Review:

Reactions of 3-Formylchromone with Active Methylene and Methyl Compounds and Some Subsequent Reactions of the Resulting Condensation Products.

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Abstract: This review presents a survey of the condensations of 3-formylchromone with various active methylene and methyl compounds, e.g. malonic or barbituric acid derivatives, five-membered heterocycles, etc. The utilisation of the condensation products for the synthesis of different heterocyclic systems, which is based on the ability of the \( \gamma \)-pyrone ring to be opened by the nucleophilic attack is also reviewed. Finally, the applications of microwave irradiation as an unconventional method of reaction activation in the synthesis of condensation products is described and the biological activity of some chromone derivatives is noted.

Keywords: 3-Formylchromone, Knoevenagel condensation, active methylene compound, active methyl compound, microwave irradiation, biological activity.
Introduction

From a synthetic viewpoint, 3-formylchromone (1, Figure 1) occupies an important position in the synthesis of various heterocyclic systems. Due to the availability of three electron deficient sites: carbon C-2, the aldehyde carbon and the C-4 carbon of the carbonyl group, 3-formylchromone is able to serve as a heterodiene as well as a dienophile or a Michael acceptor and fused heterocycles can be prepared directly by reaction of 1 with bifunctional nucleophiles.

Figure 1

Since a facile synthesis of 1 by the Vilsmeier–Haack reaction was first published [1], the interest on the chemistry of chromones and their pharmacological utilisation hasn’t decreased. Several reviews dealing with the synthesis, properties and reactions of 1 were published [2, 3], however, condensations of 1 with active methylene and methyl compounds didn’t appear to generate great interest in the earlier research.

This review presents the synthetic capability and the exploitation of the abovementioned types of condensation, achieved using the microwave irradiation method of synthesis as a new and very convenient rate enhancing method [4 - 7]. Several types of subsequent reactions of the condensation products illustrate the ability of chromone derivatives to serve as excellent precursors for the synthesis of a wide variety of heterocyclic systems.

Condensations of 1 with active methylene compounds

Condensations of 1 with malonic acid derivatives

3-Formylchromones readily react with malonic acid and its derivatives in the presence of base, mostly pyridine (Scheme 1). Reaction of 1 with malonic acid [8,9] or diethyl malonate [9,10] in the presence of pyridine afforded $E$-$\beta$-(4-oxo-4H-1-benzopyran-3-yl)acrylic acids 2a ($R^1 = H$) or ethyl acrylates 2b ($R^1 = C_2H_5$), which strongly inhibit the secretion of histamine, therefore they can serve as the suitable agents for the treatment of allergic diseases, especially bronchial asthma. Reaction of 1 with cyanoacetic acid [11,12] led to $E$-$\beta$-(4-oxo-4H-1-benzopyran-3-yl)acrylonitriles 3a ($R^1 = H$) in 56–74 % yields. Finally, condensation of 1 with malondinitrile, reported by Ellis [13] gave derivative 3b ($R = H$, $R^1 = CN$) in 72% yield after 10 min heating at 42 °C.

When 6-substituted 1 were refluxed for 8 – 12 hrs with malonic diamide in pyridine, 3-substituted 5-(2-hydroxybenzoyl)-2(1H)-pyridones 5 were obtained in 62-71% yields [14]. Cyanoacetamide reacted with 1a ($R = H$) or 1b ($R = C_2H_5$) under the similar conditions to produce the mixture of 5a (5b) together with 6a (6b). In the case of 6-nitro-3-formylchromone only 5c ($R = NO_2$) was isolated in 57% yield. Reaction of 1b with cyanoacetamide provides 2-cyano-3-(6-ethyl-(4-oxo-4H-1-
benzopyran-3-yl)acrylamide 4 in 42% yield after 5 min reflux. Whereas 4 was transformed to 5b (R = C₂H₅) in 60% yield by prolonged reflux in pyridine, in the presence of water, both 5b and 6b (1:1) were isolated (Scheme 1).

