Synthesis and Reactivity of Electron-Deficient 3-Vinylchromones

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Synthesis and Reactivity of Electron-Deficient 3-Vinylchromones

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Dedicated to Dr. V. Yu. Korotaev on the occasion of his 50th birthday

Abstract The literature data on the methods of synthesis and reactivity of electron-deficient 3-vinylchromones containing electron-withdrawing groups at the exo-cyclic double bond are summarized and systematized for the first time. The main methods for obtaining these compounds are Knoevenagel condensation, Wittig reaction, and palladium-catalysed cross-couplings. The most important chemical properties are transformations under the action of mono- and dinucleophiles, ambiphilic cyclizations, and cycloaddition reactions. The cross-conjugated and polyelectrophilic dienone system in 3-vinylchromones provides their high reactivity and makes these compounds valuable building blocks for the preparation of more complex heterocyclic systems. Chemical transformations of 3-vinylchromones usually begin with an attack of the C-2 atom and are accompanied by the opening of the pyrone ring followed by recycyclization, in which the carbonyl group of chromone, an exo-double bond or a substituent on it can take part. The mechanisms of the reactions are discussed, the conditions for their implementation and the yields of the resulting products are indicated. This review focuses on an analysis and generalization of the knowledge that has accumulated on the chemistry of electron-deficient 3-vinylchromones, mostly over the past 15 years.

1 Introduction

Chromone (4H-chromen-4-one, 4H-1-benzopyran-4-one) is the ancestor of the most important oxygen-containing heterocyclic system, which thanks to flavonoids and isoflavonoids, is very widespread in the plant kingdom. Due to their natural origin, chromones have long attracted the attention of researchers, and reviews regularly appear in the literature on their isolation from natural sources, their biological activity, and their use as preferred structural blocks in the preparation of more complex heterocycles.

The synthetic capabilities of the chromone (benzo-y-pyrene) system are mainly determined by the structural features of the γ-pyrene ring, as well as by the nature and position of the substituents on it. It is obvious that electron-withdrawing groups make the pyrone fragment more active towards nucleophiles, especially when there is no substituent at C-2 and the acceptor group is in the 3-position. Taking this into account, when considering the chemical properties of chromones, it is desirable to distinguish between 2-substituted and 3-unsubstituted chromones, as their reactivity can be very different from each other due to the different electrophilicity and steric accessibility of the C-2 atom, at which the nucleophilic attack usually begins.

Replacement of the aryl substituent at position 3 of isoflavones by an electron-withdrawing group (X = CHO, COR, CN, etc.) radically changes the reactivity of the γ-pyrene ring, transforming it into a geminally activated alkene with three electrophilic centers (C-2, C-4, group X at C-3) and a good leaving group in the form of a phenolate anion capable of performing the function of an internal nucleophile (chromones I). Such chromones include 3-formylchromone (1a) – the most popular and most widely studied representative of a number of 3-substituted chromones.

Of the three possible directions of nucleophilic attack in this series of compounds, 1A-As on the C-2 atom (favored) and 1,2-As on the 3-X group (less favored) are most often realized. Michael addition of Y-Z dinucleophiles (hydrazines, and hydroxylamines for instance) usually leads to opening of the pyrone ring and is accompanied by recycyclization, in which the phenolate anion competes for the X group with the second nucleophilic center Z. The latter, in turn, has a choice between the carbonyl and X group. In the case of 1,2-addition at the 3-X substituent, the ability of the adduct to undergo intramolecular attack at the C-2 and C-4 electrophilic centers is retained (Scheme 1). If the nucleophilicity of the Y and Z atoms is close, as, for example, in methylhydrazine, then the picture becomes
even more complicated, and issues of regiochemistry of the final products acquire special significance. The reactions of 3-substituted chromones 1 with 1,3-acetonedicarboxylate ester serve as an example that illustrates how changes in the functional groups in the pyrone ring alter the direction of reaction with the same 1,3-C,C-dinucleophile, leading to the formation of such carbo- and heterocyclic products as benzophenones, benzocoumarins, azaanthrones, and benzochromones\(^3\) (Scheme 1).

Unlike 3-formyl-\(^2\) 3-trifluoroacetyl-\(^1\) 3-cyano-\(^5\) 3-halogeno-\(^3,6\) 3-carboxy-\(^7\) 3-alkoxy carbonyl-\(^8\) 3-alkoxalyl-\(^9\) and 3-{1-alkynyl}chromones\(^10\) the chemical properties of which have already been summarized and analysed in the literature, the reactivity of electron-deficient 3-{1-alkenyl}chromones 2 has not been previously considered. Meanwhile, in recent years, interest in these readily available representatives of the family of 3-substituted chromones has been growing, and their chemistry is developing intensively, deserving a separate discussion. This review systematizes the data on 3-vinylchromones having one or two electron-withdrawing groups at the 2’-position (with the exception of 3-styrylchromones\(^10\)), published mainly over the past 15 years, as well as some earlier works necessary to create a coherent and complete picture.

### Scheme 1. Possible pathways for the reactions of dinucleophiles with 3-substituted chromones 1

This review is the first to consider 2-unsubstituted 3-{1-alkenyl}chromones 2 with electron-withdrawing substituents at the exo-double bond, which are vinylogs of chromones 1 and have an extended synthetic potential. Indeed, the polyelectrophilic nature of 3-vinylchromones 2, associated with the presence in their structure of a carbonyl carbon atom (endo-C4), a hidden aldehyde group (crypto-C2), a polarized double bond (exo-C1’), and an electron-withdrawing group X, makes these compounds even more reactive and attractive substrates than chromones 1 for the construction of a wide range of organic molecules.

The most characteristic transformations of 3-vinylchromones 2, which are a cross-conjugated diene system, having an endo-\(\alpha\)-ene fragment and an exo-cyclic double bond (at \(X = \text{COR} - \text{exo-}\alpha\)-ene), are reactions with mono- and dinucleophiles (I and II), with amphiphiles containing nucleophilic and electrophilic centers (III), as well as [4+2] and [3+2] cycloaddition reactions (IV). Scheme 2 shows the main electrophilic centers in 3-vinylchromones 2 and the main directions of the above reactions, most of which, including cycloaddition reactions, are accompanied by the opening of the \(\gamma\)-pyrone ring. It is obvious that the introduction of the second electron-withdrawing substituent at the 2’-position will lead to an increase in the electrophilicity of the exo-C1’ and crypto-C2 atoms.

