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Synthesis and Reactivity of Electron-Deficient 3-Vinylchromones

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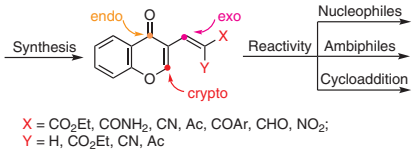
Dedicated to Dr. V. Yu. Korotaev on the occasion of his 50th birthday



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Crowd-Reviewed

Abstract The reported methods and data for the 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-catalyzed 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 recyclization, 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 are described, and the yields of the resulting products are given. 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.

Key words 3-vinylchromones, nucleophilic reactions, ambiphilic cyclizations, cycloaddition reactions, heterocycles

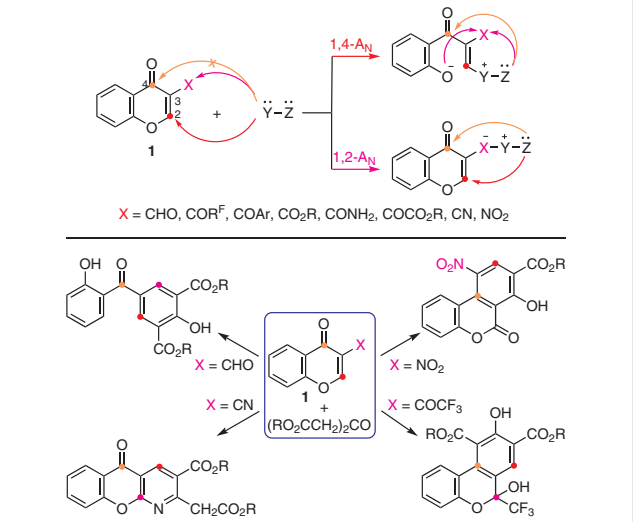
1 Introduction

Chromone (4*H*-chromen-4-one, 4*H*-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.[1]

The synthetic capabilities of the chromone (benzo-γ-pyrone) system are mainly determined by the structural features of the γ-pyrone ring, as well as by the nature and position of the substituents on it. It is clear 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 2-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 with an electron-withdrawing group (X = CHO, COR, CN, etc.) radically changes the reactivity of the γ-pyrone 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 **1**). Such chromones include 3-formylchromone (**1a**) – the most popular and most widely studied representative of the 3-substituted chromone family.[2]

Of the three possible directions of nucleophilic attack in this series of compounds, 1,4-A_N on the C-2 atom (favored) and 1,2-A_N 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 recyclization, 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 the reaction with the same 1,3-C,C-dinucleophile, leading to the formation of carbo- and heterocyclic products such as benzophenones, benzocoumarins, azaxanthones, and benzochromenes (Scheme 1).[3]



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

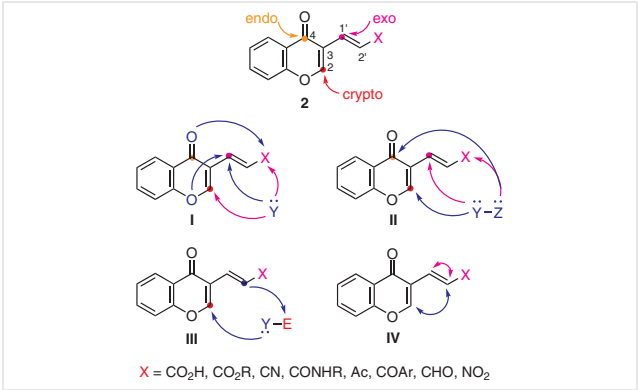
This review is the first to consider 2-unsubstituted 3-(1-alkenyl)chromones **2** with electron-withdrawing substituents at the *exo*-double bond, which are vinylogs of chromones **1** and have an extended synthetic potential. Indeed, the polyelectrophilic nature of 3-vinylchromones **2**, associated 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 dienone system, having an *endo*-α-enone fragment and an *exo*-cyclic double bond (at X = COR – *exo*-α-enone), are reactions with mono- and dinucleophiles (**I** and **II**), with ambiphiles 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 γ-pyrone ring. It is clear 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.

Unlike 3-formyl-,[2] 3-trifluoroacetyl-,[4] 3-cyano-,[5] 3-halogeno-,[3,4b,6] 3-carboxy-,[7] 3-alkoxycarbonyl-,[8] 3-alkoxalyl-,[8a] and 3-(1-alkynyl)chromones,[9] the chemical properties of which have already been summarized and analyzed 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 significantly, deserving a separate discussion. This review systematizes the data on 3-vinylchromones having one or two electron-withdrawing groups at the 2′-position (with

Biographical Sketch

Vyacheslav Y. Sosnovskikh is the Head of Department of Organic Chemistry and High Molecular Compounds at the Institute of Natural Sciences and Mathematics, Ural Federal University. He graduated from Ural State University in 1973. In 1981, he earned his Ph.D. in Organic Chemistry. In 2003, he earned a Doctor of Science Degree in Chemistry. His current research interests include organic synthesis, oxygen and nitrogen heterocycles, CF_3-containing building blocks, polyfunctional compounds, and 1,3-dipolar cycloadditions.



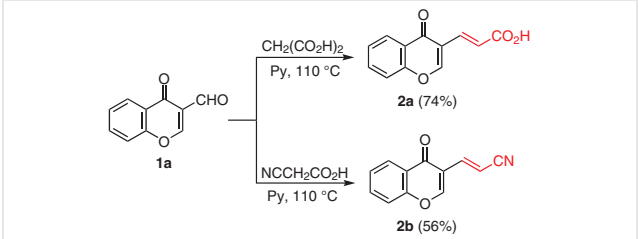
Scheme 2 Reactivity of electron-deficient 3-vinylchromones **2**

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.

2 Synthesis of 3-Vinylchromones

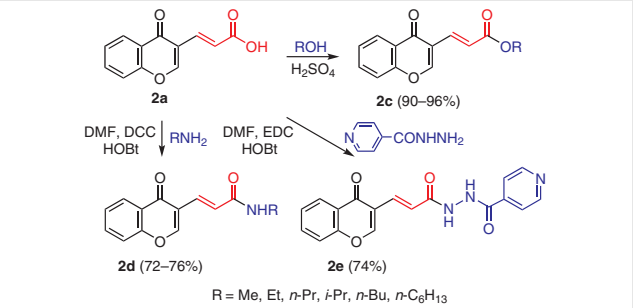
2.1 From 3-Formylchromones

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_2R, 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 coworkers[13] on heating 3-formylchromone (**1a**) with malonic and cyanoacetic acids at 110 °C in pyridine (Scheme 3).



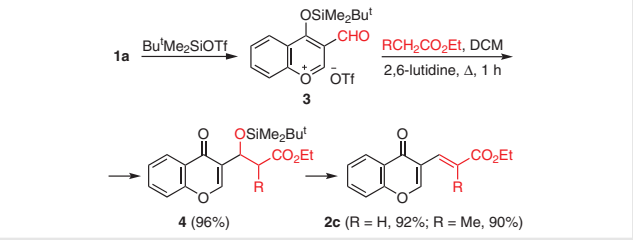
Scheme 3 First syntheses of 3-vinylchromones **2a** and **2b**

Treatment of acid **2a** with alcohols and amines gives *E*-3-(chromon-3-yl)acrylates **2c** and *E*-3-(chromon-3-yl)-acrylamides **2d**, which have antiproliferative activity.[14] The esterification reaction was catalyzed by sulfuric acid, and amidation proceeded in DMF solution in the presence of 1-hydroxybenzotriazole (HOBt) and dicyclohexylcarbodiimide (DCC) (Scheme 4). Under similar conditions, but under ultrasonic irradiation and replacing DCC with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), the reaction with isoniazid leads to hydrazide **2e**.[15]



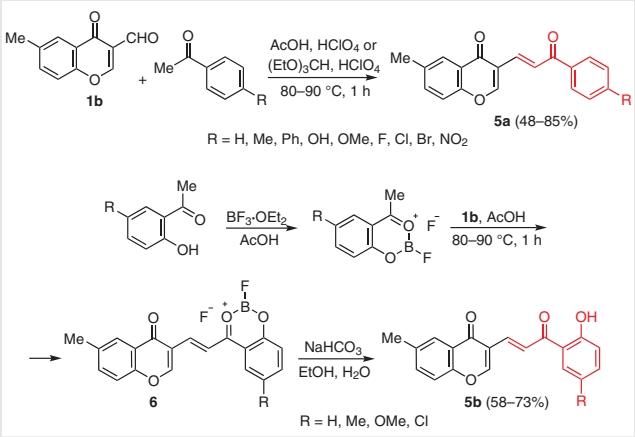
Scheme 4 Some derivatives of *E*-3-(chromon-3-yl)acrylic acid (**2a**)

Activation of 3-formylchromone (**1a**) by conversion into 4-siloxypyrylium salt **3** under the action of *tert*-butyldimethylsilyl triflate (2 equiv) allows condensation with esters to obtain acrylates **2c** (Scheme 5).[16] It was found that, to achieve a high yield with ethyl acetate, it is necessary to use 1.3 equivalents of 2,6-lutidine, with ethyl propionate – 3.0 equiv of 2,6-lutidine, and to stop the reaction at the stage of adduct **4** (R = H) – 2.2 equiv.



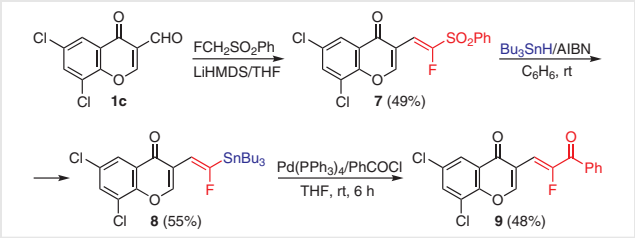
Scheme 5 Synthesis of chromones **2c** via 4-siloxypyrylium salt **3**

In this work,[17] chromone analogues 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-hydroxyacetophenones, these conditions turned out to be unsuitable; however, their complexes with BF_3 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.



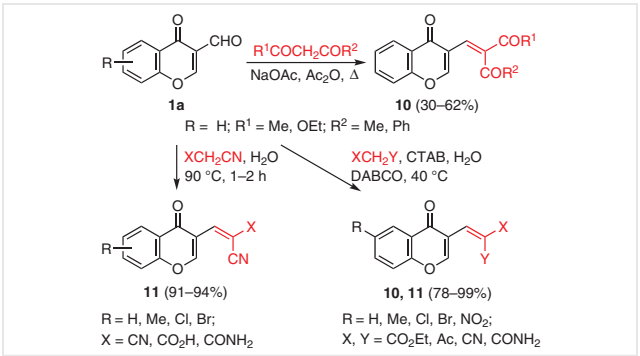
Scheme 6 Synthesis of 3-(3-oxo-3-arylprop-1-en-1-yl)chromones **5a** and **5b**

Condensation of 6,8-dichloro-3-formylchromone (**1c**) with a Horner–Wittig reagent formed in situ from fluoromethylphenylsulfone and diethylchlorophosphate in the presence of lithium hexamethyldisilazane (LiHMDS) led to vinylsulfone **7**, which was converted into fluorovinylstannane **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 $Pd(PPh_3)_4$ gave fluorochalcone **9**, which is of interest for subsequent syntheses of bioactive fluorine-containing molecules.[18]



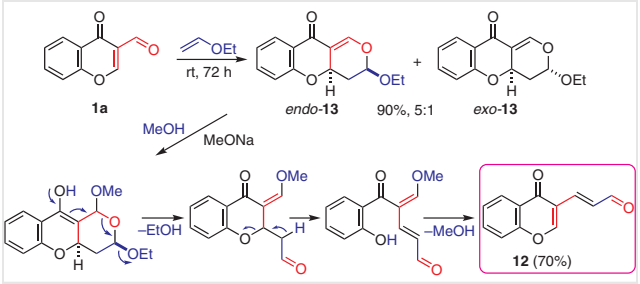
Scheme 7 Synthesis of 6,8-dichloro-3-(2-fluoro-3-oxo-3-phenylprop-1-en-1-yl)chromone **9**

3-Vinylchromones **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).[19] This procedure was further improved in terms of environmental friendliness and increased product yield. Thus, it was shown[20] 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 1,4-diazabicyclo[2.2.2]octane (DABCO).[21] The geometry of the double bond was not discussed in these reports.



