

Review

New Synthetic Routes to Furocoumarins and Their Analogs: A Review

Valery F. Traven

Department of Organic Chemistry, D. Mendeleev University of Chemical Technology of Russia
125047, Moscow, Russia. E-mail: traven@muctr.edu.ru

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Abstract: Many furocoumarins and their analogs possess a prominent photobiological activity. Some of them are successfully used as drugs in phototherapy of skin diseases. Fries rearrangement of acyloxyheteroarenes, condensation of acylhydroxyheteroarenes with α -carbonyl compounds under base catalysis and transformations of dihydrofurocoumarinones are new trends in synthesis of furocoumarins and their analogs.

Keywords: Furocoumarins; furocoumarin analogs; psoralens; Fries rearrangements.

Introduction

Furocoumarins, such as psoralene and the angelicine derivatives are naturally occurring compounds. They are known to possess a high photobiological activity [1]. Psoralene derivatives have been used for many years in the treatment of skin diseases [2]. Furocoumarin/ultraviolet therapy, known as photopheresis, has recently become an effective treatment of cutaneous T cell lymphoma, Sezary syndrome and related diseases [3, 4]. The photochemotherapeutic effects of furocoumarins are based on intercalation of the molecules between the pyrimidine bases of the microorganism's DNA. The intercalation is then followed by the UV light activated cycloaddition reactions of furocoumarins with the pyrimidine bases. These [2+2] photocycloaddition reactions result in a cross-linking of DNA and prevent a microorganism's reproduction.

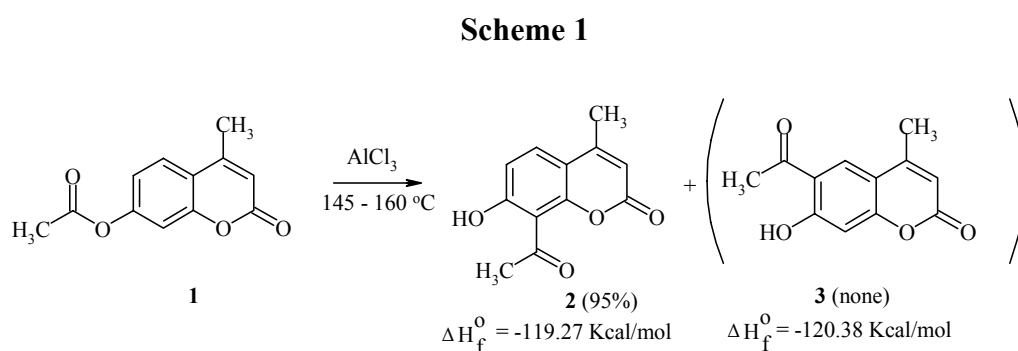
Psoralens, which are linear furocoumarins, have the highest photosensitivity. Their molecules have two active sites in the [2+2] photocycloaddition reactions: the pyrone ring and furan ring double bonds. This kind of difunctionality of the psoralens (and of the angelicines in to a lesser extent) has been suggested to cause undesirable side effects in their medical use. Mutagenicity and carcinogenicity should be mentioned among these side effects of some psoralens [5-11].

Even though some methods of furocoumarin synthesis have been known for a long time, the successful use of furocoumarins as effective medicines requires access to as many new derivatives as possible. For example, it has been found that furocoumarin analogs that contain other heteroatoms besides the oxygen atom in the lactone ring are free of some side effects [4]. Better intercalation properties and higher hydrophilicity should be also specific for new furocoumarins recommended for pharmaceutical testing. Therefore, the search for new synthetic approaches to the furocoumarins and their analogous heterocyclic compounds is a promising trend in photochemotherapy [12-19].

Fries rearrangement of acetoxyheteroarenes

Acyloxyheteroarenes are convenient intermediates in furoheteroarene synthesis. The key reaction for preparation of these intermediates is the Fries rearrangement of acyloxyheteroarenes. Nevertheless, this reaction with heteroarene derivatives has not been studied much when compared with that of benzene derivatives.

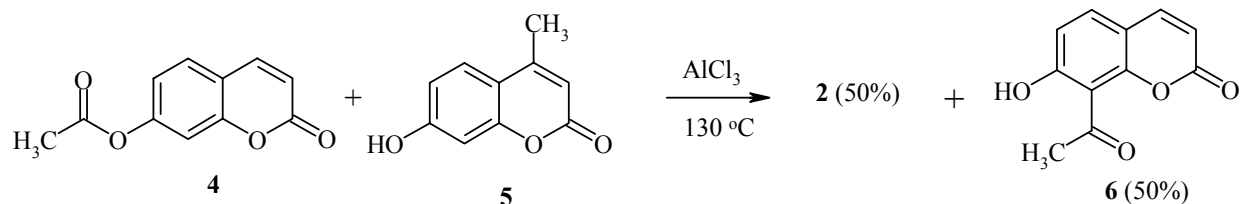
We have studied the Fries rearrangement of 7-acyloxycoumarins in detail [20-22]. Some of the results are given below. For example, 7-acetoxy-4-methylcoumarin (**1**) undergoes a smooth transformation into 8-acetyl-7-hydroxy-4-methylcoumarin (**2**) as the exclusive product of the rearrangement (Scheme 1). This rearrangement is largely temperature independent.



Kinetic factors seem to explain this result, since both 8-acetyl- and 6-acetyl-isomers (compounds **2** and **3**, respectively) possess similar thermodynamic stability.

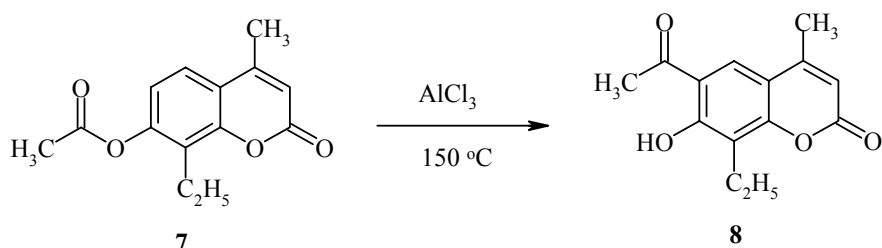
We have found that the Fries rearrangement of 7-acyloxycoumarins takes place by an intermolecular mechanism [20]. Thus, rearrangement of 7-acetoxycoumarin (**4**) in the presence of 7-hydroxy-4-methylcoumarin (**5**) results in the formation of equimolar amounts of 8-acetyl-7-hydroxy-4-methylcoumarin (**6**) and 8-acetyl-7-hydroxy-4-methylcoumarin (**2**) (Scheme 2).