### Scheme 2. Reactivity of electron-deficient 3-vinylchromones 2

#### 2 Synthesis of 3-vinylchromones

##### 2.1 From 3-formylchromones

The most important method for the preparation of electron-deficient 3-{1-alkenyl}chromones 2 is the Knoevenagel condensation of 3-formylchromones with active methylene compounds. Numerous examples of such reactions, including active methylene heterocycles, have been described in reviews by Gasparova\(^11\) and Ibragim.\(^12\) This review will focus on 3-vinylchromones with one or two electron-withdrawing groups, mainly CO\(_2\)R, Ac, ArCO, CN, at the exo-C=C double bond in the 2’-position. The first representatives of this series, \(E-3\)-(chromon-3-yl)acrylic acid (2a) and \(E-3\)-(chromon-3-yl)acrylonitrile (2b), exhibiting antiallergic properties, were synthesized in 1975 by Nohara and co-workers\(^13\) on heating 3-formylchromone (1a) with malonic and cyanoacetic acids at 110 °C in pyridine (Scheme 3).
In this work, chromone analogs of chalcones 5 were considered as a new group of biologically active compounds. To obtain them, acid-catalyzed Claisen-Schmidt condensation between 6-methyl-3-formylchromone (1b) and substituted acetophenones was used. In the case of chalcones 5a, the reaction was carried out either in acetic acid in the presence of catalytic amounts of perchloric acid, or in a mixture of triethylorthoformate with perchloric acid (Scheme 6). For 2-hydroxycetophenones, these conditions turned out to be unsuitable; however, their complexes with BF₃ readily react with chromone 1b in acetic acid to form intermediates 6, the treatment of which with sodium bicarbonate in ethanol gives chalcones 5b in good yields.

Condensation of 6,8-dichloro-3-formylchromone (1c) with an in situ generated Horner-Wittig reagent formed between fluoromethylphenylsulfonylurea and diethylchlorophosphate in the presence of lithium hexamethyldisilazane (LHMDS) led to vinylsulfonyl 7, which was converted to fluorovinylnitramine 8 under the action of tributyltin hydride (2 equiv.) and catalytic amounts of azobisisobutyronitrile (AIBN) in refluxing benzene, maintaining the double bond configuration (Scheme 7). Cross-coupling of stannane 8 with benzoyl chloride in the presence of Pd(PPh₃)₄ gave fluorochalcone 9, which is of interest for subsequent syntheses of bioactive fluorine-containing molecules.

3-Vinykromones 10, which have two carbonyl-containing groups in the 2'-position, were first synthesized in 1976 from 3-formylchromone (1a), acetylacetone, acetoacetic ether, and ethyl benzoyl acetate in acetic anhydride in the presence of sodium acetate upon heating (Scheme 8). This procedure was further improved in terms of environmental friendliness and increased product yield. Thus, it was shown that the
Knoevenagel condensation of chromones 1a with malononitrile, cyanoacetic acid, and cyanoacetamide can be carried out in distilled water without a catalyst at 90 °C for 1–2 h with an almost quantitative yield of products 11 containing at least one cyano group at the formed C=C bond. Another method for the preparation of chromones 10 and 11 involves condensation with various methylene active compounds in water in the presence of cetyltrimethylammonium bromide (CTAB) and DABCO. The geometry of the double bond was not discussed in these reports.

Compared with the above-mentioned derivatives of acrylic acid, 3-(chromon-3-yl)acrolein (12) is the most difficult to obtain representative of this group of compounds. For the first time, it was obtained in 1984 by acetylation of 3,4-dihydro-2H-pyran 13, an adduct of the hetero-Diels-Alder reaction of 3-formylchrome (1a) with ethyl vinyl ether. Later, Coutts and Wallace studied this transformation in more detail and showed that the use of MeONa as a catalyst increases the yield of aldehyde 12 from 49 to 70%. The reaction mechanism proposed by the authors is shown in Scheme 9.

The Vilsmeier-Haack reaction with 6-acetyl-4,9-dimethoxy-5H-furo[3,2-g]chromene-5-one (14, 6-acetylnorhellin) was realized and a new acrolein derivative 3-chloro-3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)prop-2-enal (15) was obtained in high yield (Scheme 10).

3-(2-Nitrovinyl)chromones 17 are synthesized by dehydration in acetic anhydride in the presence of pyridine of the corresponding nitroalcohols 16, which, in turn, can be obtained according to Henry reaction from chromones 1a and nitromethane under microwave irradiation (90 °C, 25 min) or under Barbier conditions using bromonitromethane and SnCl₂ in THF (Scheme 11).

The reaction of 3-formylchromone (1a) with stabilized methylene triphenylphosphoranes in toluene at room temperature for 4 h proceeds to give 3-vinylchromones 2c and 5a with exclusively the E-configuration of the double bond (Scheme 12). A similar transformation was used for aldehydes 18 and 20, which under the action of 2-(triphenylphosphoryl)propanol and ethyl (triphenylphosphoryl)acetate, lead to the formation of compounds 19 and 21 in high yields (Scheme 12).

### 2.2 From 3-R-chromones (R = Hal, H)

The possibility of using the palladium-catalysed Heck reaction to obtain 3-vinylchromones 2 was first demonstrated in 1987 by the synthesis of methyl 3-(chromon-3-yl)acrylate 2c from 3-bromochromene 22 (R = H) and methyl acrylate. The reaction
was carried out under pressure at 120 °C in the presence of palladium acetate and triphenylphosphine (Scheme 13).28 Subsequently, the Heck cross-coupling was extended to 3-bromo-2-methylchromone 22 (R = Me), ethyl acrylate, and acrylonitrile and was implemented with more mild conditions, at 100 °C in N-methylpyrrolidone (NMP) under a nitrogen atmosphere, which made it possible to obtain 2-methyl-3-vinylchromones 23 with ethoxycarbonyl and cyano groups at the exo-double bond, albeit with low yields.29

![Scheme 13](image)

Scheme 13 3-Bromochromones in the synthesis of 3-vinylchromones

3-Iodochromones 24, in comparison with 3-bromochromones 22, proved to be the best in the Heck reaction. Thus, an effective method was developed for the synthesis of various 3-vinylchromones 2 under microwave radiation conditions, which do not require the use of phosphine ligands or an inert atmosphere. The most optimal conditions for the Heck cross-coupling were found to be: 5 mol% Pd(OAc)₂ as a catalyst, DMF as a solvent, and triethylamine as a base (Scheme 14). Simple conditions and a short reaction time (5 min), coupled with a wide range of useful olefins, make 3-vinylchromones 2 sufficiently accessible substrates for obtaining new biologically active substances, including those with anticancer activity and activity against the hepatitis B virus.30

![Scheme 14](image)