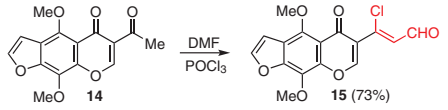
Scheme 8 Knoevenagel condensation of 3-formylchromones with methylene active compounds

Compared with the derivatives of acrylic acid mentioned above, 3-(chromon-3-yl)acrolein (**12**) is the most difficult to obtain representative of this group of compounds. It was obtained for the first time in 1984 by acid hydrolysis of 3,4-dihydro-2*H*-pyran **13**, an adduct of the hetero-Diels–Alder reaction of 3-formylchromone (**1a**) with ethyl vinyl ether.[22] Later, Coutts and Wallace studied this transformation in more detail and showed that the use of MeONa as a catalyst increased the yield of aldehyde **12** from 49 to 70%. The reaction mechanism proposed by the authors is shown in Scheme 9.[23]



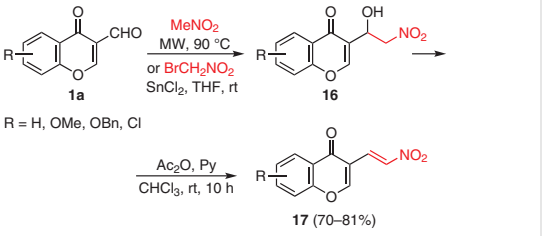
Scheme 9 Possible mechanism of transformation of adduct **13** into chromone **12**

The Vilsmeier–Haack reaction with 6-acetyl-4,9-dimethoxy-5*H*-furo[3,2-*g*]chromene-5-one (**14**, 6-acetylnorkhellin) was realized[24] and a new acrolein derivative 3-chloro-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)prop-2-enal (**15**) was obtained in high yield (Scheme 10).



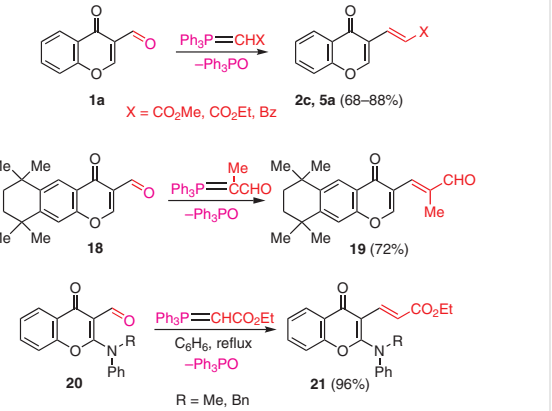
Scheme 10 Synthesis of khellin derivative **15**

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 $SnCl_2$ in THF (Scheme 11).[25]



Scheme 11 Synthesis of 3-(2-nitrovinyl)chromones **17**

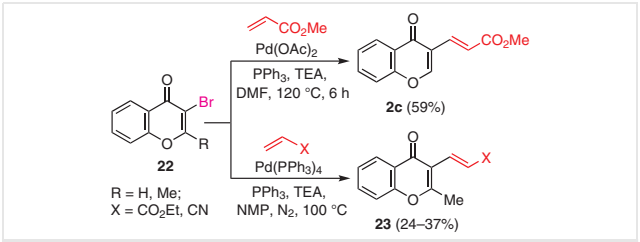
The reaction of 3-formylchromone (**1a**) with stabilized methylene triphenylphosphoranes in toluene at room temperature for 4 h proceeded to give 3-vinylchromones **2c** and **5a** with exclusively the *E*-configuration of the double bond (Scheme 12).[26] A similar transformation was used for aldehydes **18** and **20**, which, under the action of 2-(triphenylphosphoranylidene)propanal and ethyl (triphenylphosphoranylidene)acetate, led to the formation of compounds **19** and **21** in high yields (Scheme 12).[27]



Scheme 12 Wittig approach to electron-deficient 3-vinylchromones

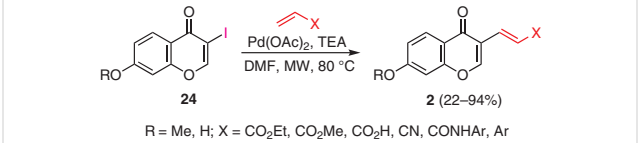
2.2 From 3-R-Chromones (R = Hal, H)

The possibility of using the palladium-catalyzed Heck reaction to obtain 3-vinylchromones **2** was first demonstrated in 1987 in the synthesis of methyl 3-(chromon-3-yl)acrylate **2c** from 3-bromochromone **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 milder 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 3-Bromochromones in the synthesis of 3-vinylchromones

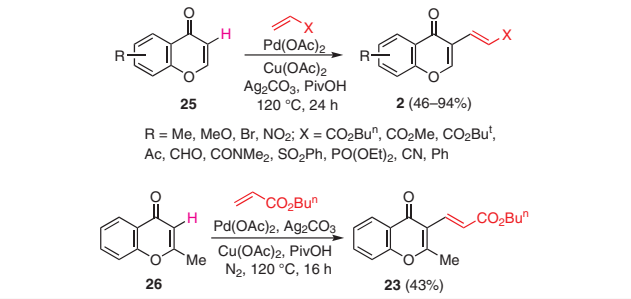
3-Iodochromones **24**, in comparison to 3-bromochromones **22**, proved to be the best in the Heck reaction. Thus, an effective method was developed for the synthesis of various 3-vinylchromones **2** under microwave radiation conditions, which does not require the use of phosphine ligands or an inert atmosphere. The 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 used 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 3-Iodochromones in the synthesis of 3-vinylchromones

In 2011, Kim and Hong[31] proposed a new method for the direct alkenylation of chromones at the 3-position without preliminary formation of 3-halochromones by palladium(II) catalyzed 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 $Cu(OAc)_2/Ag_2CO_3$ as an oxidizing agent provided the required reactivity of chromones in cross-coupling with electron-deficient alkenes. 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 3-H-chromones in the synthesis of 3-vinylchromones

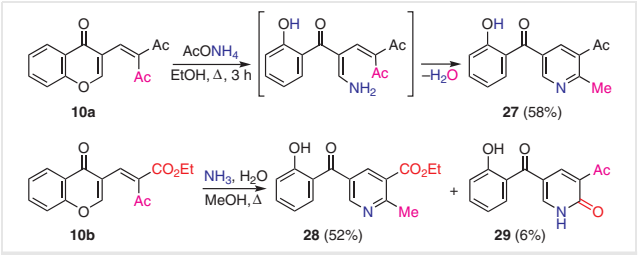
Other examples of the synthesis of alkyl 3-(chromon-3-yl)acrylates **2c** by oxidative cross-coupling of chromone **25a** (R = H) with the corresponding esters of acrylic acid are described in the reports.[33]

3 Reactions with Mononucleophiles

Various chromone derivatives, especially isoflavones and other 3-substituted chromones, for example, 3-formyl-[2] and 3-(1-alkynyl)chromones,[9] 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 polyelectrophilic 3-(1-alkenyl)chromones **2** for targeted organic synthesis of useful products.

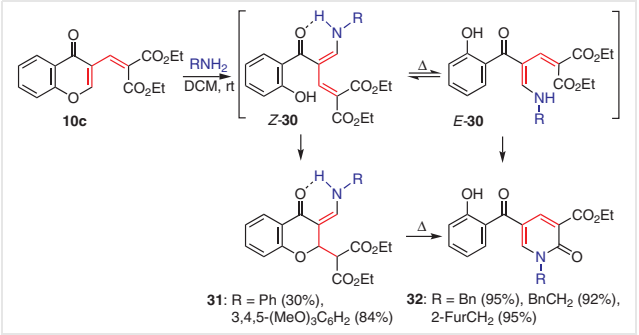
3.1 Reactions with Amines

The first data on the interaction of ammonia with 3-vinylchromones **10**, which are easily obtained by Knoevenagel condensation from 3-formylchromone and methylene active compounds and, due to this, are more accessible than 3-(3-chromon-3-yl)acrylates **2c**, appeared in 1981 in the works of Ghosh[34] and Haas.[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 chromone **10b**, the main product is pyridine **28**, formed from the acetyl group, and the side product is pyridone **29**, formed as a result of attack on the ester group (Scheme 16).[35]



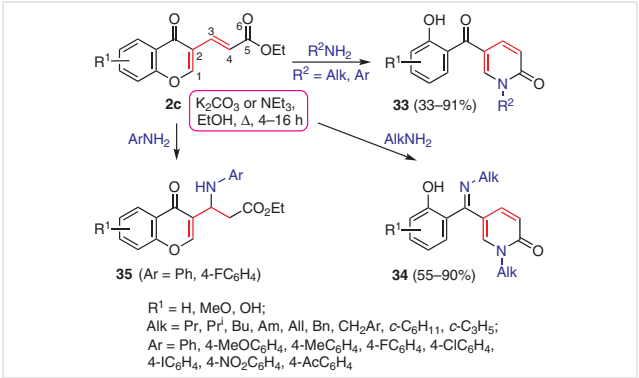
Scheme 16 Reactions of chromones **10** with ammonia

Recently, this transformation was studied in more detail in the reaction of chromone **10c** with a wide range of primary aliphatic and aromatic amines.[36] It was found that reaction with benzyl-, phenethyl-, and furfurylamines 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.



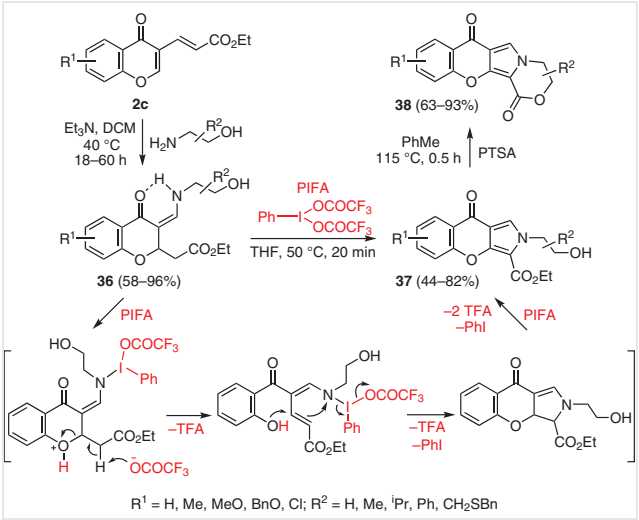
Scheme 17 Reactions of chromone **10c** with primary amines

The availability and relatively low toxicity of 2-pyridones led to increased interest among many researchers as potential inhibitors of the hepatitis B virus, c-Src kinase and acetylcholinesterase.[30c,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-A_N pathway, leading to compounds **33** and **34**, and through the 1,4-A_N 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** formed from alkyl- and benzylamines, and chromones **35** – from arylamines and morpholine.[30c,37a,38] Complete assignment of all signals in the ^1H and ^{13}C NMR spectra of a wide range of 2-pyridones **33** was carried out by Chand et al.[39]



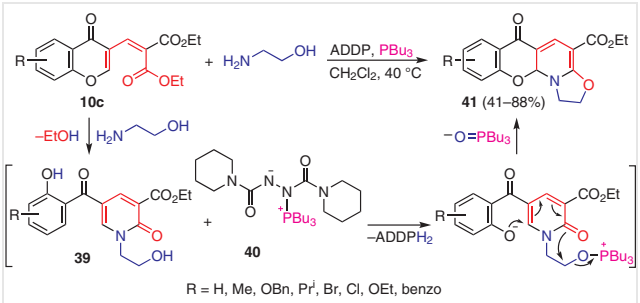
Scheme 18 Reactions of chromones **2c** with primary amines

In 2017, Daïch'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 ethanolamines under kinetic control, which, through the intermediacy of chromeno[2,3-*c*]pyrroles **37**, were transformed into a more complex heterocyclic system with a pyrrolooxazinone fragment **38**. These authors were able to show that treatment of chromanones **36** with [bis(trifluoroacetoxy)iodine]benzene (PIFA) in THF leads to chromenopyrroles **37**, which, upon treatment 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.