**Scheme 1**

**Condensations of 1 with 2,4-pentanedione**

Condensation of 1 with an excess amount of 2,4-pentanedione (Scheme 2, path a) in boiling ethanol catalysed by ammonium acetate furnished 3-acetyl-5-(5-R-2-hydroxybenzoyl)-2-methylpyridines 9 in 20–29% yields [15]. The mechanism of this reaction involves the initial base-catalysed condensation of 1 with 2,4-pentanedione to obtain 3-[(4-oxo-4H-1-benzopyran-3-yl)methylene]-pentanediones 7, followed by the cleavage of the pyrone ring at C-2 by ammonia and cyclisation of 7 to afford 9 via non-isolable intermediate 8. Product 7 was also synthesized in 60% yield by
condensation of \( \text{1} \) and 2,4-pentanedione in acetic anhydride – sodium acetate medium [16]. Benzophenones \( \text{14} \) were obtained in low yields (15–30 %) along with \( \text{7} \) (30–40 %) by the addition of a solution of \( \text{1} \) in acetic acid to a preheated (70–80 °C) mixture of 2,4-pentanedione in acetic acid containing a catalytic amount of hydrochloric acid [17]. The formation of \( \text{14} \) (Scheme 2, path c) can be explained by a mechanism which involves the acid-catalysed 1,4-addition of the enol form of 2,4-pentanedione to \( \text{1} \), followed by ring opening to generate intermediate \( \text{10} \), which then enolises to \( \text{12} \). Benzophenone \( \text{14} \) is finally obtained by cyclisation of \( \text{12} \) to \( \text{13} \) and subsequent dehydration and tautomerisation.

When the mixture of \( \text{1} \), 2,4-pentanodione and the catalytic amount of hydrochloric acid is treated in acetic acid at room temperature and then heated at 70–80°C for 2 hrs, only products \( \text{7a} \) and \( \text{7b} \), respectively, were isolated in 40–45% yields [17], which demonstrates 1,2 – addition of 2,4-pentanedione to protonated \( \text{1} \). On the other hand, the mechanism of base-catalysed condensation of \( \text{1} \) consists on the initial attack of the nucleophile at the C-2 of pyrone ring, followed by ring opening and recylisation to \( \text{11} \) with subsequent elimination of water to give \( \text{7} \) (Scheme 2, path b) [2, 16].

**Condensations of \( \text{1} \) with ethyl acylacetates**

Condensation products \( \text{15} \), prepared in 63 or 30 % yields from \( \text{1} \) and ethyl acetoacetate or ethyl benzoylacetic acid in sodium acetate – acetic anhydride medium served as the intermediates for synthesis
of diethyl 5-(2-hydroxybenzoyl)-2-methylisophthalate 16 [16] (Scheme 3). Thus, 15a (R = CH₃) on treatment with excess ethyl acetoacetate in the presence of piperidine in ethanol gives 16, which can be also formed in 80 % yield by one-step reaction of 1 with excess ethyl acetoacetate in piperidine – ethanol medium (Scheme 3, path a). The proposed mechanism involves initial condensation of 1 with ethyl acetoacetate followed by Michael addition of the second molecule of ethyl acetoacetate and subsequent rearrangement (Scheme 3, path b).

Condensations of 1 with 5-nitrofurylethylchloromethylsulphone

Product 17 [18] was formed, when 1 was treated with 5-nitrofurylethylchloromethylsulphone in glacial acetic acid in the presence of ammonium acetate and piperidine at 50–80 °C. Further 17 gave with diazomethane the cyclopropanes 18 instead of the expected pyrazoline derivatives.
These results can be explained by non-finished stepwise mechanism (Scheme 4). Nucleophilic attack of diazomethane on the polarised C=C double bond of trisubstituted ethylenes produces carbanion, which undergoes a cyclopropane forming SNi reaction with the simultaneous elimination of N₂.