Scheme 14 3-Iodochromones in the synthesis of 3-vinylchromones

In 2011, Kim and Hong31 proposed a new method for the direct alkenylation of chromones at the 3-position without preliminary formation of 3-halochromones by palladium (II) catalysed C–H functionalization, which is a dehydrogenative or oxidative cross-coupling leading to 3-vinylchromones 2 with moderate to high yields (Scheme 15). The use of pivalic acid together with Cu(OAc)₂/Ac₂O as an oxidizing agent provided the required reactivity of chromones in cross-coupling with electron-deficient allenes. This approach turned out to be applicable not only for 2,3-unsubstituted chromones 25, but also for 2-methylchromone 26, from which butyl acrylate 23 was obtained in 43% yield.32

![Scheme 15](image)

Scheme 15 3-H-chromones in the synthesis of 3-vinylchromones

Other examples of the synthesis of allyl 3-(chromon-3-yl)acrylates 2c by oxidative cross-coupling of chromone 25a (R = H) with the corresponding esters of acrylic acid are described in the report.33

3 3-Reactions with mononucleophiles

Various chromosome derivatives, especially isoflavones and other 3-substituted chromones, for example, 3-formyl-1 and 3-(1-alkynyl) chromones, are widely used as preferred structures for the creation of substances with different types of biological and pharmacological activity in the field of neurodegenerative, inflammatory and infectious diseases, as well as diabetes, asthma and cancer.1 In this regard, there is an urgent need to systematize the various chemical properties of polyether triphosphorous 3-(1-alkenyl)chromones 2 for targeted organic synthesis of useful products.

3.1 Reactions with amines

The first data on the interaction of ammonia with 3-vinylchromones 10, which are easily obtained by Knoevenagel condensation from 3-formylchromone and methane active compounds and, due to this, are more accessible than 3-(3-chromon-3-yl)acrylates 2c, appeared in 1981 in the works of Ghosh34 and Haar.35 It was shown that the attack proceeds at the 2-position of chromone 10a and is accompanied by the opening of the pyrone ring, followed by cyclization to pyridine 27 (cyclization of the type 1,5-dielectrophile + 1,1-dinucleophile).34 In the case of chromosome 10b, the main product is pyridine 28 formed due to the acetyl group and the side product is pyridine 29 as a result of the attack on the ester group (Scheme 16).35

![Scheme 16](image)

Scheme 16 Reactions of chromones 10 with ammonia

Recently, this transformation was studied in more detail on the reaction of chromosome 10c with a wide range of primary aliphatic and aromatic amines.36 It was found that reaction with benzyl-, phenethyl-, and furylamine at room...
temperature in dichloromethane gives the expected 2-pyridones 32, and with aniline and 3,4,5-trimethoxyaniline, enaminochromanones 31, which are kinetic products capable of being transformed into pyridones 32 when heated to 40 °C (Scheme 17). In other cases (with tryptamine, its derivatives and p-anisidine), mixtures of compounds 31 and 32 were obtained through the open forms Z-30 and E-30. 2-Pyridones 32 were formed exclusively under thermodynamic control conditions upon heating and/or in the presence of CsF as a catalyst.

**Scheme 17** Reactions of chromone 10c with primary amines

The availability and relatively low toxicity of 2-pyridones caused increased interest among many researchers as potential inhibitors of the hepatitis B virus, c-Src kinase and acetylcholinesterase.30,37 In this regard, the reaction of 3-(chromon-3-yl)acrylates 2c with a large number of primary amines was investigated. It has been shown that, depending on the nature of the amine, the reaction can proceed both along the 1,6-Ax pathway leading to compounds 33 and 34, and through the 1,4-Ax pathway without opening the pyrone ring, giving adducts 35 (Scheme 18). 5-Salicyloyl-2-pyridones 33 are readily formed in good yields from aliphatic and aromatic amines, imines 34 (from alkyl- and benzylamines) and chromones 35 (from amines and morpholine).30,37,38 Complete assignment of all signals in the 1H and 13C NMR spectra of a wide range of 2-pyridones 33 was carried out by Chand et al.39

**Scheme 18** Reactions of chromones 2c with primary amines

In 2017, Daich’s group,40 based on the data of their previous work on the synthesis of compounds 31,36 developed a method for the preparation of enaminochromanones 36 from 3-(chromon-3-yl)acrylates 2c and ethanamines under kinetic control, which through the intermediacy of chromeno[2,3-c]pyrroles 37 were transformed into more complex heterocyclic system with a pyrrolooxazinone fragment 38. These authors were able to show that treatment of chromanones 36 with [bis(trifluoroacetoxy)iodobenzene (PIFA) in THF leads to chromenopyrrolo[3,4-d]pyridines 37, which upon heating in refluxing toluene with p-toluenesulfonic acid (PTSA) undergo intramolecular esterification into tetracyclines 38. The mechanism of the key step 36→37 is shown in Scheme 19.

**Scheme 19** Proposed mechanistic pathway for the reaction 36→37

An interesting example of the synthesis of derivatives of chromeno[3,2-e]oxazolo[3,2-a]pyridine system 41 from diester 10c and ethanamine in the presence of 1,1′-(azodicarbonyl)diisopropylamine (ADDI) and tributylphosphine (Mitsunobu reagent) is described in this work.41 At the first stage of the transformation, the expected 2-pyridine 39 is formed, which reacts with the zwiterionic intermediate 40 and, undergoes Mitsunobu, cyclizing to compounds 41 in good yield (Scheme 20). Substituted ethanamines also enter into this reaction.

**Scheme 20** Synthesis of chromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylates 41

The cascade transformation of diacetylated 3-vinylchromone 10a under the action of propargylamines is a new method for the preparation of the indolizine system.42 The attack of the C-2 atom of chromone by the amino group, with subsequent cyclization of the pyrone ring, leads to the formation of...
intermediate pyridine A (Scheme 21). The enamine fragment of the latter attacks the triple bond by 5-exo-dig cyclization with the formation of the zwitterion B, with subsequent proton transfer and the hydrogen shift in intermediate C give indolizines 42.

Scheme 21: Synthesis of indolizines 42

It is well known that the reactivity of the pyrone ring in chromones with respect to nucleophiles increases under the influence of an electron-withdrawing substituent at the 3-position, but it was difficult to foresee that the presence of a cyano group at the exo-double bond would lead to a change in the direction of the reaction with amines. Indeed, it was shown in the work of Ibrahim and Badran43 that chromones 2b and 11 react with benzylamine and p-toluidine to form compounds 43–46, of which pairs 43/45 and 44/46 are ring-chain isomers (Scheme 22). As in all previous cases, the reaction begins with an attack by the amino group at position 2. However, in this case, the pyrone ring does not open, and the carbonyl oxygen atom as an internal nucleophile is attached at the cyano group, giving depending on the nature of the amine and substituents at the exo-C=C bond of compound 43–46. Despite the fact that the ratio of the reagents was always 1:1, in some cases, products 44 and 46 were formed, the stoichiometry of which required two equivalent of amine. When p-toluidine was used, open form 45 prevailed, and with benzylamine, cyclic forms 43 and 44 prevailed.