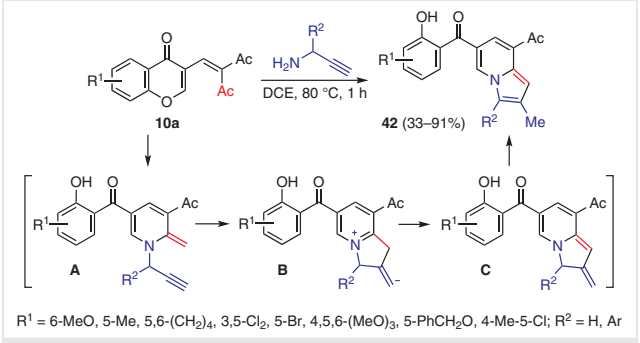
Scheme 19 Proposed mechanistic pathway for the reaction **36**→**37**

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



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

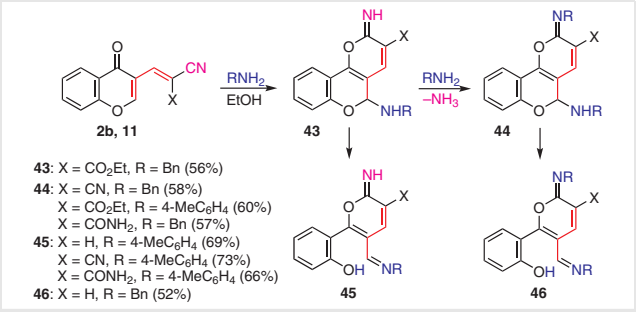
The cascade transformation of diacetylated 3-vinylchromone **10a** under the action of propargylamines is a new method for the preparation of the indolizine system.[42] Attack of the C-2 atom of chromone by the amino group, with subsequent recyclization of the pyrone ring, leads to the formation of intermediate pyridine **A** (Scheme 21). The enamine fragment of the latter attacks the triple bond by 5-*exo*-dig cyclization with the formation of zwitterion **B**, with subsequent proton transfer and hydrogen shift in intermediate **C** giving 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 Badran[43] 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, 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.

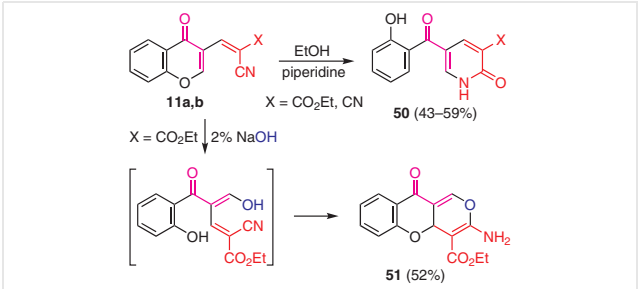


Scheme 22 Reactions of 3-(chromon-3-yl)acrylonitriles with primary amines

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]

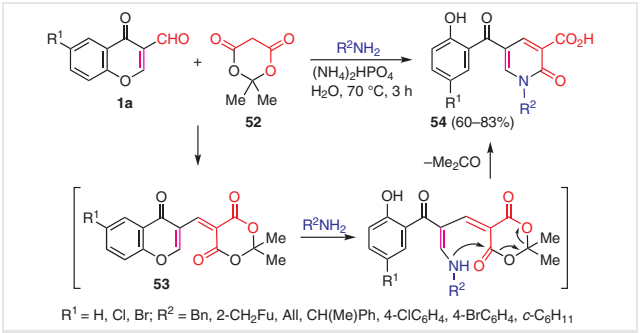
Heating chromones **11a**,**b** in refluxing 95% ethanol containing 1 drop of piperidine results in partial hydrolysis of the cyano group to the amide group, leading to 2-pyridones **50** as recyclization products of the γ-pyrone ring (Scheme 24).[45] On the other hand, treatment of chromone **11a** at X = CO_2Et 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.[45]

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 $(NH_4)_2HPO_4$ in water (Scheme 25).[46] 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



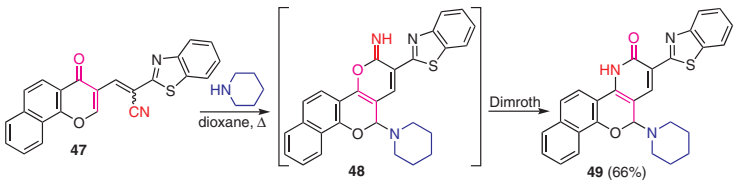
Scheme 24 Transformations of chromones **11** under basic conditions

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**.



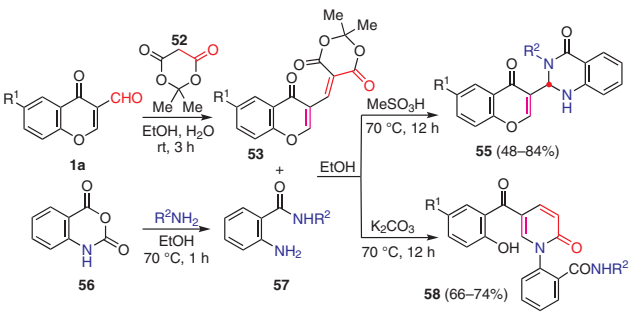
Scheme 25 Meldrum's acid condensate **53** in the reaction with primary amines

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.[47] 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 K_2CO_3 condensate **53** is more stable, and 2-aminobenzamides **57**, obtained from allyl-, benzyl- and



Scheme 23 Reaction of chromone **47** with piperidine

phenethylamines, behave like aromatic amines, giving 2-pyridones **58**. In this case, in contrast to the previous work,[46] Meldrum's acid loses not only acetone, but also carbon dioxide.

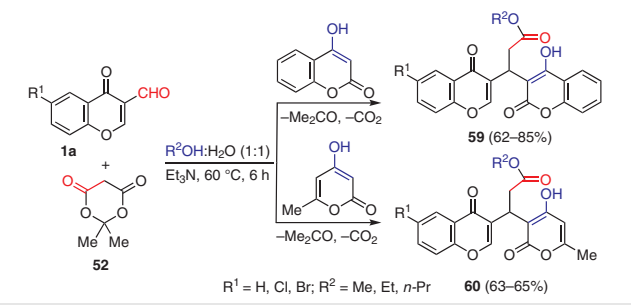


R^1 = H, Cl, Br; R^2 for **55** = All, Bn, $BnCH_2$, 4-ClC_6H_4, PhNH, 4-$MeOC_6H_4NH$, BzNH, 2-FuCONH; R^2 for **58** = All, Bn, $BnCH_2$

Scheme 26 Reactions of condensate **53** with 2-aminobenzamides

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.[48] Information on reactions with *O*- and *C*-nucleophiles is extremely limited. So, in addition to work where the reaction of chromone **11** with NaOH is described,[45] there is only one article on the reaction of 4-hydroxycoumarin and triacetic acid lactone as C-nucleophiles with adducts **53**, arising in situ from 3-formylchromonones and Meldrum's acid.[49] It was found that the four-component reaction of chromones **1a**, Meldrum's acid **52**, 4-hydroxycoumarin or 6-methyl-4-hydroxy-2-pyrone 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 cleavage of acetone from the Michael adduct, a ketene intermediate is formed, which is then attacked by the primary alcohol and decarboxylates to give the product.



R^1 = H, Cl, Br; R^2 = Me, Et, *n*-Pr

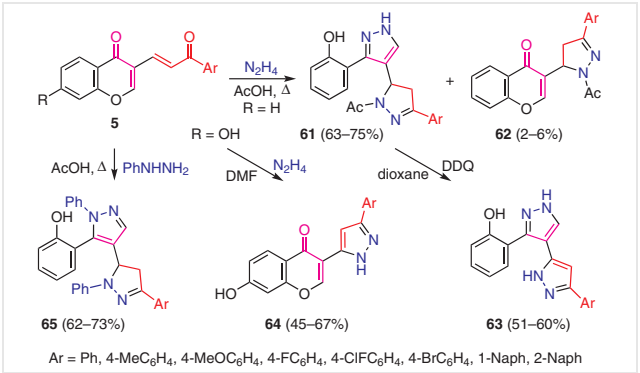
Scheme 27 Reactions of Meldrum's acid derivatives with methylene active heterocycles

4 Reactions with Dinucleophiles

4.1 Reactions with Hydrazines

3-Vinylchromones **5**, with an aroyl 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).[50] 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.

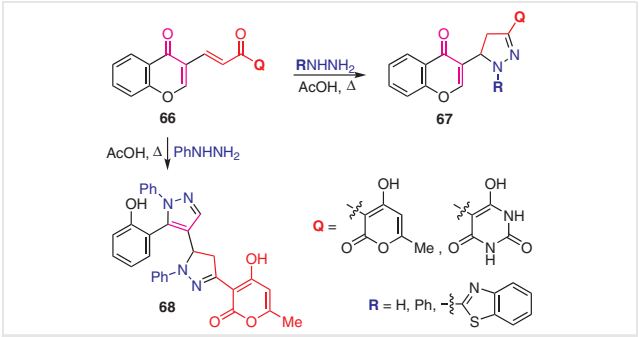
The reaction of chromones **5** (R = OH) with hydrazine hydrate in refluxing DMF for 18 h proceeds only at the *exo*-enone fragment and is accompanied by aromatization into 3-(pyrazol-5-yl)chromones **64**.[51] When treating chromones **5** with an excess of phenylhydrazine in refluxing acetic acid, pyrazolyl-2-pyrazolines **65** were synthesized, the regiochemistry of which was confirmed by HMBC and NOESY spectroscopy (Scheme 28).[52] 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**.



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$ClFC_6H_4$, 4-BrC_6H_4, 1-Naph, 2-Naph

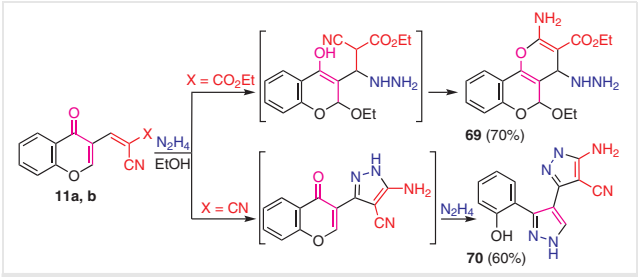
Scheme 28 Synthesis of pyrazolyl-2-pyrazolines and bipyrazoles

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 pyrazolylpyrazoline **68** after the opening of the chromonic system (the yields of compounds **67** and **68** are not indicated in the original report).[53]



Scheme 29 Reactions of heteroanalogues of chalcones **66** with hydrazines

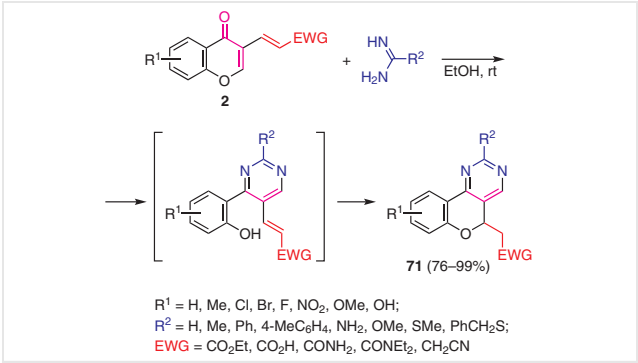
Ibrahim's group[45] studied the behavior of chromones **11a**,**b** (X = CO_2Et, CN) under the action of hydrazines. While a retro-Knoevenagel reaction was observed with phenylhydrazine, leading to the previously known pyrazole from 3-formylchromone, heating chromone **11a** with hydrazine hydrate to reflux in absolute ethanol gives ethyl 2-amino-5-ethoxy-4-hydrazinyl-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxylate (**69**) (Scheme 30). The dicyanomethylene derivative **11b** under similar conditions reacts differently, proceeding via 3-(chromon-3-yl)pyrazole intermediate to give bipyrazole **70**. With both chromones, the reaction begins with a 1,4-A_N 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 hydrazine.



