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Review

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1*H*-isochromene-1-ones and isoquinoline-1(2*H*)-ones with carbonyl group in position 3: Features of synthetic approaches and transformation

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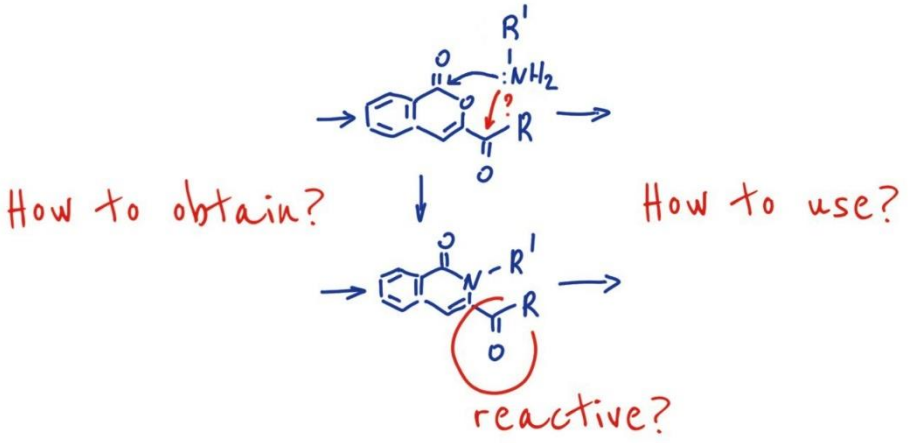
Abstract

Oxygen-containing heterocyclic 1*H*-isochromen-1-ones are core structural components of various natural products and biologically active compounds. They are used as functional substrates in the synthesis of biologically active 1*H*-isochromen-1-ones and isoquinolin-1(2*H*)-ones exhibiting different biological properties and diverse applications. Synthetic approaches to these classes of heterocyclic compounds developed in parallel from the very beginning because one of the strategies for the synthesis of isoquinolin-1-one is the recyclization of the isochromen-1-one system by the action of primary amines. In this review, we comprehensively describe the synthesis of 1*H*-isochromen-1-ones and isoquinolin-1(2*H*)-ones with a carbonyl function in position 3, summarize their use as synthons in organic chemistry and highlight their biological activities.



Keywords: Heterocyclization, recyclization, isochromenones, isoquinolinones, isocoumarins, isoquinolines.

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1. Introduction

Oxygen-containing heterocyclic scaffolds are common fragments among natural compounds with many applications in the drug design of pharmacologically relevant derivatives. The 1*H*-isochromen-1-ones (isocoumarins) are an essential oxygen-containing motif consisting of a α-pyranone ring fused to the benzene ring at 5,6-positions. Due to their attractive properties, substituted isocoumarins are becoming a prominent synthetic intermediate with various synthesis methodologies reported in recent reviews.[1,2]

Due to their biosynthetic origin, most natural isocoumarins contain a 3-alkyl (C1–C17) or a (un)substituted 3-phenyl ring on the *α*-pyranone and 8 oxygenation on the benzene ring. Among isocoumarins functionalized in the 3rd position, many biologically active compounds of both natural and synthetic origin exist. Some examples are a natural anticancer agent Cytogenin (**1**)[3] and a metabolite with antimicrobial activity Cephalosol (**2**).[4] Compound **3** was synthesized along with other derivatives as an analog of the natural antimalarial agent Cladosporin,[5] and bromoketone **4**[6,7] was used for the synthesis of 3-hetarylisocoumarins with a possible ability to treat spinal muscular atrophy (Figure 1).

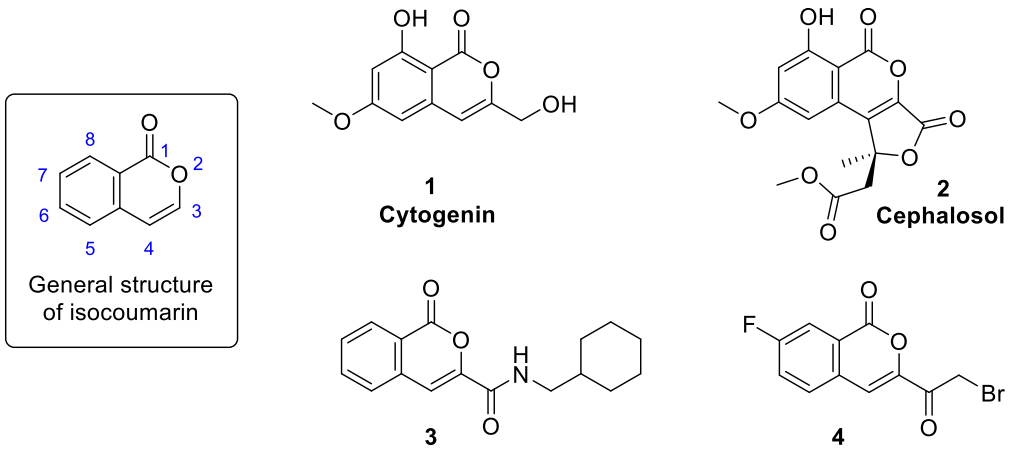
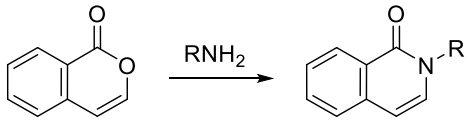


Figure 1. Representatives 1*H*-isochromen-1-ones functionalized in the 3rd position.

Recently we reviewed publications on amino acid derivatives of isocoumarins and 3,4-dihydroisocoumarins.[8]

The synthetic potential of functionalized 1*H*-isochromen-1-ones, namely derivatives with a carbonyl group in position 3 of the isocoumarin cycle, is of no less interest. The reactivity of such compounds is apparent, as is the variety of possible transformations, especially given the proximity of reaction centers. Unfortunately, relatively few studies of the methods for obtaining and using 3-acyl(formyl)isocoumarins in organic synthesis exist; this review provides an overview of these works.

The nitrogen analogs of isocoumarins, isoquinolin-1(2*H*)-ones, also known as isocarbostyrils, are found in nature and exist in equilibrium with cyclic tautomers. For this reason, the review includes isoquinolin-1-ones similar to isocoumarins with a carbonyl function. It is worth noting that the chemistry of these classes of heterocyclic compounds developed in parallel from the very beginning because one of the approaches to the formation of the isoquinolin-1(2*H*)-one **5** is the recyclization of the 1*H*-isochromen-1-ones system **6** under the action of compounds with a primary amino group (scheme 1; the results for 3-arylsubstituted derivatives are summarized and analyzed in reviews).[9,10]



6 **5**

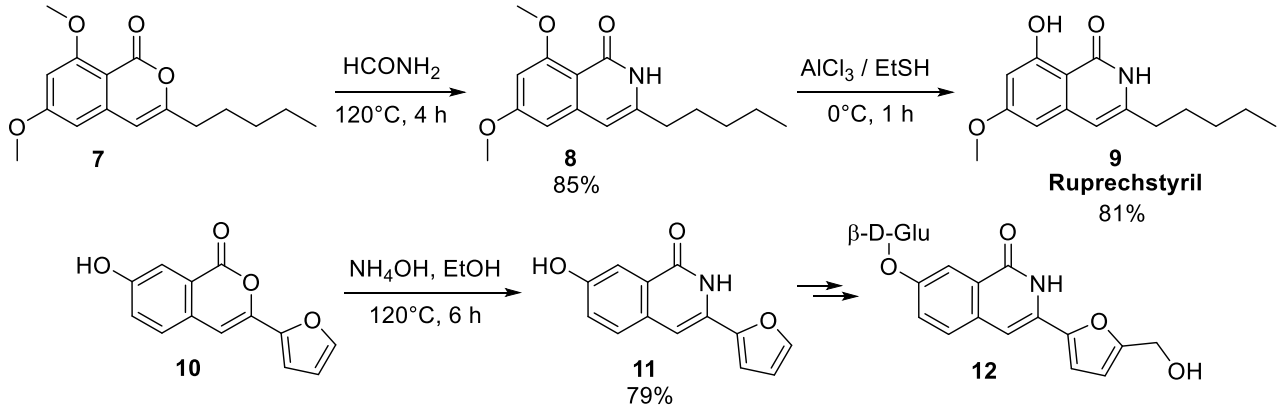
Scheme 1. Recyclization of 1*H*-isochromen-1-one system into isoquinolin-1(2*H*)-one.

Despite the significant synthetic potential of such transformations, this topic is represented by a relatively small number of works in the literature. The review covers this subject's entire period of development: from the first experiments with 3-acylisocoumarins in the 1930s to attempts to create new drugs based on 3-acylisocoumarins and isoquinolones in the 2000-2020s. Of the so far small number of patented developments in this field (the review includes 10 patents), the most significant is the Duvelisib synthesis method, which is based on the reductive amination of the acetyl group in the substituted isoquinolone.

We describe the application of various methods for implementing the transformation shown in Scheme 1. Thus, the reaction was carried out by heating with primary amines in ethanol at elevated pressure; boiling in ethanol under normal pressure but with an excess of amine; boiling in pyridine; boiling in toluene in an inert atmosphere; and when heated without solvent (for example, heat at 100-120 °C in a sealed tube or an autoclave; you can read more about variations of this technique in reviews[9,10]). Synthetic equivalents of ammonia were also used: $AcONH_4$, $(NH_4)_2CO_3$, $HCONH_2$, etc. Such diversity in the reaction procedure allows for choosing the optimal method for individual substrates, which determines the importance of this transformation in the series of isocoumarins and isoquinolones.

This approach has retained its relevance and is used, in particular, for the synthesis of natural alkaloids of the isoquinolin-1(2*H*)-one series, such as Ruprechstyril **9**[11,12] from *Ruprechtia tangarana*[13] and compound **12** from *Isatis Tinctoria*[14] (Scheme 2).

Functionalized isoquinolin-1-one appear to be as synthetically attractive as corresponding isocoumarins. Even without considering the reactivity of side functional groups, the isoquinolinone system, in contrast to the isocoumarin system, can undergo modifications in positions 1 or 2 and is therefore a promising source of various isoquinoline derivatives.

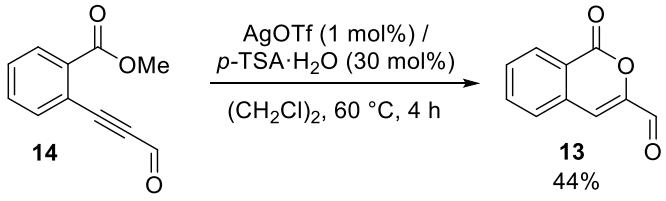


Scheme 2. Application of 1*H*-isochromen-1-ones' recyclization to the synthesis of bioactive isoquinolin-1(2*H*)-ones.