Scheme 22: Reactions of 3-(chromon-3-yl)acrylonitriles with primary amines

Chromone 47 obtained from 3-formylbenzochromone and 2-cyanomethyl-1,3-benzothiazole reacts with piperidine in refluxing dioxane in the same way as chromones 11, with the only exception that the expected product 48 at the final stage of the reaction undergoes a Dimroth rearrangement to form heterocycle 49 (Scheme 23).44

Scheme 23: Reaction of chromone 47 with piperidine

Heating chromones 11a,b in refluxing 95% ethanol containing 1 drop of piperidine results in partial hydrolysis of the cyano group to the amide group, leading to 2-pyridones 50 as cyclization products of the γ-pyron ring (Scheme 24).45 On the other hand, treatment of chromone 11a at X = CO₂Et with a 2% aqueous solution of NaOH at 70 °C gives pyrano[4,3-b]chromene 51, which is formed as a result of the attack by the hydroxide anion of the C-2 atom, opening of the pyrone ring and addition of hydroxyl groups at the activated double bond and the cyano group.46

Scheme 24: Transformations of chromones 11 under basic conditions

Derivatives of 2-pyridone-3-carboxylic acid 54 were obtained by a three-component reaction of 3-formylchromones 1a, Meldrum’s acid 52 and primary amines in the presence of catalytic amounts of (NH₄)₂HPO₄ in water (Scheme 25).47 The reaction begins with Knoevenagel condensation and the formation of chromones 53, the pyrone ring of which opens under the action of amines, and ends with an intramolecular attack of the amino group at one of the carbonyl carbon atoms of the Meldrum’s acid residue, followed by the elimination of acetone and the production of acids 54.

Scheme 25: Meldrum’s acid condensates 53 in the reaction with primary amines

Obtaining of 3-vinylchromones 53 from 3-formylchromones 1a and Meldrum’s acid 52, as well as 2-aminobenzamides 57 by
the reaction of isatoic anhydride 56 with amines, hydrazines, and hydrazides, has been described. A study of the reaction between compounds 53 and 57 showed that, under acidic conditions, when methanesulfonic acid is used as a catalyst at 70 °C, 3-vinylchromone 53 undergoes a retro-Knoevenagel reaction with elimination of Meldrum's acid and the formation of 2-(chromon-3-yl)dihydroquinazolinones 55 as products of the reaction of the aldehyde group of chromones 1a with 1,5-N,N-dinucleophiles 57 (Scheme 26). Under basic conditions in the presence of K2CO3, condensate 53 is more stable, and 2-aminobenzamides 57 obtained from allyl-, benzyl-, and phenethylamines behave like aromatic amines, giving 2-pyridones 58. In this case, in contrast to the previous work, Meldrum's acid loses not only acetone, but also carbon dioxide.

3.2 Reactions with methylene active heterocycles

It should be noted that the currently available data on the interaction of electron-deficient 3-vinylchromones with mononucleophiles are restricted almost solely to reactions with amines as N-nucleophiles, which are an important addition to the previously known methods for the synthesis of 2-pyridones of interest in medical chemistry. Information on reactions with O- and C-nucleophiles is extremely limited. So, in addition to work where the reaction of 11 with NaOH is described, there is only one article on the reaction of 4-hydroxycurarin and triacetic lactone as C-nucleophiles with adducts 53, arising in situ from 3-formylchromones and Meldrum's acid. It was found that the four-component reaction of chromones 1a, Meldrum acid 52, 4-hydroxycurarin or 6-methyl-4-hydroxy-2-pyrene and primary alcohol in water leads to products 59 or 60 with good yields (Scheme 27). The authors proposed that, at the final stage of the reaction, after the cleavage of acetone from the Michael adduct, a ketene intermediate is formed, which is then attacked by the primary alcohol and decarboxylates into the product.

4 Reactions with dinucleophiles

4.1 Reactions with hydrazines

3-Vinylchromones 5 with an aryl substituent at the double bond have two α-enone fragments in their composition, and therefore are valuable building blocks for the construction of a bipyrazole systems when interacting with hydrazines as 1,2-N,N-dinucleophiles. Indeed, in the reaction of 3-(3-aryl-3-oxoprop-1-en-1-yl)chromones 5 with an excess of hydrazine in refluxing acetic acid for 3 h, 5-(pyrazol-4-yl)-2-pyrazolines 61 are formed as the main products, with 5-(chromon-3-yl)-2-pyrazolines 62 as side products (Scheme 28). This suggests that hydrazine reacts primarily at the side α-enone chain, and only then is the C-2 chromone atom attacked with the opening of the pyrone ring and the closure of the second pyrazole ring. When compounds 61 were oxidized using DDQ in boiling dioxane bipyrazoles 63 were obtained in 51–60% yields.

The reaction of chromones 5 (R = OH) with hydrazide hydrate in refluxing DMF for 18 h proceeds only at the exo-enone fragment and is accompanied by aromatization into 3-(pyrazol-5-yl)chromones 64. When treating chromones 5 with an excess of phenylhydrazine in refluxing acetic acid, pyrazolyl-2-pyrazolines 65 were synthesized, the regiochemistry of which was confirmed by HMBC and NOESY spectroscopy (Scheme 28). The mechanism of this reaction involves the initial formation of chromonyl-2-pyrazolines 62, after which, the chromone system is attacked at C-2 by the more nucleophilic primary amino group of the second phenylhydrazine molecule and is recycled into 65.
Heteroanalogues of chalcones 66, reacting with hydrazine hydrate, phenylhydrazine, and hydrazinobenzothiazole in acetic acid, give pyrazolines 67 (Scheme 29), but in the case of phenylhydrazine and chalcone with a triacetic acid lactone residue, the reaction proceeds further and leads to pyrazolopyrazoline 68 after the opening of the chromonic system (the yields of compounds 67 and 68 are not indicated in the original report).

Ibrahim’s group studied the behavior of chalcones 11a,b (X = COEt, CN) under the action of hydrazines. While a retro-Knoevenagel reaction was observed with phenylhydrazine, leading to the previously known pyrazole from 3-formylchromone, heating chalcone 11a with hydrazine hydrate to reflux in absolute ethanol gives ethyl 2-amino-5-ethoxy-4-hydrazinyl-4H,5H-pyran[3,2-d]chromene-3-carboxylate (69) (Scheme 30). The dicyanomethylene derivative 11b under similar conditions reacts differently proceeding via 3-(chromone-3-yl)pyrazole intermediate to give bipyrrole 70. With both chromones, the reaction begins with a 1,4-As on the side C=C bond, but in the first case, the cyclization is due to the enol hydroxyl, and in the second case, the amino group of the hydrazone.