Scheme 30 Synthesis of pyrano[3,2-*c*]chromene **69** and bipyrazole **70**

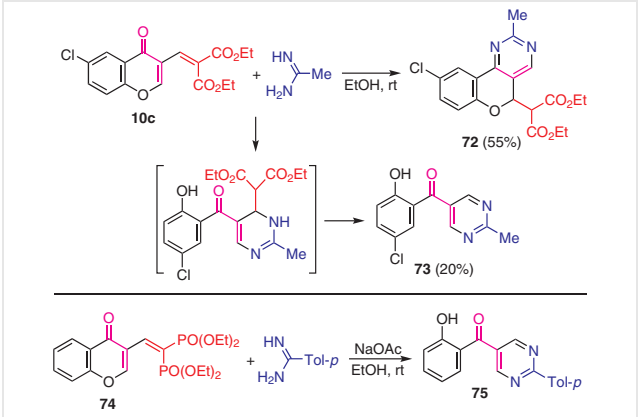
4.2 Reactions with Amidines

A simple and effective approach to the new chromeno-[4,3-*d*]pyrimidines **71** was developed through the ANRORC reaction of electron-deficient 3-vinylchromones **2** and such 1,3-N,N-dinucleophiles as amidines and guanidine.[54] The reaction proceeds under mild conditions (EtOH, ca. 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.



Scheme 31 Synthesis of chromeno[4,3-*d*]pyrimidines **71**

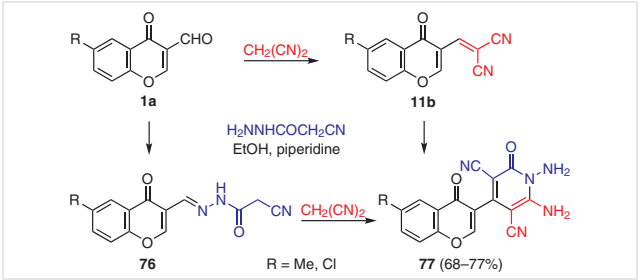
In the reaction of acetamidine with 3-vinylchromone **10c**, containing two ester groups that increase its electrophilicity compared to chromones **2**, in addition to the expected chromenopyrimidine **72**, 5-salicyloylpyrimidine **73** is formed as a result of the attack at the C-2 and C-1′ atoms, followed by cleavage of the malonic ether.[54] An analogous behavior of chromone **10c**, similar to that of 3-formylchromone, was also observed in the formation of pyrimidine **75** from toluamidine and 3-vinylchromone **74** with two phosphonate groups (Scheme 32).[55]



Scheme 32 Reactions of chromones **10c** and **74** with amidines

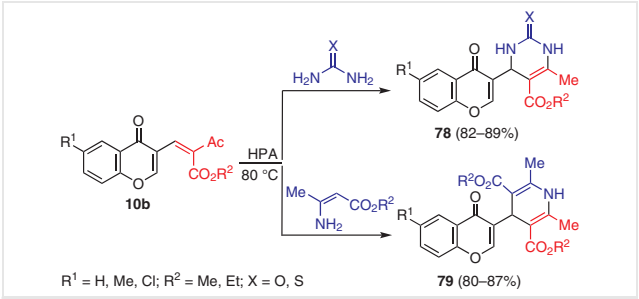
4.3 Reactions with other 1,3- and 1,4-Dinucleophiles

3-Vinylchromones **11b** obtained from 3-formylchromones **1a** and malononitrile react with cyanoacetohydrazide as a 1,3-C,N-dinucleophile on the acrylonitrile fragment, giving chromonylpyridones **77**.[56] 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).



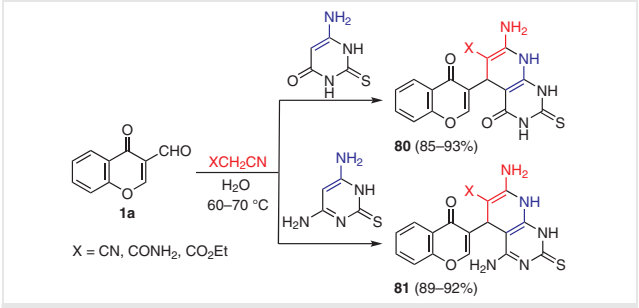
Scheme 33 Synthesis of chromonylpyridones **77**

Biginelli products **78** and Hantzsch products **79** were synthesized by reacting chromones **10b**, thiourea, and β-aminocrotonates in the presence of heteropolyacids (HPA) $H_{14}[NaP_5W_{29}MoO_{110}]$ or $H_6P_2W_{18}O_{62}{\cdot}24H_2O$ 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]



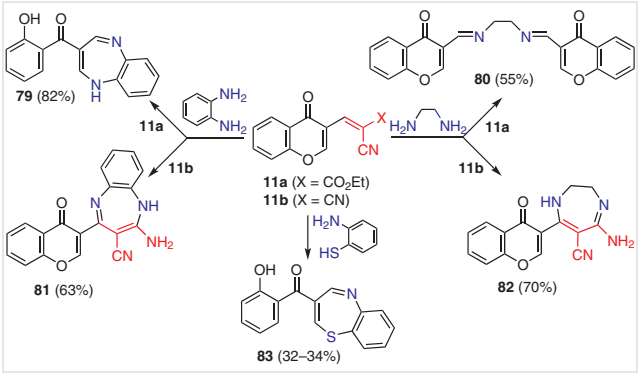
Scheme 34 Chromones **10b** in the Biginelli and Hantzsch reactions

Similarly, a three-component, one-pot reaction from 3-formylchromone (**1a**), methylene active cyanoacetic acid derivatives, 6-aminothiouracil or 4,6-diaminopyrimidine-2(1*H*)-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]



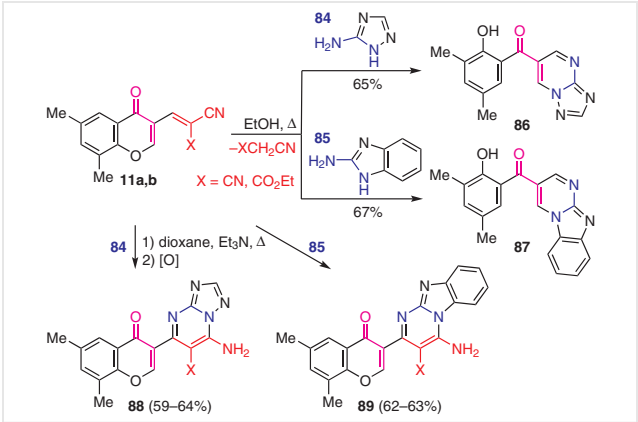
Scheme 35 Three-component synthesis of compounds **80** and **81**

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**.



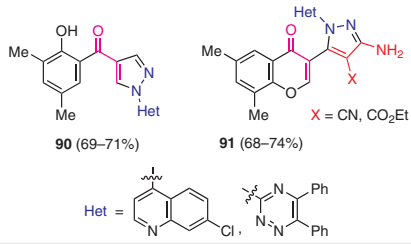
Scheme 36 Reactions of chromones **11a**,**b** with 1,4-dinucleophiles

Thus, 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 group[60] 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).



Scheme 37 Reactions of chromones **11a**,**b** with aminoheterocycles

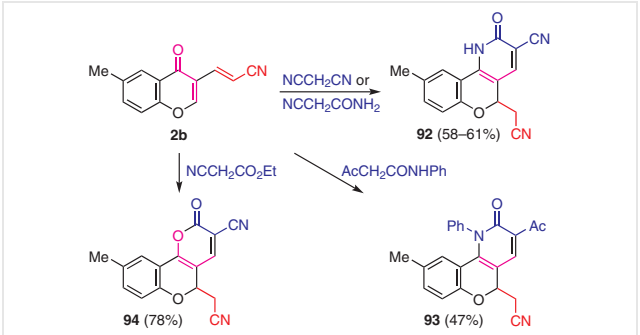
A similar outcome was observed in the reaction of chromones **11a**,**b** with 7-chloro-4-hydrazinoquinoline and 5,6-diphenyl-3-hydrazino-1,2,4-triazine, giving 4-salicyloylpyrazoles **90**. These were also obtained from 6,8-dimethyl-3-formylchromone in ethanol, while 3-aminopyrazoles **91** were formed in dioxane due to the side chain reaction (Scheme 38).[60]



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

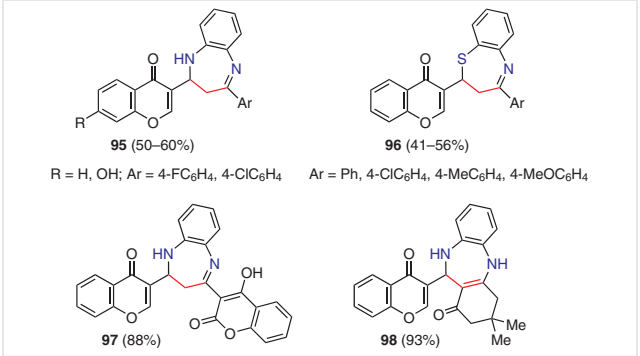
A study of the reaction of 3-(6-methylchromon-3-yl)-acrylonitrile **2b** with 1,3-*C*,*N*-dinucleophiles such as malononitrile, cyanoacetamide and acetoacetanilide showed that these molecules first attack the chromone C-2 atom via the methylene group with opening of the pyrone ring, and then with a nitrogen 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).[61] In the case of ethyl cyanoacetate, after attack at the C-2 atom and ring opening, the internal *O*-nucleophiles attack 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-5*H*-furo[3,2-*g*]-chromen-6-yl)acrylonitrile.[62]

A report[44] has described a number of reactions of chromone **47** with various dinucleophiles (Scheme 40), but the structure of the obtained compounds cannot be considered definitively proven due to the lack of 2D experiments and X-ray diffraction data.

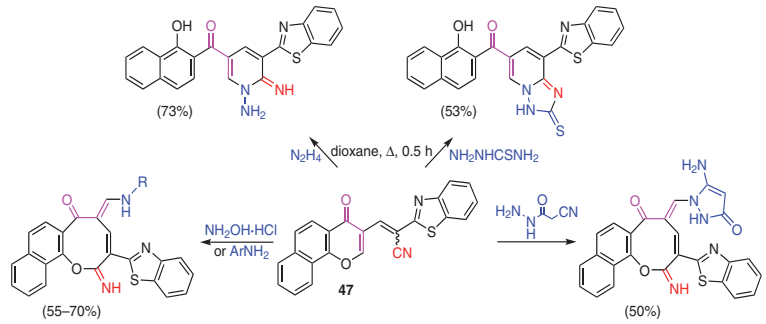


Scheme 39 Reactions of chromone **2b** with 1,3-C,N-dinucleophiles

The reaction of 3-aroylvinylchromones **5** with *o*-phenylenediamine and 2-aminothiophenol gave benzodiazepines **95** (AcOH, DMF, microwave irradiation, 15 min)[63a,b] and benzothiazepines **96** (hexafluoropropan-2-ol, r.t., 6 h or MeOH, AcOH, reflux, 2 h), respectively (Scheme 41).[63c,d] Three-component condensation of 3-formylchromone (**1a**), *o*-phenylenediamine, and 3-acetyl-4-hydroxycoumarin catalyzed by nano silica-supported *N*-propylsulfamic acid resulted in benzodiazepine **97**.[63e] Similarly, the use of 3-formylchromones **1a**, *o*-phenylenediamine, and dimedone as an active methylene component gave rise to the fused benzodiazepine **98**.[63f] This reaction requires no solvent and is catalyzed by the novel heterogeneous catalyst $Fe(OTs)_3/SiO_2$.

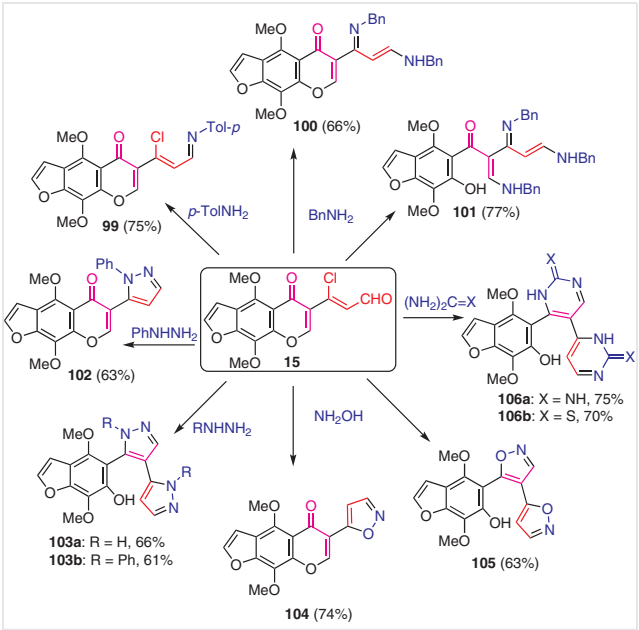


Scheme 41 Benzodiazepines and benzothiazepines prepared from 3-aroylvinylchromones **5**



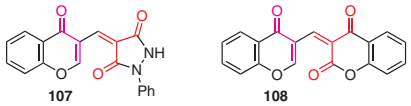
Scheme 40 Reactions of chromone **47** with various dinucleophiles

Reaction of 3-chloro-3-(4,9-dimethoxy-5-oxo-5*H*-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 biisoxazole **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 Et_3N or KOH as a catalyst was required.