**Condensations of 1 with 5,5-dimethylcyclohexane-1,3-dione and Meldrum’s acid**

When 1 was treated with 5,5-dimethylcyclohexane-1,3-dione (dimedone) in aqueous ethanol, a 2:1 adduct 21 was formed [19]. Reaction in pyridine gave the same product 21, which was dehydrated to xantone derivative 22 (73 %) by recrystallization in ethanol, containing hydrochloric acid [20] (Scheme 5).

![Scheme 5](image)

On the other hand, when condensation of 1 with dimedone took place in acetic anhydride in the presence of potassium acetate, expected adducts 19 were isolated in 54–64 % yields by reflux for 1 hr as well as under 4–6 min irradiation in microwave oven [21]. Various heterocyclic aldehydes, including 3-formylchromone, were condensed with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum’s acid). Product 20 was obtained in 63 % yield by heating of 1 with Meldrum’s acid in chloroform in the acetic acid–piperidine medium [22] (Scheme 5).

**Condensations of 1 with 1,3-indandione and the other five-membered fused heterocycles**

1,3-Indandione was used as a component for condensations with 1 under various reaction conditions. Products 23 were synthesized in 61–92% yields either by 20 min of reflux in glacial acetic acid in the presence of piperidine [23] or by 4–6 min of the microwave irradiation in acetic anhydride without any catalyst [21]. Nearly identical yields (61%) were obtained when these reactions were performed in ethanol in the absence of a catalyst at room temperature [24].
It is also possible to obtain the same product 23 in pyridine after 3 hrs at room temperature [20]. According to the same procedure there were prepared products 26 and 27 by condensations of 1 with 3-oxo-2,3dihydrobenzo[b]thiophene-1,1-dioxide and oxindole, respectively.
Reactions of 23 or 26 with aqueous ammonia led to 3-(2-hydroxybenzoyl)-5-oxoindano[3,2-b]pyridine (25) in 81% yield and 3-(2-hydroxybenzoyl)[1]benzothieno[3, 2-b]pyridine-5,5-dioxide (28) in 89% yield. In comparison with these results, adduct 27 didn’t react with ammonia, what is explained by lower electrophilicity of carbonyl group. On the other hand, reaction of 23 with hydrazine sulfate in pyridine gave pyrazole 24 in 45% yield [21]. [1,3]Thiazolo[3,2-a]benzimidazol-3(2H)-one was prepared by the cyclization of (2-benzimidazolylthio)acetic acid in acetic anhydride. The following condensation with 1 under microwave irradiation for 18–30 min as well as by the classical heating at 130°C for 1.5–3 hrs lead to high yields (60–97%) of products 29 [21].

3-Formylchromones react easily with 2-methyl[1,3]thiazolo[3, 2-b][1,2,4]triazol-5(6H)-one in acetic anhydride – sodium acetate medium. After 8 hrs of reflux 30 was produced in 68–91% yields [24]. 1,2'-Biindenylidene-3,1',3'-trione (bindone), as the derivative of 1,3-indandione, gave by treatment with 1 in acetic anhydride – potassium acetate [21] only low yields of condensation products 31 (20–43%), what is probably caused by the steric effects (Scheme 6).

Condensations of 1 with hippuric acid, N-acetylglycine and benzoylepropionic acid

In the presence of acetic anhydride and sodium acetate 1 was condensed with hippuric acid [27] to afford acrylic acid derivatives 32, which subsequently cyclised to 2-phenyl-4-[(chromon-3-yl)methylene]oxazolin–5(4H)-ones 33a in 40–52% yields.
Heating of 33a in ethanolic or methanolic solution of sodium carbonate lead to 37–78% yields of pyroles 34 (Scheme 7). Analogously it is possible to obtain products 33b from 1 and N-acetylglucine [39]. Both of the products 33a and 33b can be transformed to 36 by treatment with amines. In an alternate method, compounds 36 could also be obtained by condensations of 1 with 1,2-disubstituted imidazolin-5(4H)-ones, which were prepared from N-acetylglucine and the corresponding amine.

