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Synthesis and reactivity of 3-(1-alkynyl)chromones

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For the first time, the literature data on the methods of synthesis and reactivity of 3-(1-alkynyl)chromones are summarized and systematized. The main method for obtaining these compounds is the Sonogashira cross-coupling reaction of 3-halochromones with terminal acetylenes, and their most important chemical properties include the transformation into furans, reactions with dinucleophiles, ambiphilic [4 + 2]- and [4 + 3]-cyclizations, and also dimerization and mixed condensation of 2-methyl-3-(1-alkynyl)chromones due to the vinylogous methyl group. Except for the oxacyclization to furans, chemical transformations of 3-(1-alkynyl)chromones are accompanied by pyrone ring transformation, in which not only the carbonyl group but also the triple bond can participate. This significantly increases the synthetic value of these compounds and ensures the production of more complex heterocyclic systems based on them. The mechanisms of the reactions are discussed, the conditions for their implementation and the yields of the resulting products are indicated.
The bibliography includes 80 references.

Contents

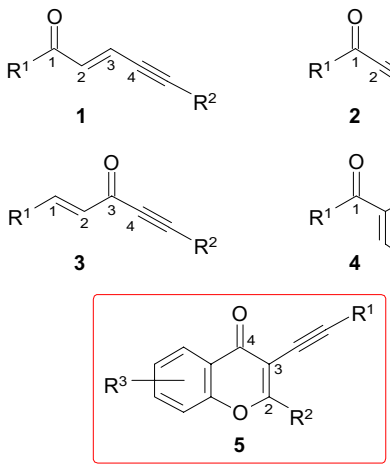
1. Introduction 511
2. Synthesis and the triple bond reactions 512
3. Conversion into furans 514
4. Nucleophilic reactions 519
5. Ambiphilic cyclizations 521
6. Reactions involving a pendant chain 525
7. Conclusion 525
8. List of acronyms and designations 526

1. Introduction

In recent years, the number of articles devoted to the synthesis and chemical properties of vinylacetylene ketones, also called enynones, has dramatically increased. Interest in these compounds stems primarily from their high reactivity towards a wide range of nucleophiles and dipoles, which makes enynones valuable building blocks for targeted organic synthesis of useful products, including natural compounds and their analogues.[1] An important role in the rapid development of the chemistry of enynones also belongs to their availability that has significantly increased due to the widespread introduction of various palladium-catalyzed cross-coupling reactions into the practice of organic synthesis.

All vinylacetylene ketones can be divided into four types: linear-conjugated enynones (alk-2-en-4-yn-1-ones **1**, alk-4-en-2-yn-1-ones **2**) and cross-conjugated enynones [alk-1-en-4-yn-3-ones **3**, 2-(alkyn-1-yl)alk-2-en-1-ones **4**]. Despite the great synthetic potential of conjugated enynones **1**–**4** and the interest in them shown in this connection, reviews on the methods of their preparation, physical and chemical properties began to appear just recently. Special attention was given to the analysis of data for classic vinylacetylene ketones **1**–**3**,[1–4] whereas 2-(alkyn-1-yl)alk-2-en-1-ones **4**, sufficiently differing from the former compounds in reactivity, were only presented in two reviews addressing their reactions catalyzed by electrophiles.[4, 5]

Structures 1 – 5



It is easily seen that the cross-conjugated system of enynones **4** is present in 3-(1-alkynyl)chromones **5**, whose chemistry began to develop only since 2004 when 3-(phenylethynyl)chromone was synthesized for the first time by the Sonogashira reaction.[6] At the same time, numerous chromone derivatives including isoflavones and other 3-substituted chromones have long been recognized as 'privileged' structures in drug discovery, and the chromone system *per se* proved to be a valuable building block for designing compounds with various biological activities. Chromone derivatives have a pharmacological effect on neurodegener-

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ative, inflammatory and infectious diseases, as well as diabetes, asthma, and cancer.[7–11]

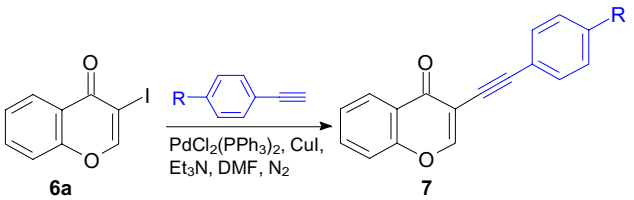
In this review, for the first time, an attempt was made to summarize and analyze all information reported over the past 15 years on the synthesis and reactivity of 3-(1-alkynyl)chromones as typical, but much less known representatives of the family of 3-substituted chromones. Indeed, in contrast to 3-formyl-,[12,13] 3-trifluoroacetyl-,[14–16] 3-cyano-,[17–19] 3-halo-,[20–22] 3-nitro-,[23] 3-carboxy-,[24] 3-alkoxycarbonyl- (Refs 23, 25), and 3-alkoxalylchromones,[25] the properties of which have been repeatedly highlighted in the literature; the chemistry of 3-(1-alkynyl)chromones has not been previously considered.

2. Synthesis and the triple bond reactions

The reactions catalyzed by transition metals (particularly, palladium) are ofter characterized by a high rate, selectivity, low amount of side products, and the ease of the product isolation, which accounts for their wide application in the synthesis of a variety of compounds with useful properties. Almost all 3-(1-alkynyl)chromones known to date have been obtained by the Sonogashira reaction, that is by the cross-coupling of 3-halochromones with terminal alkynes using a palladium catalyst and cuprous halide in the presence of triethylamine.[26,27] The Sonogashira reaction leads to the formation of the C–C bond between C(sp^2) and C(sp) atoms of a halide and an alkyne, respectively, and in contrast to other cross-coupling reactions, requires no preliminary activation of the alkyne through its conversion into an organometallic compound. Moreover, this reaction tolerates a broad range of functionalities which makes it an indispensable tool in organic synthesis, including the introduction of the triple bond into the 3-position of coumarins, which are structural isomers of chromones.[28]

In 2004, Larock and co-workers[6] used the reaction of 3-iodochromone (**6a**) and phenylacetylene to obtain the first representative of 3-(arylethynyl)chromones — 3-(phenylethynyl)chromone (**7a**, R = H) (Scheme 1). The reaction mixture was stirred in Et_3N and DMF with $PdCl_2(PPh_3)_2$ (1 mol.%) and CuI (0.5 mol.%) under nitrogen overnight at room temperature; isolation by flash chromatography gave product **7a** in high yield.

Scheme 1



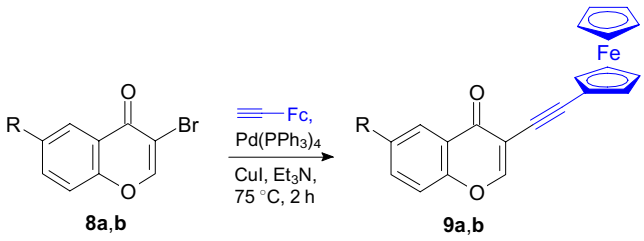
6a **7**

R = H (**a**, 91%), Me (67%), OMe, OPr^i, $OCH_2CH(Et)Bu^n$

Yang *et al.*[29] described the synthesis of a series of 3-(arylethynyl)chromones **7**, possessing various electron-donating groups in the phenyl substituent, and studied their photophysical and chemiluminiscent properties associated with structural features of these compounds (see Scheme 1). This synthesis was carried out by refluxing the reactants in THF for 10–12 h using 2 mol.% of palladium(II) chloride with the addition of PPh_3 (10 mol.%) as a catalyst. The presence of donating groups was shown to have virtually no effect on the absorption spectra of the products, while the photoluminiscence spectra changed significantly.

Under Sonogashira conditions, 3-bromochromones **8a**,**b** reacted with ethynylferrocene to afford 3-(ferrocenylethynyl)chromones **9a**,**b** (Scheme 2), which were further used to obtain ferrocenyl derivatives of furo[3,2-*c*]chromenes and furo[3,2-*c*]coumarins (see Section 3).[30]

Scheme 2

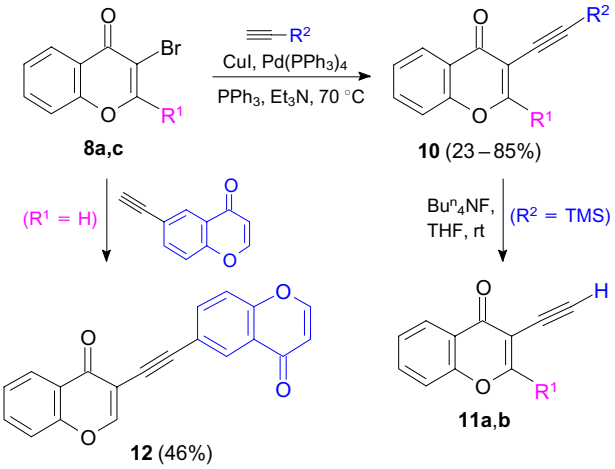


8a,**b** **9a**,**b**

R = H (**a**, 75%), F (**b**, 39%); Fc is ferrocenyl

Under similar conditions, 3-bromochromone (**8a**) and 3-bromoflavone (**8c**) react with various terminal acetylenes to provide 3-(1-alkynyl)chromones **10**.[31] 3-Ethynylchromone (**11a**) and 3-ethynylflavone (**11b**) having a terminal triple bond were obtained by the treatment of chromones **10,** bearing the trimethylsilylalkynyl moiety, with tetra-n-butylammonium fluoride in THF under nitrogen at room temperature (rt) (Scheme 3). Bis-chromone **12** was formed in a moderate yield *via* the cross-coupling of 3-bromochromone (**8a**) and 6-ethynylchromone under Sonogashira conditions at 110 °C for 2.5 h.[31]

Scheme 3



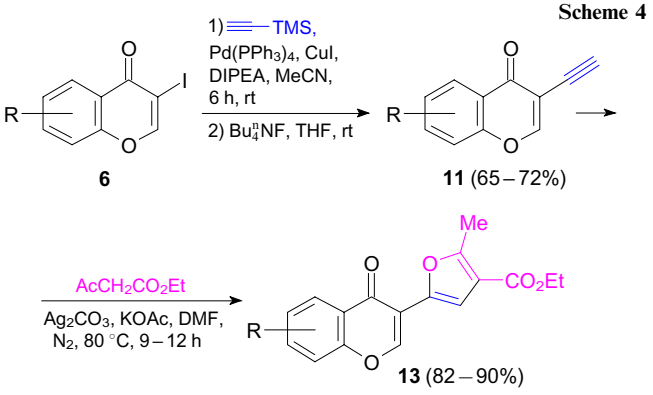
8a,c **10** (23–85%) **12** (46%) **11a,b**

R^1 = H (**8a**; **11a**, 27%), Ph (**8c**; **11b**, 72%);
R^2 = Ph, TMS, CMe_2OH; TMS = $SiMe_3$

It should be mentioned that 3-ethynylchromone (**11a**), a parent compound for chromones substituted with the triple bond in position 3, was for the first time synthesized in 1978 by the flash pyrolysis of 4-hetarylmethylene-3-methylisoxazol-5-ones.[32]

The Sonogashira reaction between 3-iodochromones **6** and trimethylsilylacetylene produced a series of 3-(trimethylsilylethynyl)chromones, which were not isolated but

Scheme 4

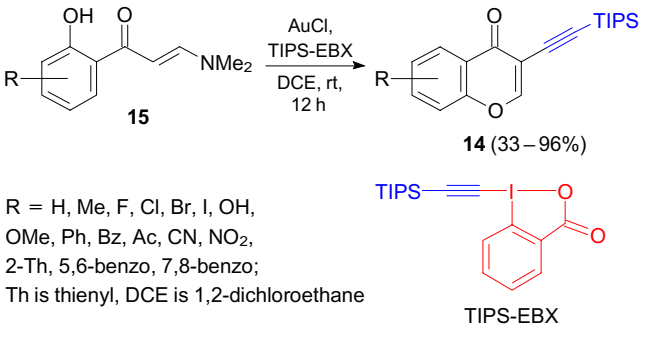


R = H, 6-OMe, 7-OMe, 7-OEt; DIPEA is diisopropylethylamine

were immediately desilylated under the above-mentioned conditions[31] to give 3-ethynylchromones **11** in 65 – 72% yields (Scheme 4). Chromones **11** react with ethyl acetoacetate in the presence of silver carbonate and sodium acetate in DMF *via* the oxidative C – H/C – H-functionalization to afford 3-(2-furyl)chromones **13** in high yields.[33]

Patil and co-workers[34] implemented another strategy for the synthesis of TIPS-alkynylchromones **14** (TIPS is triisopropylsilyl), namely, the cyclization of 1-(2-hydroxyaryl)-3-(dimethylamino)prop-2-en-1-ones **15** under the action of electrophylic reagents (Scheme 5). Earlier, this method had been widely used to introduce halogen atoms and alkyl, aryl, acyl, and various sulfur-containing substituents[35] into position 3 of chromones.[20] To obtain (triisopropylsilyl)ethynyl derivatives, the authors used 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) as a source of the alkynyl cation in the

