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# Multicomponent design of chromeno[2,3-*b*]pyridine systems

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The review summarizes and systematizes data on the methods for the preparation of chromeno[2,3-*b*]pyridines. Both multicomponent and pseudo-multicomponent synthetic approaches and one-pot transformations based on the reactions of carbonyl compounds, malononitrile or its derivatives, and CH-acids are considered. Examples of the use of various catalysts, microwave and ultrasonic radiation, as well as electric current for the implementation of multicomponent transformations of this type are given. Characteristic features of the course and mechanisms of reactions are discussed. Data on the biological activity of the obtained compounds and on other fields of application of such heterocyclic systems are presented.
The bibliography includes 109 references.

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## 1. Introduction

Heterocyclic compounds constitute more than half of known organic compounds and about 90% of active synthetic pharmaceuticals.[1] For this reason, in design of modern medicinal drugs, heterocyclic compounds are of undoubted priority. Chromeno[2,3-*b*]pyridines, one of the important classes of heterocyclic compounds, have a wide pharmacological potential, since they display antimicrobial,[2,3] antiproliferative,[4] anticancer,[5] antirheumatic,[6] antihistamine,[7] antimyopic,[8] and antiasthmatic[9] activities and are used in some areas of medicine as pharmacological preparations.[10]

Chromeno[2,3-*b*]pyridines relate to the so-called privileged medicinal structures, or scaffolds.[10] There are only a few dozen of such scaffolds, and they cover most of the physiologically active drugs. The scaffold architecture implies the presence of a common heterocyclic backbone, which is often found in molecules that actively interact with

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various biological targets.[11] This backbone is usually responsible for the recognition of a derivative of such a molecule by the target active site. Physicochemical properties of chromene[2,3-*b*]pyridines give rise to their application also as corrosion inhibitors of low-carbon steel.[12]

To obtain chromeno[2,3-*b*]pyridines, both classical (multi-step) and multicomponent methods are used. Multicomponent reactions (MCR) are processes in which several components react in one vessel and form a new compound that comprises most of the atoms that were contained in the starting compounds.[13] Such reactions have been used since the discovery of the multicomponent synthesis of dihydropyridines by Hantzsch[14] and are actively studied at the present time.

Compared to conventional synthesis methods, multicomponent processes have undoubted advantages, among which are:

— efficient consumption of reagents (most of the atoms of the starting compounds are part of the products formed in the reaction),

— reduction in the amount of organic solvents used,

— reduction in the number of steps and manipulations,

— reduction of waste and by-products,

— convergence (simultaneous interaction of more than two reagents to produce one final compound),

— high bond forming index (the number of non-hydrogen bonds formed during one multicomponent transformation).[15]

With the development of the methodology of multicomponent reactions, a simple and fast synthesis of various derivatives (the so-called 'compound libraries') became available by varying the starting components.[16]

The multi-step synthesis of chromeno[2,3-*b*]pyridine and related systems has been known since the middle of the 20th century,[17,18] but new approaches towards such compounds appear to the present time.[19–25] Currently, the development of one-pot † and multicomponent processes is highly relevant.

In this review, multicomponent, pseudo-multicomponent and one-pot procedures for the preparation of various chromene[2,3-*b*]pyridines are considered and systematized, from the very first works to the results of the last decade, which are mainly focused on. The mechanisms of these transformations are discussed, and the pharmacological properties of the known chromeno[2,3-*b*]pyridines and other fields of their application are presented.

The closest topic to this review is the work[10] published in 2011. It considers both classical and multicomponent methods for the synthesis of a wide range of heterocyclic systems, including chromene and chromenopyridine derivatives. Over the past nine years, this field has been extensively developing, and mainly towards the research of multicomponent and one-pot reactions. The latest published reviews[26,27] relate to 2020 and concern multicomponent reactions affording compounds of a similar structure, and do not focus on the synthesis of chromeno[2,3-*b*]pyridines and the reaction mechanisms. In the review article,[28] published in 2014, synthesis of chromeno[2,3-*b*]pyridines is described only partly and covers a limited number of compounds. This review focuses mainly on multicomponent and one-pot approaches to chromeno[2,3-*b*]pyridine systems proposed in the last decade, and the mechanisms of such transformations.