In the reaction of acetylamidine with 3-vinylchromone 10c, containing two ester groups that increase its electrophilicity compared to chromones 2, in addition to the expected chromenopyrimidine 72, 5-salicylpyrimidine 73 is formed as a result of the attack at the C-2 and C-1′ atoms, followed by the cleavage of the malonic ester. An analogous behavior of chromone 10c, similar to that of 3-formylchromone, was also observed in the formation of pyrimidine 75 from toluamide and 3-vinylchromone 74 with two phosphonate groups (Scheme 32).

4.2 Reactions with amidines

A simple and effective approach to the new chromenopyrimidines 71 was developed through the ANRORC reaction of electron-deficient 3-vinylchromones 2 and such 1,3-N,N-dinucleophiles as amidines and guanidine. The reaction proceeds under mild conditions (EtOH, ~20 °C), is complete within a few hours, and is applicable to a wide range of substrates (Scheme 31). This transformation proceeds following the pathway characteristic for chromones, i.e., through attack on the crypto- and endo-electrophilic centers with Michael oxacyclization in the final step.

4.3 Reactions with other 1,3- and 1,4-dinucleophiles

3-Vinylchromones 11b obtained from 3-formylchromones 1a and malononitrile react with cyanoacetoxyhydrzone as a 1,3-CN-dinucleophile on the acrylonitrile fragment, giving chromonopyridones 77. The same products, under the same conditions (boiling in ethanol in the presence of a catalytic amount piperidine), are formed from hydrazones 76 when the latter are treated with malononitrile (Scheme 33).
Biginelli products 78 and Hantzsch products 79 were synthesized by reacting chromones 10b, thiourea and β-aminocrotonates in the presence of heteropolyacids (HPA) H_{2}[NaP_{2}W_{18}MoO_{40}] or H_{2}P_{2}W_{18}O_{62}/24H_{2}O as effective catalysts. The reactions were carried out at 80 °C for brief periods (from 15 min to 1.5 h) without solvent (scheme 34).57 A three-component version of the reaction is also possible, when 3-formylchromones and acetoacetic esters are used instead of chromones 10b.57,58

Similarly, a three-component one-pot reaction from 3-formylchromone (1a), methylene active cyanoacetic acid derivatives, 6-aminothiouracil or 4,6-diaminopyrimidine-2(1H)-thione, acting as 1,3-C,N-dinucleophiles, when heated in distilled water without a catalyst, pyrido[2,3-d]pyrimidines 80 and 81 were obtained (Scheme 35).59

Condensation products of 3-formylchromone with cyanoacetic ester and malononitrile 11a,b react differently when heated to reflux in ethanol with 1,4-N,N-dinucleophiles such as o-phenylenediamine and ethylenediamine.45 Thus, chromone 11a reacts with these diamines as 3-formylchromone 1a, giving products 79 and 80, while with chromone 11b, the reaction proceeds at the dicyanomethylene fragment and leads to diazepines 81 and 82 (Scheme 36). Under the action of o-aminothiophenol, both chromones undergo a retro-Knoevenagel reaction to 3-formylchromone with the formation of benzothiazepine 83.

Thus, the cleavage of cyanoacetic ester and malononitrile by dinucleophiles is a typical process for electron-deficient 3-vinylchromones. Indeed, continuing their research in this area, Ibrahim’s group49 found that chromones 11a,b reacting with 3-amino-1,2,4-triazole 84 and 2-aminobenzimidazole 85 in refluxing ethanol give the same products 86 and 87 that had previously been obtained from 6,8-dimethyl-3-formylchromone. However, if these reactions are carried out in refluxing dioxane containing a few drops of triethylamine, the reaction course changes. In this case, the addition of 1,3-N,N-dinucleophiles 84 and 85 at the side double bond and the cyano group occurs, which leads to the formation of heterocycles 88 and 89 (Scheme 37).

A similar outcome was observed in the reaction of chromones 11a,b with 7-chloro-4-hydrazonequinoline and 5,6-diphenyl-3-hydrazino-1,2,4-triazine, giving 4-salicylpyrazolo[1,2-d]pyrimidines 90. These were also obtained from 6,8-dimethyl-3-formylchromone in ethanol, while 3-aminopyrazoles 91 were formed in dioxane due to the side chain reaction (Scheme 38).60
A study of the reaction of 3-(6-methylchromon-3-yl)acrylonitrile 2b with 1,3-C,N-dinucleophiles such as malononitrile, cyanoacetamide and acetoacetamide showed that these molecules first attack the chromone C-2 atom via the methylene group with opening of the pyrone ring, and then with nitrogen atom at the C-4 endo-electrophilic center, followed by addition of phenolic hydroxyl at the acrylonitrile moiety, ultimately giving 5-cyanomethylchromeno[4,3-b]pyridines 92 and 93 (Scheme 39).

In the case of ethyl cyanoacetate, after attack at the C-2 atom and ring opening, the internal O-nucleophile attacks the ester group and the double bond activated by the cyano- group to form 5-cyanomethylpyrano[3,2-c]chromene 94. Similar products were obtained with the same active methylene compounds based on 3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)acrylonitrile.62

The reaction of 3-aroylvinylchromones 5 with o-phenylenediamine and 2-aminophenol gave benzodiazepines 95 (AcOH, DMF, microwave irradiation, 15 min)63a,b and benzothiazepines 96 (hexafluoropropan-2-ol, rt, 6 h or MeOH, AcOH, reflux, 2 h), respectively.63a,b Three-component condensation of 3-formylchromone (1a), o-phenylenediamine, and 3-acetyl-4-hydroxycoumarin catalysed by nano silica-supported N-propylsulfamic acid resulted in benzodiazepine 97.64a Similarly, the use of 3-formylchromones 1a, o-phenylenediamine, and dimedone as an active methylene component gave rise to the fused benzodiazepine 98.64b This reaction requires no solvent and is catalysed by the novel heterogeneous catalyst Fe(OTf)/SiO₂.

A report44 has described a number of reactions of chromone 47 with various dinucleophiles (Scheme 39), but the structure of the obtained compounds cannot be considered definitively proven due to the lack of 2D experiments and X-ray diffraction data.

A reaction with various dinucleophiles 47 was required.