2. Synthesis of 3-Acyl- and 3-Formyl-1*H*-isochromen-1-ones

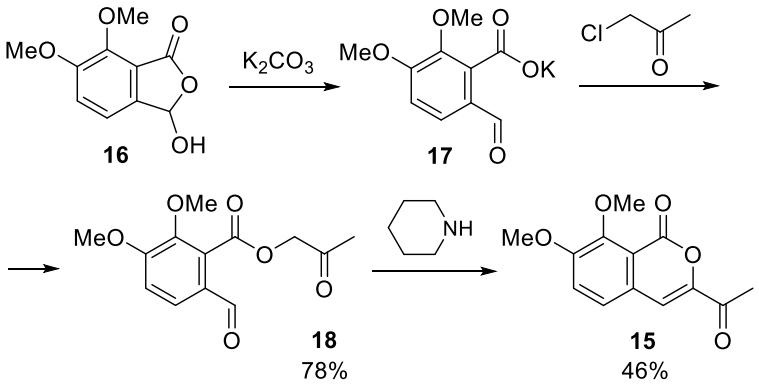
One of the widely used approaches to the synthesis of 1*H*-isochromen-1-ones – the cyclization of *ortho*-alkenyl benzoates[15] – can also be used to obtain isocoumarins with a carbonyl group in position 3, although the yields of such derivatives are not always sufficiently high. Usually, the *ortho*-alkenyl benzoates are obtained by metal-catalyzed coupling of *ortho*-iodobenzoic acids with terminal alkynes. Various acidic reagents are used for their cyclization; in some cases, the formation of *ortho*-alkenyl benzoates and their cyclization into isocoumarins takes place in one step. 3-Formylisocoumarin (**13**), the simplest isocoumarin with a carbonyl function in position 3, was synthesized with this approach. It is worth noting that this is a natural compound known under the name Artemidinal and found in the composition of *Artemisia dracunculus*.[16]

3-Formylisocoumarin (**13**) was successfully obtained with a 44% yield from methyl 2-(3-oxoprop-1-yn-1-yl)benzoate (**14**) in the study of catalytic properties of the AgOTf/*p*-TSA system (Scheme 3). It should be noted that using the same approach and under similar conditions, a considerable amount of 3-arylisocoumarins was obtained with two times higher yields.[17]



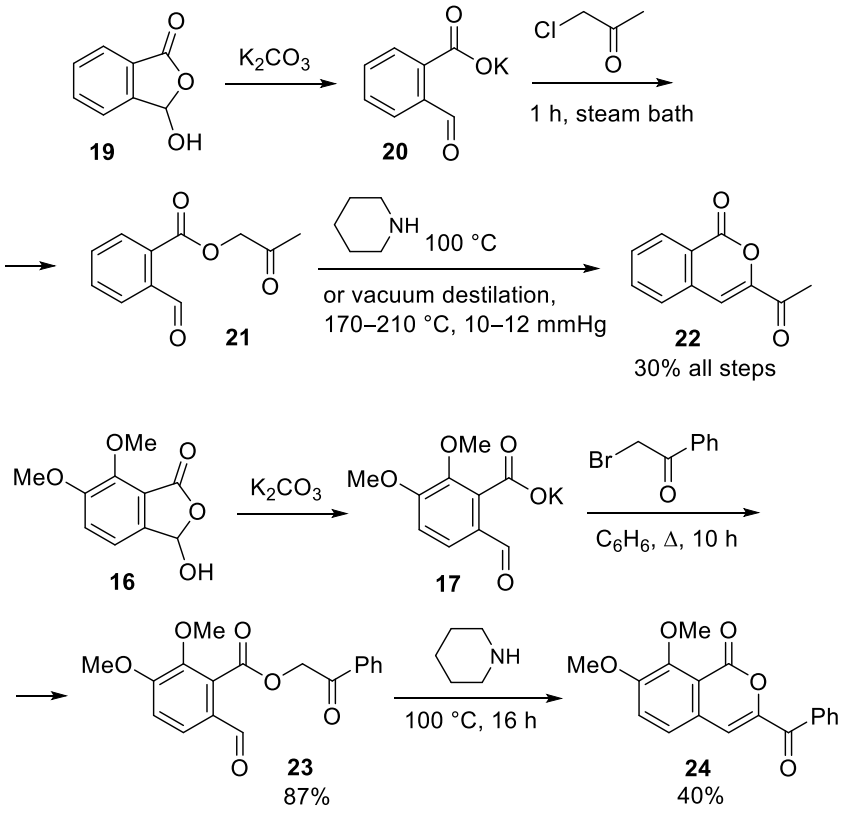
Scheme 3. Synthesis of 3-formylisocoumarin (**13**) from methyl 2-(3-oxoprop-1-yn-1-yl)benzoate (**14**).

ortho-Formylbenzoic acids are convenient substrates for the construction of 3-acylisocoumarins. These compounds form esters in reaction with halogen ketones, which are then cyclized into ketoisocoumarins by condensation of the aldehyde group and the active methylene group of the ketone. The use of this approach was first reported in the early 20th century; thus, the corresponding isocoumarin **15** was obtained from opianic acid (**16**) (Scheme 4).[18]



Scheme 4. Synthesis of 3-acetyl-7,8-dimethoxyisocoumarin (**15**) from opianic acid (**16**).

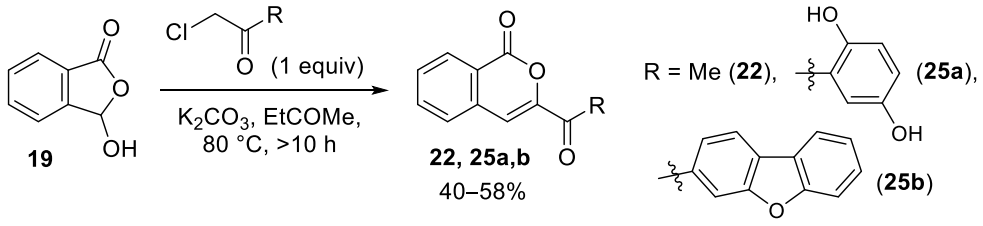
The effectiveness and duration of the 3-acylisocoumarin synthesis with this method significantly depend on the nature of the substrate substituents. For comparison, Scheme 5 represents the conditions for the interaction of *ortho*-formylbenzoic acid **19** with chloroacetone and opianic acid **16** with ω-bromoacetophenone, which allowed to obtain corresponding 3-acylisocoumarins **22** and **24**.[19]



Scheme 5. Synthesis of 3-acylisocoumarins **22** and **24** from *ortho*-formylbenzoic acid **19** and opianic acid **16**.

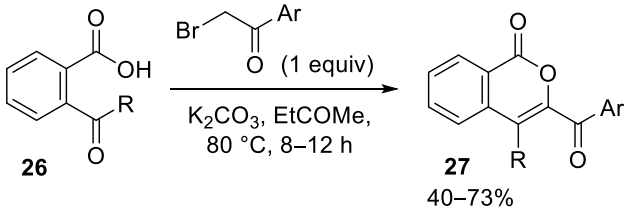
In the initial works, during the preparation of 3-acylisocoumarins from *ortho*-formylbenzoic acids, esters of type **18**, **21**, and **23** were extracted separately, but later the formation of 3-acylisocoumarins from formylbenzoic acid and haloketones was carried out in one stage, by prolonged boiling in a polar aprotic solvent with base, most often triethylamine;[20-22] the use of DBU was also successful.[23]

The synthesis of 3-acetylisocoumarins **22** and 3-aroylisocoumarins **25a,b** was also carried out during prolonged boiling in methyl ethyl ketone with K_2CO_3 as a base (Scheme 6).[24]



Scheme 6. Synthesis of 3-acylisocoumarins **22**, **25a,b** from *ortho*-formylbenzoic acid **19**.

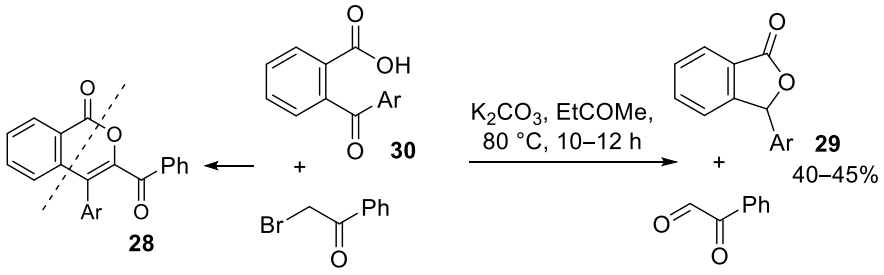
The same technique enabled a condensation of *ortho*-carboxyphenones **26** with α-bromoketones (Scheme 7);[25,26] some of the obtained 3-aroylisocoumarins **27** manifested antimicrobial, fungicidal, and anticoagulant activities, ability to lower blood pressure in rats, and anesthetic action.



R = CH_3, C_2H_5, $CH_3CH_2CH_2$
Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 2,4-$(HO)_2C_6H_3$, 2,5-$(HO)_2C_6H_3$, 4-PhC_6H_4

Scheme 7. Synthesis of 4-alkyl-3-aroylisocoumarins **27** from *ortho*-carboxyphenones.

It is worth clarifying that the attempt to obtain analogs of 3,4-disubstituted isocoumarins **28** with an aromatic substituent in position 4 was unsuccessful: heating benzophenones with α-bromoacetophenone resulted in phthalides **29** with moderate yields (Scheme 8).[25]

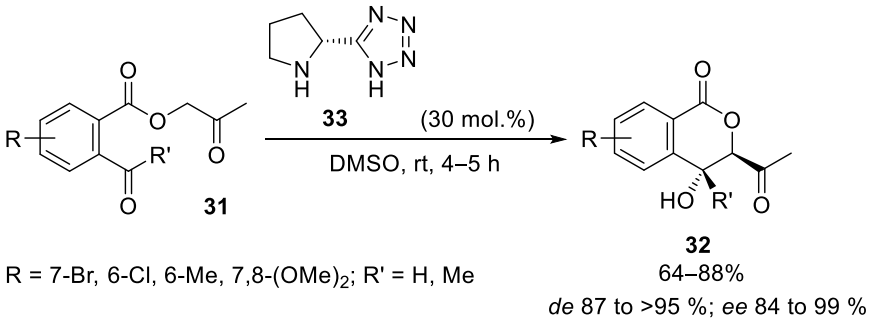


Ar = Ph, *p*-Tol, 2,4-$Me_2C_6H_3$, 3,4-$Me_2C_6H_3$, naphthalene-2-yl, 4-MeO-naphthalene-2-yl

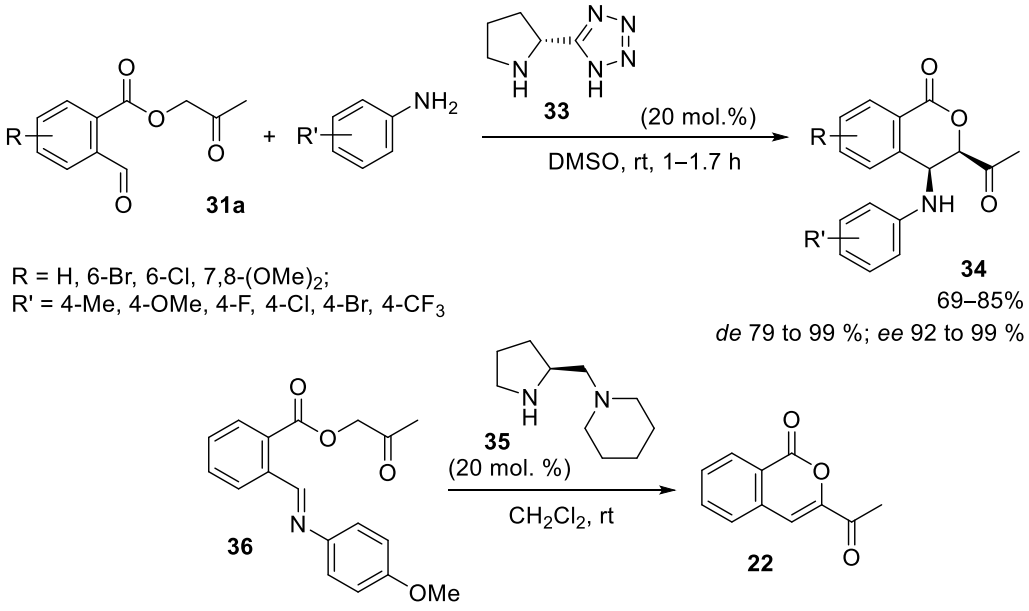
Scheme 8. Cyclization of *ortho*-carboxybenzophenones **30** into 3-aryl-2-benzofuran-1*H*-ones **29**.

Ali Ertürk and coworkers conducted a thorough study of the formation process of 3-acetylisocoumarin **13** by the condensation of *ortho*-formylbenzoic acid and chloroacetone.[27] The authors compared the effectiveness of previously published methods with synthetic procedures in which microwave irradiation was applied in different ways – an open and closed reactor and a completely closed system. However, triethylamine was recognized as the most successful base (superior to potassium carbonate, hydroxide, and phosphate), while the temperature, reaction time, and solvents varied. Some experiments, both by classical methods and with irradiation, were carried out without a solvent. It turned out that almost all methods make it possible to achieve target product yields of more than 80%, but only the use of irradiation in a completely closed system allows the synthesis of the same amount of 3-acetylisocoumarin without a solvent and in the shortest reaction time.

Derivatives **31** under mild conditions and in the presence of chiral catalysts can form 4-hydroxy-3-acyl-3,4-dihydroisocoumarins **32** with high diastereo- and enantioselectivity (Scheme 9).[28]



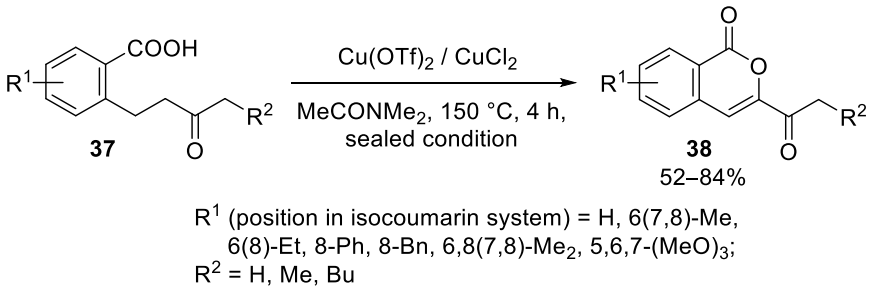
Scheme 9. Enantioselective synthesis of 4-hydroxy-3-acyl-3,4-dihydroisocoumarins **32**.