Scheme 2



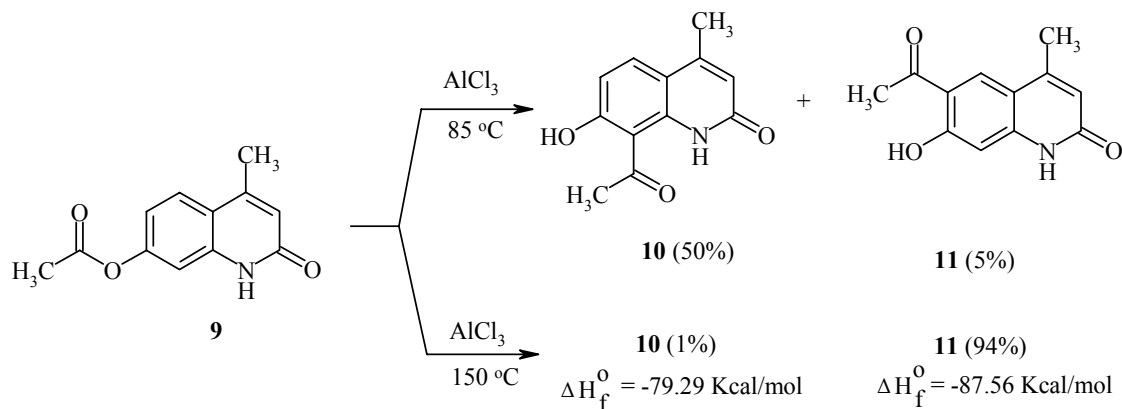
The deacylated product, 7-hydroxycoumarin, has also been found in the final reaction mixture. When the position 8 of the starting coumarin derivative is occupied (as in compound 7, Scheme 3), the acyl group rearrangement involves the 6 position.

Scheme 3



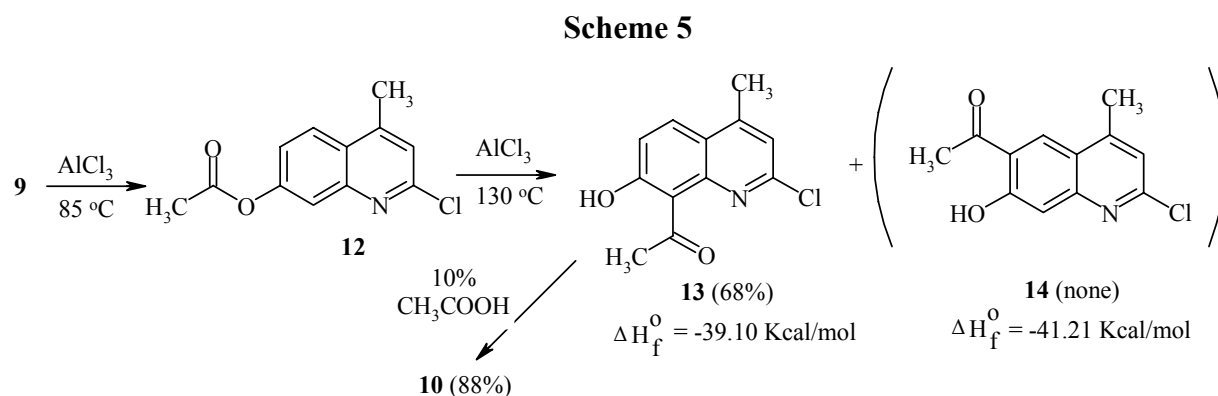
Rearrangement of 7-acetoxycoumarins thus provides intermediates for both angular and linear furocoumarins. We have found the regioselectivity of the Fries rearrangement of acyloxyheteroarenes to be very dependent on the structure of the heteroarene [23]. Regioselectivity data of rearrangements of acyloxycoumarins, bis(acyloxy)coumarins, acyloxyquinolin-2-ones, acyloxy-2-chloroquinolines and their analogs are shown below. In contrast to the reactions of acyloxycoumarins, the regioselectivity of Fries rearrangement of 7-acyloxyquinolin-2-one **9** is very dependent on the temperature.

Scheme 4



At relatively low temperature (85°C), 8-acetyl-7-hydroxy-4-methylquinolin-2-one (**10**) is the predominant product of the rearrangement: 50% of 8-isomer **10** and 5% of 6-isomer **11** have been found in the final reaction mixture. However, an increase in temperature to 150°C results in the formation of the 6-isomer **11** as the major product (Scheme 4).

It should be noted that isomers **10** and **11** possess different calculated thermodynamic stabilities. As can be seen, a high rearrangement temperature results in predominant formation of the thermodynamically more stable isomer **11**. By contrast, isomer distributions of products at lower temperatures seem to follow a kinetic trend. Substitution of a chlorine atom for the oxo-function in quinolinone **9** greatly affects the regioselectivity of the Fries rearrangement. Thus, 7-acetoxy-2-chloro-4-methylquinoline (**12**) undergoes the rearrangement with exclusive formation of the 8-acetyl-isomer **13** independent of the temperature (Scheme 5). A possible isomer **14** was not found. Heating of **13** in aqueous acetic acid furnished quinolone **10**.

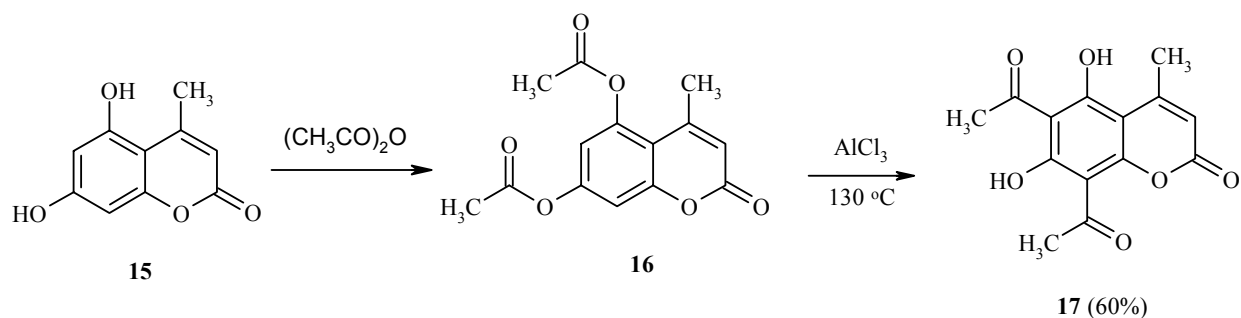


As can be seen from Scheme 5, isomers **13** and **14** exhibit similar calculated thermodynamic stabilities. Therefore, the exclusive formation of **13** appears to be a result of a kinetically controlled rearrangement. As already noted, a similar selectivity has been observed for acetoxy coumarin **1**.

The following conclusions concerning regioselectivity of the acyloxyheteroarenes Fries rearrangement agree with the given results. If two isomers, the products of the rearrangement, have different thermodynamic stabilities, one can see a definite effect of the reaction temperature on the regioselectivity. If two isomeric products of the rearrangement possess similar thermodynamic stabilities, then the regioselectivity seems to be independent of the reaction temperature.

An interesting example of the Fries rearrangement is provided by the transformation of 5,7-bis(acetoxy)-4-methylcoumarin (**16**), derived from dihydroxycoumarin **15** (Scheme 6). In the rearrangement of **16**, two acetoxy functions are simultaneously rearranged in the same molecule to give **17**. In summary, the Fries reaction seems to be a convenient method for the synthesis of heteroarenes with adjacent acyl and hydroxyl functions.