Scheme 42 Reactions of khellin derivative **15** with mono- and dinucleophiles

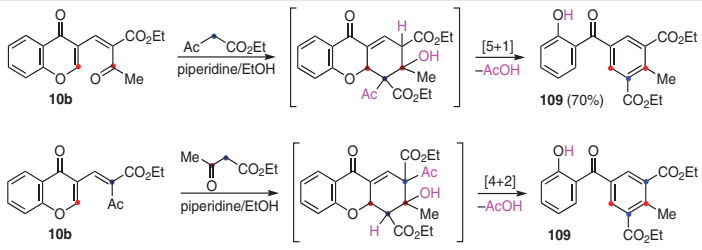
There are data in the literature on the transformations of condensation products of 3-formylchromone with 1-phenylpyrazolidine-3,5-dione and 4-hydroxycoumarin (chromones **107** and **108**, Scheme 43) under the action of various nucleophilic agents.[65] Reactions with amines, hydrazines, hydroxylamine, guanidine, 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.



Scheme 43 Methylene-linked chromones, the reactivity of which was described

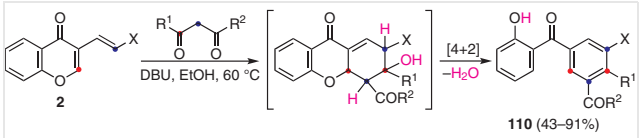
5 Ambiphilic Cyclization

In 1976, Jones and Albrecht[66] reported that treatment of 3-formylchromone with ethyl acetoacetate in the presence of AcONa/Ac_2O gave Knoevenagel product **10b** in 62% yield (Scheme 44). 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-dinucleophile (as in the reaction with amines, Scheme 16), reacting with each other by a type of intermolecular Michael addition followed by intramolecular aldol 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).



Scheme 44 Reaction of chromone **10b** with ethyl acetoacetate

A general synthesis of salicyloylbenzenes (2-hydroxybenzophenones) from 3-vinylchromones **2** with one electron-withdrawing group at the double bond was demonstrated in the work of Chen et al. in 2011.[67] 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, which do not contain such a group, do not enter into the reaction.

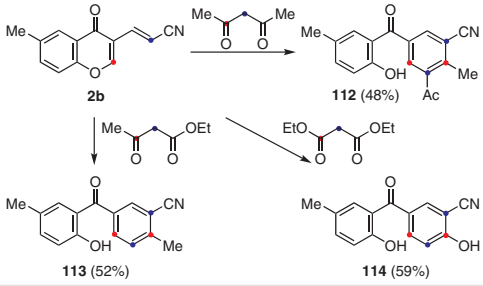


Scheme 45 Reaction of chromones **2** with 1,3-dicarbonyl compounds

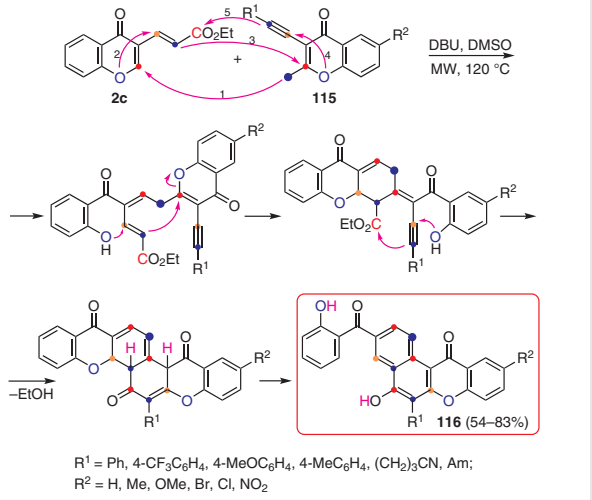
2-Hydroxybenzophenones **111**, with a different set of substituents, were obtained from chromones **2** and β-enaminoesters or β-enaminoketones by the [4+2] benzannulation reaction, catalyzed by indium(III) triflate in acetonitrile at room temperature (Scheme 46).[68] In this transformation, the role of 1,2-ambiphile was performed by ketoenamines.

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).[69]

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.[70] 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 the 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 **115** and the involvement of its triple bond in the process of double intramolecular cyclization with the formation of products **116**.

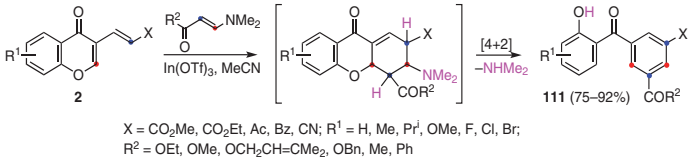


Scheme 47 Reaction of chromone **2b** with 1,3-dicarbonyl compounds

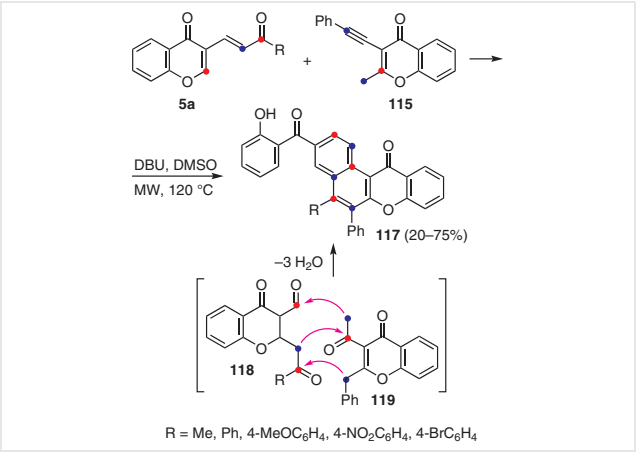


Scheme 48 Possible mechanism of benzo[*a*]xanthone formation

In addition to acrylate **2c**, chromones **5a**, containing an acylvinyl 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-12*H*-benzo[*a*]xanthen-12-one in 64% yield[69] (not shown in Scheme 49).



Scheme 46 Reaction of chromones **2** with enaminones

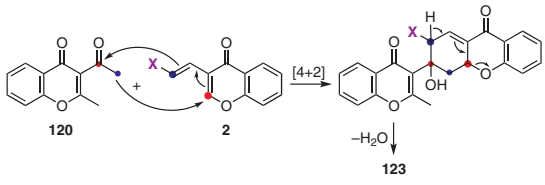


Scheme 49 Alternative mechanism of benzo[*a*]xanthone formation

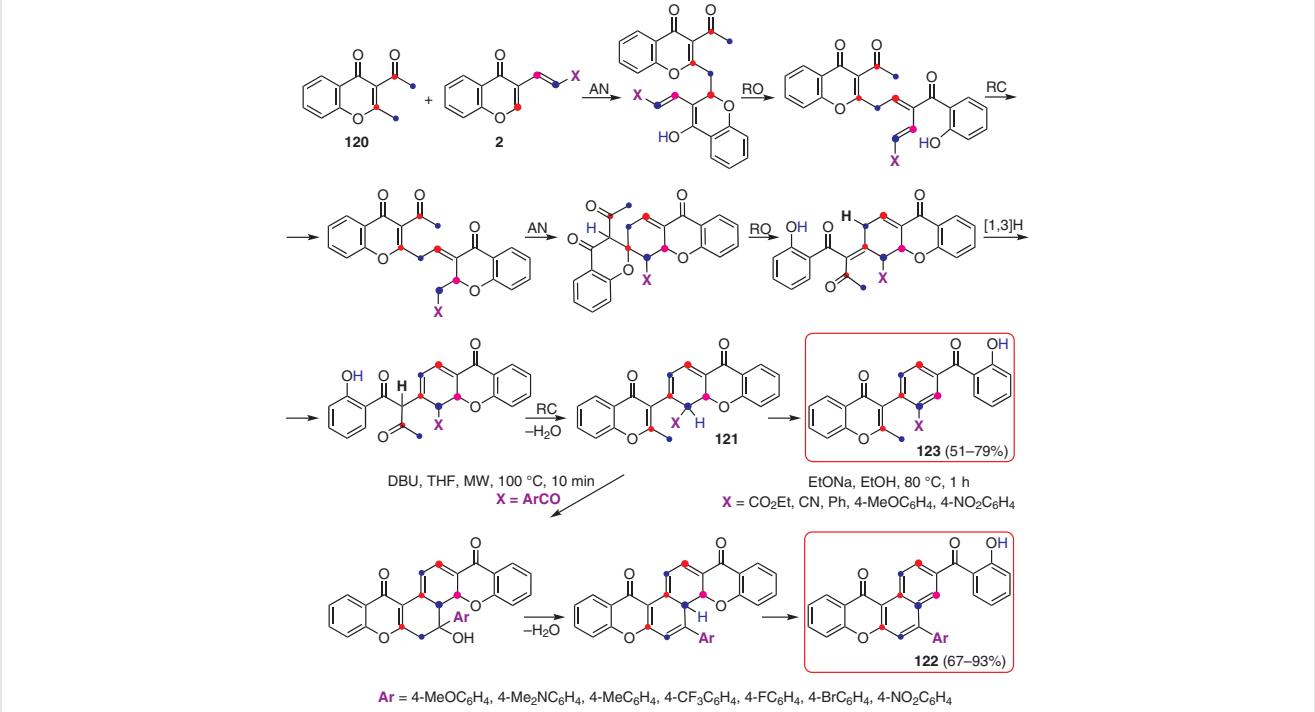
The rather extended mechanistic pathway to benzo[*a*]xanthones **116** and **117** can be replaced by a simple and illustrative scheme, including ambiphilic [4+2] cyclization in combination with aldol condensation between two hydrated forms **118** and **119**, which can hypothetically be formed during 1,4-addition of a water molecule to chromones **5a** and **115**, followed by opening of the pyrone ring and new cyclization where chromane **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.[71] 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).

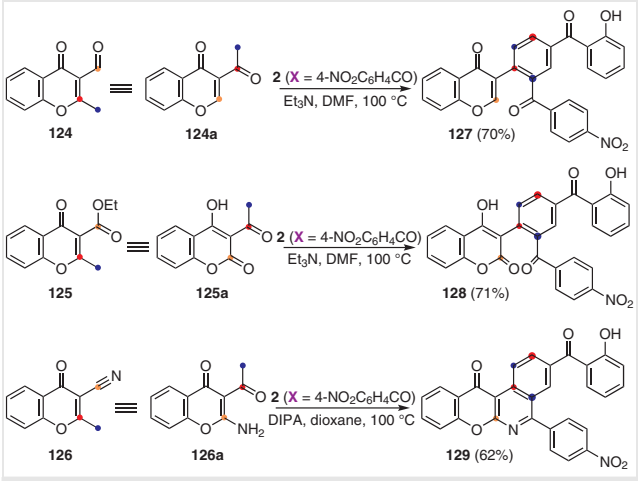


Scheme 51 Ambiphilic [4+2] carbocyclization, leading to benzophenones **123**



Scheme 50 Possible mechanism of the formation of compounds **122** and **123**

In addition to 2-methyl-3-acetylchromone (**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-$NO_2C_6H_4CO$), was studied.[71] 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).