Scheme 10. Enantioselective synthesis of 4-amino-3-acyl-3,4-dihydroisocoumarins **34** and 3-acetylisocoumarin **22**.

When a similar transformation was carried out in the presence of aromatic amines, an intramolecular Mannich reaction occurred (through the intermediate imine formation stage), resulting in 4-amino-3-acyl-3,4-dihydroisocoumarins **34** (Scheme 10).[29] Additionally, various chiral proline derivatives were tested as catalysts, but all were inferior to tetrazole **33**, resulting in either reduced yields or no conversion. The use of amine **35** resulted exclusively in the formation of 3-acetylisocoumarin **22** from the Schiff base **36** (Scheme 10).

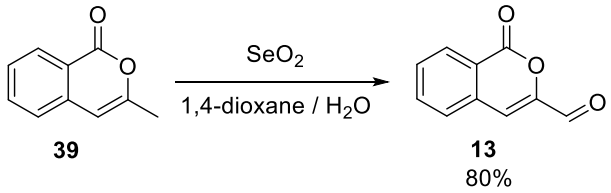
A general method of cyclization of 2-(3-oxobutyl)benzoic acids **37** into 3-acylisocoumarins **38** under the action of copper (II) trifluoromethanesulfonate in combination with copper (II) chloride as an oxidant is patented. The isocoumarin cycle is formed from successive copper-catalyzed C-O coupling and oxidative dehydrogenation, using copper triflate as an oxidant and copper chloride dihydrate as a salt (Scheme 11).[30] This transformation is unique to isocoumarin chemistry, and the mechanism undoubtedly deserves more detailed study in the future.



Scheme 11. Synthesis of 3-acylisocoumarins **38** from 2-(3-oxobutyl)benzoic acids **37**.

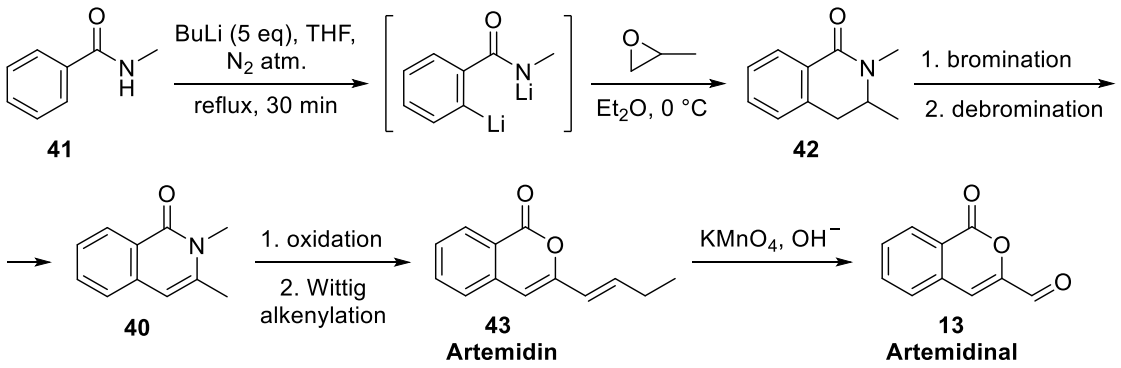
Another general strategy for the synthesis of 3-acyl(formyl)isocoumarins is based on converting the functional group in position 3 to a carbonyl.

This possibility, in particular, was illustrated by the example of product **39** methyl group conversion into a formyl group under the action of SeO_2 (Scheme 12).[31]



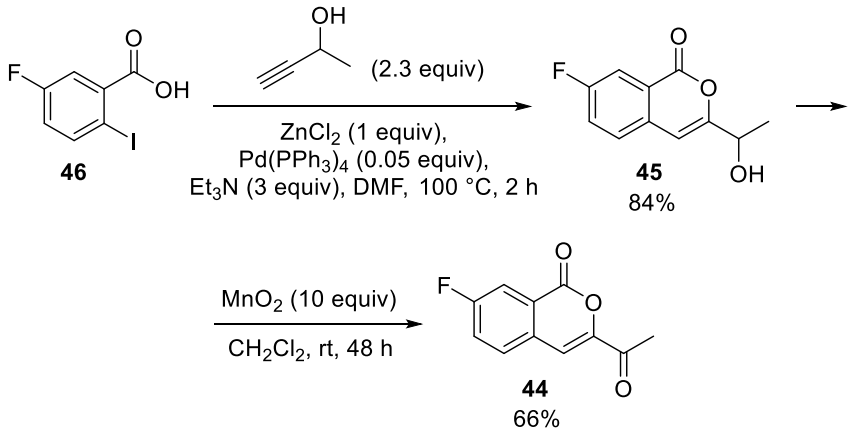
Scheme 12. Synthesis of 3-formylisocoumarin **13**.

Mallabaev and coworkers reported the oxidation of the C=C bond of natural Artemidin with $KMnO_4$ to form Artemidinal **13**,[16] which made it possible to prove the structure and relationship of these two isocoumarins of natural origin. This reaction was carried out as the last of the seven stages of the synthesis of Artemidinal (Scheme 13).[32] Interestingly, the construction of the isocoumarin system employed an uncommon approach in the chemistry of isocoumarins – the recyclization of *N*-methylisoquinolin-1(2*H*)-one **40** under the action of oxidants.



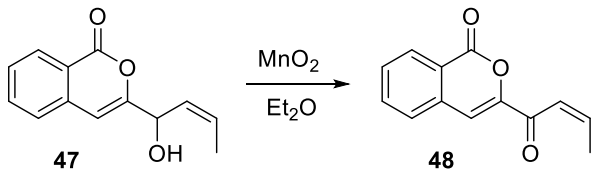
Scheme 13. Oxidation of 2,3-dimethylisoquinolin-1(2*H*)-one (**40**) as a stage of Artemidin synthesis.

Scheme 14 presents the synthesis of 3-acetyl-7-fluoroisocoumarin (**44**), which also includes the oxidation of the side hydroxyl group of isocoumarin **45**. Heterocyclization occurs during the coupling of *ortho*-iodobenzoic acid **46** and butyn-2-ol with $Pd(PPh_3)_4$ as the catalyst.[6,7]



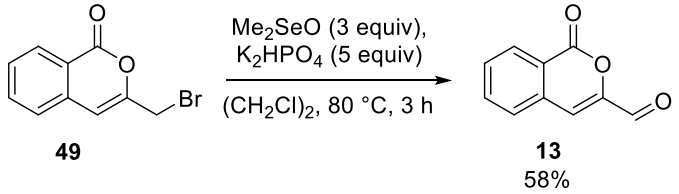
Scheme 14. Synthesis of 3-acetyl-7-fluoroisocoumarin **44**.

Oxidation of the hydroxyl group with MnO_2 was also carried out for natural isocoumarin **47** extracted from *Anthemis punctata* in order to confirm its structure (an analytical sample was used) (Scheme 15).[33]



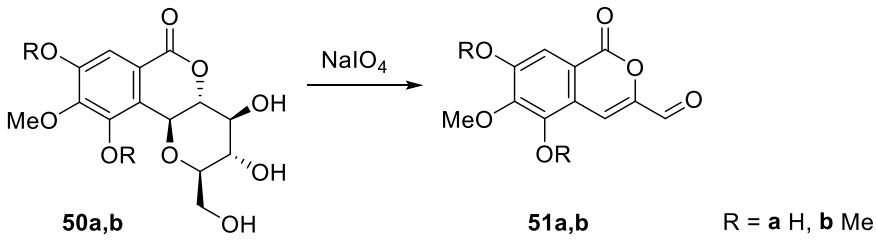
Scheme 15. Oxidation of (*Z*)-3-(1-hydroxybut-2-en-1-yl)isocoumarin (**47**) into (*Z*)-3-(but-2-enoyl)isocoumarin (**48**).

Together with a wide range of aromatic and heteroaromatic compounds with a halogenomethyl group, isocoumarin **49** took part in a large-scale study of dimethylselenoxide and potassium benzeneselenite use as oxidizing agents of the halogenomethyl group to an aldehyde group.[34] The optimal conditions for isocoumarin **49** conversion to the corresponding aldehyde **13** are given in Scheme 16.



Scheme 16. Synthesis of 3-formylisocoumarin (**13**) by the oxidation of CH_2Br group of 3-(bromomethyl)-isocoumarin (**49**).

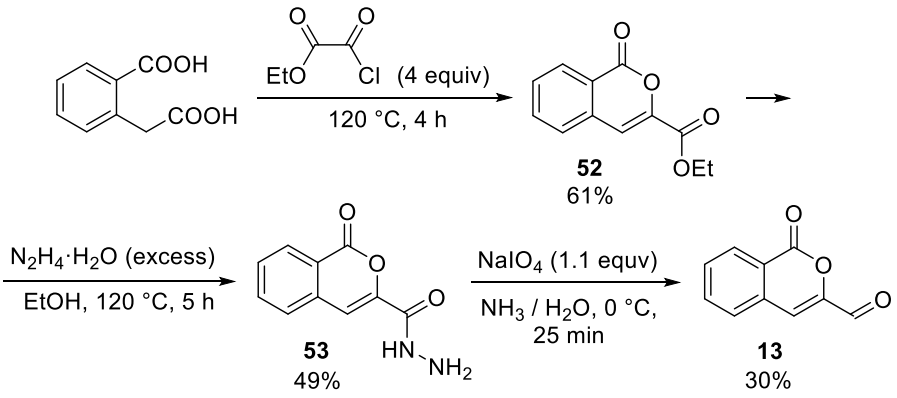
Several publications[35,36] on establishing the configuration of some natural polycyclic derivatives of a series of dihydroisocoumarins mentioned the removal of aldehyde **51a** as a result of the oxidation of Bergenine **50a** by $NaIO_4$. In this case, the alkyl fragment elimination occured in addition to the oxidative cleavage of glycol (Scheme 17). A similar transformation leading to the formation of aldehyde **51b** was described for dimethylbergenine **50b** (Scheme 17).[37,38]



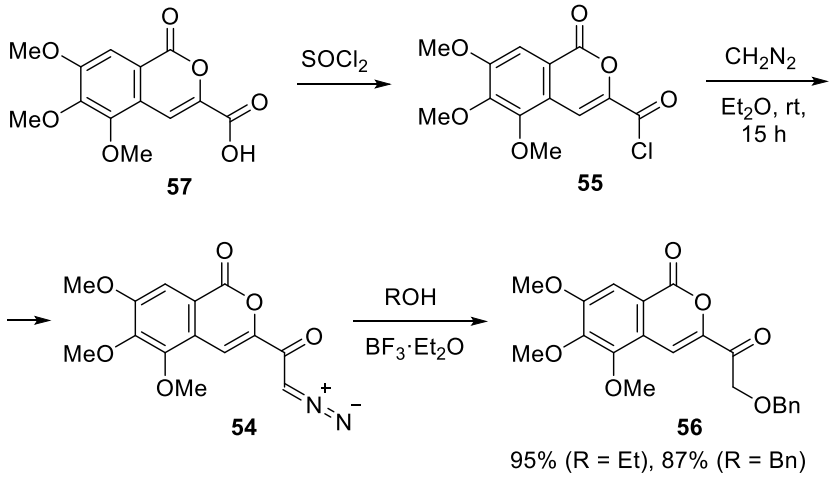
Scheme 17. Oxidation of Bergenine and dimethylbergenine into 3-formylisocoumarins **51a,b**.

Reduction as an alternative to oxidation was implemented for isocoumarin-3-carboxylic acid ester **52**, synthesized by the condensation of homophthalic acid with ethoxalyl chloride. The ester group was converted to an aldehyde via a cleavage step of the corresponding hydrazide **53** (Scheme 18).[39] Note that under these conditions - in the presence of an excess of hydrazine - the authors did not record the recyclization of the isocoumarin cycle, which is generally quite susceptible to the action of hydrazine (see review[10]). Unfortunately, the interaction of functionalized isocoumarins with hydrazine has not been studied enough to say whether this transformation is general for isocoumarin-3-carboxylic acids.