Scheme 5



R = H, Me, F, Cl, Br, I, OH, OMe, Ph, Bz, Ac, CN, NO_2, 2-Th, 5,6-benzo, 7,8-benzo; Th is thienyl, DCE is 1,2-dichloroethane

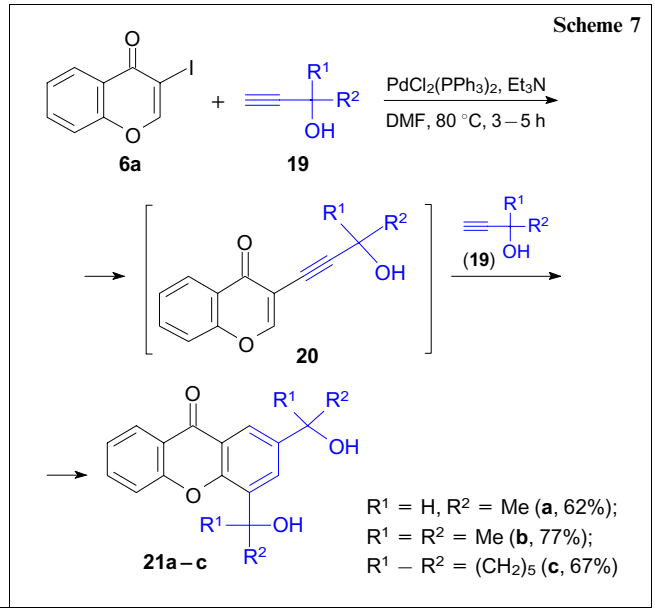
presence of AuCl as a catalyst. The reaction proceeds in dichloroethane at room temperature to provide a variety of 3-(isopropylsilylethynyl)chromones **14** in yields from low to high.[34]

The removal of the TIPS group and conversion to chromones **11** were carried out using a combination of Bu^n_4NF with camphor-10-sulfonic acid (CSA) (Scheme 6). Transformations of chromone **11a** giving rise to 3-substituted chromones **7a** and **16** – **18** demonstrated high reactivity of the terminal triple bond in position 3 of the chromone.[34] The Sonogashira cross-coupling and Cu-catalyzed azide – alkyne cycloadditions provided phenylethynyl, benzofuranyl, and triazole derivatives **7a**, **16**, and **17**, respectively. Also, the use of Bu^tONO as a nitrogen source and 2-picoline *N*-oxide as an oxidizing agent[36] led to 3-cyanochromone **18** in a moderate yield.[34]

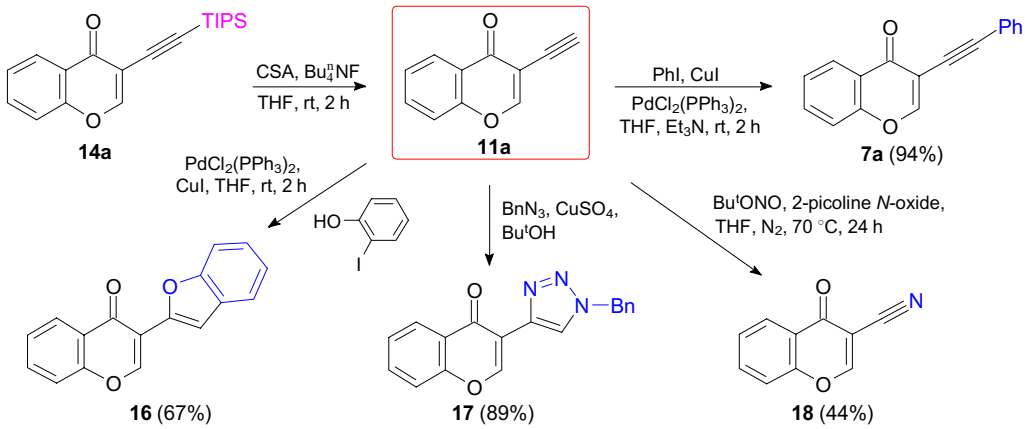
Starting from 3-iodochromones, a novel Pd-catalyzed multi-component coupling reaction to construct a fused benzene ring has been developed (Scheme 7). Heating the solutions of the starting 3-iodochromone (**6a**) and propargyl alcohols **19** in DMF or dioxane in the presence of triethylamine at 80 °C gives intermediate chromones **20** and then, furnishes xanthones **21** in good yields.[37]

The synthesis of 3-alkynyl- and 3-alkenynyl-substituted flavones and thioflavones has been described in a series of works by Indian chemists,[38 – 40] and the data on the enyne derivatives of thioflavones were summarized in a review.[41]

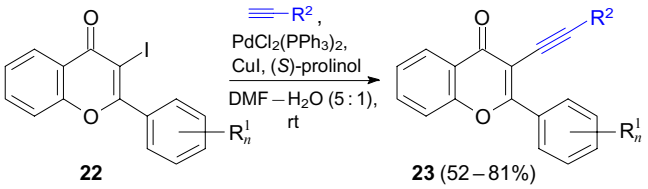
Scheme 7



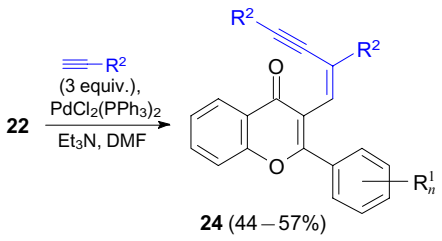
Scheme 6



Scheme 8



R^1_n = 3,4-$(OMe)_2$, 3,4-$(OMe)_2$-5-NO_2;
R^2 = EtCH(OH), Me_2C(OH), Ph, $(CH_2)_2$OH



R^1_n = H, 3,4-$(OMe)_2$; R^2 = 4-$MeOC_6H_4OCH_2$, EtCH(OH), 2-$MeC_6H_4OCH_2$, 4-$O_2NC_6H_4OCH_2$

Pal *et al.*[38] demonstrated that (*S*)-prolinol promotes the cross-coupling reaction between terminal alkynes and 3-iodoflavones **22** under palladium – copper catalysis in aqueous DMF, thus providing a sufficiently effective synthetic route to 3-alkynyl-substituted flavones **23**, which are compounds with a potential biological activity (Scheme 8).[38]

Various enyne derivatives of flavones **24** were obtained using a palladium catalytic system free of cuprous salts, in Et_3N and DMF medium.[39] The best results were attained with 3 equivalents of a terminal alkyne; 3-alkenynylflavones **24** were formed regio- and stereoselectively in moderate yields. Flavonic and acetylenic moieties at the double bond are arranged in the *cis*-configuration relative to each other. It is important to emphasize that the above-mentioned reaction does not require the presence of CuI and thus, oxidative homocoupling of terminal alkynes (the Glaser reaction) is avoided and the purification procedure for the product is simplified. With CuI being present in the catalytic system, the reaction terminates after the formation of 3-alkynylflavones **23**. The plausible reaction mechanism, outlined in Scheme 9 and explaining its high stereoselectivity, includes the reduction of Pd^{II} to Pd^0 in the presence of a terminal alkyne and Et_3N at the initial step. The authors attributed the uniqueness of the process in the absence of CuI to the structural peculiarity of terminal alkynes containing an alcohol or ester oxygen atom capable of coordinating intramolecularly to the palladium atom at the step of iodide substitution.[39, 40]

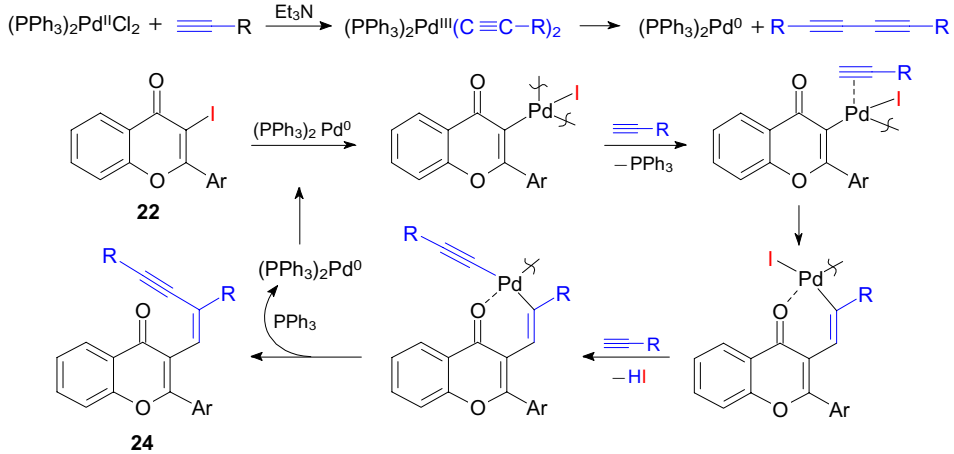
3. Conversion into furans

In 2004, Larock and co-workers[6, 42] developed a procedure to obtain trisubstituted furans *via* cyclization of 2-(alkyn-1-yl)alk-2-en-1-ones **4** under the action of nucleophiles, catalyzed by transition metals or initiated by electrophiles. This unique cyclization proved to be very useful from the synthetic point of view since it allows the formation of the C – O bond and the nucleophilic 'domino' attack on double and triple bonds to be accomplished thus providing a novel approach towards diverse polysubstituted furans.[43] This reaction turned out to apply not only to various enynones **4**, but also to 3-(1-alkynyl)chromones, which cyclize under the same conditions to give 4*H*-furo[3,2-*c*]chromenes, similar to the natural pterocarpenes and coumestanes. Scheme 10 provides a general view of oxacyclization reactions of these substrates to afford furans and furochromenes under metal catalysis conditions and under the action of electrophiles.

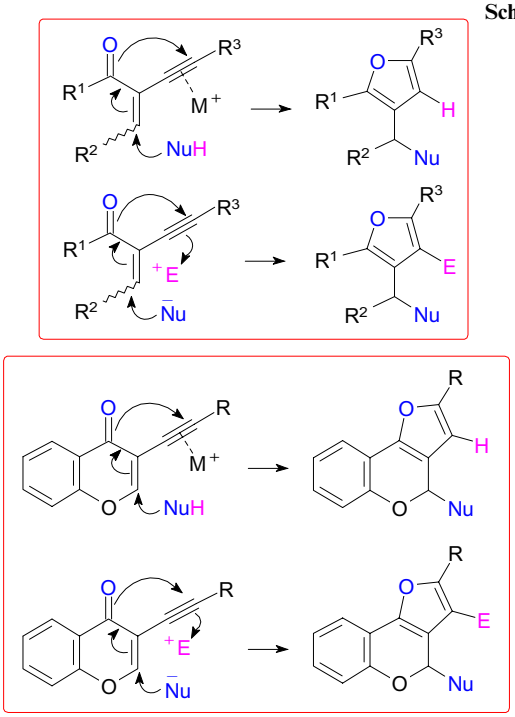
Among a wide range of platinum, palladium, rhodium, gold, silver, and copper catalysts, the best results in oxacyclization (higher product yields over a shorter reaction time) were achieved for $AuCl_3$.[42] Thus, 3-(phenylethynyl)chromone (**7a**) reacted with methanol in the presence of $AuCl_3$ in dichloromethane at room temperature to give 4-methoxy-2-phenyl-4*H*-furo[3,2-*c*]chromene (**25**) in 62% yield (Scheme 11). However, subsequently, by the example of the same reaction of chromone **7a** with methanol, it was shown that in addition to $AuCl_3$, highly efficient catalytic systems for activating the triple bond can be represented by CuBr (10 mol.%) in DMF,[44] $PtCl_2$ (5 mol.%),[45] and $Bu^n_4N[AuCl_4]$ (1 mol.%) in a stable and recirculating ionic liquid such as 1-n-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4).[46]

Along with catalysis by the transition metal salts, this process can make use of the typical electrophilic agents such as I_2, *N*-iodosuccinimide (NIS), PhSCl acting as a triple bond activator and promoting the nucleophilic attack at the C(2) atom of the chromone **7a** thereby giving compound **26** (Scheme 12). The highest product yields were attained using

Scheme 9

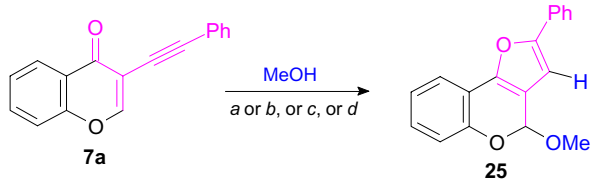


Scheme 10



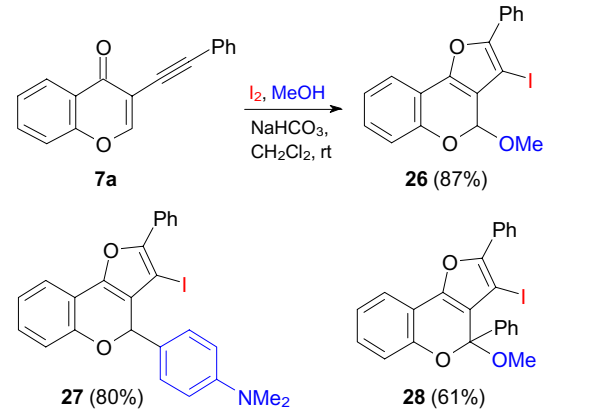
M is metal, NuH is nucleophile, E is electrophile