**Scheme 38** Reactions of chromones 11a,b with hetarylhydrazines

**Scheme 39** Reactions of chromone 2b with 1,3-C,N-dinucleophiles

**Scheme 40** Reactions of chromone 47 with various dinucleophiles

**Scheme 41** Benzodiazepines and benzothiazepines prepared from 3-aroylvinylchromones 5

Reaction of 3-chloro-3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromene-6-yl)prop-2-enal 15 with amines, hydrazines, hydroxylamine, guanidine, and thiourea was studied in detail in the work.64 In the examples with p-toluidine and benzylamine, it was shown that the aldehyde group is attacked first (compound 99), then the chlorine atom is replaced (compound 100), and the pyrone ring is opened last (compound 101). In a similar way, norkhellin 15 reacts with hydrazines and hydroxylamine, giving first pyrazole 102 and isoxazole 104, and then bipyrazoles 103 and biiisoxazole 105, the regiochemistry of which was not discussed. Only bipyrimidines 106 were isolated with guanidine and thiourea (Scheme 42). Reactions with amines and hydrazines were carried out in absolute ethanol at room temperature or at reflux, while in other cases, the use of Et₃N or KOH as a catalyst was required.
There are data in the literature on the transformations of condensation products of 3-formylchromone with 1-phenylpyrazol-3-5-dione and 4-hydroxycoumarin (chromones 107 and 108, Scheme 43) under the action of various nucleophilic agents. Reactions with amines, hydrazines, hydroxylamine, thiourea, o-phenylenediamine, o-aminophenol, o-aminothiophenol, ethylenediamine, thioglycolic acid, ethyl cyanoacetate, malononitrile, cyanoacetamide, cyanothioacetamide and other nucleophiles were studied, which react both along the pyrone ring and along the exo-enone fragments. Unfortunately, conclusions about the structure of the obtained products were made on the basis of spectroscopic data without strict assignment of all signals and without single crystal X-ray diffraction studies, which does not allow complete confidence about the regiochemistry of the reactions.

5 Ambiphilic cyclization

In 1976, Jones and Albrecht reported that treatment of 3-formylchromone with ethyl acetoacetate in the presence of AcONa/Ac2O gave Knoevenagel product 10b in 62% yield. However, when the reaction was carried out with a twofold excess of ethyl acetoacetate and using piperidine in ethanol, isophthalate 109 was formed. The authors interpreted this transformation as a formal [5+1] cycloaddition, in which chromone 10b acts as a 1,5-dielectrophile, and ketoester as a 1,1-dnucleophile (as in the reaction with amines, Scheme 16), reacting with each other by the type of intermolecular Michael addition followed by intramolecular alkol condensation (in Scheme 44, electrophilic centers are marked in red, while nucleophilic centers are marked in blue). However, currently, such reactions are referred to as ambiphilic cyclizations, in which the starting molecules contain both electrophilic and nucleophilic centers. In this case, chromone 10b plays the role of the 1,4-ambiphile, and ethyl acetoacetate plays the role of the 1,2-ambiphile, which is ultimately accompanied by elimination of acetic acid and the formation of the aromatic ring as a result of formal [4+2] cycloaddition (Scheme 44).

A general synthesis of salicylophenzenes (2-hydroxybenzophenones) from 3-vinylchromones 2 with one electron-withdrawing group at the double bond was demonstrated in the work of Chinese chemists in 2011. It was shown that chromones 2 as 1,4-ambiphiles when heated in ethanol in the presence of DBU react with a wide range of β-diketones and β-ketoesters, acting as 1,2-ambiphiles, and after dehydration and opening of the 4,4a-dihydroxanthone system, give benzophenones 110 (Scheme 45). In β-ketoesters, only the more electrophilic ketone C=O group takes part in intramolecular cyclization; for this reason malonic esters, in which such a group is absent, do not enter into the reaction.

2-Hydroxybenzophenones 111 with a different set of substituents were obtained from chromones 2 and β-enaminoesters or β-enaminoketones by the reaction [4+2] benzannulation, catalysed by indium(III) triflate in acetonitrile at room temperature (Scheme 46). In this transformation, the role of 1,2-ambiphile was performed by ketoamines.

Heating 3-(6-methylchromon-3-yl)acrylonitrile (2b) for 2 h in refluxing ethanol containing a catalytic amount of piperidine with acetylacetone gave the expected benzophenone 112, while with acetoacetic or malonic esters under these conditions, cleavage of the ester group was observed after hydrolysis and decarboxylation to form compounds 113 and 114 (Scheme 47).
A more complex cascade process leading to the production of substituted benzo[a]xanthones 116 from 2-methyl-3-(1-alkynyl)chromones 115 and electron-deficient 3-vinylchromones 2 was described by Hu and co-workers. In this case, the reaction is initiated by deprotonation of the vinylogous methyl group of chromone 115 by DBU (marked with an enlarged blue circle in Scheme 48), with attack at the 2-position of chromone 2c beginning a cascade process consisting of five nucleophilic addition steps, indicated by numbered arrows. This transformation proceeds in DMSO in the presence of DBU under microwave irradiation, and its mechanism is presented in Scheme 48 using the example of ethyl (E)-3-(chromon-3-yl)acrylate 2c. After opening pyrone ring of chromone 2c, the phenolate anion attacks the double bond of the acrylic fragment, which leads to the creation of a xanthone system with the simultaneous opening of chromone bond of the acrylic fragment, which leads to the creation of a ring of chromone 115 and the involvement of its triple bond in the process of double intramolecular cyclization with the formation of products 116.

In addition to acrylate 2c, chromones 5a, containing an acetylvinyl substituent in position 3, also react with 2-methyl-3-(phenylethynyl)chromone 115. In this case, benzo[a]xanthones 117, which have methyl or aryl substituents instead of OH groups are formed in low to high yields (Scheme 49). Use of (E)-3-(chromon-3-yl)acrylonitrile (2b) leads to 5-amino-3-salicyloyl-6-phenyl-12H-benzo[a]xanthene-12-one in 64% yield (not shown in Scheme 49).

The rather extended mechanistic pathway to benzo[a]xanthones 116 and 117 can be replaced by a simple and illustrative scheme, including ambiphilic [4+2] cyclization in combination with aldol condensation between two hydrated forms 118 and 119, which hypothetically can be formed during 1,4-addition of a water molecule to chromones 5a and 115, followed by opening of the pyrone ring and new cyclization where chromone 118 acts as a synthetic equivalent of chromone 5a (Scheme 49).

Another interesting example of the construction of complex aromatic structures consisting of chromone and benzophenone moieties was described by the same research group. It was shown that 2-methyl-3-acetylchromone (120) reacts with 3-vinylchromones 2 (X = ArCO) in THF in the presence of DBU under microwave irradiation and heating to 100 °C resulting in a cascade formation of benzo[a]xanthones 122, which differ from compounds 117 only in the absence of a phenyl group at the 6-position. The reaction mechanism is shown in Scheme 50 and includes two ANRORC sequences, leading to intermediate 121, which cyclizes due to the vinylogous Me group and aroyl carbonyl, followed by dehydration and opening of the pyrone ring to the final products 122. When the reaction is carried out in ethanol in the presence of EtONa, which is a stronger base than DBU, and in the absence of a carbonyl group at the exo-double bond, intermediates 121 are deprotonated and open to compounds 123.
The formation of benzophenones 123 can also be represented in a simpler form through ambiphilic [4+2] carbocyclization occurring between chromones 2 as 1,4-ambiphile and 120 as 1,2-ambiphile (Scheme 51).