Conversion of the carboxyl group in position 3 of isocoumarin to the carbonyl group was also successfully carried out with the help of diazomethane. Thus, diazoketone **54** was obtained from anhydride **55,** and diazomethane[40] and oxyacetyl derivatives **56** were obtained upon treatment with alcohol in the presence of a Lewis acid (Scheme 19).[41]

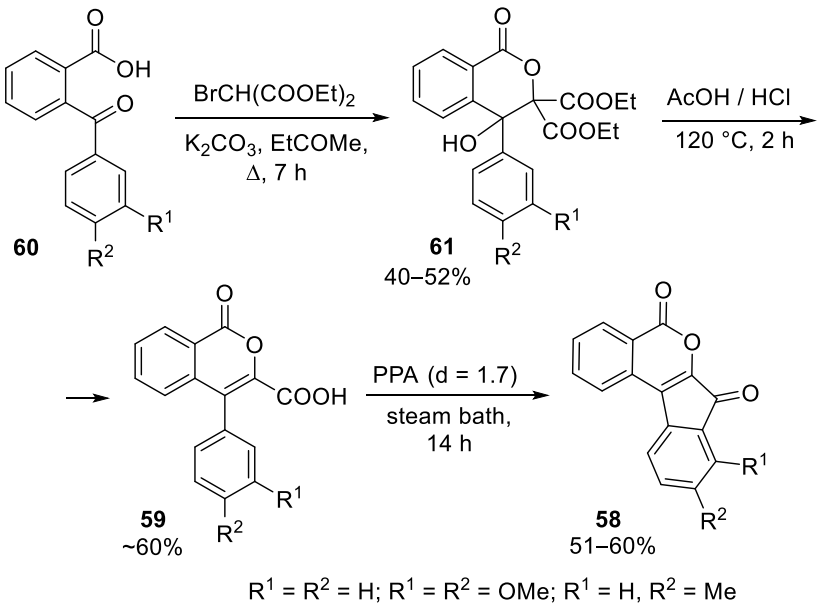


Scheme 18. Conversion of isocoumarin-3-carboxylic acid hydrazide **53** into 3-formylisocoumarin **13**.



Scheme 19. Synthesis of isocoumarin **56**.

Annulated products **58** are a rather remarkable and, at the same time, understudied variety of 3-acylisocoumarin derivatives (Scheme 20). Such compounds were successfully obtained by the intramolecular Friedel–Crafts reaction upon heating of 4-arylisocoumarin-3-carboxylic acids **59** in polyphosphoric acid, which were synthesized by cyclization of *ortho*-aroylbenzoic acids **60** with bromomalonate with subsequent acid hydrolysis of adducts **61**.[42]

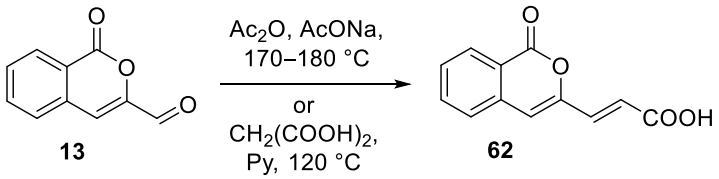


Scheme 20. Intramolecular Friedel–Crafts reaction of 4-arylisocoumarin-3-carboxylic acids **59**.

3. Transformation of 3-Acyl- and 3-Formyl-1*H*-isochromen-1-ones

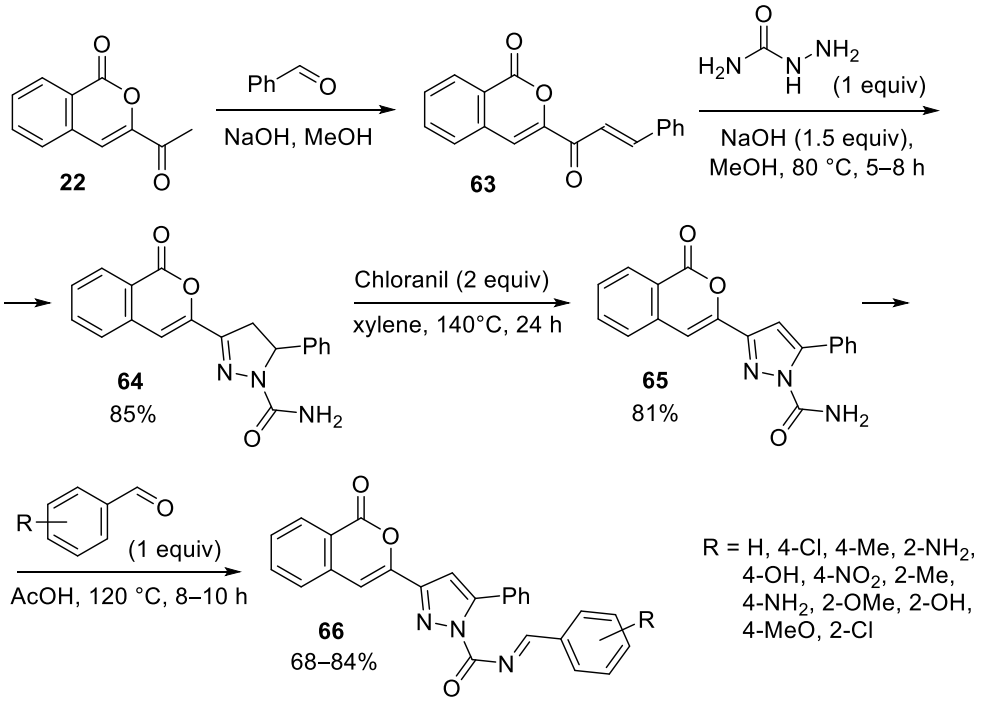
Firstly, it should be noted that the reactions that lead to the transformation of 3-acylisocoumarins into the corresponding 3-acylisoquinolones will be considered in the next section as methods for the synthesis of the latter.

Several transformations of 3-acyl- and 3-formylisocoumarins that do not affect the heterocyclic system but occur exclusively at the side keto group are known. Thus, the condensation of the above-mentioned aldehyde **13** with an active methylene compound led to acrylic acid **62** (Scheme 21).[31]



Scheme 21. Application of 3-formylisocoumarin in Perkin and Debner condensation.

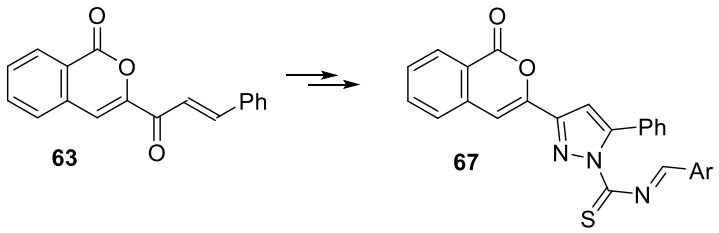
Condensation of 3-acetylisocoumarin **22** with benzaldehyde results in the formation of chalcone **63**; its subsequent heterocyclization made it possible to obtain the corresponding pyrazole derivatives **64–66** with 68-84% yields (scheme 22).[22]



Scheme 22. Synthesis of chalcone **63** and its transformation into 3-(1*H*-pyrazol-3-yl)isocoumarin derivatives **64-66**.

It is worth noting that the synthesis of pyrazoles **66** was carried out to search for new antibiotics and antifungal drugs. Most substances of this group displayed sufficiently high bioactivity, and the derivative **66** with R = 4-NO_2 (Scheme 22) was the most effective: its antimicrobial and antifungal activity was similar to comparison drugs Chloramphenicol and Ketoconazole, respectively.[22]

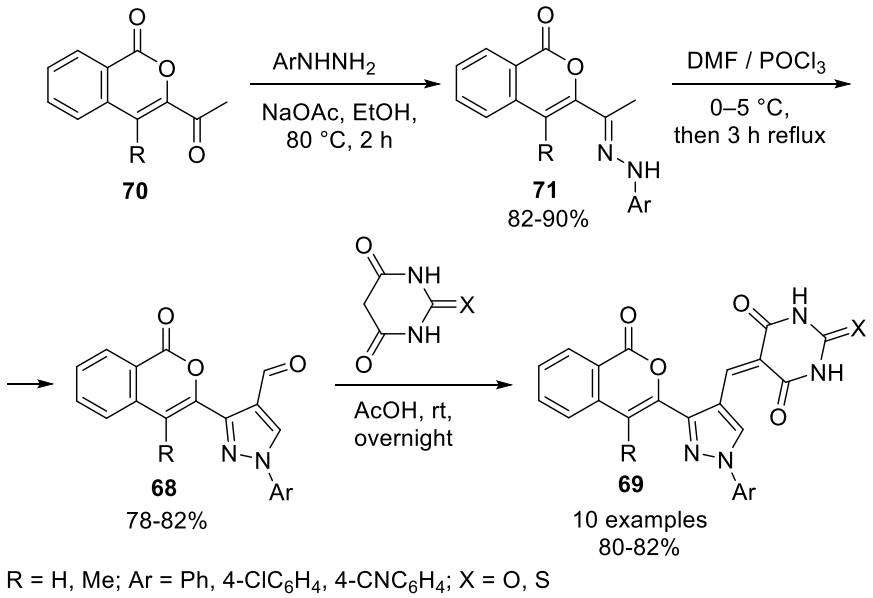
Pyrazoles **67** (Scheme 23) were recently obtained from ketone **63** using a similar approach and tested for antimicrobial activity with other heterocyclic derivatives.[43]



Scheme 23. Application of chalcone **63** for the synthesis of 3-(1*H*-pyrazol-3-yl)isocoumarin **67** with antimicrobial activity.

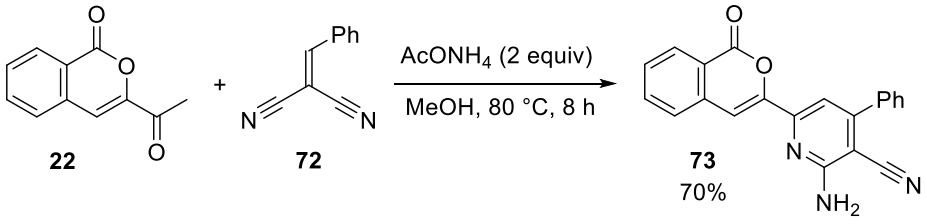
The synthesis of similar pyrazolylisocoumarins was recently reported via a slightly different sequence – the initial formation of arylhydrazones **71** from the keto group of 3-acetylisocoumarins **70**[44] (also for the synthesis of the latter see[27]) and their subsequent formylation (Scheme 24). The excess of the formylating agent leads to both the pyrazole cycle closure and its formylation. Aldehydes **68** were condensed with barbituric acid, and the resulting derivatives **69** were investigated for their interaction with four human (h) CA isoforms, hCA I,

II, IX and XII, known to be important drug targets. The inhibition constants ranged between 2.7–78.9 μM against hCA IX and 1.2–66.5 μM against hCA XII. Therefore, such isocoumarins represent a new class of CA inhibitors.



Scheme 24. Application of 3-acetylisocoumarins **70** in the synthesis of the new class of CA inhibitors – 3-(1*H*-pyrazol-3-yl)isocoumarins **69**.

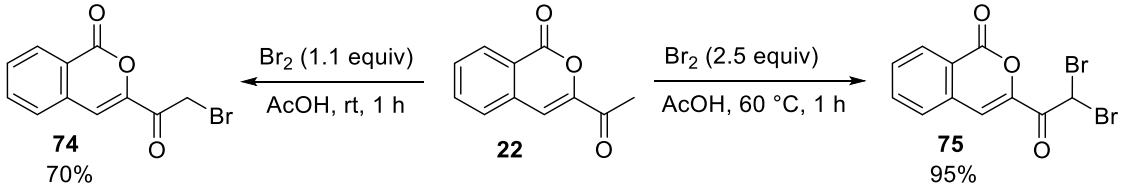
Condensation of 3-acetylisocoumarin **22** with 2-benzylidenemalononitrile (**72**) resulted in aminocyanopyridine **73** – a new fluorescent sensor with high selectivity for detecting Hg^{2+} and Fe^{3+} ions (upon chelation with metal cations, the initial fluorescence of compound **73** disappears) and with low cytotoxicity (Scheme 25).[45] The latter makes it possible to use such compounds in biological environments.



Scheme 25. Synthesis of 2-amino-6-(isocoumarin-3-yl)-4-phenylnicotinonitrile from 3-acetylisocoumarin.