Scheme 11



(*a*) $AuCl_3$, CH_2Cl_2, rt, 1 h (62%);[6,42] (*b*) CuBr, DMF, 80°C (71%);[44] (*c*) $PtCl_2$, 40°C, 10 h (78%);[45] (*d*) $Bu^n_4N[AuCl_4]$, [bmim]BF_4, rt, 3 h (76%) [46]

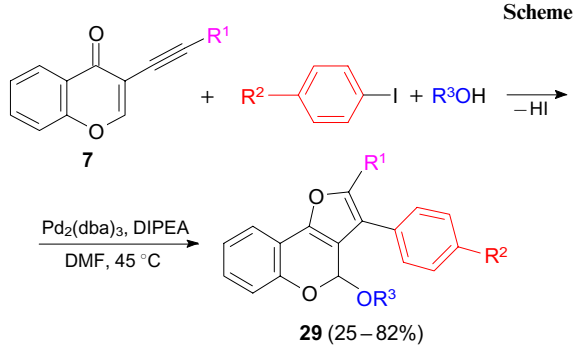
Scheme 12



iodine in the presence of $NaHCO_3$ in dichloromethane. Except for methanol, *N*,*N*-dimethylaniline can be used as a nucleophile, affording 3-iodofurochromene **27**. Despite the presence of the phenyl substituent in position 2, which hampers a nucleophile approach, 2-phenyl-3-(2-phenylethynyl)chromone also reacts with methanol under similar conditions to yield the product **28**.[42]

Hu and co-workers [47] demonstrated that tris(dibenzylideneacetone)dipalladium(0) complex, taken in the amount of 10 mol.%, in the presence of DIPEA provides the cascade reactions involving 1,4-nucleophilic addition of an alcohol molecule to chromone **7a**, cyclization into furan, and cross-coupling with aryl iodides. This gives rise to furochromenes **29** bearing an aryl substituent in position 3 (Scheme 13). The maximum product yield (82%) was achieved when the electron-withdrawing CO_2Me group was present in the aryl iodide and the electron-donating methoxy group was present in the arylethynyl substituent. 2-Iodo- and 3-iodothiophenes also enter this reaction to give the corresponding products in yields of 62 and 55% respectively. The authors believe that the oxidative addition of ArI converts Pd^0 to Pd^{II}, which acts as a Lewis acid first catalyzing the conjugate addition of alcohol, and then coordinating to the triple bond thus initiating the cyclization. Following the reductive elimination, product **29** is formed and Pd^0 is regenerated.

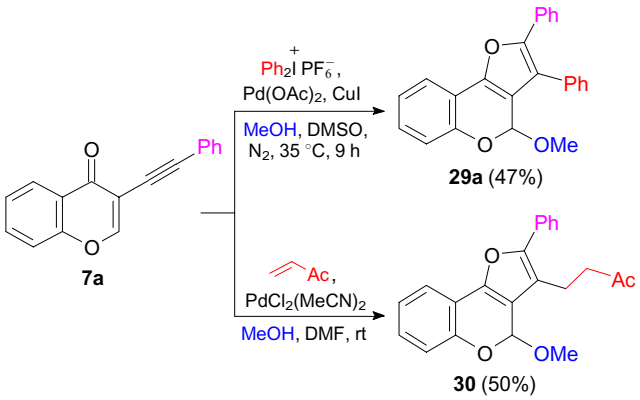
Scheme 13



R^1 = Ph, 4-$MeOC_6H_4$, 2-FC_6H_4, 4-$F_3CC_6H_4$, $(CH_2)_3CN$, Am, Bu^t; R^2 = H, Me, OMe, CO_2Me; R^3 = Me, Pr^i, Bn; dba is dibenzylideneacetone, Am is n-pentyl (amyl)

To obtain tetrasubstituted furans from enynones **4**, Li and Zhang [48] used diaryliodonium salts as precursors to aryl iodides to be utilized as reactants for the cross-coupling reaction. When chromone **7a** was used a similar three-component 'domino' reaction catalyzed by $Pd(OAc)_2$ and CuI, furochromene **29a** was obtained in a moderate yield (Scheme 14). The authors suggest that the furanyl carbocation, generated from enynone and incorporated in the

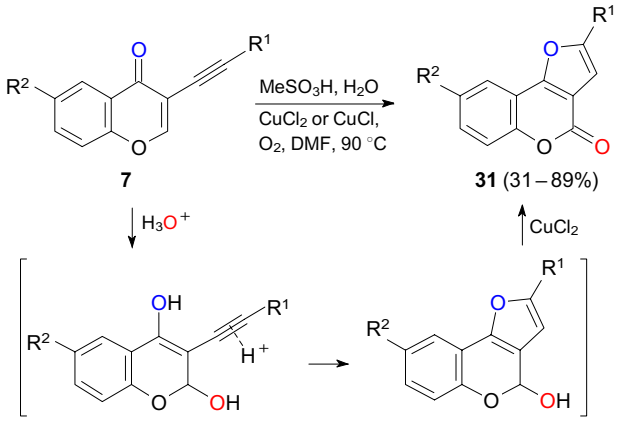
Scheme 14



palladium complex, is captured by methanol and then enters the coupling reaction *via* the oxidative addition at the palladium centre. A similar approach was also used in the cross-coupling of chromone **7a** with methyl vinyl ketone in the presence of $PdCl_2(MeCN)_2$, which resulted in the formation of product **30**.[49]

The transformation of 3-(1-alkynyl)chromones into furochromenes was further developed by Cheng and Xu.[50, 51] These authors proposed a novel one-pot procedure to obtain furo[3,2-*c*]coumarins **31**, which are of natural origin and possess high biological activity, *via* the cascade addition – cyclization – oxidation (Scheme 15). The construction of a furocoumarine scaffold with the product yields ranging from moderate to high has been realized using $MeSO_3H$ as an acid catalyst in the presence of water, while a copper(II) salt in DMF at 90 °C acted as an oxidizing agent.[50] In the follow-up study, it was shown that $CuCl_2$ can be replaced with CuCl and atmospheric oxygen.[51]

Scheme 15

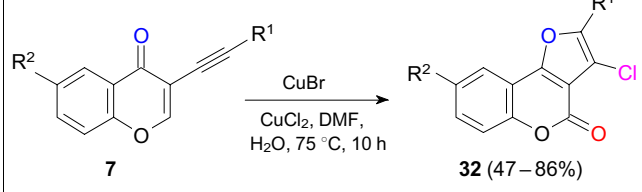


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, Am, Bu^t, $(CH_2)_3CN$;
R^2 = H, Cl, Me, OMe, NO_2

The use of catalytic amounts of CuBr (0.1 equiv.) and $CuCl_2$ (4.2 equiv.) as an oxidizing agent and chlorinating agent, respectively, provides an access to 3-chloro-4*H*-furo[3,2-*c*]chromen-4-ones **32** in good yields (Scheme 16). For 6-nitro-3-(phenylethynyl)chromone (**7b**), the reaction requires more harsh conditions (heating at 90 °C for 10 h, then another 10 h at 110 – 120 °C), while 3-(trimethylsilylethynyl)chromone (**7c**) furnishes dichloro derivative **32** (R^1 = Cl, R^2 = H).[51]

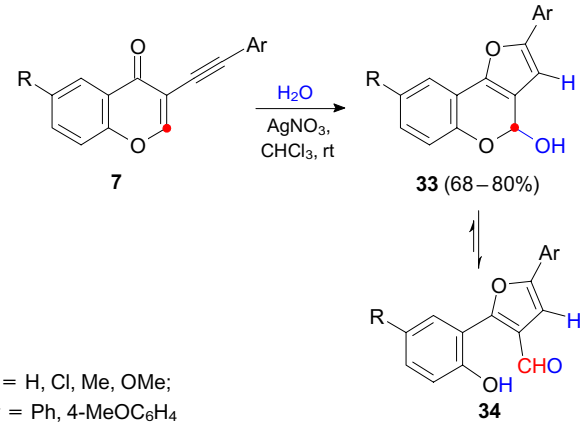
Effective conversion of 3-(1-arylalkynyl)chromones **7** into furochromones **33** and 2-(2-hydroxyphenyl)-5-aryl-

Scheme 16



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, Am, Bu^t, $(CH_2)_3CN$, TMS; R^2 = H, Cl, Me, OMe, NO_2

Scheme 17

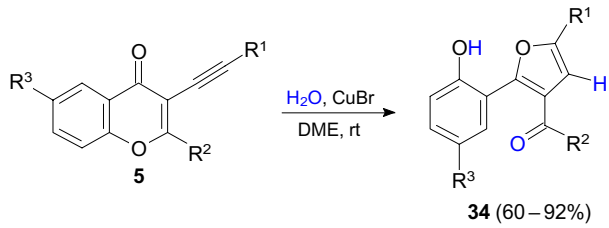


R = H, Cl, Me, OMe;
Ar = Ph, 4-$MeOC_6H_4$

furan-3-carbaldehydes **34** under the action of water and $AgNO_3$ as a catalyst has been reported (Scheme 17).[52] Study of the ring – chain tautomerism revealed that in $CDCl_3$ and DMSO solutions, these compounds exist mostly in the open form **34**, and with R = OMe, the cyclic tautomer **33** dominates.

2-Substituted 3-(1-alkynyl)chromones **5** react with water in the presence of CuBr (0.2 equiv.) under mild conditions in dimethoxyethane (DME) to afford 3-acylfurans **34** in high yields (Scheme 18).[53] In this case, no ring – chain tautomerism was observed, which is associated with the lower electrophilicity of the acyl carbon atom (R^2 = Alk, Ar) compared to the formyl one (R^2 = H).

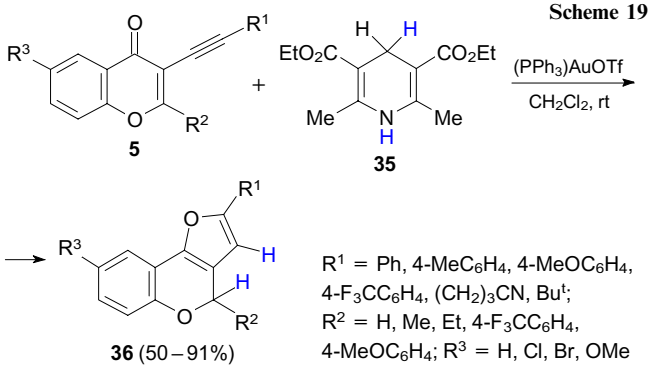
Scheme 18



R^1 = Ph, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 3-Th, $(CH_2)_3CN$, Bu^t;
R^2 = Me, Et, Pr^i, Ph; R^3 = H, OMe, NO_2

The gold-catalyzed reduction of chromones **5** proceeding under the action of the Hantzsch ester **35**, which acts as a source of the hydrogen molecule, *via* the cascade process that involves the addition of a hydride ion, oxacyclization, and the proton transfer, provides compounds **36** in high

Scheme 19

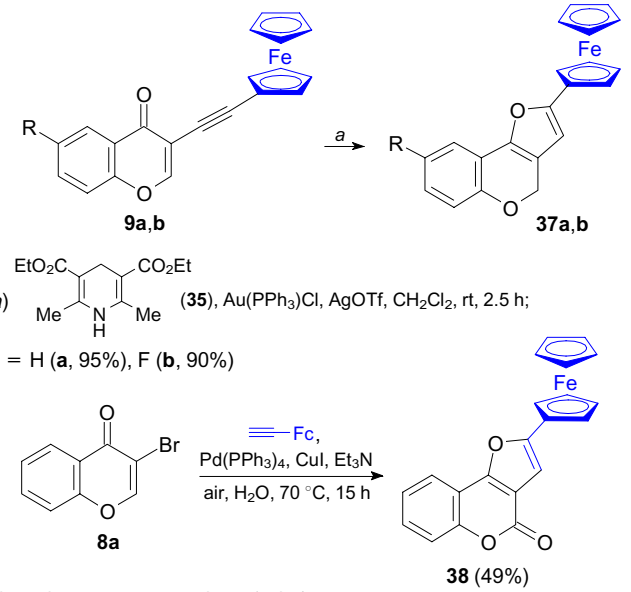


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, $(CH_2)_3CN$, Bu^t;
R^2 = H, Me, Et, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$; R^3 = H, Cl, Br, OMe

yields (Scheme 19). This reaction occurs under mild conditions and affords furochromenes bearing various substituents, including the hydrogen atom, in position 4.[54]

Implementing the above-mentioned synthetic strategy,[54] Kowalski *et al.*[30] obtained ferrocenyl derivatives of 4*H*-furo[3,2-*c*]chromene **37a**,**b** (Scheme 20). Moreover, the authors found the conditions optimal for the synthesis of the ferrocenyl derivative **38**, which is structurally similar to coumestans, directly from 3-bromochromone (**8a**) and ethynylferrocene *via* a one-pot process involving the Sonogashira reaction, the nucleophilic addition of the water molecule, cyclization onto the triple bond, and oxidation with atmospheric oxygen.