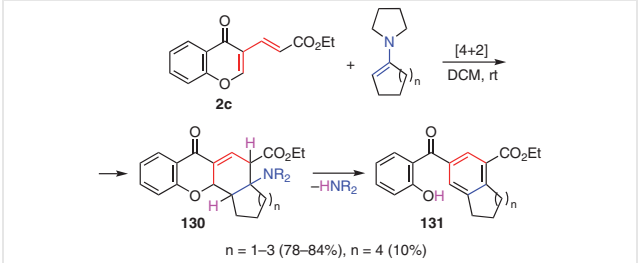


Scheme 52 [4+2] Carbocyclization via chemical equivalents **124a**–**126a**

6 Cycloaddition Reactions

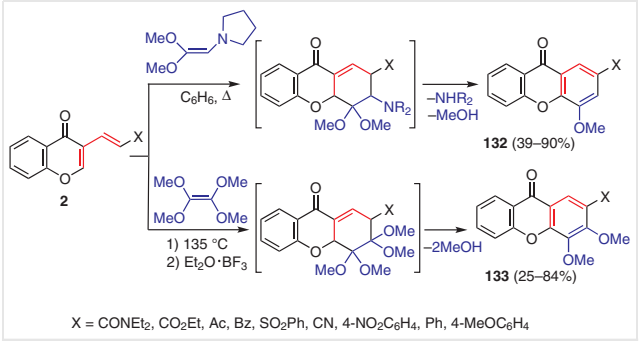
6.1 [4+2] Cycloaddition

The first data 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.[72] 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 eight-membered derivative (Scheme 53).



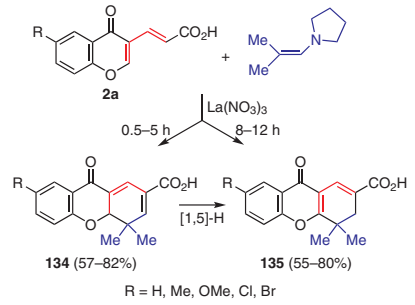
Scheme 53 Chromone **2c** in the inverse electron demand Diels–Alder reaction with enamines

When using such π-excess alkenes as 1-(2,2-dimethoxyvinyl)pyrrolidine or tetramethoxyethylene, due to the methoxy leaving-group, the pyrone ring does not open, which makes it possible to obtain 4-methoxyxanthones **132** and 3,4-dimethoxyxanthones **133** (Scheme 54).[73] 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** depend substantially 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**

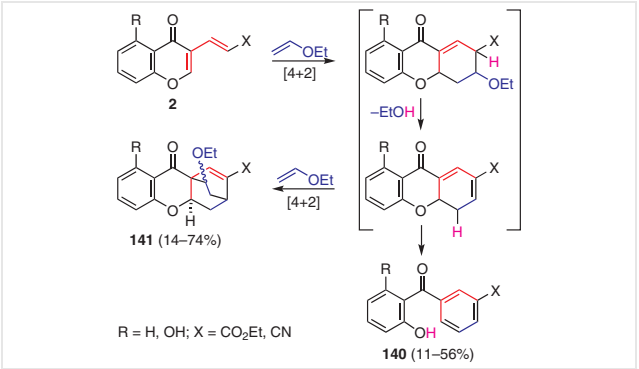
In another report,[74] [4+2] cycloaddition between chromonylacrylic acids **2a** and enamines from isobutyric aldehyde and pyrrolidine or piperidine led to the preparation of 4,4a-dihydroxanthones **134** in 43–81% yields (Scheme 55). Further study of this reaction using the example of a more active enamine with a pyrrolidine fragment showed that, if the reaction is carried out with the addition of $La(NO_3)_3$ 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**

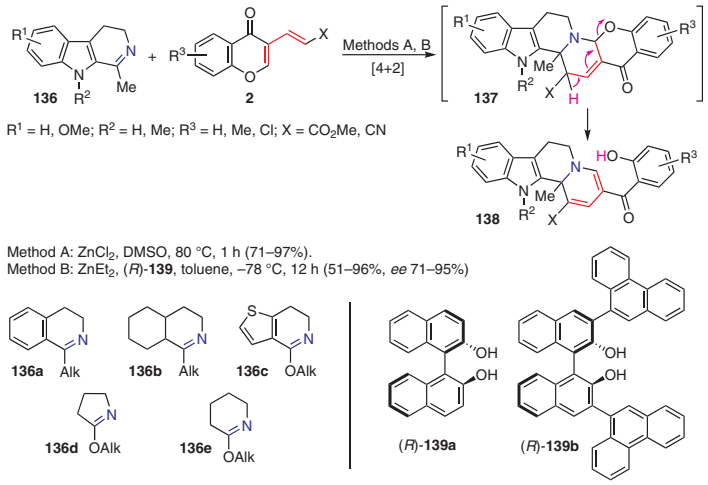
Interestingly, the IEDDA reaction with the electron-deficient diene system of 3-vinylchromones involves not only π-donor enamines, which is predictable, but also π-acceptor imines. The first, and so far, only example of an imino-Diels–Alder reaction with inverse electron demand (IEDIDA) between chromones **2** and cyclic imines **136a–e** has been described.[75] The reaction was catalyzed 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 IEDIDA reaction, chiral Lewis acids based on binol ligands **139a** or **139b** and $ZnEt_2$ 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.[76] The highest yield of tetracycles **141** (R = OH, X = CO_2Et) 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 with 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).

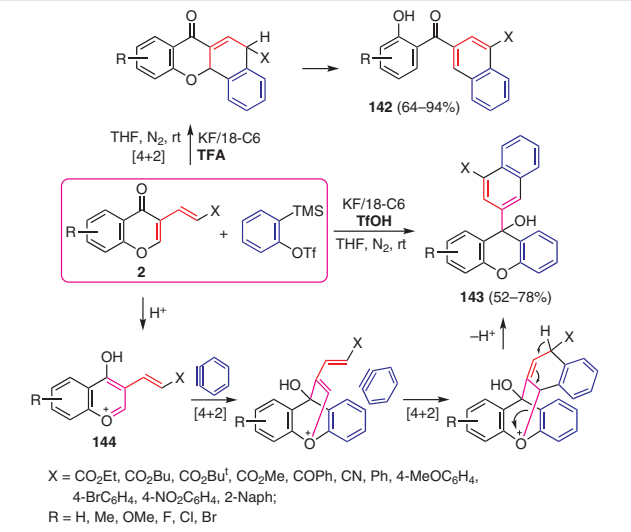


Scheme 57 Ethyl vinyl ether in the IEDDA reaction with chromones **2**

Reaction of 3-vinylchromones **2** with dehydrobenzene formed in situ from 2-(trimethylsilyl)phenyltriflate in the presence of KF/18-C6 in THF has been studied,[77] and it was shown that, in 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.



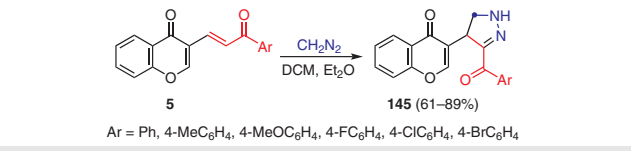
Scheme 56 Enantioselective IEDIDA reaction of chromones **2** with cyclic imines **136a–e**



Scheme 58 Reactions between chromones **2** and benzyne

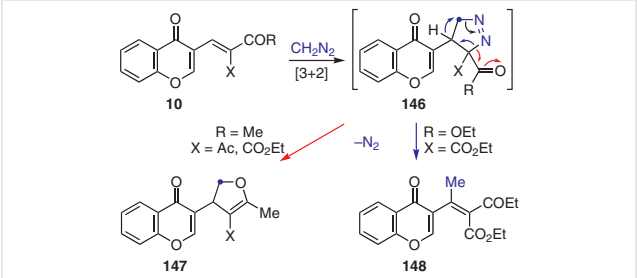
6.2 [3+2] Cycloaddition

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-aroyl-4-(chromon-3-yl)-2-pyrazolines **145** as the only isolated products (Scheme 59).[78] 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.



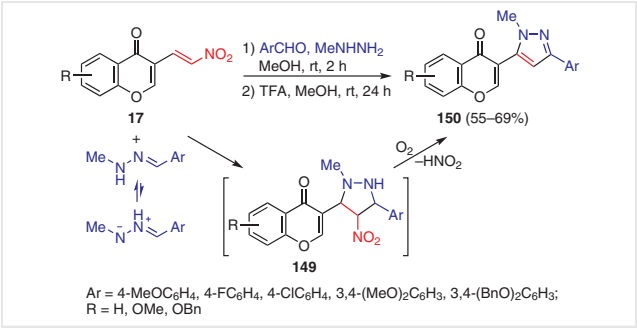
Scheme 59 Reaction of chromones **5** with diazomethane

Diazomethane also reacts with disubstituted 3-vinylchromones **10** (Scheme 60). In the case of condensates of 3-formylchromone with acetylacetone and acetoacetic ether, 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).[79]



Scheme 60 Reaction of chromones **10** with diazomethane

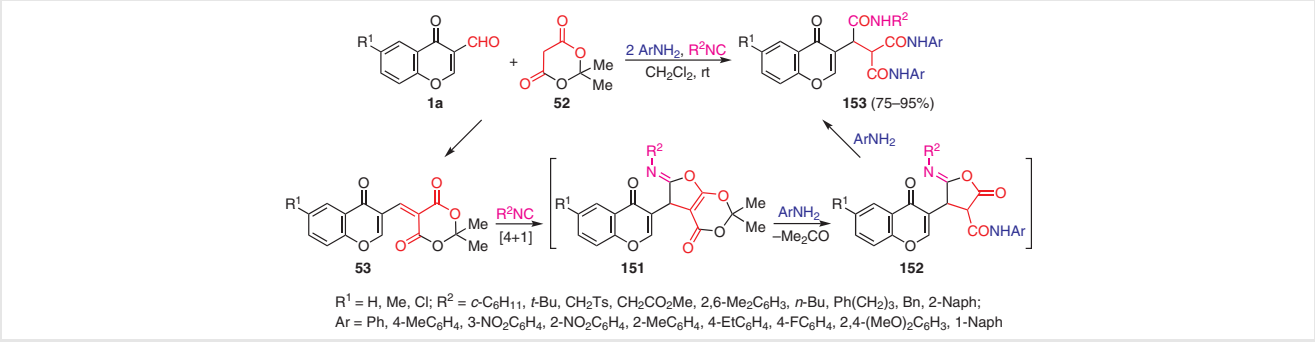
[3+2] Cycloaddition of 3-(2-nitrovinyl)chromones **17** with in situ generated *N*-methylhydrazones of aromatic aldehydes, which act as 1,3-dipoles, in the presence of a catalytic amount of trifluoroacetic acid in methanol, proceeds through pyrazolidine **149** (Scheme 61). The latter, after oxidation and elimination of HNO_2, gives the corresponding 3-(3-aryl-1-methyl-1*H*-pyrazol-5-yl)chromones **150** in good yields.[25a,80] Among the synthesized compounds, derivatives exhibiting α-glucosidase inhibitory activity were found.



Scheme 61 [3+2] Cycloaddition between chromones **17** and *N*-methylhydrazones

6.3 [4+1] Cycloaddition

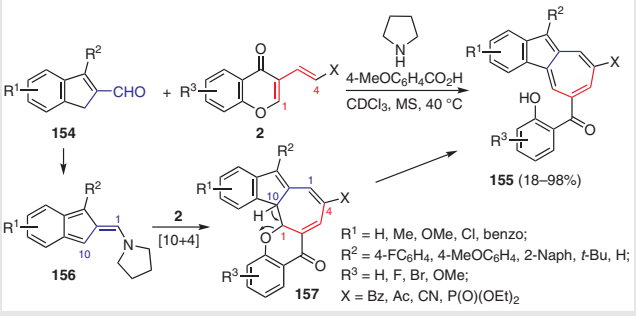
Teimouri et al.[81] reported the pseudo-five-component reaction of 3-formylchromones **1a**, Meldrum's acid **52**, primary aromatic amines and isonitriles under mild conditions, as an effective method for the synthesis of tripeptides containing a chromone moiety. The reaction begins with Knoevenagel 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 irrespective of the bulk or electronic nature of substituents in the starting compounds. However, with aliphatic amines, this transformation did not occur.