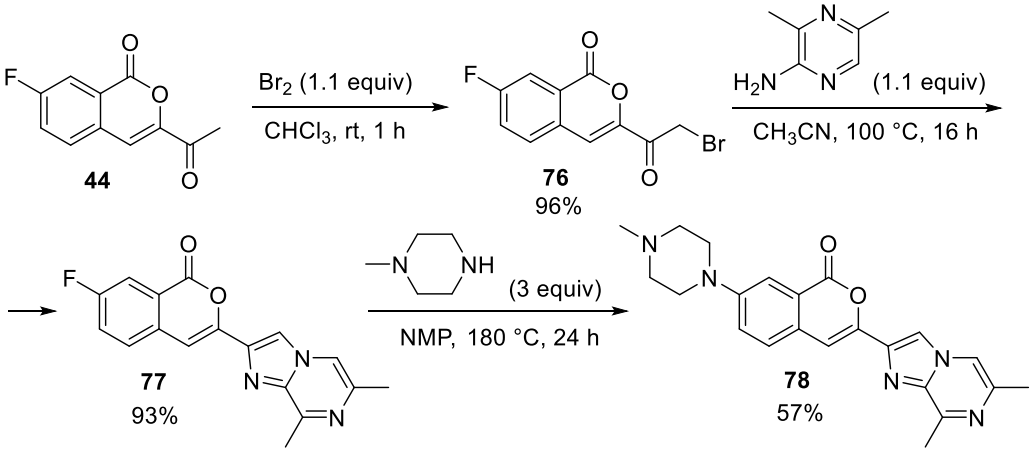
In addition to the target monobromo derivative **74**, the dibromo derivative **75** was discovered in the reaction mixture during the bromination of 3-acetylisocoumarin **22** in acetic acid,[46] (Scheme 26). The product **75** was also synthesized using 2.5 equiv. of bromine. Based on bromoketone **74**, the authors successfully obtained isocoumarins with thiazol-2-yl, 6-R-imidazo[1,2-*a*]pyridin-2-yl, imidazo[2,1-*b*]thiazole and quinoxaline substituents. The monobromo derivative **74** and the dibromo derivative **75** were used to construct the quinoxaline system.[21,47] It is noteworthy that the obtained 3-hetarylisocoumarins were subsequently used to synthesize new 1-amino-3-hetarylisoquinolines – potential anticancer agents.[47,48] Bromination of 3-acetylisocoumarin **22** in acetic acid at 5 °C resulted in the formation of 3-(*α*-bromo)acetylisocoumarin (**74**).[49] Its

subsequent interaction with a methacrylic acid salt resulted in the formation of an ester; the authors studied the temperature decomposition parameters of the specified methacrylate polymer in detail.



Scheme 26. Synthesis of mono- and dibromo derivatives **74** and **75**.

Bromination of acetylisocoumarin **44** was carried out in chloroform, and the bromoacetyl derivative **76** was successfully used as a starting product for the construction of the imidazopyrazine ring; fluorine was replaced with the *N*-methylpiperazine fragment (Scheme 27).[6,7]

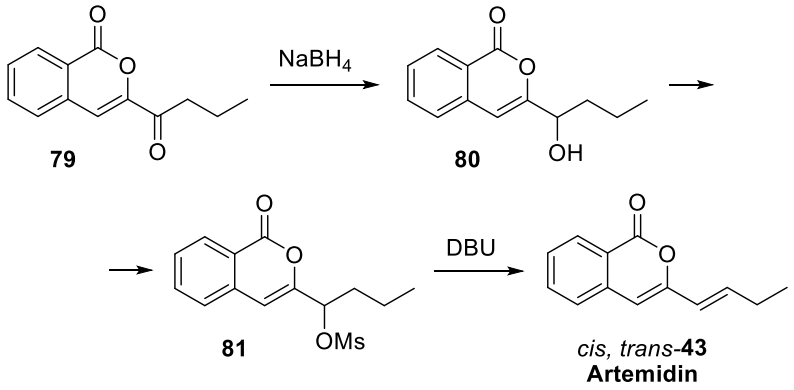


Scheme 27. Synthesis of 3-(6,8-dimethylimidazo[1,2-*a*]pyrazin-2-yl)-7-(4-methylpiperazin-1-yl)isocoumarin (**78**).

3-Hetarylisocoumarin **78**'s potential to treat spinal muscular atrophy was also investigated; the product showed high activity *in vitro* but, unfortunately, revealed a weak negative effect on the brain and/or blood plasma when administered orally to rats.[6,50] In order to diversify the list of potential agents for the treatment of spinal muscular atrophy, other isocoumarins with an *N*-methylpiperazine substituent in position 7 and a heterocyclic substituent (imidazo[2,1-*b*]thiazole-6-yl, 8-chloroimidazo[1,2-*a*]pyridin-2-yl, 1,3-dimethyl-pyrrolo[1,2-*a*]pyrazin-7-yl) in position 3 were successfully obtained through a similar synthetic sequence starting from the *α*-bromoacetyl derivative **74**.[7]

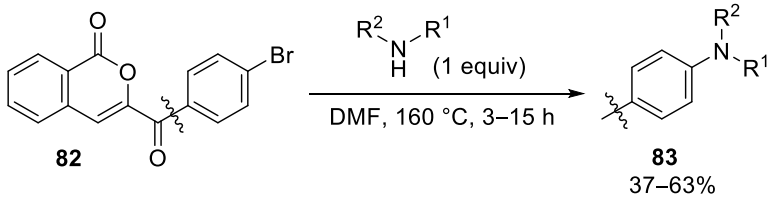
Although the isocoumarin system has been reduced by relatively mild reducing agents such as sodium borohydride, there are several examples in the literature where the side C=O-group in 3-acyl- or 3-formylisocoumarins reduces faster.

Thus, sequential reduction of the carbonyl group of isocoumarin **79** to the hydroxy group followed by elimination of the mesylate **81** (Scheme 28) was used for the synthesis of *cis*- and *trans*-isomers of Artemidin **43**.[51]



Scheme 28. Conversion of 3-butyrylisocoumarin **79** for the synthesis of Artemidin.

The 3-acylisocoumarin-based transformation where the lactone fragment and the keto group were preserved was of particular interest. Thus, the interaction of the 4-bromobenzoyl derivative **82** with 1 equiv. of amine completed with the substitution of just the bromine atom by the amine residue, despite the relatively harsh conditions of the transformation (prolonged boiling in DMF) (Scheme 29).[24] Certain amines **83** showed significant antibacterial and fungicidal activity during the initial screening.



R^1R^2NH = *p*(*m*)-nitroaniline, 3-aminocoumarin, 2,5-dichloroaniline, sulphanilic acid, *p*-aminobenzoic acid, glycine, *N*-methyl aniline, acridon

Scheme 29. Amination of 4-bromobenzoylisocoumarin **82**.

To summarize, we would like to note that a comprehensive study[52] of various chemical transformations of probably the best-known natural representatives of 3-acylisocoumarins – tricyclic derivatives of Brevifolin **84** and Brevifolincarboxylic acid **85** (Figure 2) - was also conducted. The study included the extraction of target compounds from natural raw materials, alkylation, acylation and esterification of functional groups, cleavage of rings, and reactions with *N*-nucleophiles.

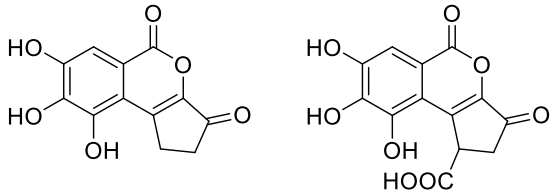
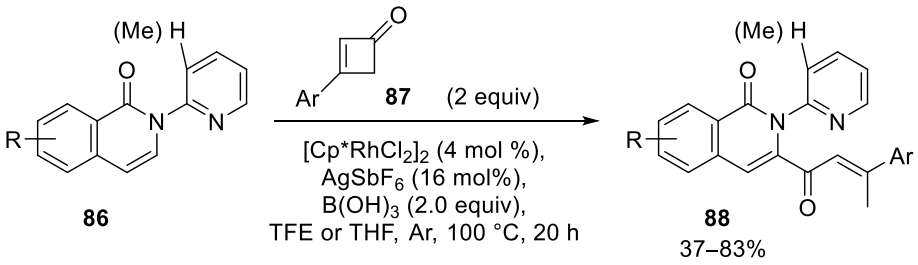


Figure 2. Examples of tricyclic derivatives of isocoumarins – Brevifolin (**84**) and Brevifolincarboxylic acid (**85**).

4. Synthesis of 3-Acyl- and 3-Formyl-isoquinolin-1(2*H*)-ones

We start this subsection with the review of methods for the construction of 3-acylisoquinolin-1(2*H*)-ones through the direct addition of a keto group to the isoquinolin-1(2*H*)-one cycle.

Thus, the catalytic coupling of isoquinolones **86** with cyclobutenones **87** (Scheme 30) was described.[53] The isoquinolone derivatives involved in the reaction contained an α-pyridyl substituent at the nitrogen atom (a directing residue capable of chelation with the catalyst metal), and the corresponding chalcones **88** were isolated as reaction products.



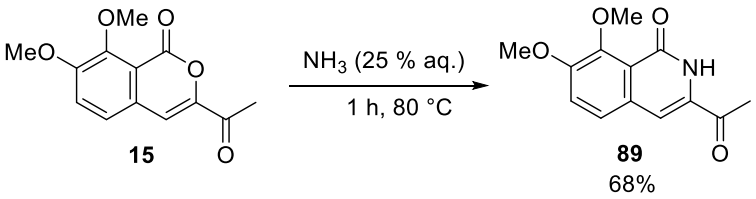
R = H, 6-MeO, 6-Ph, 6-Cl(Br), 5-Br; Ar = Ph, 3-$CH_3C_6H_4$

Scheme 30. Synthesis of chalcone-type products by coupling of 2-(pyridin-2-yl)isoquinolin-1(2*H*)-ones with cyclobutenones.

The keto group was successfully introduced into the isoquinolin-1-one system by the transformation of the side group in position 3. Thus, the oxidation of the acetyl group in the 3rd position of methylisoquinolin-1(2*H*)-one by SeO_2 resulted in 3-formylisoquinolin-1(2*H*)-one with 80% product yield.[31]

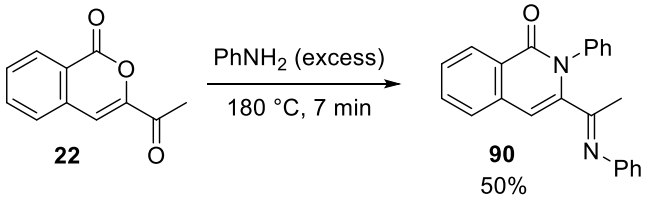
The following methods are based on the formation of the isoquinolone cycle during a recyclization reaction.

The first and early publications devoted to the synthesis of 3-acylisocoumarins noted the possibility of their transformation into the corresponding isoquinolones. Thus, isocoumarin **15**, obtained from opianic acid **16**, gave product **89** (Scheme 31)[54,19] when heated in aqueous ammonia (a similar transformation is described for 3-acetylisocoumarin[19]).



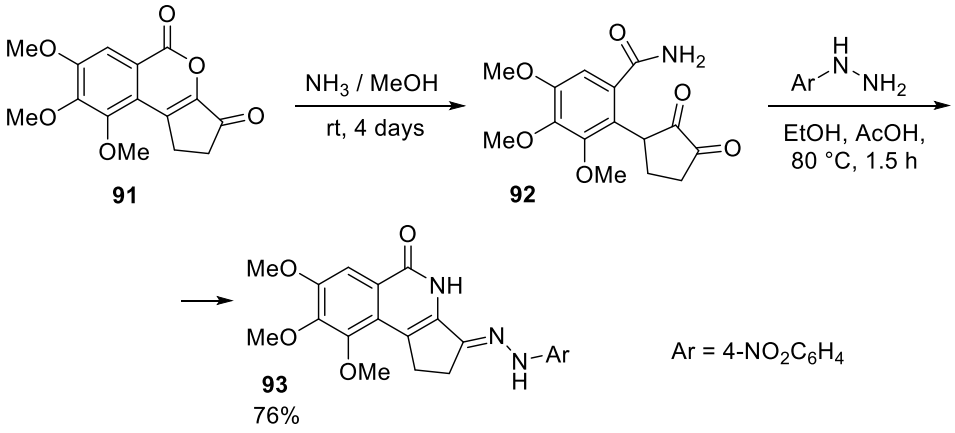
Scheme 31. Recyclization of 3-acylisocoumarin **15** into 3-acylisoquinolin-1(2*H*)-one **89** without ketogroup involvement.

Interestingly, the interaction of 3-acylisocoumarin **22** with aniline resulted in the formation of isoquinolone **90** with an imino group (Scheme 32).[19]



Scheme 32. Recyclization of 3-acylisocoumarin **22** into 3-acylisoquinolin-1(2*H*)-one **90** with ketogroup transformation into imine.

In contrast, treating Brevifolin trimethyl ether **91** with an alcoholic solution of ammonia yielded benzamide **92**; the authors noted that the cyclization to the isoquinolone cycle occurred while obtaining the hydrazone **93** (Scheme 33).[52]



Scheme 33. Brevifolin trimethyl ether (**91**) conversion into isoquinolin-1(2*H*)-one **93** with hydrazone group.