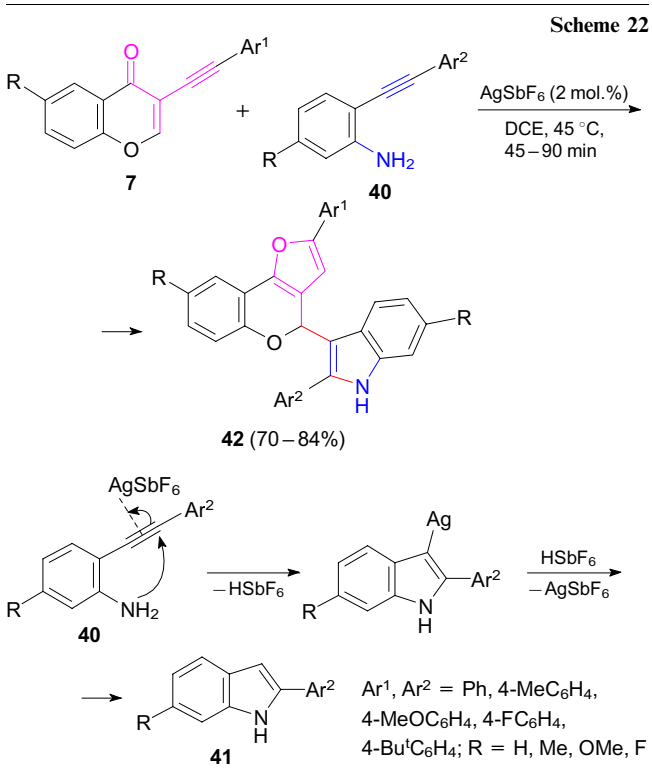
Scheme 20



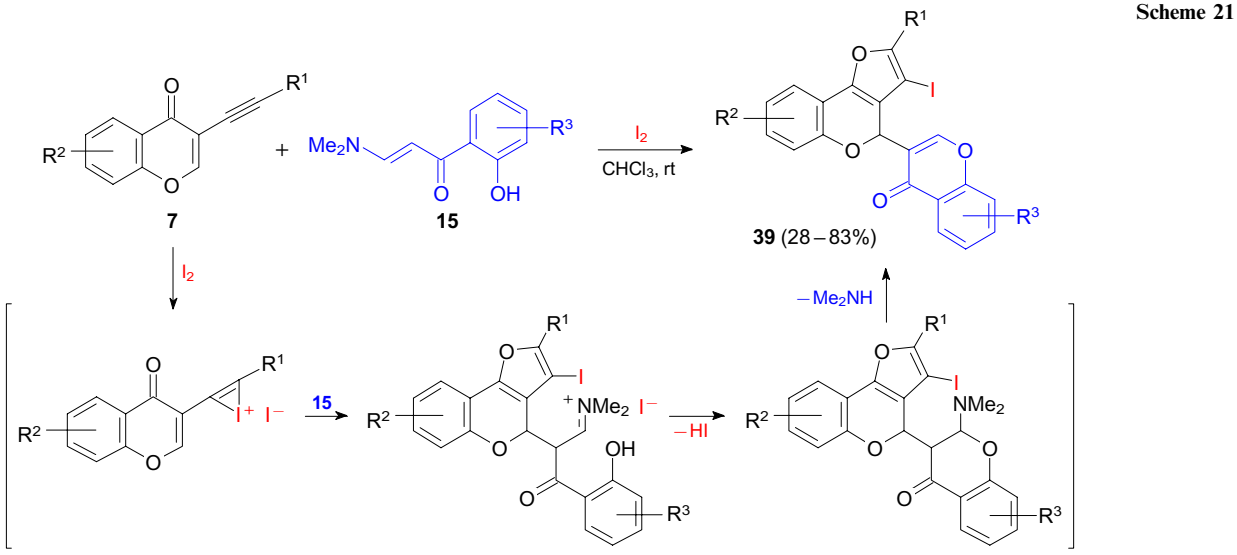
An interesting example of constructing a hybrid structure composed of the furochromene and chromone moieties has been reported by Indian chemists.[55] 4-(3-Chromonyl)-furo[3,2-*c*]chromenes **39** were obtained through the iodine-catalyzed cascade reaction of 3-(1-alkynyl)chromones **7** with 1-(2-hydroxyaryl)-3-dimethylaminoprop-2-en-1-ones **15** serving as a nucleophile. The mechanism of this reaction is illustrated in Scheme 21 and includes steps of electrophilic and nucleophilic addition, double cyclization into furan and chromane, and elimination of dimethylamine.

Samanta and co-workers[56] suggested an atom-economical and efficient synthetic approach to another class of hybrid compounds containing an indole ring in position 4 of 4-furo[3,2-*c*]chromene (Scheme 22). At the first step, the $AgSbF_6$-catalyzed intramolecular hydroamination of the triple bond in 2-alkynylaniline **40** occurs to afford indole **41**, which subsequently attacks the C(2) atom of chromone **7** as a C-nucleophile and initiates the cyclization onto the triple bond activated with the same silver catalyst. 2-Aryl-

Scheme 22



Scheme 21

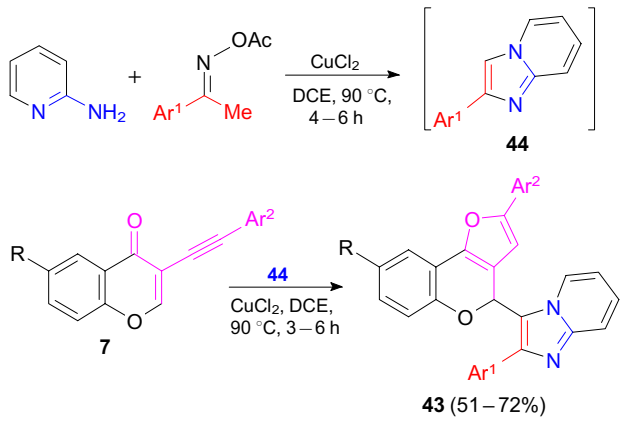


R¹ = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, TMS, Am; R² = H, Me, OMe, Cl; R³ = H, Me, OMe, Cl, Br, NO$_2$

substituted indoles **42**, bearing a furochromene moiety in position 3, are formed under mild conditions and in high yields.

Recently, the same authors[57] obtained a series of furo[3,2-*c*]chromenes **43**, containing an imidazo[1,2-*a*]pyridine moiety in position 4, from 2-aminopyridine, *O*-acetyl oximes, and 3-(1-alkynyl)chromones **7** (Scheme 23). The first step includes the radical reaction of 2-aminopyridine with *O*-acetyl oxime in the presence of $CuCl_2$ in dichloroethane (90 °C, 4 – 6 h) providing imidazo[1,2-*a*]pyridine **44**, to which a chromone **7** was added. Then, the mixture was stirred at the same temperature for 3 – 6 h (the second step). Copper(II) chloride catalyzes both the first and second steps of this transformation, and imidazo[1,2-*a*]pyridine **44** acts as a C-nucleophile, attacking the C(2)-electrophilic centre of chromone **7** followed by the cyclization into furane.

Scheme 23



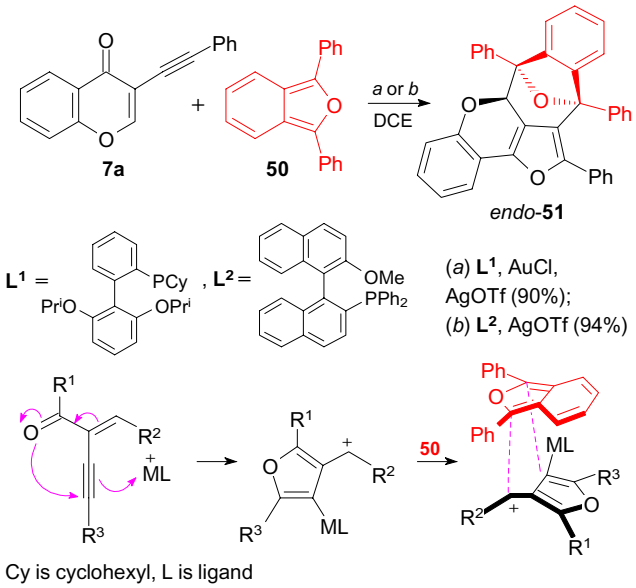
Ar^1 = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 2-Th, 1-Naph; R = H, Me, OMe; Ar^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$Bu^tC_6H_4$; Naph is naphthyl

The double bond modification of chromones **7** expands significantly their synthetic potential. Thus, Zhand and Schmaltz[58] showed that the reaction of 3-(phenylethynyl)-chromone (**7a**) with trimethylsulfoxonium iodide in the presence of NaH gives 3-phenylethynyl-2,3-methanochromanone (**45**) in low yield. This product is converted into a homologue of 4-methoxy-2-phenyl-4*H*-furo[3,2-*c*]chromene (**25**) — 5-methoxy-2-phenyl-4,5-dihydrobenzo[*b*]furo[2,3-*d*]-oxepine (**46**) in high yield under the action of methanol and $(Ph_3P)AuOTf$ (1 mol.%) (Scheme 24). Oxirano[2,3-*b*]chromanone **47**, obtained on treating chromone **7** with 30% hydrogen peroxide solution in THF, reacts under similar conditions with nucleophiles such as methanol, indole, or allyl alcohol to afford furodioxepines **48**. In the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), compounds **48** generate furanone **49** as a product of methanolysis, oxidation, and nucleophilic addition of methanol.[59]

Gao *et al.*[60] studied the reaction of 2-(alkyn-1-yl)alk-2-en-1-ones **4** with 1,3-diphenylisobenzofuran **50**, proceeding as a tandem oxacyclization and formal [4 + 3]-cycloaddition (Scheme 25). This reaction is of interest in that the use of complexes of phosphine ligands $\mathbf{L}^1$ and $\mathbf{L}^2$ with gold and silver salts allows the *exo*/*endo* selectivity in the synthesis of bridged polyheterocycles to be 'switched'. However, it turned out that with both catalytic systems, chromone **7a** gives solely an *endo*-cycloadduct **51** (the diastereomer ratio > 20 : 1), whose structure was confirmed by the X-ray diffraction data and whose formation route was demonstrated by the example of the enynone system.

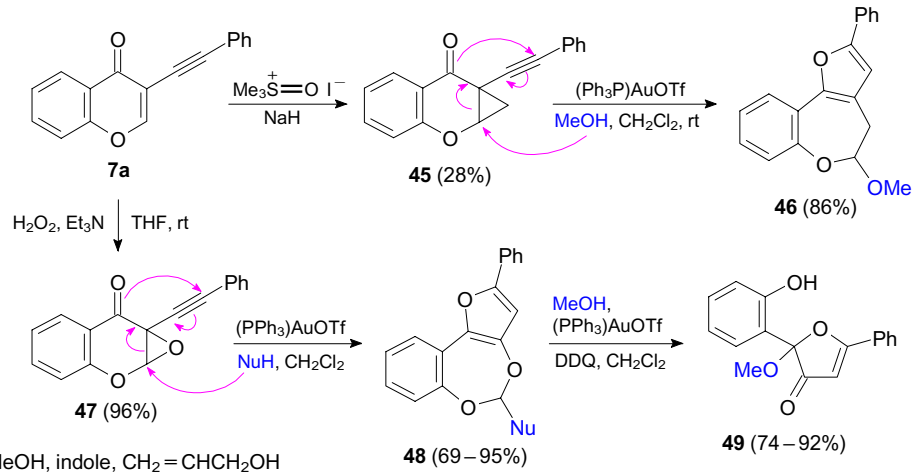
Based on their own experience in studying the transformation of enynones **4** into substituted furans, Xiao and

Scheme 25



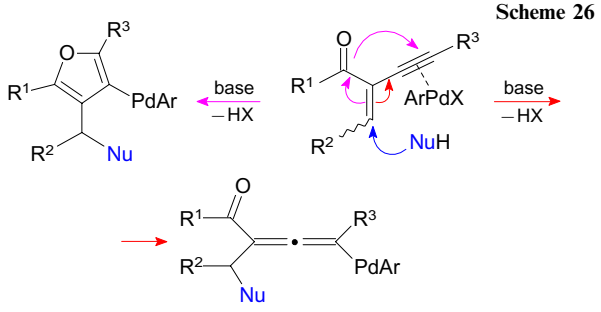
Cy is cyclohexyl, L is ligand

Scheme 24

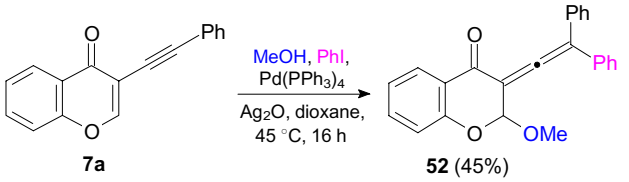


NuH: MeOH, indole, $CH_2=CHCH_2OH$

Scheme 26



Scheme 27



Zhang[61] suggested that the use of aryl halides and Pd^0 in place of Pd^{II} catalysts would change the reaction direction towards the formation of tetrasubstituted allenes (Scheme 26). Indeed, they succeeded in showing that the reaction of 2-(alkyn-1-yl)alk-2-en-1-ones **4** with methanol and aryl iodides in the presence of $Pd(PPh_3)_4$ catalyst and Ag_2O base produced allenes in high yields. Chromone **7a** also enters this reaction to give the corresponding allene **52**, though in a moderate yield (Scheme 27).