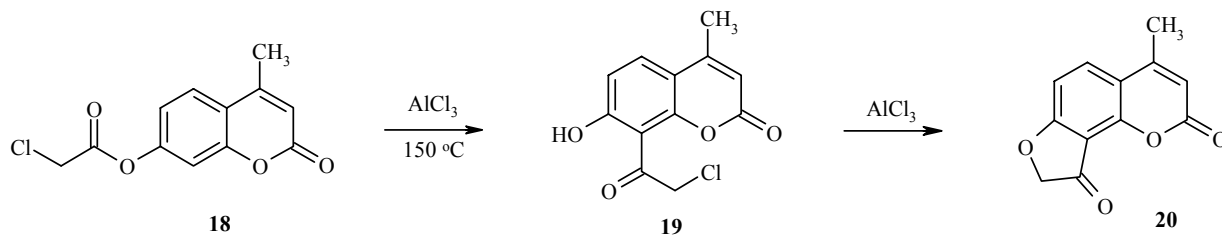
Scheme 6



Unusual Fries rearrangements of chloroacetoxyheteroarenes

Unusual results have been found for the treatment of 7-chloroacetoxyheteroarenes with excess aluminum trichloride [22]. Unexpectedly, the classical rearrangement is followed by an intramolecular cyclization of an intermediate chloroacetyl hydroxy derivative with formation of a condensed dihydrofuranone. As an example, the rearrangement of 7-chloroacetoxy-4-methylcoumarin (**18**) to give the final product **20** via the intermediate **19** is shown in Scheme 7.

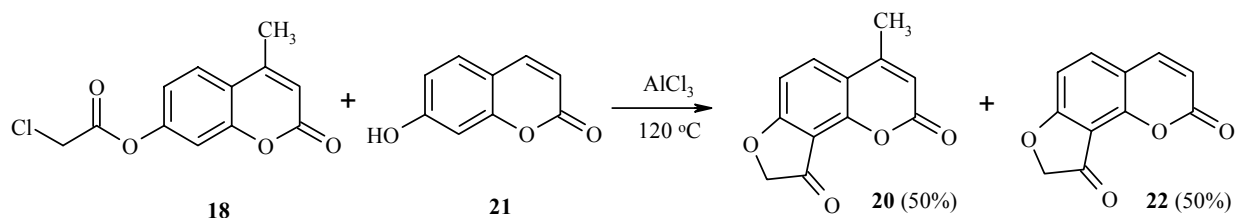
Scheme 7



Thus, compound **18** and similar 7-chloroacetoxy substituted coumarins are important substrates for the synthesis of angular furocoumarins.

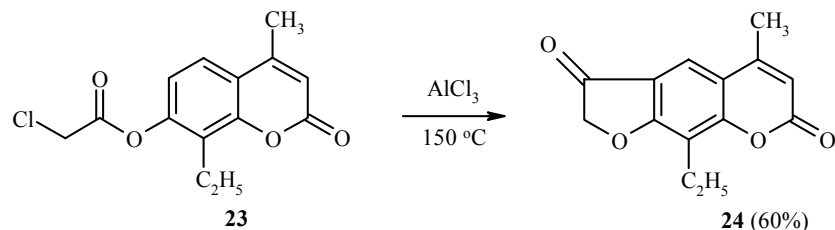
As with 7-acetoxycoumarins, 7-chloroacetoxy coumarins undergo this unusual Fries rearrangement by an intermolecular mechanism as well. Thus, rearrangement of **18** in the presence of 7-hydroxy-4-methylcoumarin (**21**) gives equimolar amounts of a 4-methyl derivative **20** and its analog **22**, lacking the methyl group (Scheme 8) [20].

Scheme 8



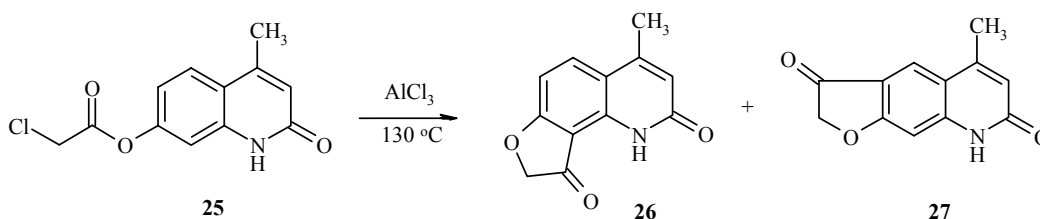
Substrates which have a substituent at position 8 of the coumarin ring system, undergo rearrangement into position 6 [22]. This is illustrated in Scheme 9 by the synthesis of **24** from **23**.

Scheme 9



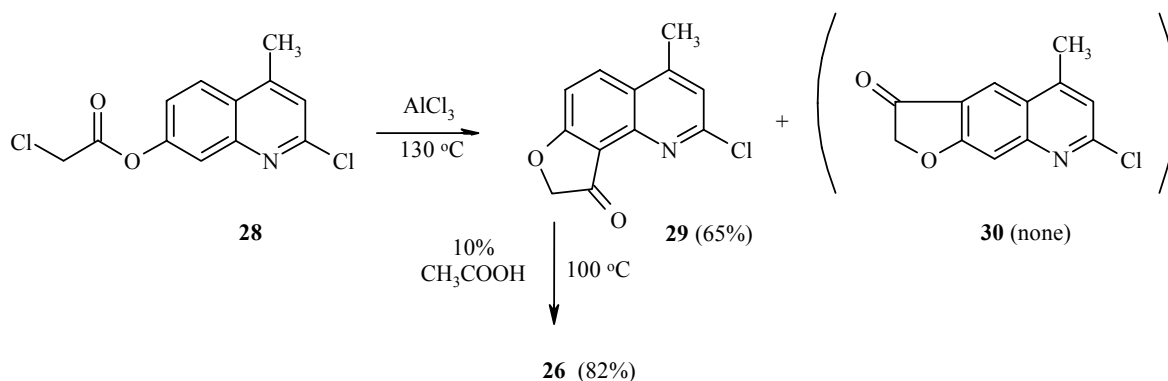
7-Chloroacetoxy-4-methylquinolin-2-one (**25**) also undergoes the a Fries rearrangement that is followed by an intramolecular cyclization to give a mixture of furoquinolines **26** and **27** (Scheme 10). Due to low regioselectivity, this reaction does not have much synthetic value.

Scheme 10



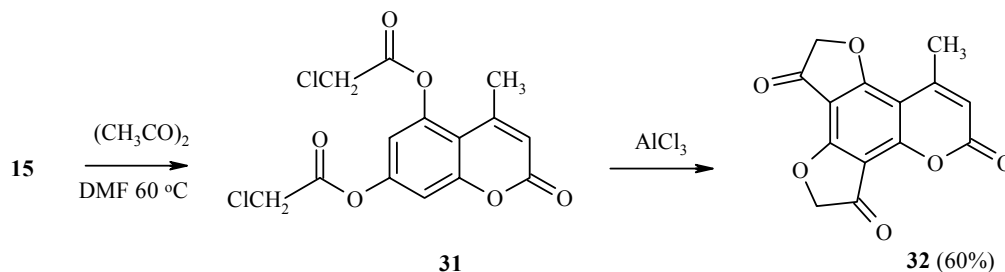
As with 7-acetoxy derivatives, regioselectivity of the Fries rearrangement of 7-chloroacetoxy-substituted substrates is much affected by substitution of the chlorine atom for the 2-oxo function. Exclusive formation of **29** without traces of isomer **30** by rearrangement of **28** can be noted (Scheme 11). The chlorine atom in **29** can be replaced by an oxo or amino function, as exemplified by hydrolysis of **29** to furoquinolinone **26**.

Scheme 11



Two dihydrofuranone rings in the same heteroarene molecule can be constructed under Fries rearrangement as well (Scheme 12). For example, 5,7-bis(chloroacetoxy)coumarin **31** has been prepared by chloroacetylation of compound **15**. Heating of **31** with a large excess of aluminum trichloride gave **32** in good yield.