Substituted benzoylpropionic acids cyclized readily with 1 to 35 [26]. Classical heating in acetic anhydride in the presence of potassium acetate gave 78% of products 35, while the irradiation in microwave oven in the same medium needed only 1–4 min to prepare 35 in 62–84% yields.

3-Formylchromones were condensed with substituted 4-coumarinylacetic acids in acetic anhydride in the presence of potassium carbonate as the catalyst either by heating at 80–90 °C for 3 hrs or by 4–10 min of irradiation in microwave oven. The expected products 38 were not obtained directly and the reaction led to arising of 2-hydroxy derivatives 37, which were transformed to 2-ethoxy derivatives 40 by reflux in ethanol. Compounds 38 were formed only by reflux of 37 or 40 in acetic acid.

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\text{Scheme 8}
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Derivatives 37, 38 and 40 were able to change into each other as it is indicated in scheme 8. It was proved that only chromone parts of molecules of 37, 38 and 40 reacted with primary amines or formamide. After nucleophilic attack the pyrone ring was opened to cause the rearrangement of chromone system into pyridine derivatives 41 and 42, respectively [28].

On the other hand, Shingare and co-workers [29] described the condensations of substituted 3-formylchromones with 6,8-dimethylcoumarin-4-acetic acid. Even if the reactions were carried out in pyridine, after 6 hrs of reflux the opening of the pyrone ring was not observed. Condensation products 38 were obtained in 46–69 % yields.

When substituted 3-formylchromones were treated with 3- or 4-coumarinylacetic acids in acetic anhydride–potassium acetate either by heating at 90–100°C for 1–2 hrs or by microwave irradiation for 10 min, products 43a and 44a (R² = CH₃CO), respectively were obtained in 80–86 % yields (Scheme 9).

Their subsequent alcoholysis with various alcohols at 60–100 °C in the presence of p-toluenesulfonic acid gives ethers 43 and 44 (R² = CH₃, C₂H₅, CH₂CH=CH₂) in about 80% yields. It was also found, that all prepared compounds 43 and 44 underwent a rearrangement by heating with acetic acid at 60–80 °C to afford products 45 and 46 in about 75 % yields [30] (Scheme 10).
3-Formylchromone was easily condensed with several pyrimidine derivatives [20, 31]. Product 47 was obtained in 94% yield after 10 min of reflux of 1 and barbituric acid in pyridine [20] (Scheme 10). Two types of condensation products were synthesized by treatment of 1 with 1,3-dimethyl-4-iminouracil depending on the reaction conditions [31].

When the reaction took place in water, a Knoevenagel type product 48 was produced in 39% yield. On the other hand using of the ethanol–water medium (1:1) in the presence of a catalytic amount pyridine led to product 49 in 28% yield.
Substituted barbituric or thiobarbituric acids reacted with 1 in acetone under triethylamine–pyridine catalysis to afford products 50 in 13–21 % yields, while an acetic acid–acetic anhydride medium has been identified as suitable for preparing pyrimidopyranopyrimidines 51, which were obtained in 12–64 % yields [31].

**Condensations of 1 with 5-membered heterocycles**

**Reactions with 2-thioxoimidazolidin-4-one**

Condensation products 52 were prepared in 74–78 % yields by refluxing 1 with 2-thioxoimidazolidin-4-one (thiohydantoin) in glacial acetic acid in the presence of piperidine for 20 min [23]. A subsequent method is based on 0.5–2 hr heating of the reaction mixture in acetic anhydride and catalysed by potassium acetate [32]. Microwave irradiation shortened the reaction times to 4–10 min and gave comparable yields (62–96 %) of 52 (Scheme 11).

**Reactions with 2-thioxothiazolidin-4-one**

2-Thioxothiazolidin-4-one (rhodanine) gives with 1 in acetic anhydride under sodium acetate catalysis [27] products 53 (R = H or R = 5-CH₃, 6-CH₃O) in 43 and 66 % yields. Products 53 have been utilised for the preparation of thiophene carboxylic acids 55. Thus, on treatment of 53 in aqueous sodium hydroxide after 1 hr of reflux afforded 55 (R = H, CH₃) in 44 and 80 % yields, respectively.