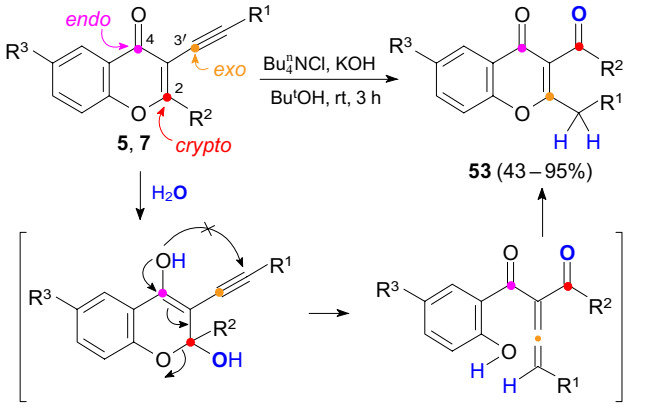
4. Nucleophilic reactions

Electrophilic nature of 2-substituted (**5**, $R^2 \neq H$) and 2-unsubstituted (**7**, $R^2 = H$) 3-(1-alkynyl)chromones related to the presence a carbonyl group [the *endo*-C(4) atom], a latent aldehyde group [*crypto*-C(2)], and the triple bond [*exo*-C(3′)] makes these compounds valuable substrates in reactions with nucleophiles. However, given the ease with which chromones **5** and **7** are converted into furo[3,2-*c*]chromenes when the *crypto*-C(2) atom is attacked by O- and C-nucleophiles, one would expect that the opening of the γ-pyrone ring, which is typical of other 3-substituted chromones, followed by cyclization at the C=O and(or) the triple bond would be hampered.

In fact, it turned out that if 3-(1-alkynyl)chromones **5** and **7** are treated with a saturated aqueous KOH solution under phase transfer catalysis conditions (Bu^n_4NCl, Bu^tOH, ~20 °C, 3 h), then instead of oxacyclization, the pyrone ring opens, which is accompanied by the addition of the phenoxide anion to the allene intermediate to afford 2-substituted 3-acyl chromones **53** (Scheme 28).[62] In this reaction, the pyrone ring opening occurs faster than the cyclization of the substrate into furan, and 3-alkynyl chromone acts as a 1,3-dielectrophile, with which water (an external nucleophile) reacts at the *crypto*-C(2) atom, while the phenol hydroxyl group (an internal nucleophile) reacts at the *exo*-C(3′) atom. This reaction provides a general synthetic approach towards previously elusive 2-alkyl-3-acylchromones.[63]

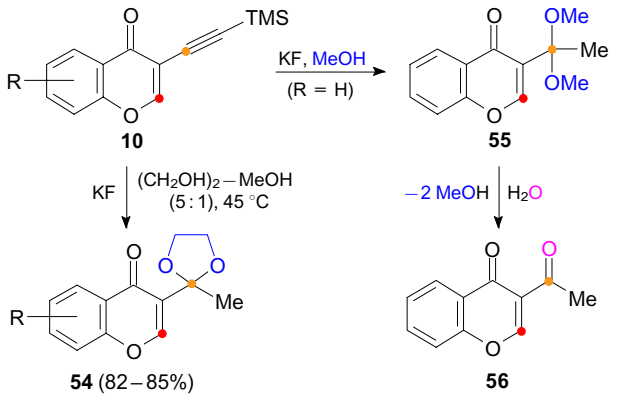
The conversion of 3-TMS-ethynyl chromones **10** to cyclic ketals **54** under the action of ethylene glycol – methanol mixture (5 : 1) has been reported.[64] Using only methanol, an unstable ketal **55** is formed, which hydrolyzes readily to give 3-acetylchromone **56** (Scheme 29). At first glance, it might seem that after removal of the trimethylsilyl protecting group under the action of KF, the triple bond is hydrated to afford 3-acetylchromone followed by its ketalization. However, the authors proposed another route of this reaction, which includes several steps of 1,4-nucleophilic addition – elimination of an alcohol molecule at the C(2) and C(3′) atoms leading to an allene intermediate without the pyrone ring opening. This mechanism, although not typical of the chemistry of chromones, is quite believable for this specific case.

Scheme 28



R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 4-Py, 3-Th, $(CH_2)_3CN$, Am;
R^2 = H, Me, Et, Pr^i, Ph; R^3 = H, OMe, Br; Py is pyridyl

Scheme 29

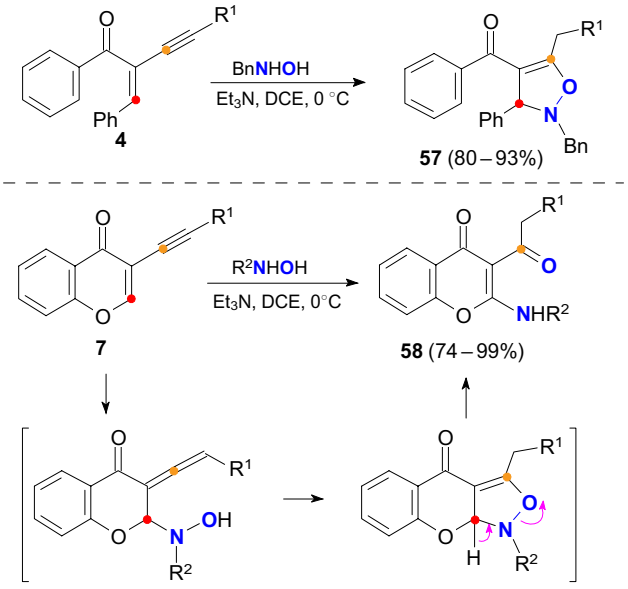


R = H, Me, OMe, OBn, benzo

Another example of a nucleophile reactions of which proceed with retention of the pyrone ring are hydroxylamines. Zhang and co-workers[65] demonstrated that the reaction of enynones **4** with *N*-substituted hydroxylamines in the presence of Et_3N occurs as a formal [3 + 2]-addition and generates 2,3-dihydroisoxazoles **57**, whereas 3-(arylethynyl)chromones **7** react differently and furnish 2-amino-3-acylchromones **58**. This process includes the 1,4-addition of the hydroxylamine molecule at the *crypto*-C(2) atom to give an allenic intermediate, which undergoes an intramolecular cyclization involving oxygen atoms and *exo*-C(3′) to yield 2,3-dihydroisoxazole. The reaction is not terminated at this step, as with enynones **4**, but is accom-

panied by the opening of the pyrone ring and leads to products **58** (a known transformation [66]). It should be noted that 2-amino-3-acylchromones **58** with R^2 = H exist in the iminoenol form (Scheme 30).

Scheme 30

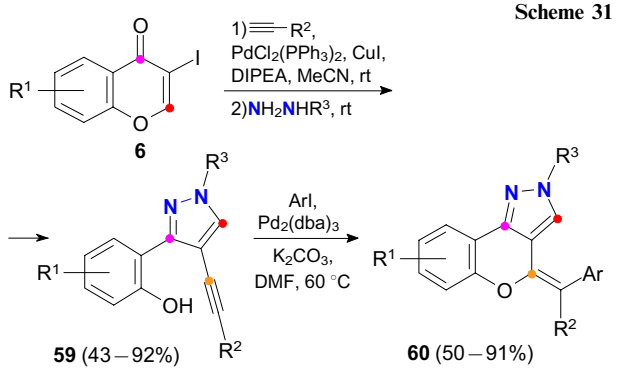


R^1 = Ph, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$; R^2 = H, Me, Bn

3-Alkynyl chromones react with hydrazines and amidines like typical chromones, at the C(2) and C(4) atoms with the pyrone ring opening and formation of pyrazoles and pyrimidines. Thus, the Sonogashira cross-coupling of 3-iodochromones **6** with terminal alkynes provided an access to a wide range of 3-alkynylchromones which were not isolated but treated with alkyl hydrazines to give alkynyl pyrazoles **59**, proposed as drugs against hepatitis C (Scheme 31).[67] Treatment of **59** with aryl iodides in the presence of $Pd_2(dba)_3$ and potassium carbonate led to 4-methylene-2,4-dihydrochromeno[4,3-*c*]pyrazoles **60** as products of an intramolecular addition across the triple bond and arylation. Regio- and stereochemistry of compounds **59** and **60** were not discussed.

A three-component one-pot approach was also used to synthesize benzopyrano[4,3-*d*]pyrimidines **61**

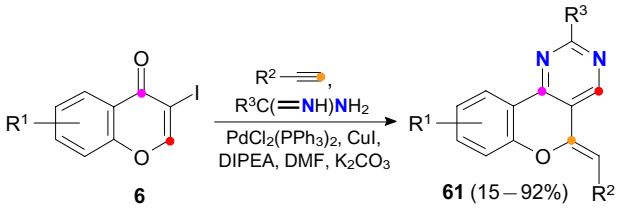
Scheme 31



R^1 = H, Me, Cl, Br, NO_2; R^2 = 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, Bu^n, Bu^t, CH_2OMe, CMe_2OH, $(CH_2)_3Cl$, $(CH_2)_3CN$, CF_3, NH_2, 2-Py; R^3 = Me, Bn, CH_2CH_2OH; Ar = 4-AcC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-ClC$_6$H$_4$

(Scheme 32).[68] These compounds were obtained from 3-iodochromones **6**, terminal acetylenes, and amidines *via* three consecutive reactions: the Sonogashira cross-coupling, chromone ring opening with the simultaneous formation of a pyrimidine [an attack at the *crypto*-C(2) and *endo*-C(4) atoms], and cyclization involving the phenol hydroxyl group and the triple bons. Thus generated C=C bond has *Z*-configuration, as confirmed by the X-ray diffraction data. All reactants were loaded in one reactor and dissolved in DMF; the resulting mixture was stirred for 2 h at room temperature, and then heated at 60 °C for 6 h. This simple combinatorial method provided access to a large library of pyrimidines **61**, their yields varied in a wide range depending on the nature of substituents.

Scheme 32



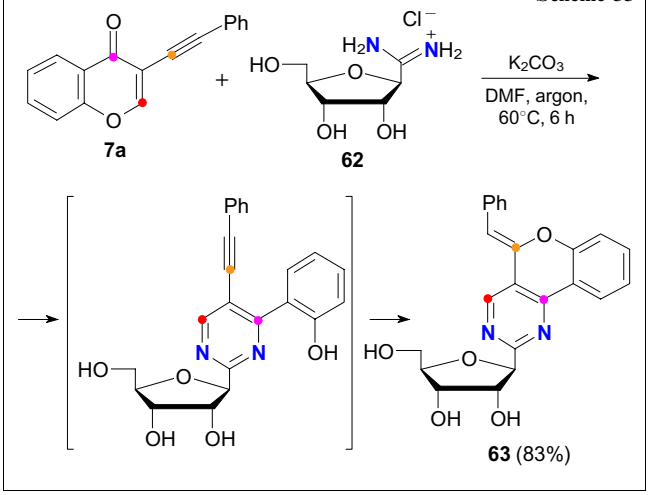
R^1 = H, Me, OMe, NO_2, Br;
R^2 = Ph, 4-F$_3$CC$_6$H$_4$, 4-MeOC$_6$H$_4$, Bu^t, $(CH_2)_3CN$;
R^3 = OMe, SMe, 4-H$_2$NC$_6$H$_4$, 4-ClC$_6$H$_4$, Me, Bu^t, Bn, $(CH_2)_2OH$

Similarly, the treatment of 3-(phenylethynyl)chromone (**7a**) with 1-(β-D-ribofuranosyl)formamidine hydrochloride (**62**) in the presence of K_2CO_3 and molecular sieves in DMF affords benzopyrano[4,3-*d*]pyrimidine **63** bearing a glycosyl residue at the C(2) atom (Scheme 33). As in the previous case, this transformation proceeds *via* the initial formation of pyrimidine followed by the intramolecular nucleophilic addition of the hydroxyl group across the triple bond.[69]

Therefore, 3-alkynylchromones, like the majority of representatives of chromone systems, react with hydrazines and amidines at the C(2) and C(4) atoms with pyrone ring transformation to pyrazoles and amidines, and the triple bond participates in the process only at the last step.