Interestingly, the carboxyl group was not involved in the transformation of the isocoumarin cycle of acrylic acid **62** (see scheme 21) to isoquinolone under the action of ammonia.[31]

The main idea for the design and synthesis of a series of 2-benzoyl-3-acyl-4-arylisoquinolones[55,56] was the high ability to inhibit JNK (c-Jun N-terminal protein kinase), inherent in the derivatives **94a-c** shown in Figure 3.

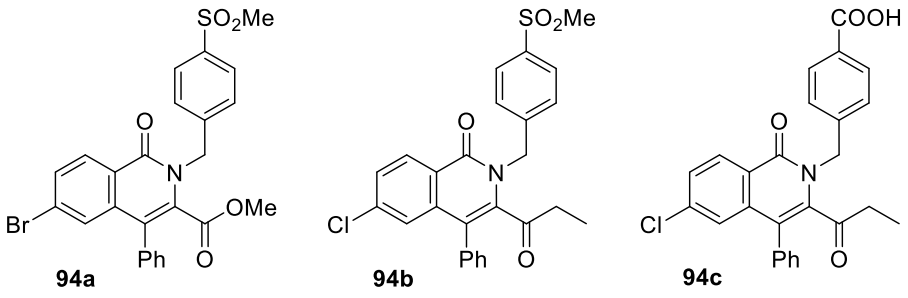
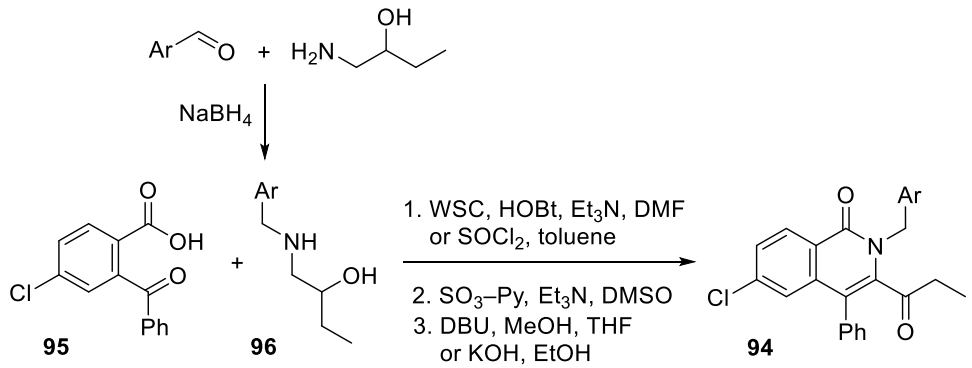


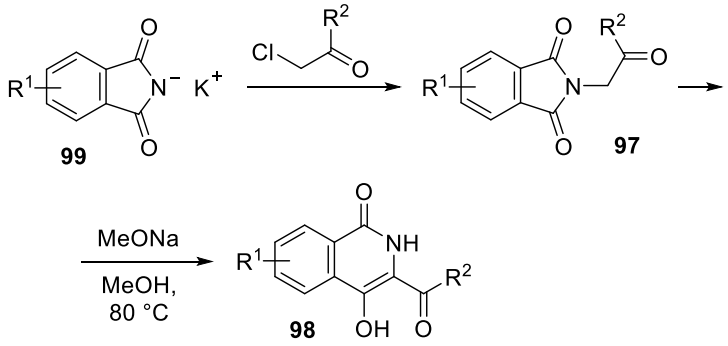
Figure 3. 2-Benzoyl-3-acyl-4-arylisoquinolin-1(2*H*)-ones **94a-c** as inhibitors of JNK.

The isoquinolone system of such potential inhibitors (Scheme 34; structure **94** as an example) was obtained from *ortho*-carboxybenzophenone **95** in a manner similar to the synthesis of isocoumarins from *ortho*-formylbenzoic acid. Although considerable efforts were directed to the synthesis of the starting substrates – amino alcohols **96**, it was successfully possible to synthesize the key products **94** in three stages in one-pot manner.[55]



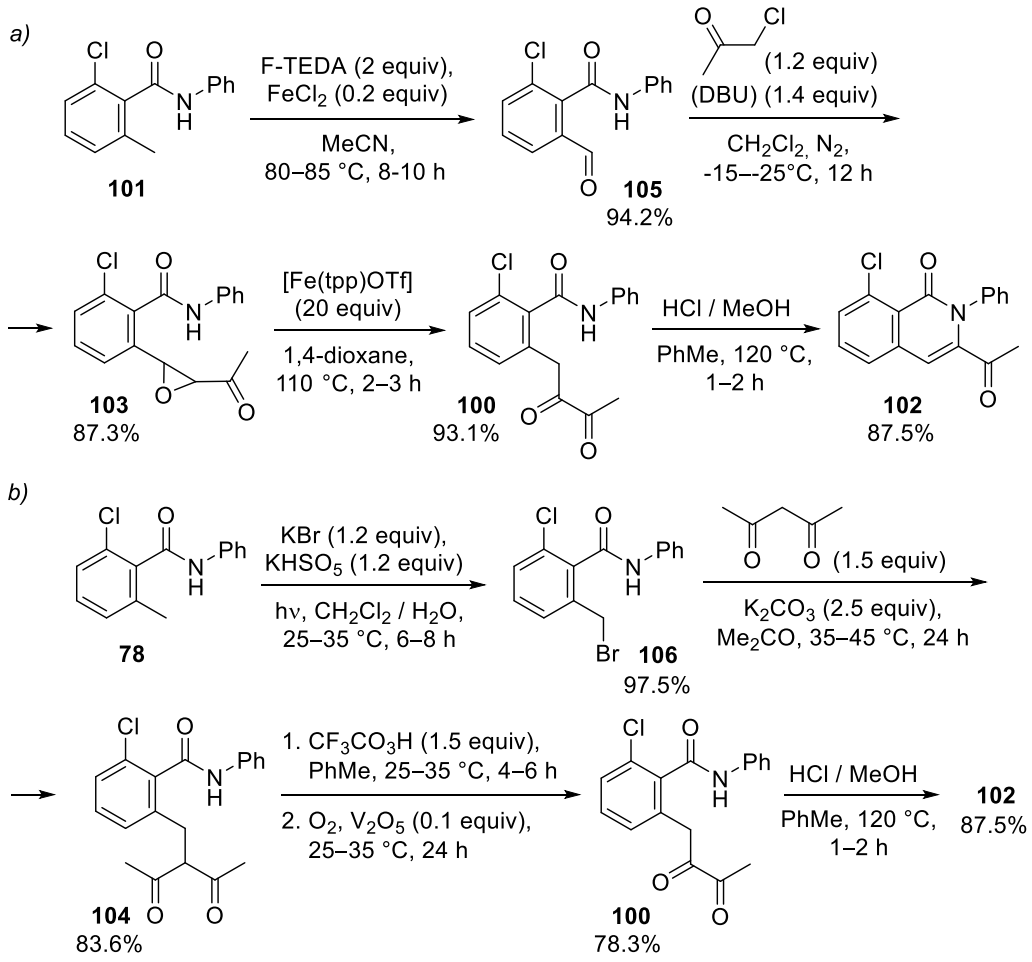
Scheme 34. Synthesis of 2-benzoyl-3-acyl-4-arylisoquinolin-1(2*H*)-ones **94**.

The same group of methods also includes the recyclization of phthalimides **97** to 3-acetyl-4-hydroxyisoquinolones **98** (Scheme 35).[57-59]



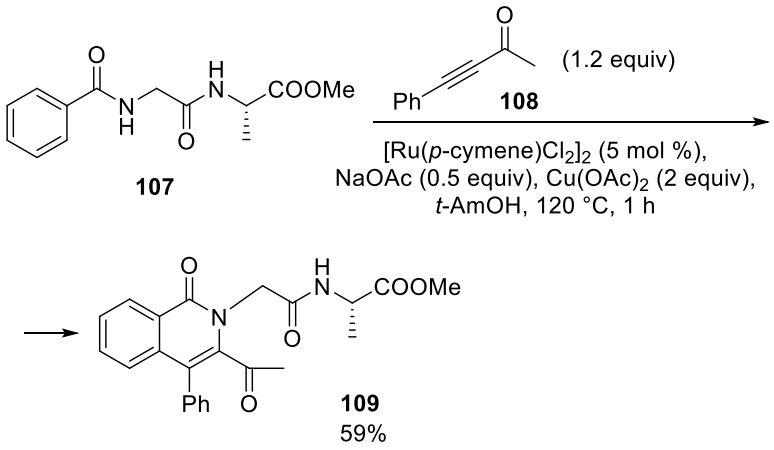
Scheme 35. Recyclization of *N*-(2-oxoalkyl)phthalimides **97** to 3-acetyl-4-hydroxyisoquinolin-1(2*H*)-ones **98**.

Cyclization of ketone **100** formed from benzamide **101** (scheme 36) resulted in the formation of 3-acetylisoquinolone **102**.[60,61] Moreover, two methods are described for the transformation of product **100** into product **101** – through rearrangement of epoxide **103** (scheme 36a)[60] and oxidative cleavage of β-diketone **104** (Scheme 35b).[61]



Scheme 36. Synthesis of 3-acetyl-8-chloro-2-phenylisoquinolin-1(2*H*)-one (**102**).

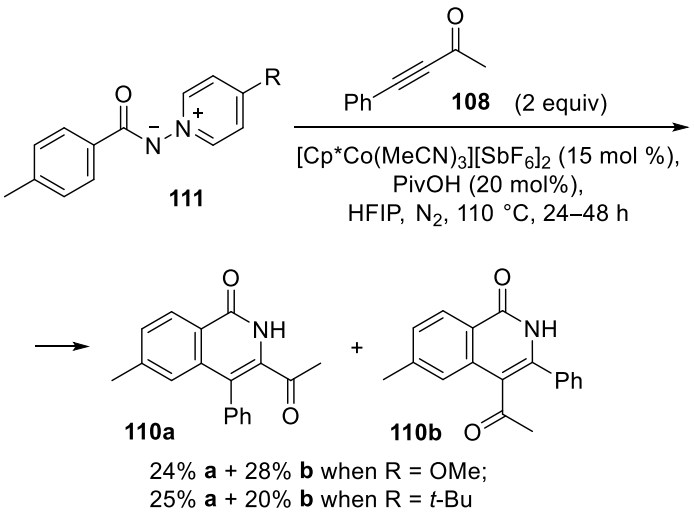
However, the most effective approach to the synthesis of 3-acylisoquinolones is the coupling of benzamides and similar compounds with alkynes containing either a keto group or another group capable of converting to a carbonyl fragment.



Scheme 37. Synthesis of 3-acetyl-4-phenylisoquinolin-1(2*H*)-one **109**.

Thus, Ruthenium-catalyzed coupling with C–H activation made it possible to complete the isoquinolin-1(2*H*)-one cycle to the benzoylated *N*-terminal of oligopeptide **107** (Scheme 37).[62] Most of the isoquinolin-1(2*H*)-ones obtained in this work contained phenyl substituents in position 3, and only a few contained functional groups such as Ac, COOMe, and CH_2CH_2OH in this position.

Apparent problems of using asymmetrical alkynes, such as the ketone **108** mentioned above, in similar transformations are probably related to regioselectivity. Indeed, two possible isomers **110a,b** were formed during the construction of isoquinolin-1(2*H*)-one from ketone **108** and *N*-iminopyridinium ylide **111** with a cobalt catalyst (Scheme 38).[63]



Scheme 38. Synthesis of 3(4)-acetyl-4(3)-phenylisoquinolin-1(2*H*)-ones **110a,b**.

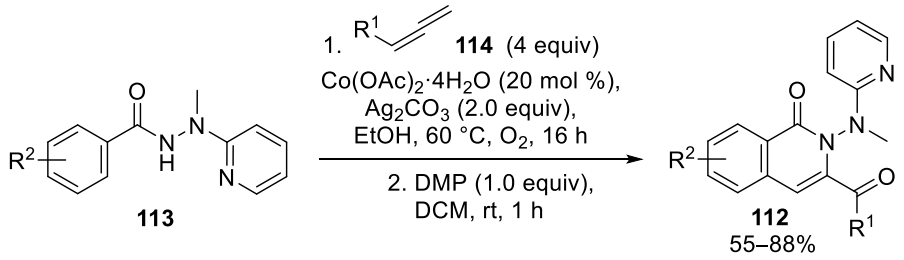
It also turned out that it is unnecessary to use compounds with an already existing acyl group to synthesize 3-acylisoquinolones from benzamides and unsaturated compounds as the group can be formed during the reaction.