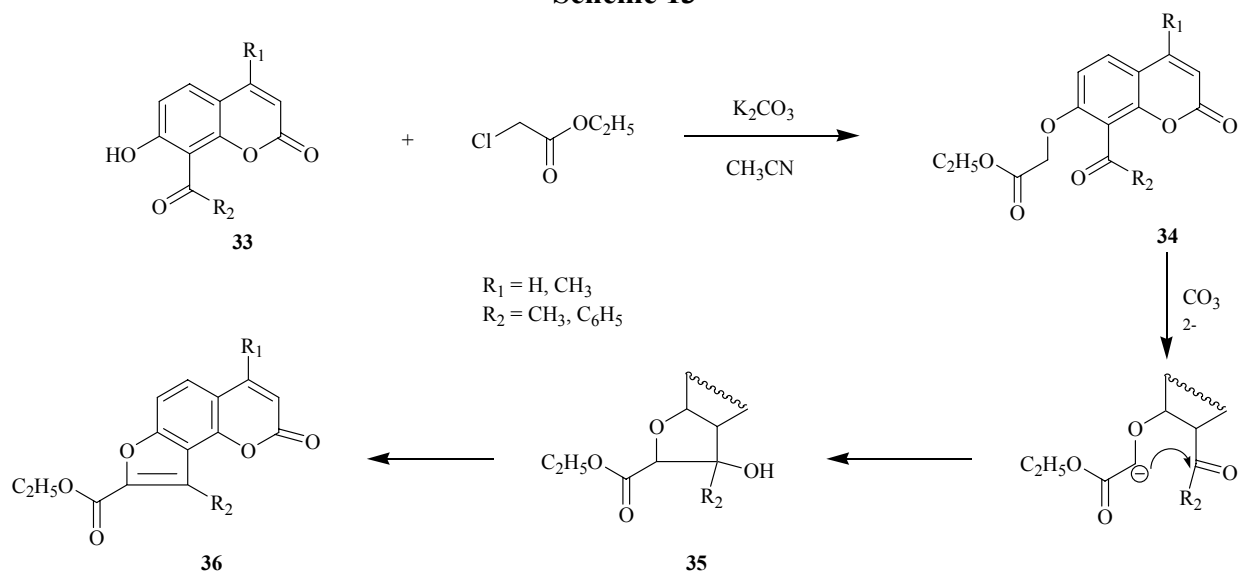
Scheme 12



Base-catalyzed condensation of acetylhydroxyheteroarenes with α -halocarbonyl compounds

Base-catalyzed condensation of acetylhydroxyheteroarenes with α -halocarbonyl compounds is a preparative method for the construction of a furan ring in condensed heteroarenes [23, 24]. This approach is shown in Scheme 13 for condensation of 8-acyl-7-hydroxycoumarins **33** with ethyl chloroacetate.

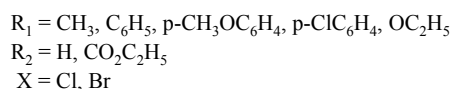
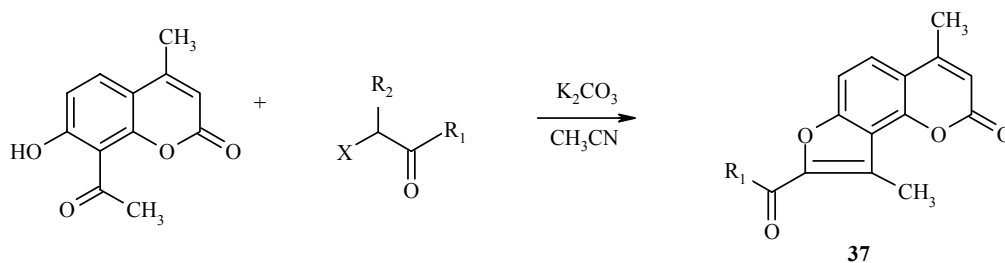
Scheme 13



Ethyl coumarinyloxyacetate **34** is formed in the first step of the reaction. This step is followed by ionization of the oxymethylene group and intramolecular cyclization with successive formation of intermediate **35**. Compound **35** undergoes dehydration to 8-(ethoxycarbonyl)furo[2,3-*h*]coumarin **36** which is an angelicine analog. These transformations provide a convenient way for preparation of furocoumarins with hydrophilic functional groups at the furan ring of the final furoheteroarene.

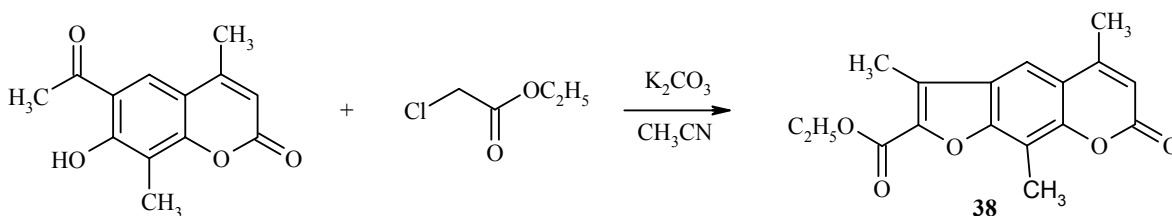
A similar condensation takes place with α -haloketones, as shown in Scheme 14 for the preparation of angelicine derivative **37**.

Scheme 14



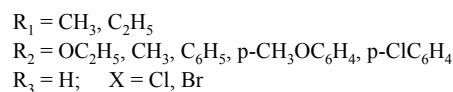
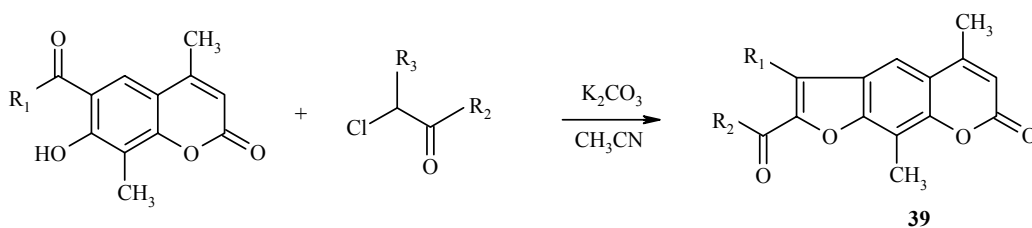
Base-catalyzed condensation of acylhydroxycoumarins with ethyl chloroacetate is also a useful reaction for preparation of psoralen derivatives, as exemplified in Scheme 15 by the synthesis of a substituted psoralen **38**.

Scheme 15



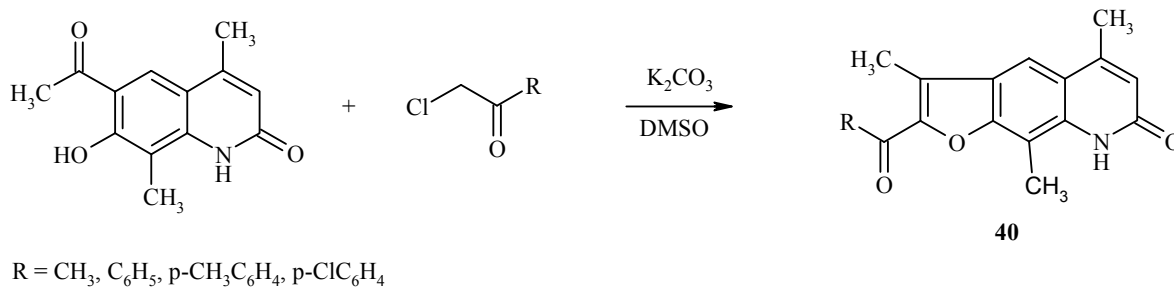
Similar condensations leading to other psoralen derivatives **39** are shown in Scheme 16.