Their peculiar feature is the reaction with hydroxylamine proceeding at the C(2) and C(3′) atoms with the

Scheme 33



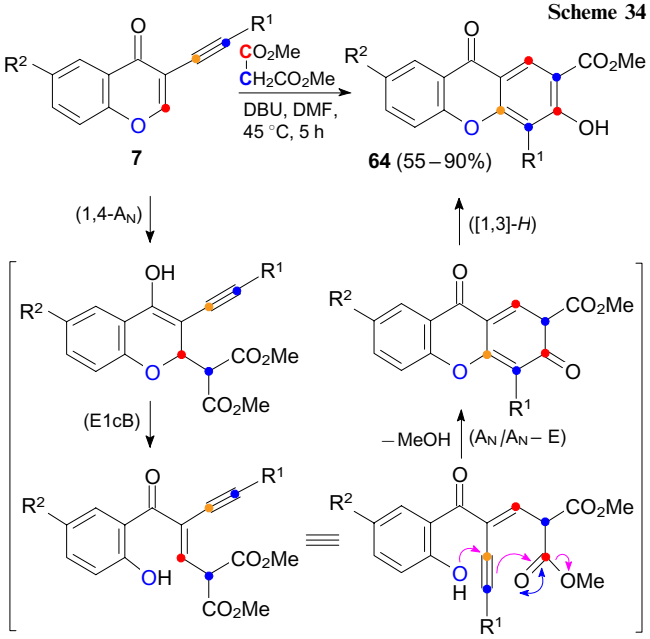
opening of the isoxazoline ring to provide 2-amino-3-acylchromones.

5. Ambiphilic cyclizations

The main contribution to the studies of amibiphilic cyclization on the base of 3-alkynylchromones was made by Hu and co-workers (see below). These authors showed that chromones **7** acting as 1,4-ambiphiles can react with a variety of 1,2- and 1,3-ambiphiles to afford xanthones, azaxanthones, cyclohepta[*b*]chromones, and chromeno[2,3-*d*]azepines as a result of [4 + 2] or [4 + 3] carbo- and heterocyclizations. Of specific importance are xanthone derivatives which display a wide spectrum of biological activity depending on the nature and location of substituents in dibenzo-γ-pyrone structure.[70, 71] In this regard, the development of novel methods to obtain substituted xanthones is not only of synthetic but also of significant practical interest.

Hu and co-workers[72] were the first to demonstrate the ambiphilic properties of 3-alkynylchromones, in 2009 by performing the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed tandem reaction giving functionalized xanthones **64**. 3-(1-Alkynyl)chromones **7** reacted with 1,3-dicarbonyl compounds under mild conditions without metal complex catalysis. This transformation involving malonates, β-ketoesters, and β-diketones is shown in Scheme 34 by the example of dimethyl malonates (electrophilic centres are marked in red and brown colours, and nucleophilic ones are in blue). The mechanism of the reaction proposed by the authors[72] includes the following steps: the Michael addition (1,4-A_N), the pyrone ring opening (E1cB-elimination), cyclization (A_N), 1,2-nucleophilic addition – elimination (A_N – E; shown by a blue arrow in the Scheme), and 1,3-hydrogen shift.

Scheme 34



R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, $(CH_2)_3CN$, Am, H;
R^2 = H, Cl, NO_2, OMe

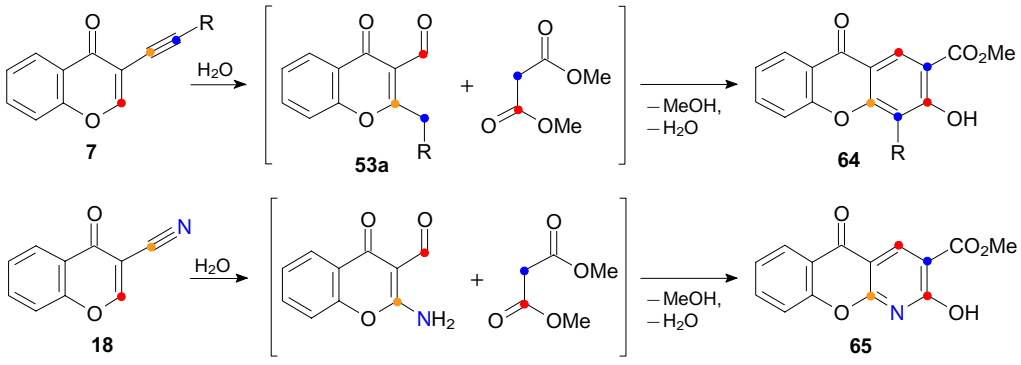
However, given that 2-unsubstituted 3-alkynylchromones can recyclize to give 2-alkyl-3-formylchromones **53a** on reacting with water (R^2 = H in Scheme 28),[62] an easy-to-understand reaction path could be proposed according to which the nucleophilic methylene group of chromone **53a** attacks the electrophilic methoxycarbonyl group of the malonate, and the malonate methylene group attacks the formyl functionality (Scheme 35). For comparison, the same Scheme illustrates the synthesis of 4-azaxanthone **65** from dimethyl malonate and 3-cyanochromone **18**, which is known[19] to readily undergo the rearrangement to afford 2-amino-3-formylchromone.

Substituted acetonitriles such as arylacetonitriles, cyanoacetamide, and malononitrile also react with chromones **7** providing 3-aminoxanthones **66** in high yields (Scheme 36).[73] The reaction follows a similar mechanism and under the same conditions, but because of lower electrophilicity of the CH_2 group compared to 1,3-dicarbonyl compounds, it requires more drastic conditions, namely microwave irradiation (MW) at 90 °C for 10 min.

Due to steric hindrances at the C(2) atom, which is first involved in the nucleophilic attack, 2-substituted chromones usually prove to be less reactive than 2-unsubstituted ones. Nevertheless, by replacing a base (DBU with Bu^tOK) and using microwave irradiation at 150 °C for 15 min, the chemists accomplished the reaction of 2-methyl-3-(1-alkynyl)chromones **5** with 3-bromophenylacetonitrile and obtained xanthones **67** substituted by R^1 = Ph, $(CH_2)_3CN$ in yields of 74% and 60%, respectively (Scheme 37). Product **66a** synthesized from cyanoacetamide condense with various aldehydes to provide linear heterocyclic xanthones **68**, which are of interest for medicinal chemistry, in good yields.[73]

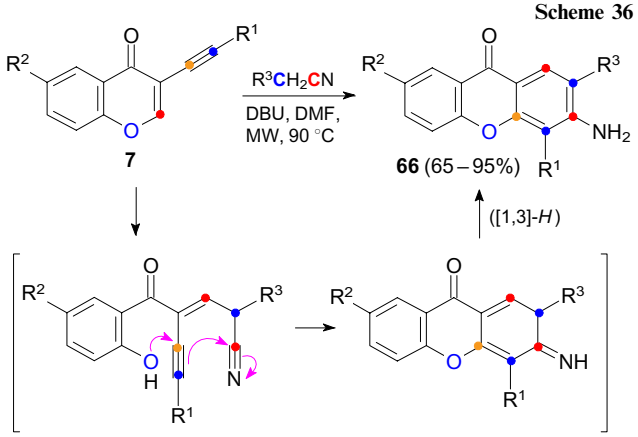
Hu and co-workers[74] demonstrated that using NH-aldimines, generated *in situ* from aromatic aldehydes and ammonium acetate, as 1,2-ambiphiles makes it possible to

Scheme 35



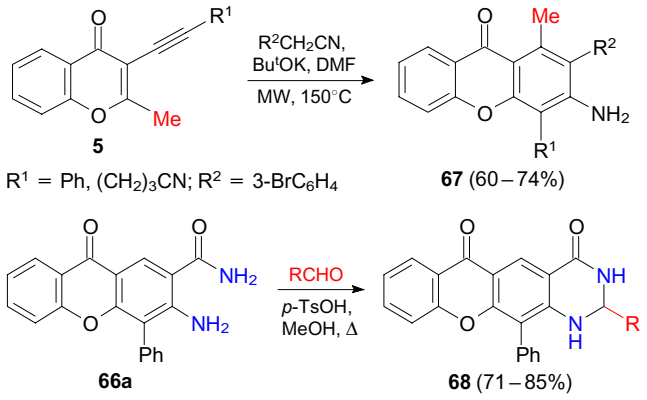
R = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, $(CH_2)_3CN$, Am, H

Scheme 36



R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, $(CH_2)_3CN$, Am, Bu^t;
R^2 = H, Me, OMe, Cl, NO_2;
R^3 = Ph, 3-BrC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, $C(O)NH_2$, CN

Scheme 37



R^1 = Ph, $(CH_2)_3CN$; R^2 = 3-BrC_6H_4

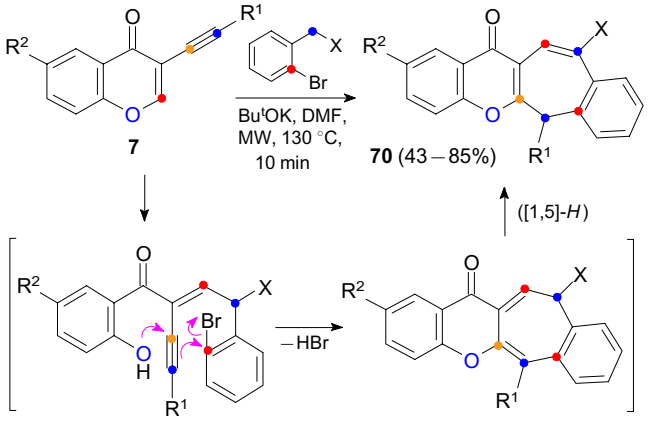
R = Ph, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, Bu^n, 3-Fu;
p-TsOH is *para*-toluenesulfonic acid, Fu is furyl

obtain 2-azaxanthones **69** whose yields significantly depend on the nature of a substituent in the benzene ring of the aldehyde (Scheme 38). The highest yields (74 – 82%) were reached for aldehyde with electron-donating substituents (OH, OMe), while the lowest ones (21%) were observed for *p*-trifluoromethylbenzaldehyde. The reaction mechanism includes an attack of the position 2 of a chromone with the aldimine nitrogen atom followed by the double cyclization and aromatization at the final step under the action of atmospheric oxygen.

An interesting example of ambiphilic cyclization of [4 + 3]-type leading to cyclohepta[*b*]chromones derived from 3-alkynylchromones has been reported.[75] It turned out that when phenylacetonitrile is replaced with 2-bromophenylacetonitrile, the direction of the reaction changes and instead of the expected 3-aminoxanthones,[73] cyclohepta[*b*]chromones **70** are formed as a result of intramolecular nucleophilic substitution of the bromine atom. In this case, 2-bromophenylacetonitrile acts as a 1,3-ambiphile, in which the replacement of the bromine atom with chlorine or fluorine, or replacement of the cyano group with an ester or amide one, does not affect the course of the reaction. 2-Methyl-3-(phenylethynyl)chromone can also be used as a 1,4-ambihile, however, the steric hindrances at the C(2) atom lead to a low yield (28%) of the corresponding product. The mechanism of this transformation does not differ basically from [4 + 2]-cyclocondensation discussed above and is illustrated in a shortened form in Scheme 39.