Scheme 62 Synthesis of tripeptides **153**

6.4 [10+4] Cycloaddition

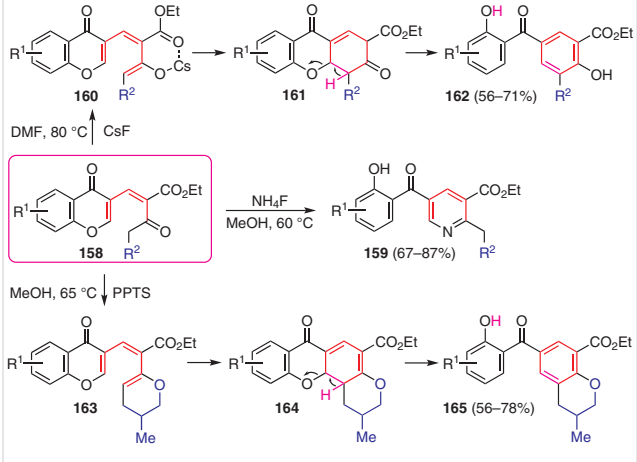
In a recent example, Jørgensen et al.[82] proposed the use of electron-deficient 3-vinylchromones **2** as readily available 4π-components in the construction of polysubstituted benzo[*a*]azulenes **155** by [10+4] cycloaddition. The role of the 10π-component was performed by indene-2-carbaldehyde **154** 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.



Scheme 63 Synthesis of benzo[*a*]azulenes **155**

7 Other Reactions

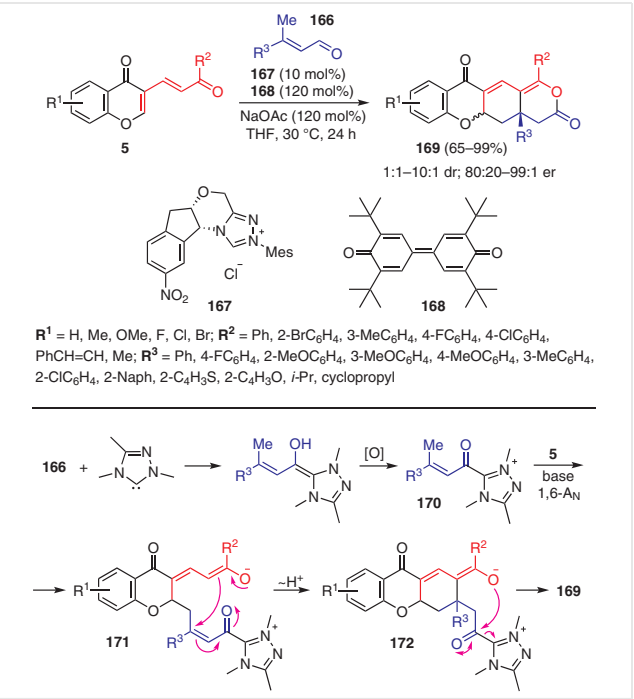
3-Vinylchromones **158**, with ester and acyl groups at the *exo*-double bond, were chosen as highly active substrates for the preparation of new derivatives of pyridines, benzophenones, and benzopyrans.[83] The authors proposed that the presence of such electrophilic centers as C-2 and C-1′, and nucleophilic centers such as CH_2 and OH (after removal of the *tert*-butyldimethylsilyl 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 in 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 NH_4F, the reaction followed the pathway of 6π-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 due to the liberated OH group added to the acyl carbonyl to obtain a hemiacetal, dehydration of which led to the hexatriene intermediate **163**. The latter, via electrocyclization and elimination of the phenolic residue from intermediate **164**, led to the formation of benzopyrans **165** in good yields.



Scheme 64 Transformations of 3-vinylchromones **158**

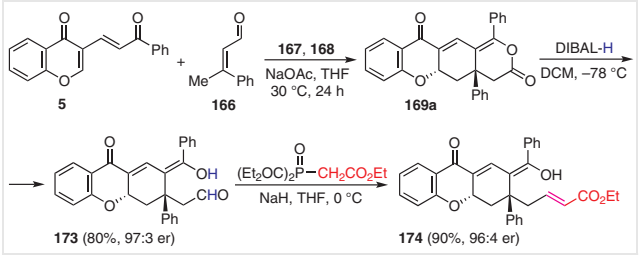
A cascade reaction between chromones **5** and β-methylacroleins under the action of *N*-heterocyclic carbene (NHC catalysis) has been described,[84] which provides a rapid approach to tetracyclic lactones **169** with a quaternary chiral carbon center (Scheme 65). To implement this diastereo- and enantioselective transformation, tetracyclic triazolium NHC **167** was used as a catalyst, quinone **168** as an oxidiz-

ing 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 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]



Scheme 65 Synthesis of compounds **169** and mechanism their formation

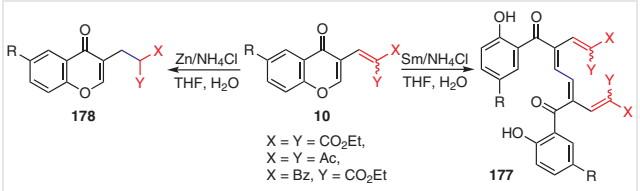
To demonstrate the synthetic potential of heterocycles **169**, by selective reduction of optically pure compound **169a**, chiral aldehyde **173** was obtained, which can be used in further transformations. For example, chiral α,β-unsaturated ester **174** was synthesized with excellent enantioselectivity via the Horner–Wadsworth–Emmons reaction (Scheme 66).[84]



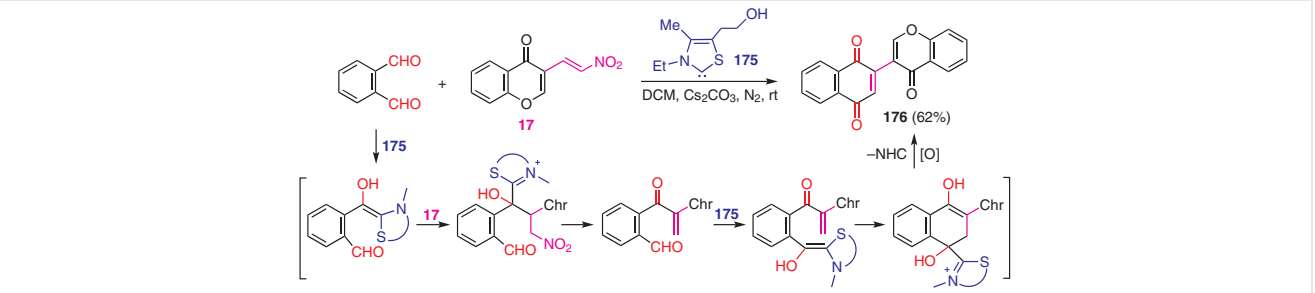
Scheme 66 Synthetic potential of heterocycles **169**

Another interesting, albeit single example, of a cascade reaction catalyzed by *N*-heterocyclic carbene **175** between 3-(2-nitrovinyl)chromone **17** and phthalaldehyde, leading to 2-(chromon-3-yl)naphthoquinone **176**, has also been described.[86] This reaction proceeds under mild conditions via a double Stetter reaction, the mechanism of which is shown in Scheme 67.

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 NH_4Cl, 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).[87]



Scheme 68 Reduction of 3-vinylchromones **10**



Scheme 67 Synthesis of compound **176** and mechanism for its formation

8 Conclusion

The chemistry of electron-deficient 3-vinylchromones containing two conjugated polarized double bonds has attracted increasing attention. It has been shown that these readily available representatives of the 3-substituted chromone family exhibit high reactivity towards nucleophilic 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 opening of the pyrone 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-vinylchromones with active methylene compounds and 2-methylchromones lead to the construction of an aromatic ring and the production of substituted *o*-hydroxybenzophenones. 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*-methylhydrazones of aromatic aldehydes having currently been reported.

Conflict of Interest

The authors declare no conflict of interest.

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References

(1) (a) Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. *Eur. J. Med. Chem.* **2014**, *78*, 340. (b) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (d) Abu-Hashem, A. A.; El-Shazly, M. *Eur. J. Med. Chem.* **2015**, *90*, 633. (e) Verma, A. K.; Pratap, R. *Tetrahedron* **2012**, *68*, 8523. (f) Sharma, S. K.; Kumar, S.; Chand, K.; Kathuria, A.; Gupta, A.; Jain, R. *Curr. Med. Chem.* **2011**, *18*, 3825. (g) Reis, J.; Gaspar, A.; Milhazes, N.; Borges, F. *J. Med. Chem.* **2017**, *60*, 7941.

(2) (a) Ghosh, C. K.; Chakraborty, A. *ARKIVOC* **2015**, *(vi)*, 288. (b) Sepay, N.; Dey, S. P. *J. Heterocycl. Chem.* **2014**, *51*, E1. (c) Plaskon, A. S.; Grygorenko, O. O.; Ryabukhin, S. V. *Tetrahedron* **2012**, *68*, 2743. (d) Shatokhin, S. S.; Tuskaev, V. A.; Gagieva, S. C.; Oganesyan, É. T. *Russ. Chem. Bull., Int. Ed.* **2021**, *70*, 1011.

(3) Sosnovskikh, V. Y. *Chem. Heterocycl. Compd.* **2020**, *56*, 243.

(4) (a) Sosnovskikh, V. Y. In *Fluorine in Heterocyclic Chemistry*; Nenajdenko, V. G., Ed.; Springer: Switzerland, **2014**, 211. (b) Tomé, S. M.; Silva, A. M. S.; Santos, C. M. M. *Curr. Org. Synth.* **2014**, *11*, 317. (c) Isakova, V. G.; Khlebnikova, T. S.; Lakhvich, F. A. *Russ. Chem. Rev.* **2010**, *79*, 849.

(5) (a) Ghosh, C. K.; Chakraborty, A. *ARKIVOC* **2015**, *(vi)*, 417. (b) Sosnovskikh, V. Y.; Moshkin, V. S. *Chem. Heterocycl. Compd.* **2012**, *48*, 139. (c) Ghosh, C. K.; Karak, S. K. *J. Heterocycl. Chem.* **2005**, *42*, 1035.

(6) Sosnovskikh, V. Y. *Russ. Chem. Rev.* **2003**, *72*, 489.

(7) Kornev, M. Y.; Sosnovskikh, V. Y. *Chem. Heterocycl. Compd.* **2016**, *52*, 71.

(8) (a) Sosnovskikh, V. Y. *Chem. Heterocycl. Compd.* **2020**, *56*, 1111. (b) Ibrahim, M. A.; El-Gohary, N. M.; Said, S. *Heterocycles* **2015**, *91*, 1863.

(9) Sosnovskikh, V. Y. *Russ. Chem. Rev.* **2021**, *90*, 511.

(10) Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Levai, A.; Patonay, T. *ARKIVOC* **2004**, *(vii)*, 106.

(11) Gašparová, R.; Lácová, M. *Molecules* **2005**, *10*, 937.

(12) Ibrahim, M. A.; Ali, T. E.; El-Gohary, N. M.; El-Kazak, A. M. *Eur. J. Chem.* **2013**, *4*, 311.

(13) (a) Nohara, A.; Kuriki, H.; Saijo, T.; Ukawa, K.; Murata, T.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1975**, *18*, 34. (b) Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1977**, *20*, 141.

(14) (a) Chand, K.; Tiwari, R. K.; Kumar, S.; Shirazi, A. N.; Sharma, S.; Van der Eycken, E.; Parmar, V. S.; Parang, K.; Sharma, S. K. *J. Heterocycl. Chem.* **2015**, *52*, 562. (b) Kumar, S.; Singh, B. K.; Pandey, A. K.; Kumar, A.; Sharma, S. K.; Raj, H. G.; Prasad, A. K.; Van der Eycken, E.; Parmar, V. S.; Ghosh, B. *Bioorg. Med. Chem.* **2007**, *15*, 2952.

(15) Joshi, R. S.; Mandhane, P. G.; Badadhe, P. V.; Gill, C. H. *Ultrason. Sonochem.* **2011**, *18*, 735.

(16) Iwasaki, H.; Kume, T.; Yamamoto, Y.; Akiba, K. *Heterocycles* **1988**, *27*, 1599.

(17) Tuskaev, V. A.; Oganesyan, É. T.; Mutsueva, S. K. *Pharm. Chem. J.* **2002**, *36*, 309.

(18) (a) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476. (b) McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T. *Tetrahedron Lett.* **1990**, *31*, 5449. (c) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45.

(19) (a) Jones, W. D.; Albrecht, W. L. *J. Org. Chem.* **1976**, *41*, 706. (b) Borrell, J. I.; Teixidó, J.; Schuler, E.; Michelotti, E. L. *Mol. Diversity* **2000**, *5*, 163.