Scheme 16

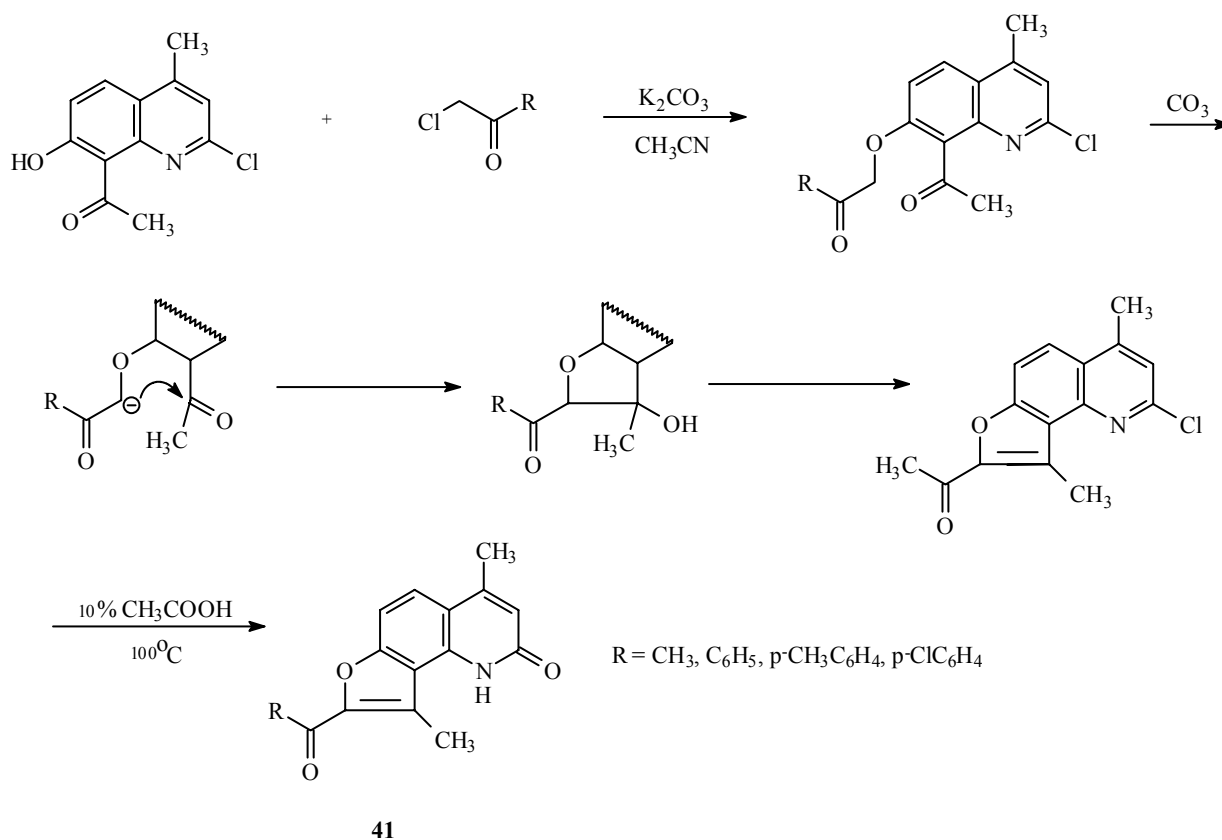


The base-catalyzed condensation of the acyl/hydroxyl functionality with α -halocarbonyl compounds can also be used for the synthesis of other fused furoheteroarenes as well (**23**, **24**). For example, both linear (**40**, Scheme 17) and angular furoquinolines (**41**, Scheme 18) have been prepared by this method.

Scheme 17



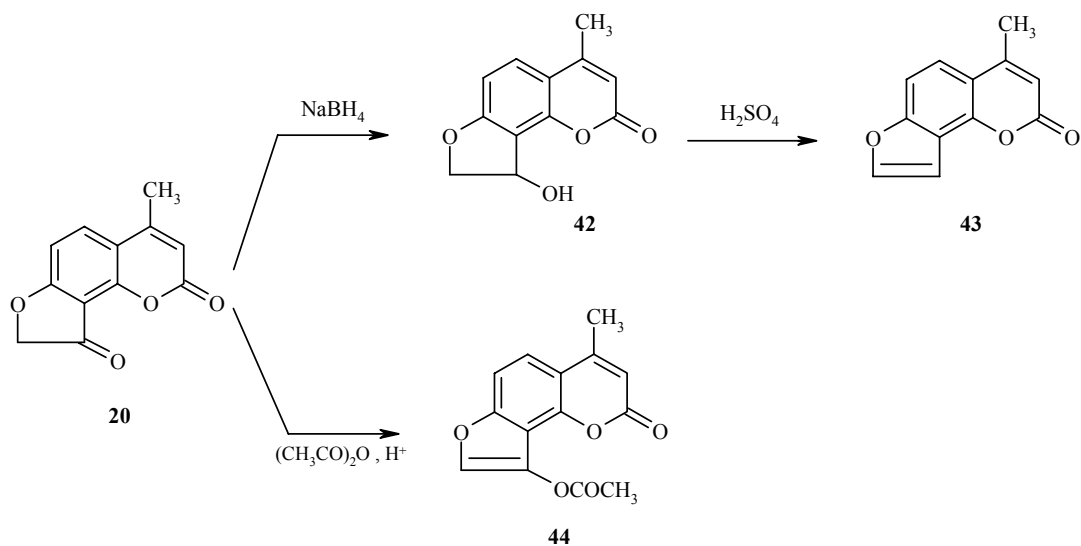
Scheme 18



Dihydrofuroheteroarenes – key intermediates of condensed furoheteroarenes

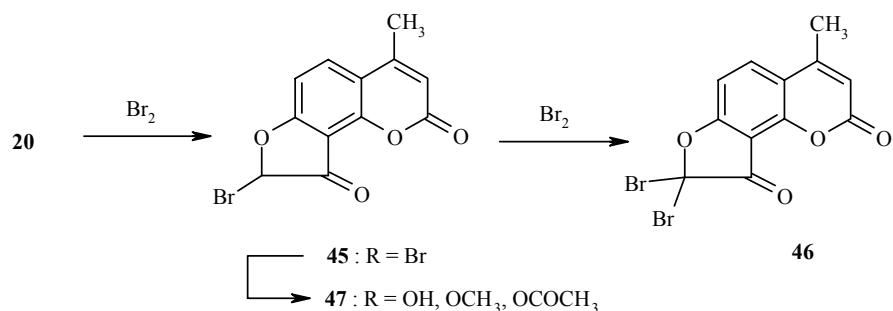
The transformations discussed above proceed with the intermediacy of dihydrofuroheteroarenes (for an example, see **35** in Scheme 13). We have shown that other dihydrofuroheteroarenes can efficiently be aromatized to condensed furoheteroarenes [25]. Two independent examples are shown in Scheme 19. As can be seen, reduction of the keto function in **20** followed by dehydration of the resultant alcohol **42** gives furocoumarin **43**. In the second example, the acetoxy-substituted furocoumarin **44** is produced by acetylation of the enol form of **20**.