In addition to 2-methyl-3-acetylcromone (120), the behavior of 2-methyl-3-formylchromone (124), 2-methyl-3-carboethoxychromone (125), and 2-methyl-3-cyanochromone (126) in the reaction with 3-vinylchromone 2, which has the most electron-withdrawing p-nitrobenzoyl substituent at the double bond (X = 4-NO₂C₆H₄CO), was studied. In the presence of bases such as triethylamine or diisopropanolamine (DIPA), polycyclic aromatic compounds 127–129 were obtained in good yields, the formation of which can be easily explained if again we proceed from ambiphilic [4+2] carbocyclization between chemical equivalents 124a–126a of chromones 124–126 (Scheme 52).
6 Cycloaddition reactions
6.1 [4+2] Cycloaddition

The first details on the participation of electron-deficient 3-vinylchromones, obtained from 3-formylchromone according to Horner-Wadsworth-Emmons, as 1,3-dienes in the Diels-Alder reaction with inverse electron demand (IEDDA) were described in the work of Bodwell in 2003. It was found that chromone 2c reacts under mild conditions with various pyrrolidine-based enamines acting as a dienophile in [4+2] cycloaddition, giving functionalized benzophenones, the yields of which strongly depend on the structure of the starting enamine. Thus, in the case of enamines from the homologous series of cycloalkanones, the reaction proceeds through intermediate 130 and, after cleavage of pyrrolidine and ring opening leads to products 131 in high yields, except for the 8-membered derivative (Scheme 53).

![Scheme 53 Chromone 2c in the inverse electron demand Diels-Alder reaction with enamines](image)

When using such π-excess alkenes as 1-(2,2-dimethoxyvinyl)pyrrolidine or tetramethoxyethylene, due to the methoxy leaving-group, the pyrrole ring does not open, which makes it possible to obtain 4-methoxyxanthones 132 and 3,4-dimethoxyxanthones 133 (Scheme 54). In the first case, the reaction was carried out in refluxing benzene, and in the second, by heating to 135 °C without solvent, followed by treatment with boron trifluoride etherate in dichloromethane. The yields of products 132 and 133 substantially depend on the nature of the substituent at the double bond of chromone 2, reaching a maximum value at X = Ac, Bz and dropping to almost zero in the case of 3-styrylchromones.

![Scheme 54 Synthesis of xanthones 132 and 133](image)

In another report, [4+2] cycloaddition between chromonylacrylic acids 2a and enamines from isobutyric aldehyde and pyrrolidine or piperidine led to the preparation of 4,4a-dihydroxanthones 134 in 43–81% yields (Scheme 55). Further study of this reaction using the example of a more active enamine with a pyrrolidine fragment showed that, if the reaction is carried out with the addition of La(NO₃)₃ as a Lewis acid for 0.5–5 h, 4,4a-dihydroxanthones 134 are formed. However, with an increase in the reaction time to 8–12 h, the thermodynamically more stable 3,4-dihydroxanthones 135 become the main products as a result of a sigmatropic [1,5] hydrogen shift, characteristic not only for acids 134, but also for their ethyl esters.

![Scheme 55 Synthesis of dihydroxanthones 134 and 135](image)

Interestingly, the IEDDA reaction with the electron-deficient diene system of 3-vinylchromones involves not only π-donor enamines, which is predictable, but also π-acceptor imines. The first, and so far, only example of an imino-Diels-Alder reaction with inverse electron demand (IEDDA) between chromones 2 and cyclic imines 136a–e has been described. The reaction was catalysed by zinc chloride (DMSO, 80 °C, 1 h, method A) and leads in high yield to tetrahydroindoloquinolizines 138 via [4+2] adduct 137 (Scheme 56). For the enantioselective version of the IEDDA reaction, chiral Lewis acids based on binol ligands 139a or 139b and ZnEt₂ in toluene at −78 °C (method B) have been proposed.
As with enamines, ethyl vinyl ether enters into a IEDDA reaction with chromones 2 and through tetra- and dihydroxanthone intermediates leads to a mixture of benzophenone 140 with two diastereomers 141, the composition of which depends on the nature of substituents and solvent. The highest yield of tetracycles 141 (R = OH, X = CO₂Et) was observed in ethyl vinyl ether (74%) and methanol (64%), and benzophenones 140 in acetone (56%). The replacement of the ester group at the C=C bond by the cyano-group also contributed to an increase in the benzophenone content in the mixture. Tetracyclic compounds 141 are formed in the course of two successive reactions [4+2] cycloaddition of ethyl vinyl ether, first at the diene system of chromone 2, and then at the cyclohexadiene fragment of the intermediate dihydroxanthone (Scheme 57).

As the presence of trifluoroacetic acid (TFA), the reaction proceeds as a normal [4+2] cycloaddition of one aryne molecule followed by opening of the pyrone ring and obtaining benzophenones 142 (Scheme 58). However, the replacement of TFA with trifluoromethanesulfonic acid (TfOH) radically changes the direction of the reaction; as a result of which xanthenes 143 become the main products of double annulation. In this case, the first aryne molecule is attacked via the enone system of the pyrylium cation 144 (oxa-Diels-Alder reaction), and the second via the resulting diene fragment.

Scheme 56 Enantioselective IEDIDA reaction of chromones 2 with cyclic imines 136a-e

Scheme 57 Ethyl vinyl ether in the IEDDA reaction with chromones 2

Scheme 58 Reactions between chromones 2 and benzene

6.2 [3+2] Cycloaddition

A study of the 1,3-dipolar cycloaddition of 3-(3-aryl-3-oxopropenyl)chromones 5 with diazomethane in a mixture of dichloromethane and diethyl ether (1:1) at 0 °C showed that the
reaction leads to 3-aryl-4-(chromon-3-yl)-2-pyrazolines 145 as the only isolated products (Scheme 59). The initially formed 1-pyrazolines spontaneously tautomerize to the thermodynamically more stable 2-pyrazolines, in which the methylene group of diazomethane is linked to the β-carbon atom of the side enone fragment. Despite the fact that the double bond of chromones can also react with diazomethane, the formation of such cycloadducts was not observed.