Similarly, 1 with 3-ethylrhodanine gave product 54 (R = H) in 95 % yield in potassium acetate–absolute ethanol medium [53]. Products 54 were also prepared in acetic anhydride–potassium acetate medium after 5 minutes of the microwave irradiation, while classical heating lead in these cases to comparable amounts (65–74 %) of products 54 after 1 hr [32].

Condensations of various aldehydes, including 1 with acylated 3-aminorhodanines were also published [33]. The acylation of 3-amino group of rhodanine was taken place by the reflux of 3-aminorhodanine with acylhalogenides in tetrahydrofuran. Subsequent condensation of 3-aminoacetylrhodanine with 1 in ethanol gave product 56.

**Reactions with 2-imino-1-methylimidazolidin-4-one**

Reactions of 1 with 2-imino-1-methylimidazolidin.4-one (creatine) provide several types of products, depending on the reaction medium [32]. When substituted 1 were condensed with creatine in acetic anhydride at catalysis by potassium acetate under microwave irradiation for 1 - 4 min as well as at classical heating for 1–2 hrs, 2-iminogroup was acetylated to yield products 57 in 40–84%.

The convenient synthesis of 1-methyl-4-oxo-[(6-R-4-oxo-4H-1-benzopyran-3-yl)methylidene]-4,5-dihydroimidazol-2-carbamoic acids 58 was accomplished by reaction of creatinine with ethyl chloroformate in dimethylformamide at 0–5°C over 30 min, followed by subsequent condensation with 1. Products 58 were obtained after 4–6 hrs in 69–71% yields by both the classical and microwave irradiation methods, even under anhydrous conditions. Unsubstituted condensation products 59 were prepared in 68–98% by heating of the mixture of 1 and creatinine in dimethylsulfoxide under boric acid catalysis for 3 hrs.
Reactions with 3-substituted isoxazol-5(4H)-ones

Knoevenagel products 60 of 1 with 3-methylisoxazol-5(4H)-one [34] or with 3-methyl- and 3-phenylisoxazol-5(4H)-one, respectively [34] were synthesized either in chloroform – ethanol medium at room temperature [34], or by 3 hr heating in ethanol [32] in 81-89 % yields. Condensation products 60 serve as convenient starting materials for the synthesis of benzopyranylacetylenes 60. Chromon-3-
ylacetylene 61 (R⁴ = H) was prepared from appropriate 60 by flash pyrolysis at 750°C [34]. 2-Methyl or 2-phenylchromonylacetylenes 61 (R⁴ = CH₃, C₆H₅) were synthesized in good yields (79–89%) after reduction of 60 (R³ = CH₃, C₆H₅) with sodium borohydride–methanol for 3 hr at room temperature and exposure to aqueous sodium nitrite–ferrous sulfate in acetic acid [35] (Scheme 11).

Reactions with substituted pyrazolin-5-(4H)-ones

Substituted 1 condensed readily with 3-methyl-1-phenylpyrazolin-5-(4H)-one [36] in acetic acid to give products 62 in 47–80% yields. When the mixture of 1 and 3-methyl-1-phenylpyrazolin-5-(4H)-one in solvent free conditions was exposed to microwave irradiation for 3-5 min derivatives 62 were isolated in 54–85% yields. Comparable yields of 62 (56–86 %) were obtained by microwave irradiation of 1 and 3-methyl-1-phenylpyrazolin-5-(4H)-one on alumina support or by “classical” heating in dioxane–triethylamine medium for 45 min [37] (Scheme 12).
Reactions of 6-substituted 3-formylchromones with 4-hydroxy-1-methyl-3-(5-oxo-2-pyrazolin-3-yl)quinolin-2(1H)-one [38] were carried out in glacial acetic acid in the presence of sodium acetate to give quinoline derivatives 63 (Scheme 12). When compound 63a (R = H) was treated with hydrazine hydrate in a 1:1 molar ratio in boiling ethanol the product of pyrone ring opening and pyrazole ring closure 64a (A = NH) was obtained in 66% yield. Treatment of 63a with the excess of hydroxylamine in boiled dimethylformamide led to product 65a in 56%. Furthermore 65a was obtained in 89% yield by refluxing 64a with excess hydrazine hydrate in dimethylformamide (Scheme 12). Similar results were acquired by reaction of 63a with hydroxylammonium chloride in a mixture of ethanol–dimethylformamide. When a 1:1 molar ratio was used, product 64b (A = O) was obtained in 84% yield, while using excess of hydroxylationm chloride led to 65b in 71% yield. Treatment of 64b with the excess of hydroxylammonium chloride also yielded 65b in 85% yield (Scheme 12).