Thus, *N*-aminoisoquinolones **112** with a carbonyl group were obtained *via* cobalt-catalyzed annulation of hydrazides **113** with allenes **114** and simultaneous oxidation with air oxygen (Scheme 39).[64] In general, the synthetic procedure successfully gave more than 30 representatives of *N*-aminoisoquinolone; the furan analog **112a** was also obtained under these conditions, albeit with a low yield (28%).

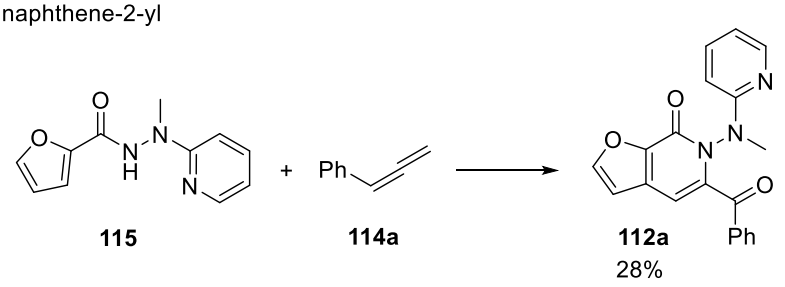
An alternative method for obtaining 3-acylisoquinolin-1(2*H*)-ones is also described.[65] Thus, using Rhodium results not only in the C–H activation of the *ortho* position of *N*-ethoxybenzamide **116** and its coupling with alkyne **117**, but also in the opening of the strained cycle of cyclobutanol (rarely cyclopropanol) with the formation of a product **118**; isoquinolone **118a** was obtained with a yield of 92% (Scheme 40). According to the reaction mechanism given in the publication, Rhodium (III) was reduced to Rhodium (I) as a result of the coupling process, and the reverse oxidation stage in the catalytic cycle was carried out by the N–OEt fragment of the substrate, which in turn was reduced to the N-H group.

N-methoxybenzamides **120** were successfully employed in a similar transformation, but the reaction conditions were slightly changed – sodium acetate (1 equiv.) was used as the base, and the reaction was carried out in toluene at 80 °C.[66,67] As a result, 26 representatives of 3-butyroylisoquinolin-1(2*H*)-ones **121** were obtained. The use of 1-propargylcyclopropanol **122** in this reaction resulted in the formation of the corresponding 3-propanoylisoquinolin-1(2*H*)-one **123** (Scheme 41). At the same time, we note that 1-

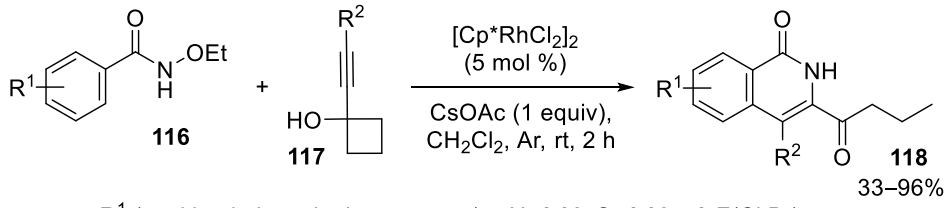
propargylcyclopentanol turned out to be inert under the given reaction conditions, demonstrating the importance of the ease of ring opening for the success of the transformation. The obtained products **121** and **123** showed anticancer activity in an *in vitro* study.



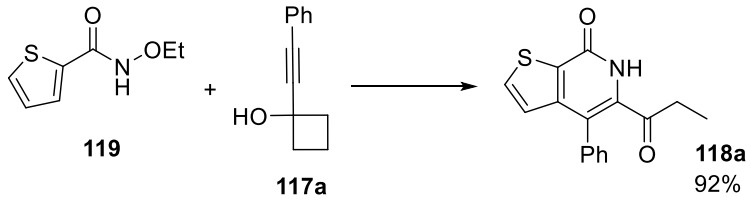
R^1 = Ph, R^2 (position in isoquinolone system) = H, 6(7)-Me, 6-*t*-Bu, 6(7,8)-MeO, 6-Ph, 6-OPh, 6-SMe, 6-NMe_2, 6-F(Cl,Br,I), 6-CF_3, 6-OCF_3, 6-Ac, 6-CO_2Me, 5,7-Me_2, 5,6,7-$(MeO)_3$;
R^2 = H, R^1 = 2(3,4)-MeC_6H_4, 4-*t*-BuC_6H_4, 4-$MeOC_6H_4$, 2(3)-ClC_6H_4, 3(4)-BrC_6H_4, CH_2CH_2Ph, naphthene-2-yl



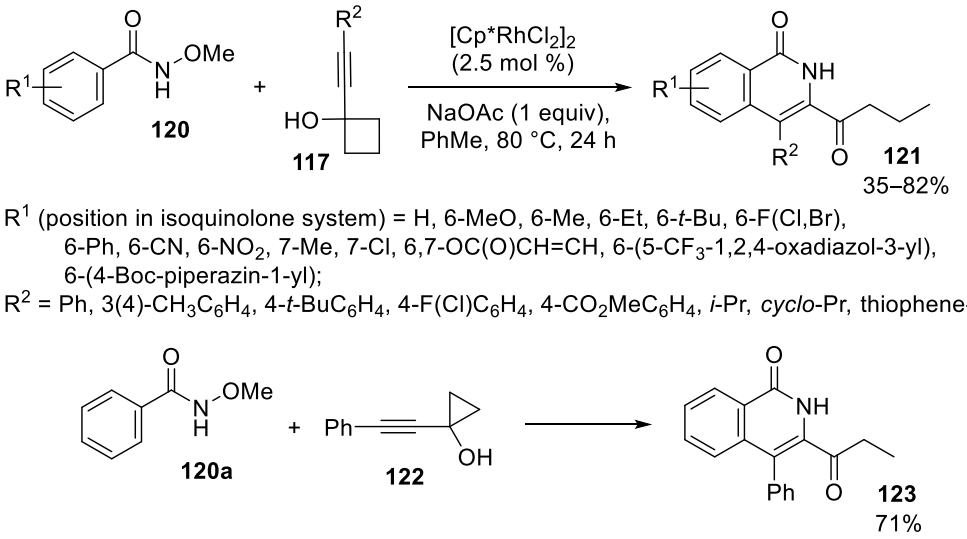
Scheme 39. Synthesis of 3-acyl-2-(methyl(pyridin-2-yl)amino)isoquinolin-1(2*H*)-ones **112** and their furan analog.



R^1 (position in isoquinolone system) = H, 6-MeO, 6-Me, 6-F(Cl,Br), 6-CN, 6-NO_2, 6-CO_2Me, 7-Me, 7-Cl(Br), 5,7-Cl_2, 6,7-benzo;
R^2 = Ph, 3(4)-MeC_6H_4, 3(4)-Cl(Br)C_6H_4, 2-ClC_6H_4, 2(3,4)-$MeOC_6H_4$, 3,5-$(MeO)_2C_6H_3$, *n*-Bu, CH_2CH_2Ph, naphthene-2-yl, thiophene-2-yl



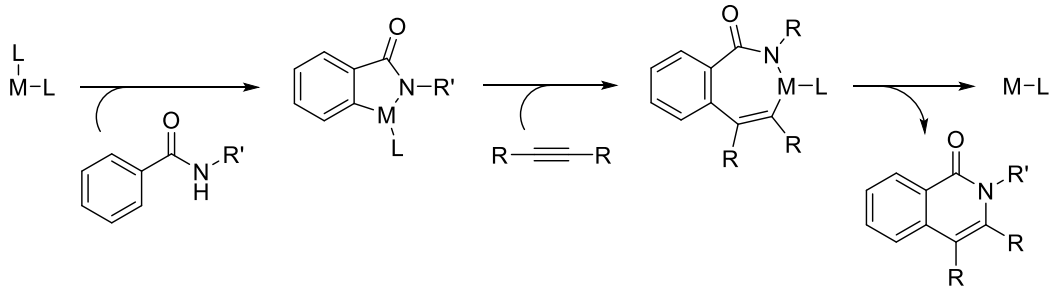
Scheme 40. Synthesis of 4-substituted 3-butyrylisoquinolin-1(2*H*)-ones **118** and their thiophene analog.



R^1 (position in isoquinolone system) = H, 6-MeO, 6-Me, 6-Et, 6-*t*-Bu, 6-F(Cl,Br), 6-Ph, 6-CN, 6-NO_2, 7-Me, 7-Cl, 6,7-OC(O)CH=CH, 6-(5-CF_3-1,2,4-oxadiazol-3-yl), 6-(4-Boc-piperazin-1-yl);
R^2 = Ph, 3(4)-$CH_3C_6H_4$, 4-*t*-BuC_6H_4, 4-F(Cl)C_6H_4, 4-$CO_2MeC_6H_4$, *i*-Pr, *cyclo*-Pr, thiophene-3-yl

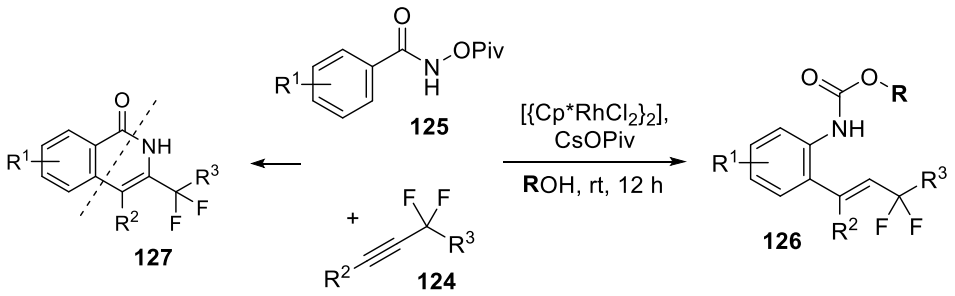
Scheme 41. Synthesis of 4-substituted 3-acylisoquinolin-1(2*H*)-ones **121** and **123**.

In general, it is worth noting that the considered set of metal-catalyzed cyclizations allows for a wide variation of substituents, although in some cases, the structure of the starting substrates can make the reaction impossible. As for the key stage of the metal-catalyzed coupling of benzamides with alkynes, the following general scheme is relevant for the above reactions (Scheme 42; M is metal, L is ligands). Moreover, R' can contain a functional group capable of coordination with a metal (as in Schemes 37, 39, 40, and 41). It is believed that additional chelation of R'–M at the intermediate complex formation stage is one of this transformation's success factors.



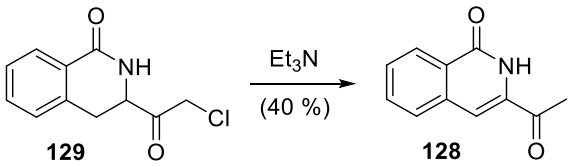
Scheme 42. General mechanism of metal-catalyzed coupling of benzamides with alkynes.

In particular, the coupling of alkynes **124** with a difluoromethylene group with benzamides **125** under the conditions of a Ruthenium-catalyzed reaction resulted not in the isoquinolones but the products of the Lossen rearrangement **126** (Scheme 43).[68]



Scheme 43. An unexpected Lossen rearrangement of benzamide derivatives.

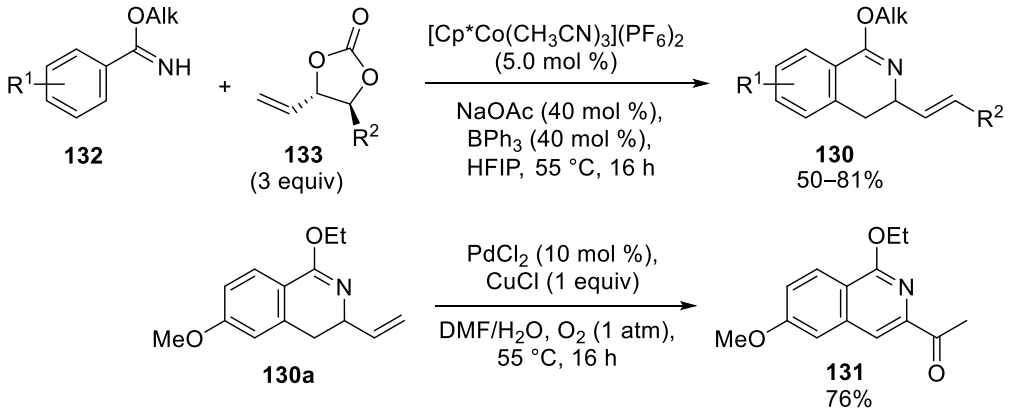
Several examples of reactions leading to the formation of 3-acylisoquinolones and their analogs are also known but have not yet found widespread use. An approach to the synthesis of α,β-unsaturated ketones during the dehydrohalogenation of α-amino-α'-halogenoketones was described.[69] Thus, the corresponding isoquinolone **128** was obtained in the 40% yield from the cyclic aminohalogenoketone **129** in this reaction (Scheme 44).