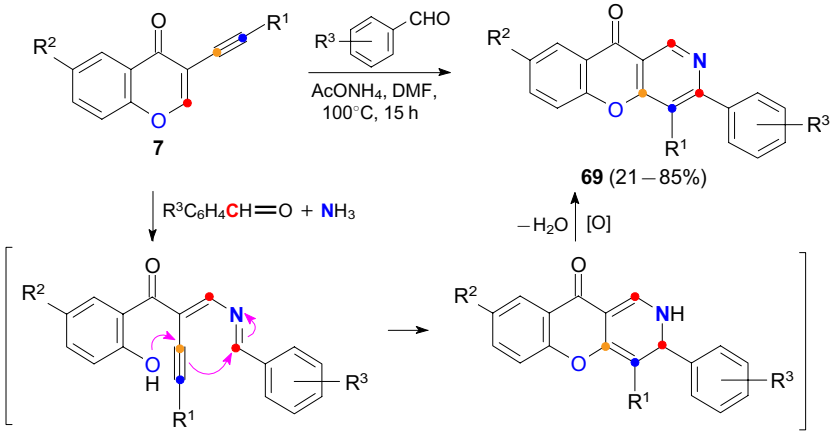
Another example of a cascade [4 + 3]-cyclization providing an approach to chromeno[2,3-*d*]azepines **71** was found when studying the reaction of 3-(1-alkynyl)chromones **7** and pyridinium ylides in the presence of Et_3N in dichloromethane (Scheme 40).[76] With aliphatic substituents at the chromone triple bond (R^2 = H: R^1 = Pr^n, Bu^t) the lowest

Scheme 39



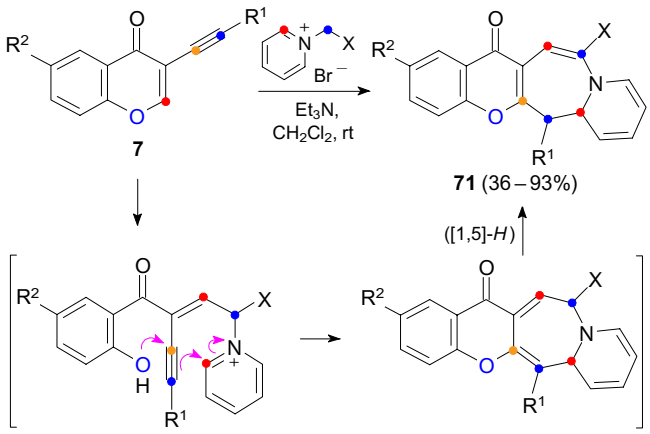
R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 2-Py, 4-Py, 2-Th, Bu^n, Bn, Bu^t;
R^2 = H, OMe, NO_2; X = CN, CO_2Et, C(O)NHMe, $C(O)NEt_2$

Scheme 38

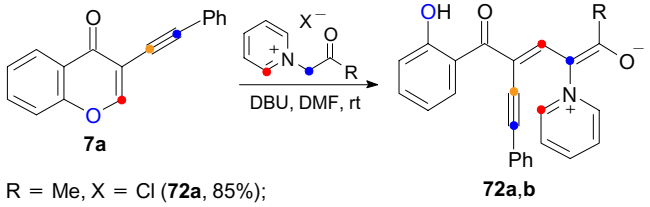


R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, Bu^n, Bu^t;
R^2 = H, OMe, Cl, NO_2;
R^3 = H, OMe, OH, Cl, CF_3, CO_2Et

Scheme 40



R^1 = Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-$F_3CC_6H_4$, 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, 4-Py, Pr^n, Bu^t; R^2 = H, OMe, F, Cl; X = CN, CO_2Et, $C(O)NMe_2$



R = Me, X = Cl (**72a**, 85%);
R = Ph, X = Br (**72b**, 88%)

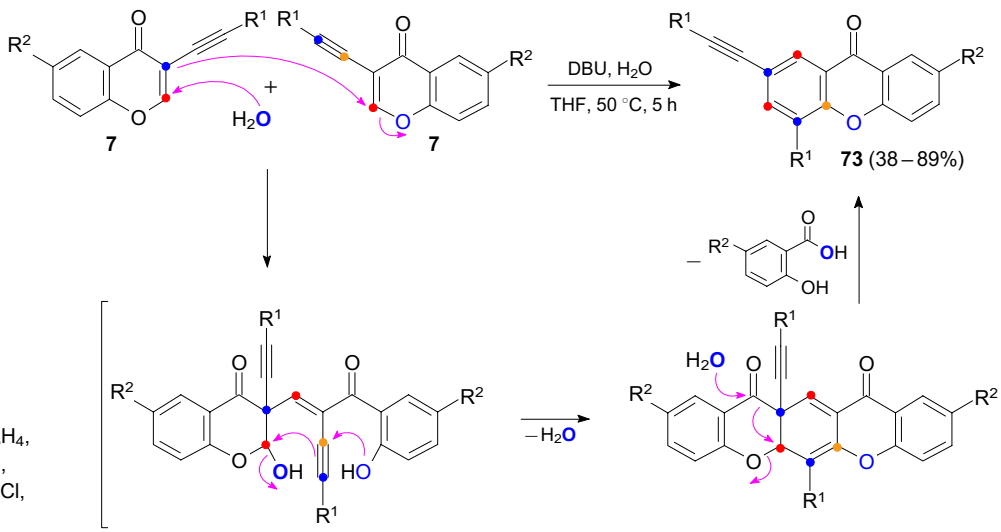
yields were observed (45 and 36% respectively). In the case of acetyl- and benzoyl-substituted pyridinium ylides the reaction terminates after the formation of acyclic ylides **72a**,**b**, whose zwitter-ionic nature was confirmed by X-ray diffraction analysis.

Studying the reaction of 3-ethynylchromones **7** with arylamines, Hu and co-workers [77] unexpectedly found the self-condensation reaction of these chromones, which is initiated by water and is accompanied by the elimination of a salicylic acid molecule to produce eventually 2-alkynylxanthones **73**. The search for optimal conditions demonstrated that the highest yields of such products are reached when using DBU solution in THF as a base. The reaction mechanism proposed by the authors is shown in Scheme 41.

In a simplified and easy-to-understand way, the formation path to xanthones **73** can be represented by the following transformations: hydration followed by the rearrangement of the chromone **7** into 2-alkyl-3-formylchromone **53a**, ambiphilic [4 + 2]-carbocyclization, and finally, the water-induced elimination of salicylic acid to afford xanthone **73** (Scheme 42).

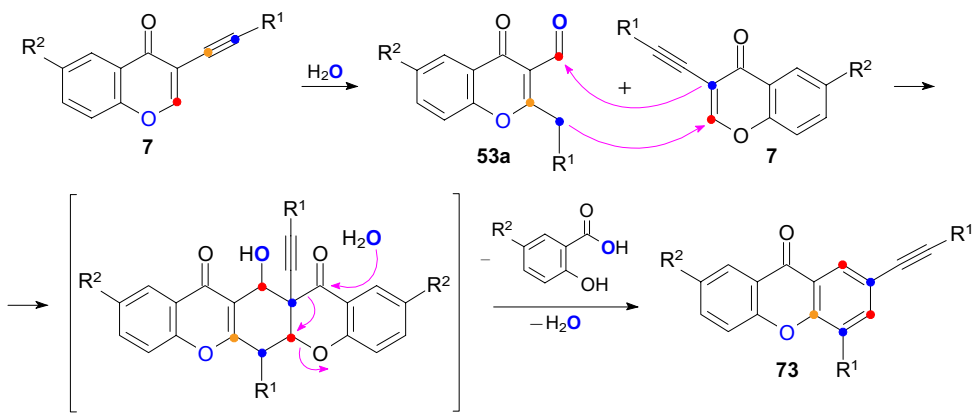
Also, it was shown [78] that under more drastic conditions including microwave irradiation, both dimerization of 3-(1-alkynyl)-2-methylchromones **5**, and their mixed condensation with 2-unsubstituted 3-alkynylchromones **7** can be accomplished, which leads to the formation of xanthones **74** and **75**, whose C(3) atom is bonded to the chromone C(3) atom. These transformations become possible due to the presence of a vinylogous methyl group in the chromone **5**,

Scheme 41

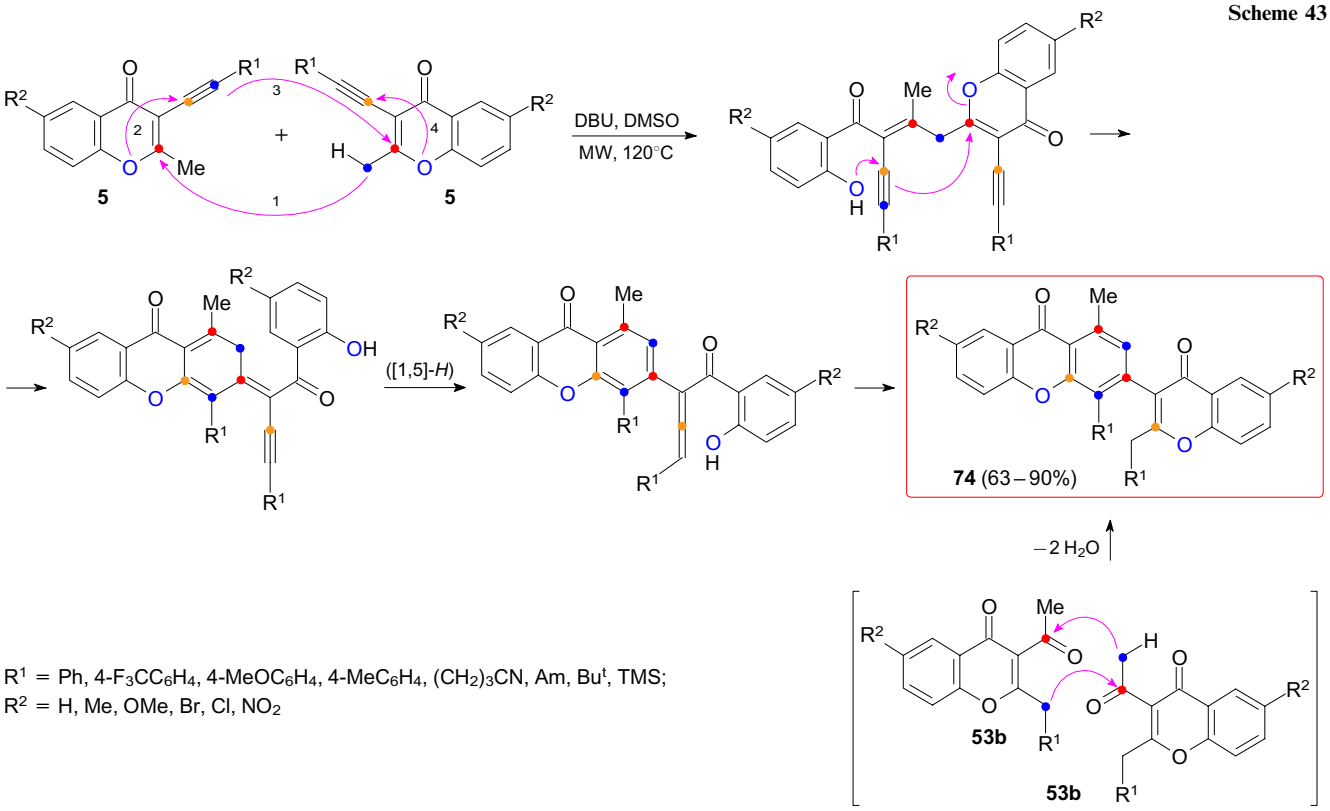


R^1 = H, Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, $(CH_2)_3CN$, Am, Bu^t; R^2 = H, Me, Cl, NO_2, OMe

Scheme 42



Scheme 43



R^1 = Ph, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, $(CH_2)_3CN$, Am, Bu^t, TMS;
R^2 = H, Me, OMe, Br, Cl, NO_2

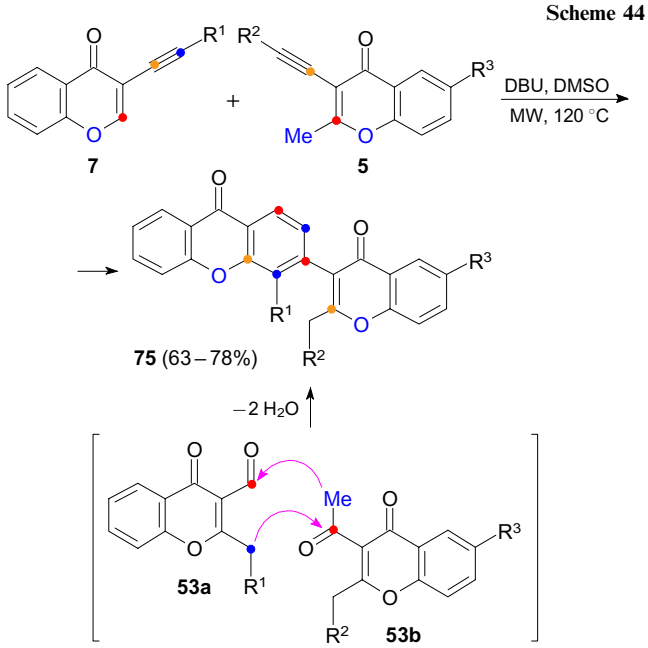
which is deprotonated under the action of DBU and attacks the C(2) atom of the second molecule, thus starting a cascade process. The mechanism of dimerization of compounds **5** is illustrated in Scheme 43 and comprises four consecutive nucleophilic attacks as indicated by the numbered arrows.

Like in the previous case (see Scheme 42), this transformation can be represented in a simplified way through [4 + 2]-cyclization of two molecules of 2-alkyl-3-acetylchromone **53b** (R^2 = Me in Scheme 28), one of which acts as a 1,4-ambiphile, and the other one serves as a 1,2-ambiphile (see Scheme 43).