(20) Hangarge, R. V.; Sonwane, S. A.; Jarikote, D. V.; Shingare, M. S. *Green Chem.* **2001**, *3*, 310.

(21) Kumar, V.; Chatterjee, A.; Banerjee, M. *Synth. Commun.* **2015**, *45*, 2364.

(22) Ghosh, C. K.; Tewari, N.; Bhattacharyya, A. *Synthesis* **1984**, 614.

(23) Coutts, S. J.; Wallace, T. W. *Tetrahedron* **1994**, *50*, 11755.

(24) Ali, T. E.; Assiri, M. A.; Ibrahim, M. A.; Yahia, I. S. *Russ. J. Org. Chem.* **2020**, *56*, 845.

(25) (a) Soengas, R. G.; Silva, V. L. M.; Ide, D.; Kato, A.; Cardoso, S. M.; Paz, F. A. A.; Silva, A. M. S. *Tetrahedron* **2016**, *72*, 3198. (b) Rodríguez, J. M.; Pujol, M. D. *Tetrahedron Lett.* **2011**, *52*, 2629. (c) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Banerjee, S. *J. Chem. Res., Miniprint* **2003**, 847.

(26) Abdou, W. M.; Khidre, M. D.; Mahran, M. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *61*, 83.

(27) (a) Sun, W.; Carroll, P. J.; Soprano, D. R.; Canney, D. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4339. (b) Singh, G.; Singh, G.; Ishar, M. P. S. *Helv. Chim. Acta* **2003**, *86*, 169.

(28) Davies, S. G.; Mobbs, B. E.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2597.
(29) Patonay, T.; Vasas, A.; Kiss-Szikszai, A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Aust. J. Chem.* **2010**, *63*, 1582.
(30) (a) Zhang, Y.; Lv, Z.; Zhong, H.; Zhang, M.; Zhang, T.; Zhang, W.; Li, K. *Tetrahedron* **2012**, *68*, 9777. (b) Zhang, Y.; Zhong, H.; Lv, Z.; Zhang, M.; Zhang, T.; Li, Q.; Li, K. *Eur. J. Med. Chem.* **2013**, *62*, 158. (c) Lv, Z.; Sheng, C.; Wang, T.; Zhang, Y.; Liu, J.; Feng, J.; Sun, H.; Zhong, H.; Niu, C.; Li, K. *J. Med. Chem.* **2010**, *53*, 660.
(31) Kim, D.; Hong, S. *Org. Lett.* **2011**, *13*, 4466.
(32) Debbarma, S.; Sk, M. R.; Modak, B.; Maji, M. S. *J. Org. Chem.* **2019**, *84*, 6207.
(33) (a) Gigant, N.; Bäckvall, J.-E. *Chem. Eur. J.* **2013**, *19*, 10799. (b) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, *551*, 489.
(34) Ghosh, C. K.; Khan, S. *Synthesis* **1981**, 903.
(35) Haas, G.; Stanton, J. L.; von Sprecher, A.; Wenk, P. *J. Heterocycl. Chem.* **1981**, *18*, 607.
(36) Pintiala, C.; Lawson, A. M.; Comesse, S.; Daïch, A. *Tetrahedron Lett.* **2013**, *54*, 2853.
(37) (a) Chand, K.; Prasad, S.; Tiwari, R. K.; Shirazi, A. N.; Kumar, S.; Parang, K.; Sharma, S. K. *Bioorg. Chem.* **2014**, *53*, 75. (b) Chand, K.; Alsoghier, H. M.; Chaves, S.; Santos, M. A. *J. Inorg. Biochem.* **2016**, *163*, 266.
(38) Zhang, Y.; Lv, Z.; Zhang, M.; Li, K. *Tetrahedron* **2013**, *69*, 8839.
(39) Chand, K.; Sharma, A. K.; Sharma, S. K. *Magn. Reson. Chem.* **2016**, *54*, 91.
(40) Lepitre, T.; Denhez, C.; Moncol, J.; Othman, M.; Lawson, A. M.; Daïch, A. *J. Org. Chem.* **2017**, *82*, 12188.
(41) (a) Lepitre, T.; Denhez, C.; Sanselme, M.; Othman, M.; Lawson, A. M.; Daïch, A. *J. Org. Chem.* **2016**, *81*, 8837. (b) Monier, M.; El-Mekabaty, A.; Abdel-Latif, D.; Elattar, K. M. *Synth. Commun.* **2019**, *49*, 2591.
(42) Lepitre, T.; Biannic, R. L.; Othman, M.; Lawson, A. M.; Daïch, A. *Org. Lett.* **2017**, *19*, 1978.
(43) Ibrahim, M. A.; Badran, A.-S. *ARKIVOC* **2018**, *(vii)*, 214.
(44) Abozeid, M. A.; El-Sawi, A. A.; Elmorsy, M. R.; Abdelmoteleb, M.; Abdel-Rahmana, A.-R. H.; El-Desoky, E.-S. I. *RSC Adv.* **2019**, *9*, 27996.
(45) Ibrahim, M. A.; El-Gohary, N. M. *Heterocycles* **2014**, *89*, 413.
(46) (a) Mehrparvar, S.; Balalaie, S.; Rabbanizadeh, M.; Ghabraie, E.; Rominger, F. *Mol. Diversity* **2014**, *18*, 535. (b) Shelke, K. F.; Sapkal, S. B.; Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. *Cent. Eur. J. Chem.* **2010**, *8*, 12.
(47) Balalaie, S.; Bijanzadeh, H. R.; Mehrparvar, S.; Rominger, F. *Synlett* **2016**, *27*, 782.
(48) (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757. (b) Amer, M. M. K.; Aziz, M. A.; Shehab, W. S.; Abdellattif, M. H.; Mouneir, S. M. *J. Saudi Chem. Soc.* **2021**, *25*, 101259.
(49) Mehrparvar, S.; Balalaie, S.; Rabbanizadeh, M.; Rominger, F.; Ghabraie, E. *Org. Biomol. Chem.* **2014**, *12*, 5757.
(50) (a) Lévai, A.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Alkorta, I.; Elguero, J.; Jekö, J. *Eur. J. Org. Chem.* **2004**, 4672. (b) Santos, C. M. M.; Silva, V. L. M.; Silva, A. M. S. *Molecules* **2017**, *22*, 1665.
(51) Hatzade, K.; Taile, V.; Gaidhane, P.; Ingle, V. *Turk. J. Chem.* **2010**, *34*, 241.
(52) (a) Santos, C. M. M.; Silva, A. M. S.; Jekő, J.; Lévai, A. *ARKIVOC* **2012**, *(v)*, 265.
(53) Siddiqui, Z. N.; Praveen, S.; Musthafa, M.; Ahmad, A.; Khan, A. U. *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 84.
(54) Chernov, N. M.; Shutov, R. V.; Potapova, A. E.; Yakovlev, I. P. *Synthesis* **2020**, *52*, 40.
(55) Xiang, H.; Qi, X.; Xie, Y.; Xub, G.; Yang, C. *Org. Biomol. Chem.* **2012**, *10*, 7730.
(56) (a) Ali, T. E.-S.; Ibrahim, M. A. *J. Braz. Chem. Soc.* **2010**, *21*, 1007. (b) Abdel-Megid, M.; Ibrahim, M. A.; Gabr, Y.; El-Gohary, N. M.; Mohamed, E. A. *J. Heterocycl. Chem.* **2013**, *50*, 615.
(57) (a) Sanchez, L. M.; Pasquale, G.; Sathicq, Á.; Ruiz, D.; Jios, J.; de Souza, A. L. F.; Romanelli, G. P. *Heteroat. Chem.* **2016**, *27*, 295. (b) Sanchez, L. M.; Sathicq, Á. G.; Jios, J. L.; Baronetti, G. T.; Thomas, H. J.; Romanelli, G. P. *Tetrahedron Lett.* **2011**, *52*, 4412.
(58) (a) Ghosh, C. K.; Ray, A.; Patra, A. *J. Heterocycl. Chem.* **2001**, *38*, 1459. (b) Ghosh, C. K.; Karak, S. K.; Patra, A. *J. Chem. Res., Synop.* **2002**, 311.
(59) Ali, T. E.; Assiri, M. A.; Shati, A. A.; Alfaifi, M. Y.; Elbehairi, S. E. I.; El-Kott, A. F. *Heterocycles* **2021**, *102*, 930.
(60) Badran, A.-S.; El-Gohary, N. M.; Ibrahim, M. A.; Hashiem, S. H. *J. Heterocycl. Chem.* **2020**, *57*, 2570.
(61) Ibrahim, M. A.; El-Gohary, N. M. *Tetrahedron* **2018**, *74*, 512.
(62) Assiri, M. M.; Ali, T. E.; Ibrahim, M. A.; Badran, A.-S.; Yahia, I. S. *Polycyclic Aromat. Compd.* **2019**, *41*, 1357.
(63) (a) Patil, R. B.; Sawant, S. D.; Reddy, K. V.; Shirsat, M. *Res. J. Pharm. Biol. Chem. Sci.* **2015**, *6*, 381. (b) Sharma, V. P.; Kumar, P. *Asian J. Chem.* **2014**, *26*, 3992. (c) Albanese, D. C. M.; Gaggero, N.; Fei, M. *Green Chem.* **2017**, *19*, 5703. (d) Shanker, M. S. S.; Reddy, R. B.; Chandra, Mouli. G. V. P.; Reddy, Y. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1989**, *44*, 143. (e) Tarannum, S.; Siddiqui, Z. N. *Monatsh. Chem.* **2017**, *148*, 717. (f) Tarannum, S.; Siddiqui, Z. N. *RSC Adv.* **2015**, *5*, 74242.
(64) See ref. 24
(65) (a) Khodairy, A. *J. Chin. Chem. Soc.* **2007**, *54*, 93. (b) Badran, A.-S.; Ibrahim, M. A.; Ahmed, A. *Synth. Commun.* **2021**, *51*, 1868.
(66) See ref. 19a
(67) Chen, H.; Xie, F.; Gong, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 8495.
(68) Cai, H.; Xia, L.; Lee, Y. R. *Chem. Commun.* **2016**, *52*, 7661.
(69) See ref. 61
(70) Gong, J.; Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3848.
(71) Gong, J.; Xie, F.; Ren, W.; Chen, H.; Hu, Y. *Org. Biomol. Chem.* **2012**, *10*, 486.
(72) Bodwell, G. J.; Hawco, K. M.; da Silva, R. P. *Synlett* **2003**, 179.
(73) Dang, A.-T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 233.
(74) Chernov, N. M.; Shutov, R. V.; Sharoyko, V. V.; Kuz'mich, N. N.; Belyakov, A. V.; Yakovlev, I. P. *Eur. J. Org. Chem.* **2017**, 2836.
(75) Eschenbrenner-Lux, V.; Küchler, P.; Ziegler, S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 2134.
(76) Heredia-Moya, J.; Krohn, K.; Flörke, U.; Pessoa-Mahana, H.; Weiss-López, B.; Estévez-Braun, A.; Araya-Maturana, R. *Heterocycles* **2007**, *71*, 1327.
(77) Huang, X.-J.; Tao, Y.; Li, Y.-K.; Wu, X.-Y.; Sha, F. *Tetrahedron* **2016**, *72*, 8565.
(78) Lévai, A.; Jekő, J. *J. Heterocycl. Chem.* **2002**, *39*, 1333.
(79) Ghosh, C. K.; Biswas, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1784.
(80) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505.
(81) Teimouri, M. B.; Akbari-Moghaddam, P.; Golbaghi, G. *ACS Comb. Sci.* **2011**, *13*, 659.
(82) Giardinetti, M.; Jessen, N. I.; Christensen, M. L.; Jørgensen, K. A. *Chem. Commun.* **2019**, *55*, 202.
(83) Waldmann, H.; Kühn, M.; Liu, W.; Kumar, K. *Chem. Commun.* **2008**, 1211.
(84) Sun, J.; Xu, J.; Nie, G.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2020**, *22*, 2595.

(85) (a) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (b) Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 1943.
(86) Mitra, R. N.; Show, K.; Barman, D.; Sarkar, S.; Maiti, D. K. *J. Org. Chem.* **2019**, *84*, 42.
(87) Saha, S.; Ghosh, T.; Bandyopadhyay, C. *Synth. Commun.* **2008**, *38*, 2429.