Scheme 44. Synthesis of 3-acetylisoquinolin-1(2*H*)-one **128**.

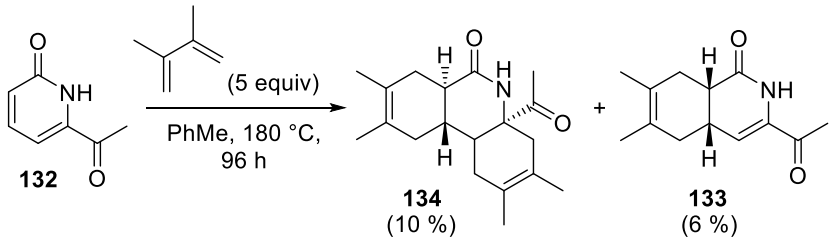
The possibility of the 3-methylisoquinolin-1(2*H*)-one methyl group oxidation to the formyl group by SeO_2 was also mentioned: the reaction is similar to the one given above for 3-methylisocoumarin (Scheme 12).[31]

An approach to the synthesis of vinyl derivatives **130** was developed.[70] The oxidation of compound **130a** to 1-ethoxy-3-acetylisoquinoline **131** was successfully carried out to demonstrate the synthetic capabilities of the obtained products (Scheme 45).



Scheme 45. Synthesis of 1-ethoxy-3-acetylisoquinoline **131**.

The Diels-Alder reaction using pyridone **132** as a starting compound resulted in a mixture of products that contained isoquinolone **133** with a partially hydrogenated carbocycle together with product **134**; however, the product yield was relatively low (Scheme 46).[71]



Scheme 46. The Diels-Alder reaction of 6-acetylpyridin-2(1*H*)-one **132** with 2,3-dimethylbuta-1,3-diene.

4. Transformation of 3-Acyl- and 3-Formylisoquinolin-1(2*H*)-ones

Active functional groups can participate in many transformations without affecting the isoquinolone system or the carbonyl fragment. Thus, numerous modifications by the pyrazole fragment of 3-acylisoquinolones such as compound **94** (see above in scheme 34, Ar – functionalized pyrazole) were carried out in work[55] to find more effective JNK inhibitors: oxidation of the mercapto group to the sulfoxide, hydrolysis of the ester group to carboxyl and its subsequent interaction with amines, *N*-alkylation of pyrazole, *N*-acylation of pyrazole with isocyanates. According to the assay results, compound **94d** showed the highest ability to inhibit JNK (and therefore showed prospects in treating heart failure) (Figure 4).

The formation of the Schiff base based on the acetyl group of isoquinolone **135** followed by asymmetric reduction of the imine was patented as a method for the synthesis of Duvelisib **136** – leukemia and lymphoma treatment drug (Scheme 47).[60,61] Moreover, two alternative methods for reducing imine **137** in the presence of chiral catalysts were developed: catalytic hydrogenation[60] and the action of trichlorosilane.[61]

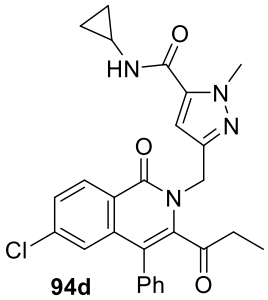
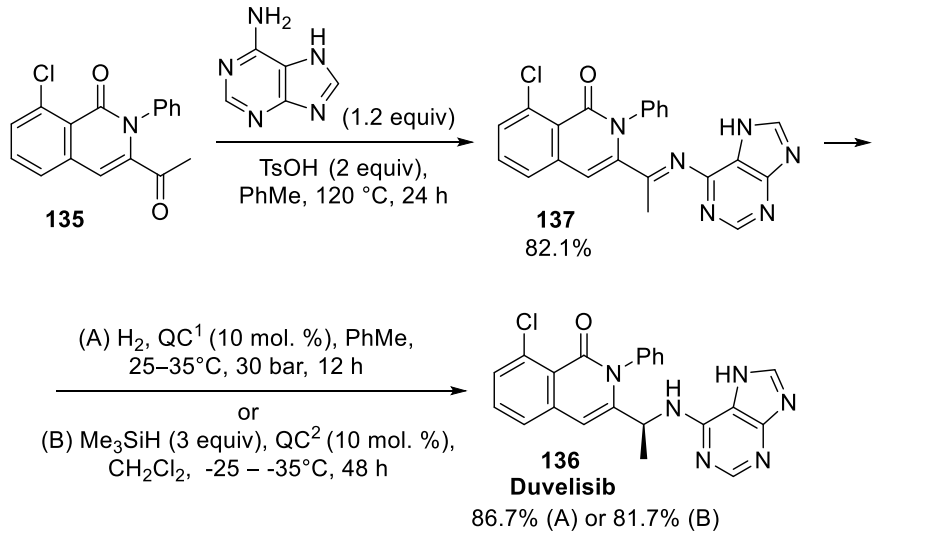


Figure 4. The most active of 2-(pyrazolylmethyl)-3-acyl-4-arylisoquinolin-1(2*H*)-ones JNK inhibitor.

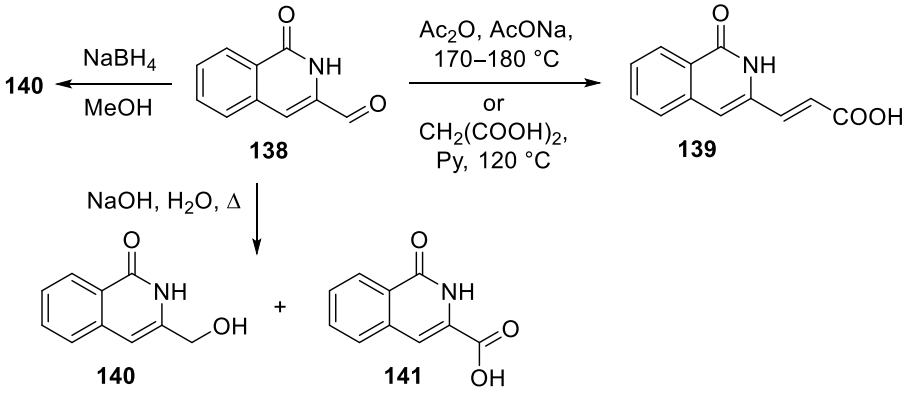


QC[1]: (*S*)-6,12-bis(3,5-di-*tert*-butylphenyl)-9-methylene-9,10-dihydro-8*H*-dinaphtho[2,1-*f*:1',2'-*h*][1,5]dioxonine + cocatalyst bis(pentafluorophenyl)borane;
QC[2]: (*S*,*E*)-*N*-(4-(phenyldiazenyl)phenyl)-1-pivaloylpyrrolidine-2-carboxamide

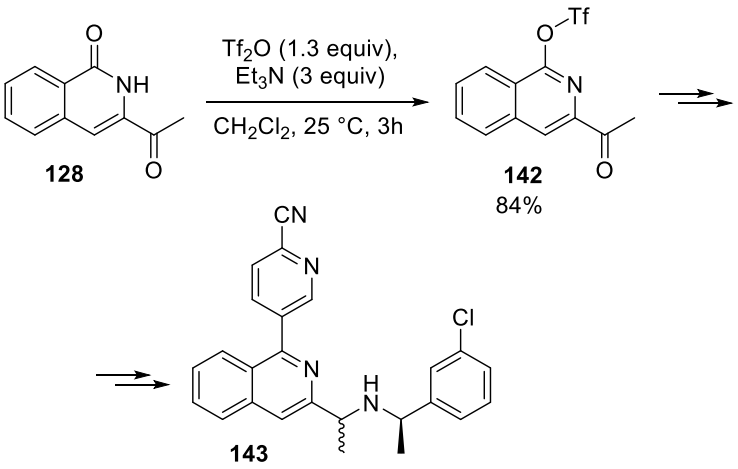
Scheme 47. Synthesis of Duvelisib from 3-acetyl-8-chloro-2-phenylisoquinolin-1(2*H*)-one **135**.

For 3-formylisoquinolin-1(2*H*)-one **138**, reduction with sodium borohydride to the corresponding alcohol, Perkin or Debner condensation with the formation of acrylic acid **139** with an isoquinolone substituent, as well as the Cannizzaro reaction were described (Scheme 48).[31]

O-Acylation or *O*-alkylation occurs through the formation of the enol form of the isoquinolone, which provides prospects for additional modification at position 1 of the heterocycle. Scheme 49 depicts an example of using this strategy to synthesize the isoquinoline **143** as a potential modulator of calcium-sensitive receptors.[72] A Palladium-catalyzed coupling with appropriate boronic acids was used for arylation, and sodium borohydride was used at the reductive amination stage.

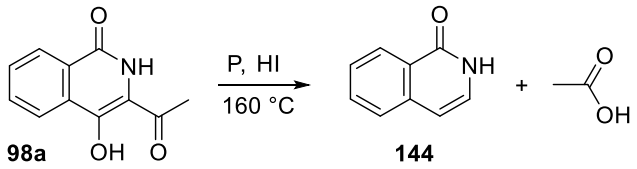


Scheme 48. Application of 3-formylisoquinolin-1(2*H*)-one in the condensation, oxidation, and reduction reactions.



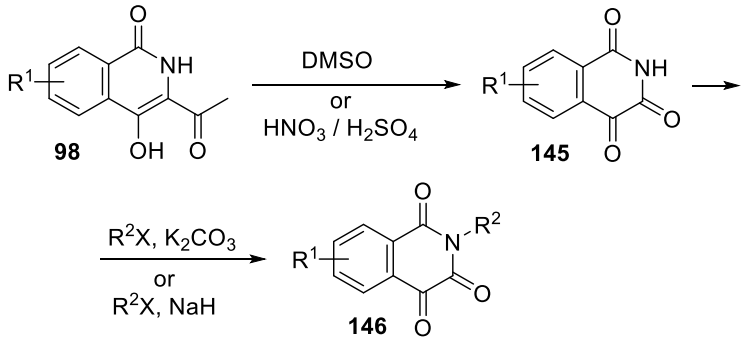
Scheme 49. Synthesis of isoquinoline **143** as a potential modulator of calcium-sensitive receptors.

It was also found that 3-acetyl-4-hydroxyisoquinolone **98a** (synthesis is shown in Scheme 35) undergoes deacetylation into the unsubstituted isoquinolone **144** (Scheme 50) under reducing conditions.[57]



Scheme 50. Synthesis of isoquinolone **144** by deacetylation of 3-acetyl-4-hydroxyisoquinolone.

In addition to reduction, oxidation of 3-acetyl-4-hydroxyisoquinolone derivatives **98** is also known. Thus, isoquinoline-1,3,4-triones **146** were obtained as drug-like compounds for nervous regressive disease treatment (Scheme 51).[73]



Scheme 51. Oxidation of 3-acetyl-4-hydroxyisoquinolones **98** to isoquinoline-1,3,4-triones **146**.

The synthetic potential of functionalized isoquinolones (in particular, compounds with a keto group) and their analogues is also indicated by the patented development devoted to the search for new phosphoinositide

3-kinase (PI3K) inhibitors, which mentions the possibility of introducing new substituents into the isoquinoline fragment by coupling at positions 1 and 4 and reductive amination of the carbonyl group.[74]

5. Conclusions

The importance of the 1*H*-isochromen-1-one and isoquinolin-1(2*H*)-one derivatives arises from their widespread occurrence in nature, versatility as suitable substrates for functionalization, and remarkable bioactivity. Developing various synthetic methodologies to obtain these heterocycles has continually attracted the attention of synthetic organic chemists. The synthetic approaches to these two classes of heterocyclic compounds have developed in parallel from the beginning since one of the strategies for synthesizing isoquinolin-1(2*H*)-one is the recyclization of the 1*H*-isochromen-1-one system by the action of primary amines. Furthermore, the isochromenone and isoquinolinone scaffolds are essential intermediates in organic chemistry. Further, various significant bioactivities have been associated with these scaffolds and reported in the literature. The present review focuses on the studies of new pharmacologically important 1*H*-isochromen-1-ones and isoquinolin-1(2*H*)-ones with a carbonyl function in position 3 and their structural analogs. The review also highlights developments towards alternative approaches, and efficient strategies. It also summarizes their use as privileged scaffolds in drug design and discovery.

Acknowledgments

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