Scheme 19



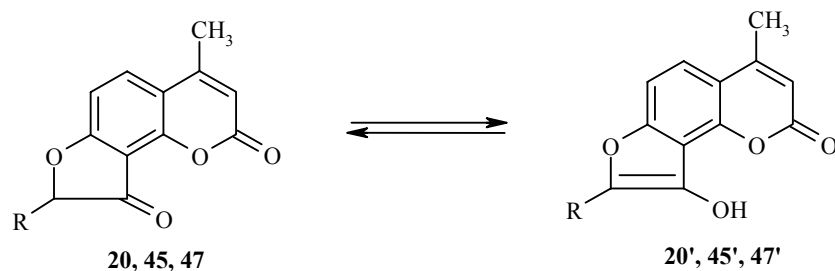
Ketones, such as **20**, are easily halogenated at the position α - to the carbonyl group. Chlorination and bromination have been performed [26]. For example, bromination of **20** to give **46** through the intermediacy of **45** is quantitative in dry dioxane (Scheme 20). Depending on the reaction conditions, compound **45** can also be isolated in high yield. Electrophilic formylation of dihydrofurocoumarinone **20** has been carried out as well. The bromine atom in **45** is highly reactive in nucleophilic displacement reactions (Scheme 20) [26].

Scheme 20



To a large extent, the reactivity of dihydrofurocoumarinones such as **20**, **45** or **47** is based on their keto-enol tautomerism (Scheme 21). Tautomeric transformations of these compounds have been studied by spectral and computational methods [27, 28].

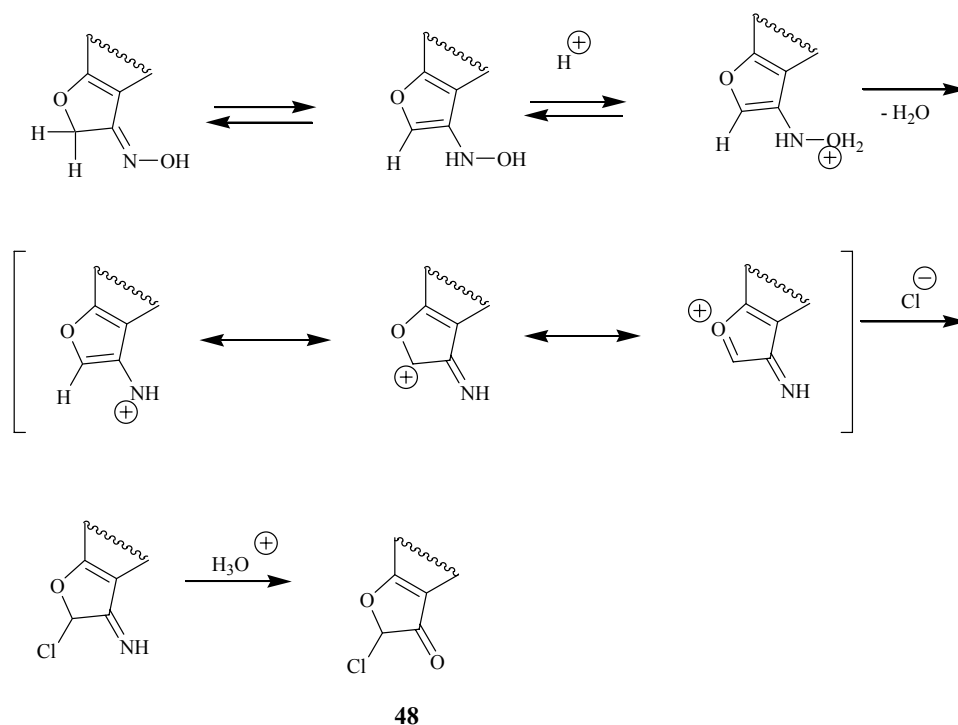
Scheme 21



For example, the longest-wavelength absorption band in the UV spectrum of **20** is at 330 nm in methanol and at 285 nm in carbon tetrachloride. The bands at 330 nm and 285 nm have been assigned to the enol form **20'** and the keto form **20**, respectively. Both semiempirical and nonempirical quantum mechanical calculations are fully consistent with these assignments.

Tautomeric transformations of the oxime of **20** are the key steps of its halogenation in the presence of hydrogen chloride or hydrogen bromide in acetic acid [29-31]. The chlorination which furnishes α -chloroketone **48** is shown in Scheme 22.

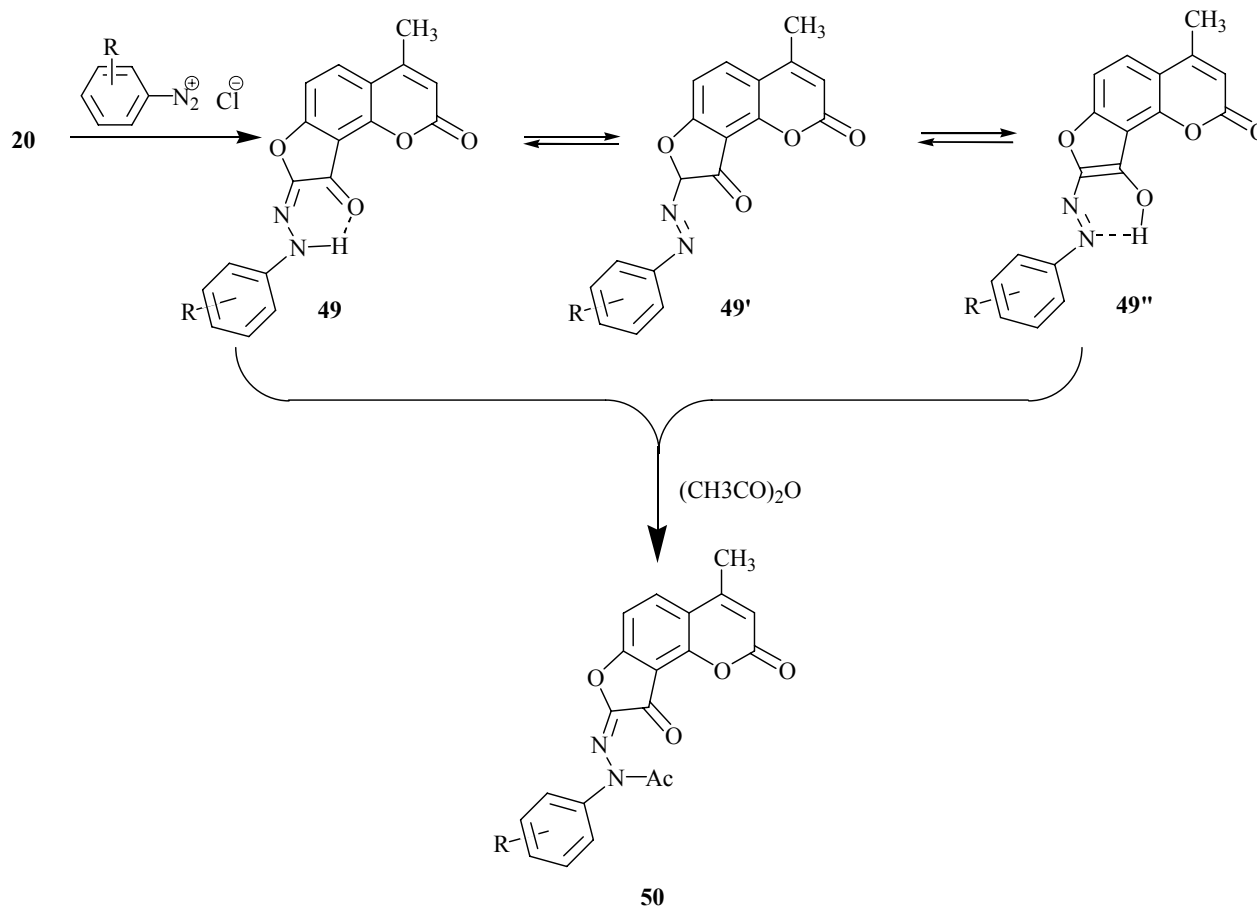
Scheme 22



One of the useful synthetic transformations of dihydrofurocoumarinone **20** is the coupling reaction with arenediazonium salts [32, 33]. Depending on the solvent and pH conditions, the substitution takes place at the 8 or 6 positions. The coupling in an acetic acid-dioxane mixture in the presence of a weak base (pyridine, sodium acetate) involves the 8 position and yields product **49** as a major tautomer