Diazomethane also reacts with disubstituted 3-vinylchromones 10 (Scheme 60). In the case of condensates of 3-formylchromone with acetylacetone and acetooacetic ester, the initial adducts of [3+2] cycloaddition 146 after extrusion of the nitrogen molecule are converted into dihydrofurans 147 through the oxygen atom of the acetyl group, while the adduct with malonic ester yields chromone 148 via the [1,2] hydrogen shift (product yields were not specified).

[3+2] Cycloaddition of 3-(2-nitrovinyl)chromones 17 with in situ generated N-methylhydrazones of aromatic aldehydes, which act as 1,3-dipoles, in the presence of a catalytic amount of trifluoroacetic acid in methanol, proceeds through pyrazoline 149 (Scheme 61). The latter, after oxidation and elimination of HNO₂, gives the corresponding 3-(3-aryl-1-methyl-1H-pyrazol-5-yl)chromones 150 in good yields. Among the synthesized compounds, derivatives exhibiting α-glucosidase inhibitory activity were found.

6.3 [4+1] Cycloaddition
Teimouri et al. reported the pseudo-five-component reaction of 3-formylchromones 1a, Meldrum’s acid 52, primary aromatic amines and isonitriles under mild conditions, as an effective method for the synthesis of tripeptides containing a chromone moiety. The reaction begins with Knoevenagel condensation leading to chromones 53, which then react with an isonitrile by a formal [4+1] cycloaddition giving iminolactone intermediates 151 and 152, which are opened under the action of anilines to give tripeptides 153 (Scheme 62). These products are formed in high yields regardless of the bulk or electronic nature of substituents in the starting compounds. However, with aliphatic amines, this transformation did not occur.

6.4 [10+4] Cycloaddition
In a recent example, Jørgensen et al. proposed the use of electron-deficient 3-vinylchromones 2 as readily available 4π-components in the construction of polysubstituted benzo[a]azulenes 155 by [10+4] cycloaddition. The role of the 10π-component was performed by indene-2-carbaldehyde 154 in the presence of pyrrolidine as a catalyst with the addition of molecular sieves and p-methoxybenzoic acid (Scheme 63). The mechanism of formation of azulenes 155 includes the generation of electron-rich 10π-enamine 156 from aldehyde 154 and pyrrolidine, the addition of which to chromones 2 followed by elimination of pyrrolidine leads to the production of unstable [10+4] intermediate 157, stabilized by opening the pyrone ring.
lactones 169 with a quaternary chiral carbon center (Scheme 65). To implement this diastereom- and enantioselective transformation, tetracyclic triazolium NHC 167 was used as a catalyst, quinone 168 as an oxidizing agent, and AcONa as a base. The reaction turned out to be tolerant to a wide range of substituents in the starting chromones and acroleins, giving tetracycles 169 in high yields. The reaction mechanism is shown in Scheme 65 and involves the formation of a acylazolium intermediate 170 with a vinylogous methyl group that attacks the C-2 atom of the chromone in a 1,6-nucleophilic manner. The resulting adduct 171 undergoes Michael cyclization to intermediate 172, the lactonization of which gives the final product 169,84,85

7 Other reactions
3-Vinylchromones 158 with ester and acyl groups at the exo-double bond were chosen as highly active substrates for the preparation of new derivatives of pyridines, benzophenones, and benzopyrans.83 The authors proposed that the presence of such electrophilic centers as C-2 and C-4, and nuclophilic centers such as CH2 and OH (after removal of the tert-butylmethyisilyl) protecting group), would make possible the participation of chromones 158 in various domino transformations and would significantly expand their synthetic potential. Indeed, the formation of pyridines 159 occurred already on an attempt to desilylate the corresponding chromone with ammonium fluoride in methanol at room temperature (the silyl protecting group was only removed when the reaction was carried out at 60 °C). When CsF (2 equiv.) in DMF was used instead of NH4F, the reaction followed the pathway of π-electrocyclization of intermediate 160 followed by opening of the xanthone system 161 to give benzophenones 162 (Scheme 64). Finally, a weakly acidic catalyst such as pyridinium p-toluenesulfonate (PPTS) allowed smooth silyl deprotection and the liberated OH group added to the acyl carbonyl to obtain a hemiacetal dehydration of which led to the hexatriene intermediate 163. The latter, in electrocyclization and elimination of the phenolic residue from intermediate 164, led to the obtaining of benzopyrans 165 in good yields.

A cascade reaction between chromones 5 and β-methylacroleins under the action of N-heterocyclic carbene (NHC catalysis) has been described,84 which provides a rapid approach to tetracyclic
Another interesting, albeit a single example, of a cascade reaction catalysed by N-heterocyclic carbenes 175 between 3-(2-nitrovinyl)chromone 17 and phthaldehyde, leading to 2-(chromon-3-yl)naphthoquinone 176, has also been described. This reaction proceeds under mild conditions and proceeds via a double Stetter reaction, the mechanism of which is shown in Scheme 67.

![Scheme 67 Synthesis of compound 176 and mechanism its formation](image)

There are also reports on the reduction of electron-deficient 3-vinylchromones by metals. Thus, when precursors 10 are treated with powdered samarium in aqueous THF containing NH₄Cl they undergo reductive dimerization, giving compounds 177, while under the action of zinc under similar conditions, the exo-double bond is reduced to form chromones 178 (Scheme 68).³⁸

![Scheme 68 Reduction of 3-vinylchromones 10](image)

8 Conclusion

The chemistry of electron-deficient 3-vinylchromones containing two conjugated polarized double bonds has attracted more and more attention. It has been shown that these readily available representatives of the 3-substituted chromone family exhibit high reactivity towards nucleophile and ambiphilic molecules. In addition, 3-vinylchromones are able to act as dienes and alkenes in [4+2] and [3+2] cycloaddition reactions, which makes them valuable building blocks for creating more complex heterocyclic systems with potential biological activity and useful photophysical properties.

It is important to note that the reactions of 3-vinylchromones with amines always begin with an attack at the C-2 atom, followed by the opening of the pyrrole ring and cyclization to 5-salicyloyl-2-pyridones, while 1,2- and 1,3-dinucleophiles primarily react on the exo-enone fragment, after which it becomes possible to attack the C-2 and C-4 atoms of the chromone system. Ambiphilic cyclizations of 3-vinylchromines with active methylene compounds and 2-methylchromines lead to the construction of an aromatic ring and the production of substituted o-hydroxybenzenophenones. Attention is also drawn to the fact that, in contrast to [4+2]-cycloadditions, reactions of 3-vinylchromones and 1,3-dipoles have not yet been extensively studied with only examples with diazomethane and N-methyldihydrazones of aromatic aldehydes having currently been reported.

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**Conflict of Interest**

The authors declare no conflict of interest.

**References**


Biosketches

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