As it was mentioned above [15, 20], the action of ammonia to chromone derivatives led to their conversion into substitutes 3-(2-hydroxybenzoyl)pyridines. Thus, the reflux of 63a with ammonium acetate in dimethylformamide for 3 hrs furnished 3-(pyrazolo[3,4-b]pyridinyl)quinoline 66 in 80% yield (Scheme 13).

Condensation product 63a underwent reactions with bidentate nucleophiles [38]. Thiobarbituric acid, which is one of the most useful precursors of polyaza-fused heterocycles, reacted with 63a in sodium ethanolate-ethanol medium to give pyrano[2,3-d]pyrimidinone 67 in 68% yield. Using phase-transfer catalysis conditions (potassium carbonate–dioxane–tetrahydroammonium bromide) compound 63a reacted with sulfanylacetic acid to give after 2 hrs of heating 53% of thiophene-2-carboxylic acid 68 via nucleophilic γ-pyrene ring opening followed by thiophene ring closure. The subsequent dehydration of 68 with polyphosphoric acid (PPA) yielded thiophene-2-carboxylic acid 68 in 52% yield.

The addition of ketene-S,S-acetal to compound 63a was carried out by in situ reaction of ethyl cyanocetate and carbon disulfide under similar phase-transfer catalysis conditions. Product 70 was obtained after 30 min heating in 77% yield. Thiapyridone 71 was prepared in 73% yield by reaction of cyanothioacetamide with 63a at sodium ethanolate–ethanol.

The reaction of 63a with 1,4-S,N-nucleophiles led to the formation of thiazepine derivatives, thus the reaction of 63a with 2-aminothiophenol in sodium ethoxide–ethanol medium furnished benzo[1,5]thiazepine 72 in 51% yield. Similarly, its treatment with 4-amino-5-triflourmethyl-4H-[1,2,4]triazole-3-thiol gave 65% yield of triazolo[3,4-b][1,5,6]thiadiazepine 73.

Finally, thiourea and guanidine hydrochloride served as suitable precursors of pyrimidine derivatives. The pyrimidinethione 74 was furnished in 85% yield by treatment of 63a with thiourea in potassium hydroxide–ethanol medium, while using guanidine hydrochloride at the similar conditions led to arising of aminopyrimidine 75 in 79% yield (Scheme 13).

Condensations of 1 with phenylacetic acids, aryl- or heteroarylsubstituted acetonitriles and six-membered fused heterocycles

The condensation of 1 with phenylacetic acid [40] in acetic anhydride in the presence of piperidine as a catalyst furnished the products 76 in 47–68% yields. The spectral data showed the presence acetyl instead of the carboxy group, which could be explained by decarboxylation followed by acetylation in situ (Scheme 14).
1-Naphtylacetonitrile condenses with 1 to give only moderate yields (30–38 %) of products 77 after 17–20 hrs of heating at 150 °C. Under the influence of microwave irradiation the yields of 77 were increased only marginally (39–46 %), but the reaction times were shortened to 10 min [26].