(Scheme 23). This conclusion was derived from spectral studies and supported by quantum mechanical calculations. Acetylation of the tautomeric mixture **49**, **49'** and **49''** gave a single acetyl derivative **50**.

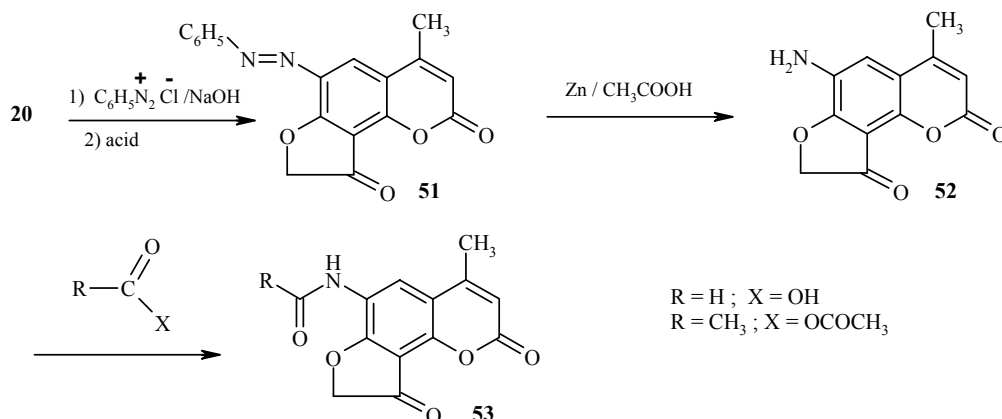
Scheme 23



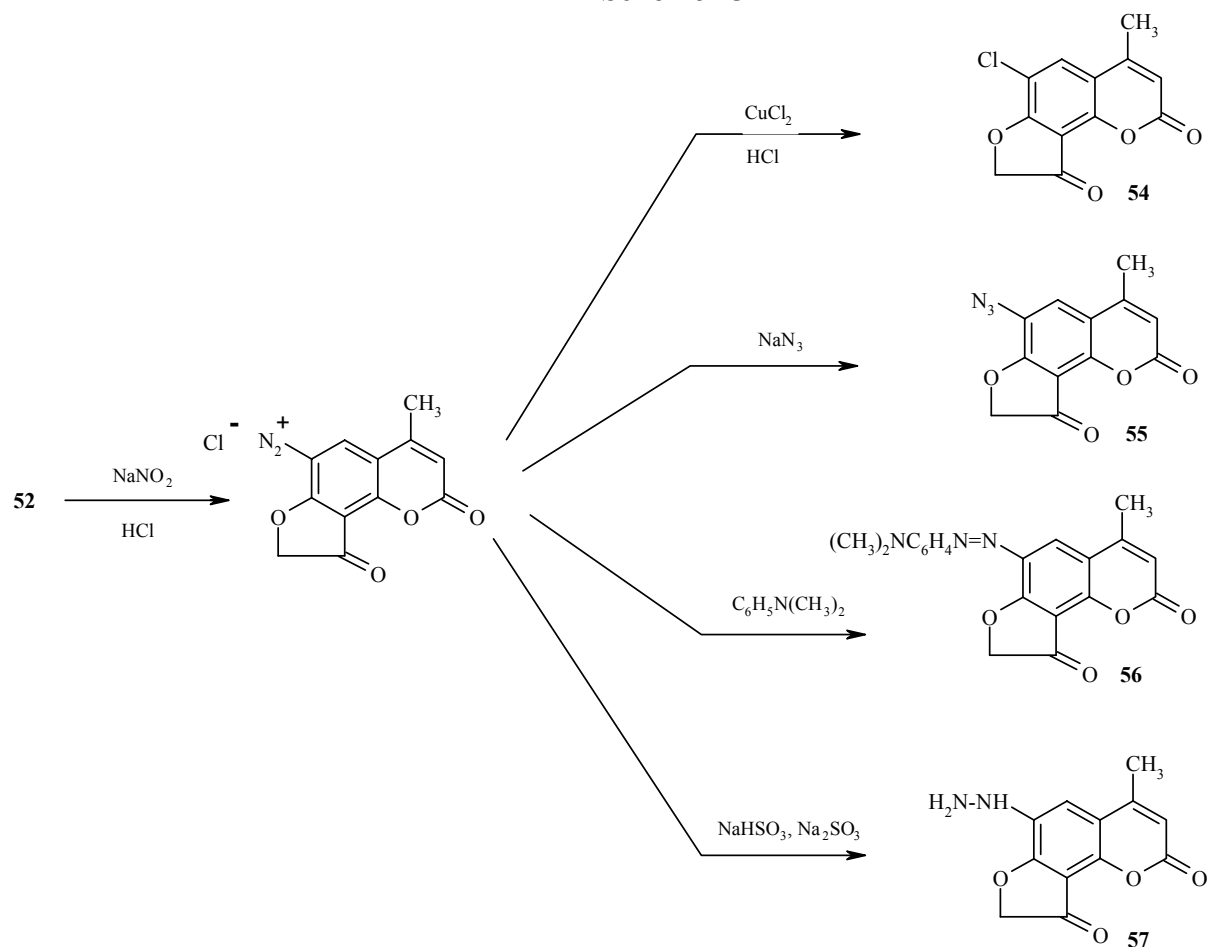
Dihydrofurocoumarinones as intermediates of angelicine analogs

Dihydrofurocoumarinone **21** and analogs are important intermediates in the synthesis of 6-substituted angelicines [34,35]. These intermediate compounds are obtained by coupling of dihydrofurocoumarinones with arenediazonium salts in the presence of sodium hydroxide. In the presence of NaOH the 6-membered lactone undergoes ring opening, thus leaving the 6 position of the coumarin as the only reactive site. The lactone is reinstated upon acidification (Scheme 24). Reduction of the azo-coupled product **51** provides an easy access to the amino derivative **52**.