A mixed condensation of 3-(1-alkynyl)chromones **7** with 2-methyl-3-(1-alkynyl)chromones **5** proceeds under similar conditions and provides high yields of compounds **75**, which, in contrast to the products of dimerization of chromone **5**, contain no methyl group in position 1 of the xanthone.[78] The reaction mechanism is similar to that illustrated in Scheme 43, and the formation of xanthones **75** can be formally explained by the ambiphilic [4 + 2]-carbocyclization of two hydrated forms **53a** and **53b**, which should be considered as synthetic equivalents of 3-(1-alkynyl)chromones **7** and 2-methyl-3-(1-alkynyl)chromones **5** (Scheme 44). It should be noted that 3-acetyl- (**53b**) and 3-formyl-2-alkylchromones (**53a**) are known, but there is no information about their dimerization to 3-(chromon-3-yl)xanthones.[63]

An even more complicated cascade process providing an access to substituted benzo[*a*]xanthones **76** from 2-methyl-3-(1-alkynyl)chromones **5** and electron-deficient 3-oxovinylchromones **77**, has been reported.[79] As in the previous case, the reaction starts with deprotonation by the action of DBU of a vinylogous methyl group of chromone **5** (designated by an enlarged blue circle in the Scheme), which further attacks position 2 of chromone **77** and thus begins a cascade process

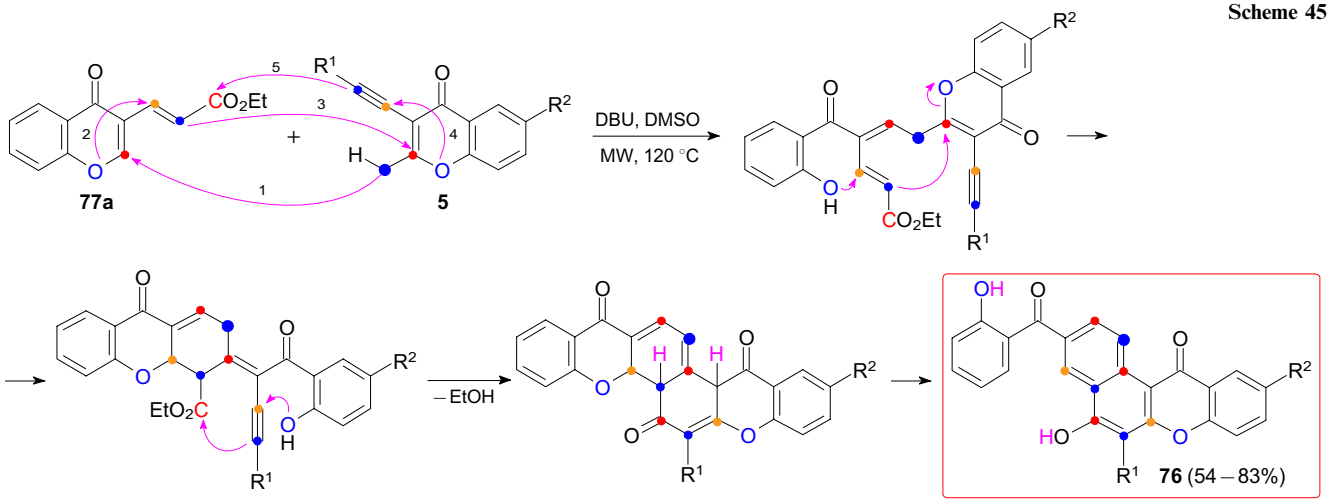
Scheme 44



R^1 = Ph, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$; R^2 = Ph, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, $(CH_2)_3CN$; R^3 = H, OMe, NO_2

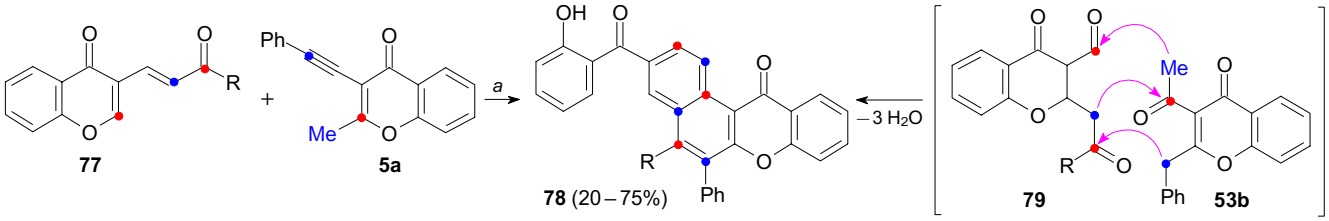
consisting of five steps of nucleophilic addition. This transformation proceeds under conditions similar to those for the dimerization reaction, and its mechanism is illustrated in Scheme 45 by the example of the reaction of ethyl (*E*)-3-(chromon-3-yl)acrylate (**77a**). After the pyrone ring opening in chromone **77a**, the phenolate anion attacks the double bond of the acrylic moiety to generate a xanthone

Scheme 45



R^1 = Ph, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, $(CH_2)_3CN$, Am; R^2 = H, Me, OMe, Br, Cl, NO_2

Scheme 46



(*a*) DBU, DMSO, MW, 120 °C; R = Me, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-BrC_6H_4

scaffold with simultaneous ring opening in chromone **5** and the involvement of the triple bond of this compound in the double intramolecular cyclization thus affording the products **76**.

In addition to acrylate **77a**, chromones **77** bearing an acylvinyl substituent in position 3 also react with 2-methyl-3-(phenylethynyl)chromone (**5a**). In this case, benzo[*a*]xanthones **78** containing methyl or aryl substituents in place of OH group are formed in low to high yields (Scheme 46). The use of (*E*)-3-(chromon-3-yl)acrylonitrile leads to 5-amino-3-salicyloyl-6-phenyl-12*H*-benzo[*a*]xanthen-12-one [79] (not shown in Scheme 46) in 64% yield. A rather long way to benzo[*a*]xanthones **76** and **78** can be replaced by a simple and clear scheme including ambiphilic [4 + 2]-cyclization in combination with aldol condensation of two hydrated forms (**79** and **53b**). These forms, hypothetically, can be generated in the course of 1,4-addition of a water molecule to chromones **77** and **5**, which is accompanied by opening of the pyrone ring and subsequent recyclization (chromane **79** acts as a synthetic equivalent of chromone **77**).

6. Reactions involving a pendant chain

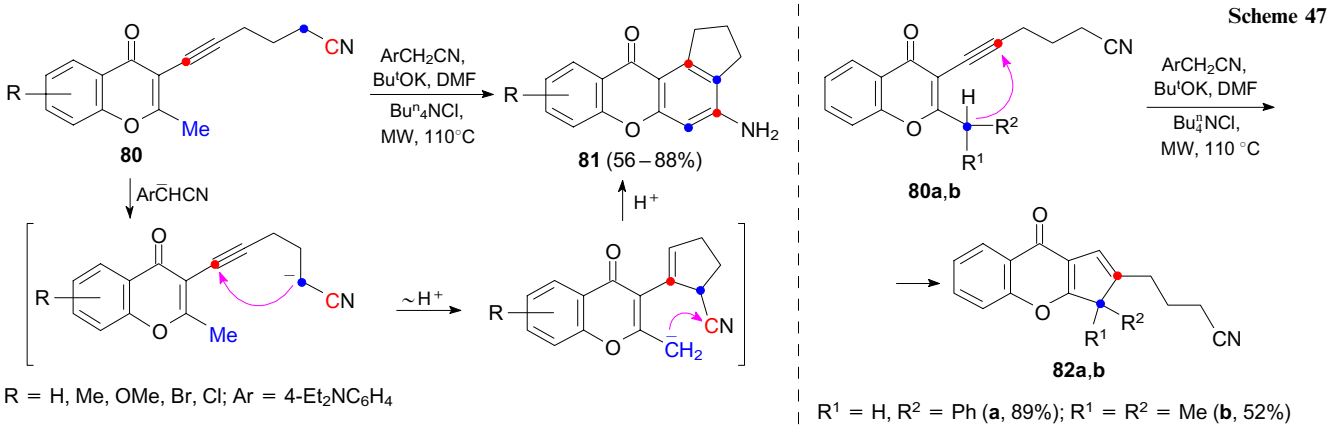
Interesting variants of intramolecular ambiphilic [4 + 2]-carbocyclization occurring both without and with the involvement of a chromone system are described by the example of 2-methyl-3-(1-alkynyl)chromones bearing a long-chain alkyl substituent at the triple bond.[62, 80] It was found [80] that the reaction of 2-methyl-3-(3-cyanopropylethynyl)chromone (**80**) with 3-bromophenylacetonitrile in the presence of Bu^{t}OK in DMF gives 4-amino-2,3-dihydrocyclopenta[*a*]xanthen-11(1*H*)-one (**81**) as the main reaction product, rather than an expected 3-aminoxanthone with a cyanopropyl group in position 4 (Scheme 47).[73] Further examination of this process demonstrated that under phase transfer catalysis conditions, arylacetonitriles deprotonated with Bu^{t}OK, in turn, undergo the abstraction of a proton adjacent to the CN group thereby initiating the double intramolecular cyclization to afford xanthones **81**. *p*-(Diethylaminophenyl)acetonitrile (Ar = 4-$Et_2NC_6H_4$) proved to be the most effective, its reactions are shown in Scheme 47. It should also be noted that when 2-benzyl- and 2-isopropylchromones **80a**,**b** are used, the reaction path changes and the addition of a deprotonated alkyl group across the triple bond leads to cyclopenta[*b*]chromen-9(3*H*)-ones **82a**,**b** in good yields.[80]

Under similar conditions, 3-(hepta-1,6-diyn-1-yl)chromones **83** are first hydrated and rearranged into the intermediate 2-alkyl-3-acylchromones **84** whose triple bond is involved in the intramolecular cyclization of [4 + 2] type and provides the synthesis of 2,3-dihydrocyclopenta[*c*]xanthen-6(1*H*)-ones **85** in 40 – 80% yields (Scheme 48).[62] This reaction is rather general and take place with both 2-unsubstituted and 2-substituted chromones, however, the introduction of a phenyl substituent at the 2-position of the chromone decreases the yield down to 28% due to the steric factor.

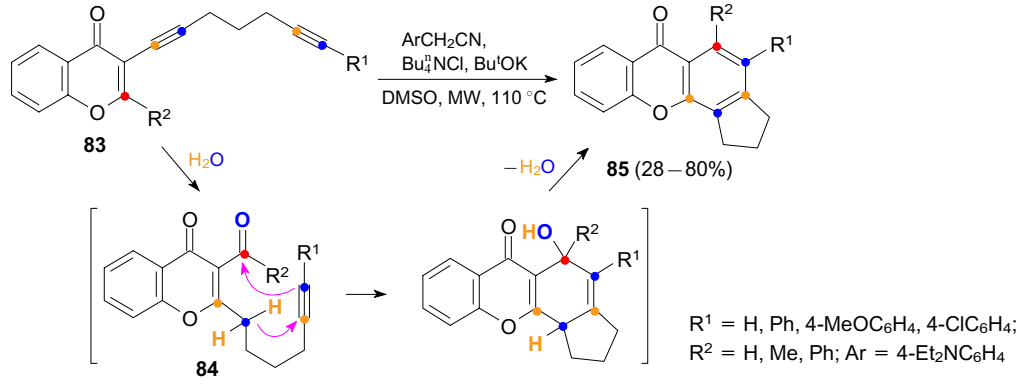
7. Conclusion

Chemistry of 3-(1-alkynyl)chromones containing the enynone scaffold attracted the attention of researchers 15 years ago, and since then, thanks to the increased interest in conjugated enynones and related systems, it has been

Scheme 47



Scheme 48



intensively developing. To date, it has been established that the Sonogashira cross-coupling reaction with 3-halochromones and terminal acetylenes provides access to a variety of derivatives of 3-ethynylchromone, which is an ancestor of a family of chromones bearing the triple bond in position 3.

A study of reactivity of 3-alkynylchromones has shown that although these compounds have their specific features, in general, their similarities both with enynones and chromones is obvious. Thus, transformation into furans is typical of both enynones and 3-alkynylchromones, and ambiphilic cyclizations of 3-alkynylchromones shows their similarity with 2-alkyl-3-acylchromones. Nucleophilic and ambiphilic transformations of 3-alkynylchromones are generally accompanied by pyrone ring transformation involving the triple bond, and the presence of a vinylogous methyl group in position 2 enables not only their dimerization, but also a mixed condensation with other 3-substituted chromones, *e.g.*, with 3-oxovinylchromones. All the above-mentioned features of 3-alkynylchromones make them valuable building blocks for constructing complex heterocyclic systems with potential biological activities and useful photophysical properties.

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8. List of acronyms and designations

Am — n-pentyl (amyl),
bmim — 1-n-butyl-3-methylimidazolium,
CSA — camphor-10-sulfonic acid,
Cy — cyclohexyl,
dba — dibenzylideneacetone,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCE — 1,2-dichloroethane,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DIPEA — diisopropylethylamine,
DME — dimethoxyethane,
E — electrophile,
Fc — ferrocenyl,
Fu — furyl,
L — ligand,
M — metal,
MW — microwave irradiation,
Naph — naphthyl,
NIS — *N*-iodosuccinimide,
NuH — nucleophile,
p-TsOH — *p*-toluenesulfonic acid,
Py — pyridyl,
rt — room temperature,
Tf — trifluoromethanesulfonyl (triflyl),
TIPS — triisopropylsilyl,
TMS — trimethylsilyl,
Th — thienyl.

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