Knoevenagel products 78 were obtained in low yields (15–43%) by heating 1 with 2H-1,4-benzothiazin-3(4H)-one in acetic anhydride–potassium acetate medium for 6–10 hrs. Using microwave irradiation reaction times were shortenned to 7–20 min with an increase in yields to 33–62%.
Treatment with hydrazine led to the conversion of 78 to the pyrazine derivatives 79 [21] (Scheme 14), similarly to the indandione derivative 24 (Scheme 6).

A series of condensation products of [2-amino-4-(3,5,5-trimethyl-2-pyrazolino)-1,3,5-triazin-6-yl]acetonitrile with various aromatic or heterocyclic aldehydes including 1 were synthesized in high yields by reflux in ethanol–piperidine medium. Derivative 80 was obtained in 95 % yield. All the products were screened for their activities against 60 tumor cell lines [41]. Harnish [42] has described the condensation of 1 with 2-benzimidazoloylacetonitrile. The reaction took place in ethanol at room temperature to give 96 % of 81 (Scheme 14).

Reaction of 1 with 4-chromanone [43] in ethanol–triethylamine medium gave after 3 hrs of reflux benzopyran-2,3-dihydrobenzopyranones 82 in high yields (67–80 %). In the next step compounds 82 were refluxed for 2 hrs with ammonia in aqueous methanolic medium or with ammonium acetate in acetic acid to give benzopyran[4-3-b]pyridines 83 in 50 – 63 % yields. The o-hydroxybenzoyl moiety of 83 can be converted either to the coumarine or to benzofuran systems. Thus, the reaction of 83 with phenylacetyl chloride in the presence of aqueous K₂CO₃ in the conditions of phase-transfer catalysis using tetrabutylammonium hydrogenosulfate and dichlormethane lead to 3-(2-oxo-3-phenylcoumarin-4-yl)-5H-1-benzopyran[4,3-b]pyridines 84 in 48–70 % yields, while similar reaction with 4-chlorophenacyl bromide gives 3-(2-benzoylbenzo[b]furan-3-yl)-5H-1-benzopyran[4,3-b]pyridines 85 in 60–84% yields (Scheme 14).

Condensations of 1 with active methyl compounds

Condensations with acetaldehyde and arylmethylketones

Ghosh and co-workers [44] published synthesis of 3-(4-Oxo-4H-1-benzopyran-3-yl)acroleines 86 in moderate yields (21–49 %) via cycloaddition of 1 with ethylvinylether and subsequent hydrolysis of benzopyranopyrane intermediumtes. More efficient method, described by Polyakov [45], consists of the reaction of 1 with acetaldehyde in dimethylformamide, catalysed with aqueous piperidine at low temperatures, followed with acidic hydrolysis. Acroleins 86 were thus prepared in 70–99% yields (Scheme 16). Substituted acetophenones served as a versatile reagents in the synthesis of a new chromonylechalcones 87 [46, 47]. Reaction took place in methanolic potassium acetate at room temperature for 3 hrs to give 70–76 % of products (Scheme 15).

Condensations of 1 with 3-alkyl-4-phenyl-3-cyclobuten-1,2-diones and 3-methylthiazine

The reaction of 1 with 3-methyl or 3-ethyl-4-phenylcyclobut-3-en-1,2-diones was reported to yield derivatives 88. The synthesis consists of the treatment of a mixture of 1 and 3-methyl-4-phenyl-3-cyclobuten-1,2-dione in aluminium chloride–dichlormethane medium for 3.5 hrs to yield 41% of 88 (R = H). 3-Ethyl-4-phenyl-cyclobut-3-en-1,2-dione reacted with 1 in concentrated hydrochloric acid to give 88 (R = CH₃) in 26 % yield [48]. Arylvinylthiazolines, including 89, show antifungal activity and antiparasitic activity on Molinema dessetae [49] (Scheme 15).
Condensations of 1 with methyl-substituted oxygen heterocycles

The chromone derivatives 90 – 92 were prepared by two procedures. Condensations of 1 with 3-R^1-4,5,5-trimethyl-2,5-dihydrofuran-2-ones or 3-R^1-4,6,6-trimethyl-5,6-dihydropyran-2-ones carried out in acetic anhydride in the temperature range 80 – 90 °C yielded products 90, 91 in 65 – 75 %. Products 92, which contained amide group as R^1, were prepared by reaction of 1 and 4-methylcoumarin in refluxing toluene [50] (Scheme 15).