Scheme 24



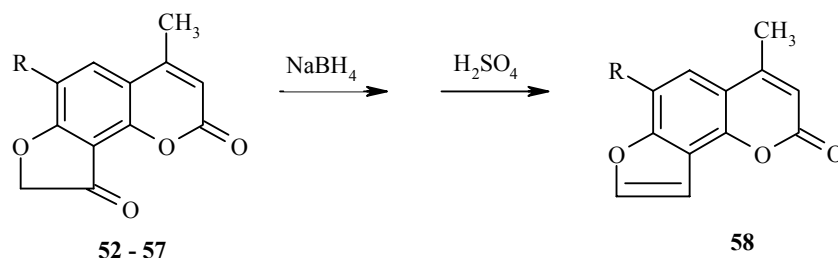
Scheme 25



As expected, 6-aminodihydrofurocoumarinone **52** possesses properties of an aromatic amine. Its transformations to **53** (Scheme 24) and **54-57** (Scheme 25) are provided for illustration.

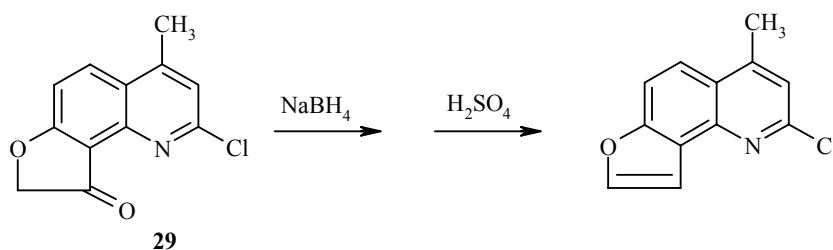
All 6-substituted dihydrofurocoumarinones **52-57** have been transformed into the corresponding 6-substituted angelicines **58**, as shown in Scheme 26.

Scheme 26

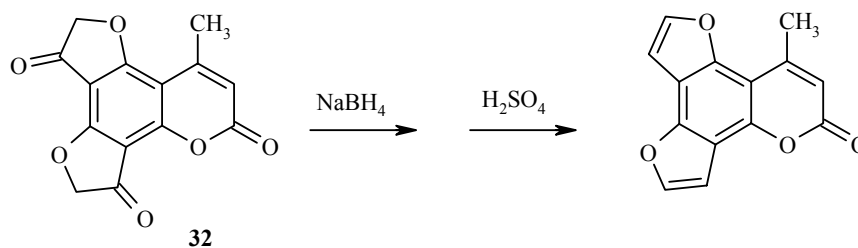


New angelicine analogs have been synthesized from **29** (Scheme 27) and **32** (Scheme 28) by using a similar reduction/dehydration methodology. The furocoumarins are fluorescent in water and strongly fluorescent in isopropanol [36].

Scheme 27



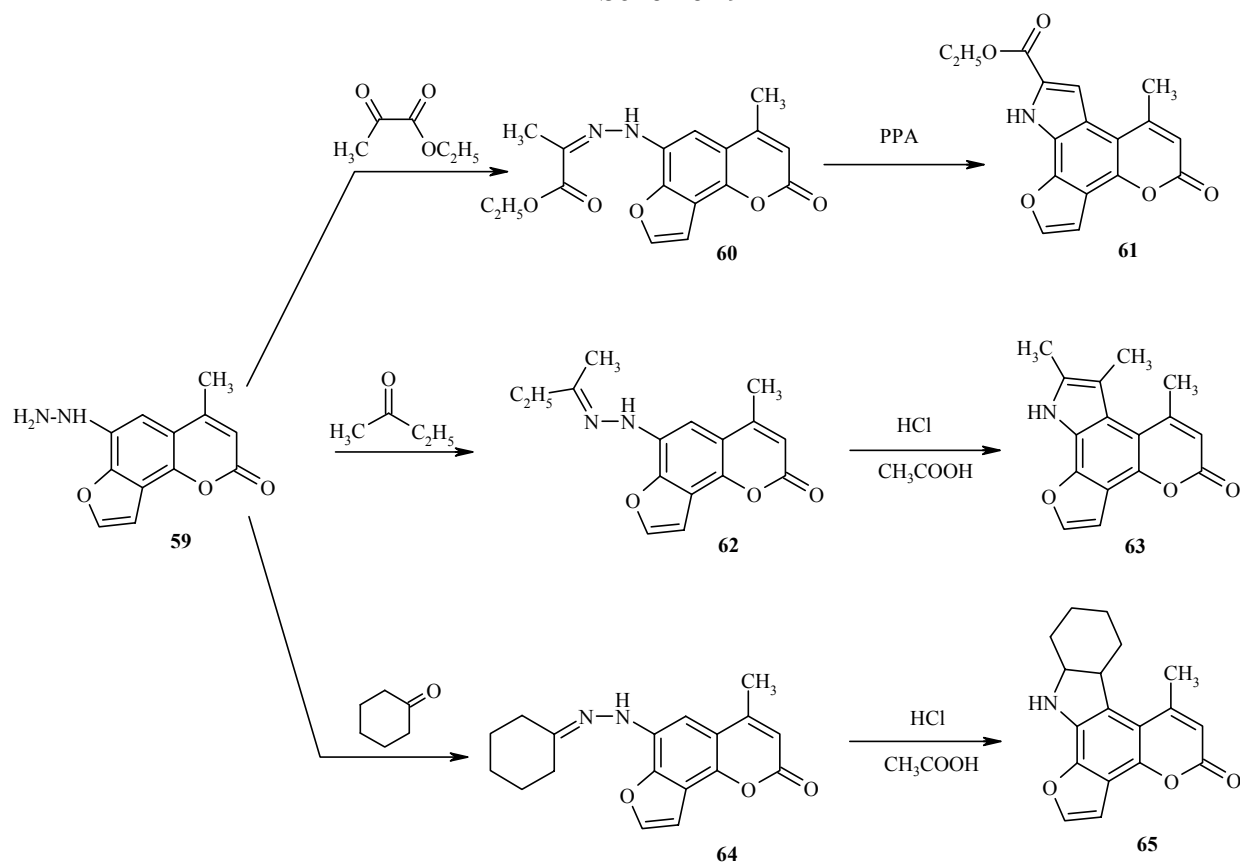
Scheme 28



Pyrrolofurocoumarins

6-Hydrazino substituted furocoumarin **59** (Scheme 29) is obtained in good yield upon diazotization of the amine **58** ($R = \text{NH}_2$) followed by reduction of the resultant diazonium salt with tin dichloride in concentrated hydrochloric acid [34]. As shown in this scheme, the hydrazine **59** is a practical starting material for high-yield syntheses of pyrrole-fused furocoumarins **61**, **63** and **65** through the intermediacy of the respective hydrazones **60**, **62** and **64**. Since these hydrazones are quite unstable compounds, their Fisher cyclization should be performed immediately after their preparation to ensure high yields of the cyclized products.

Scheme 29



A success of the Fisher cyclization of hydrazones depends on the structure of hydrazone, acid catalyst, temperature and other factors. As a rule, strong mineral acids are required for the Fisher reaction. We have successfully used several different acid media such as sulfuric acid – acetic acid, hydrogen chloride – acetic acid, thionyl chloride – ethanol, and polyphosphoric acid.

Under optimized conditions, polyphosphoric acid is the best solvent for cyclization of **60** to **61**. On the other hand, compounds **63** and **65** are obtained in yields greater than 85% when the Fisher cyclization of the respective hydrazones **62** and **64** are conducted in a mixture of hydrochloric and acetic acids.

Conclusions

Fries rearrangement of acyloxyheteroarenes, condensation of acylhydroxyheteroarenes with α -carbonyl compounds and transformations of dihydrofuroheteroarenes provide useful synthetic routes to new photosensitive linear and angular furocoumarins, furoquinolones and furoquinolines as well as to their functional and condensed derivatives.

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