2-Methyl-3-acetylchromone contains two active methyl groups, which can react by aldol condensation. Products 93 were obtained by the reaction of 1 with substituted 2-methyl-3-acetylchromones in acetic anhydride–potassium acetate medium by the classical method, which required the heating at 120–130 °C for 2–3 hrs as well as by 40 sec–2 min irradiation in the microwave oven (Scheme 15). In both cases the reaction occurred only at the 2-methyl group [51].

Condensations of 1 with 2-methylbenzothiazole and 2-methylbenzimidazole derivatives

An effective method for synthesis of benzothiazolium salts 94 consists on the preparing of 3-alkyl or 3-aryl-2-methylbenzothiazolium halides and their subsequent condensations with 1 [52].
benzothiazolium salts were synthesized either by 2–20 hr of heating of 2-methylbenzothiazole with alkyl or arylhalides in acetonitrile or nitromethane or by 10–30 min of the irradiation of reaction mixture in microwave oven (Scheme 16, path a). In the following step 2-methylbenzothiazolium salts were treated with 6-substituted 1 in acetonitrile to give 29–85% of 94 after 3–35 min of the microwave irradiation or 0.5–8 hrs of heating. The opposite sequence of reaction steps was used at the synthesis of 94c, as well as the products 96 (Scheme 16, path b).

Condensations of 1 with 2-methylbenzothiazole or 2-methylbenzimidazole carried out in dimethylsulfoxide–boric acid medium at 120 °C to give compounds 96 in 50 - 68 % yields. Decreasing of the reaction temperature to 60°C lead to products 97a, 97b, which were prepared in 81, 85 % yields (Scheme 16). Most of products 94 showed antialgal activity towards *Chlorella vulgaris* [53]. Products 95 were prepared by the treatment of 94 with ethanol, dimethylamine or 2,3-dimethylbenzothiazolium methylmetasulphate in acetonitrile in the presence of triethylamine [54].
Condensations of 1 with 4-nitro and 2,4-dinitrotoluene. Subsequent reactions of 3-styrylchromones.

3-Styrylchromones 98a (R<sup>1</sup> = NO<sub>2</sub>, R<sup>2</sup> = H) were synthesized in 24–50 % yields [39] by 8 hrs of reflux of 1 with p-nitrotoluene in ethanol. Different 3-styrylchromones 98b (R<sup>1</sup>, R<sup>2</sup> = NO<sub>2</sub>) were obtained by condensation of 3-formylchromones with 2,4-nitrotoluene in pyridine [55].

![Scheme 17](image)

The other 3-styrylchromones 98c, 98d (R<sup>1</sup> = H, Cl) where methyl group of toluene is not sufficiently activated, were prepared by Wittig reaction of 1 with benzylidenediaryl phosphoranes [56] and their subsequent reactions were extensively studied. 4-Styryl-3-(2-hydroxyphenyl)pyrazoles 99 have been prepared by reaction of 98c and 98d, respectively with hydrazine hydrate [57]. Diels-Alder reactions of 98c, 98d under microwave irradiation with dimethyl acetylenedicarboxylate led to xanthone derivatives 100 [58] and with N-methyl or N-phenylmaleimide [59] to derivatives 101 (Scheme 17).

Conclusions

Knoevenagel condensations of 3-formylchromone with active methylene and methyl compounds, described in this review, represent not only a convenient synthetic route leading to many biologically
active compounds, but combined with the cleavage of the pyrone ring by the attack of nucleophiles and subsequent rearrangement, they are widely utilised in the synthesis of new heterocyclic systems. The microwave irradiation method of reaction activation was in many cases successfully used for increasing the yields, as well as to achieve a considerable shortening of reaction times.

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