The following abbreviations are used in the review:
B — base,
ESI-MS — electrospray ionization mass spectrometry,
Fu — furyl,
MCR — multicomponent reactions,
MW — microwave radiation,
Naph — naphthyl,
Pip — piperidine,
Py — pyridyl,
rt — room temperature,
Th — thienyl,
US — ultrasonic irradiation.

## 2. Synthesis of 5-C-substituted chromeno[2,3-*b*]pyridines

The synthesis of 5-C-substituted chromeno[2,3-*b*]pyridines is based mainly on condensation, addition and cyclization reactions. The reagents for these transformations are carbonyl compounds in combination with malononitrile or its derivatives, as well as other CH-acids. The synthesis conditions are varied, in many cases the reactions take place under base catalysis, for example, with amines. However, examples of the use of nanocatalysts are known, which make it possible to simplify the work-up of the reaction mixture after the completion of the process, and to reuse the regenerated catalyst. Increased temperature or microwave irradiation leads to the rapid formation of chromene[2,3-*b*]-pyridines. The structure of the resulting product depends on the nature of the carbonyl compound and the presence of additional functional groups in the CH-acid, which can result in the cyclization of the intermediate. Despite the variety of functional groups and, consequently, the reaction pathways, the examples considered below are generally characterized by the preparation of one class of compounds.

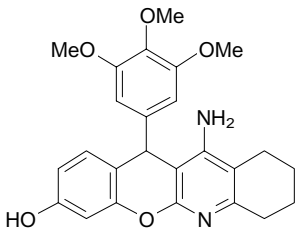
Among the synthesized 5-C-substituted chromeno[2,3-*b*]pyridines, pharmacologically active compounds were found. For example, chromenotacrine (**1**) is an antioxidant and neuroprotective agent that selectively inhibits acetylcholinesterase; these properties are highly relevant for its use in the treatment of Alzheimer's disease.[29]

Chromeno[2,3-*b*]pyridines **2** exhibit an inhibitory effect on mitogen-activated protein kinase MK-2 and suppress the expression of tumour necrosis factor TNF-α,[30] thus offering prospects for the development of drugs for the treatment of inflammatory diseases such as psoriasis and rheumatoid arthritis.

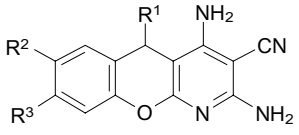
### 2.1. Reactions involving aldehydes, malononitrile, and cyclohexanediones

Cyclohexanediones, entering the multicomponent reactions, can give rise to a variety of products. 1,3-Diketones react

**Structures 1, 2**




**1**




**2**

$R^1 = CH(CN)_2$, Ph; $R^2$ = OMe, Br, OH; $R^3$ = OMe, OH

† One-pot-processes imply a sequence of chemical transformations taking place in a reactor.

both as CH-acids in the case of condensation and as enol compounds resulting in cyclization.

Thus, multicomponent transformation of benzaldehydes, malononitrile dimer and cyclohexane-1,3-dione (or dimedone) under microwave (MW) irradiation furnished tetrahydro-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **3** (Scheme 1).[31] The reaction proceeds in boiling ethanol in the presence of triethylamine (1 equiv.) for 16 – 20 min.

The mechanism of formation of tetrahydro-5*H*-chromeno[2,3-*b*]pyridines **3** is illustrated in Scheme 1. The reaction starts from the Knoevenagel condensation of aldehyde with malononitrile under the action of triethylamine. As a result, unsaturated adduct **4** is formed, entering the Michael addition with 1,3-diketone. Further transformations lead to intermediate **5**. Intermediate **5** undergoes two successive intramolecular Pinner cyclizations, followed by the formation of tetrahydro-5*H*-chromeno[2,3-*b*]pyridines **3** as a result of tautomeric transformations of imines **6**.

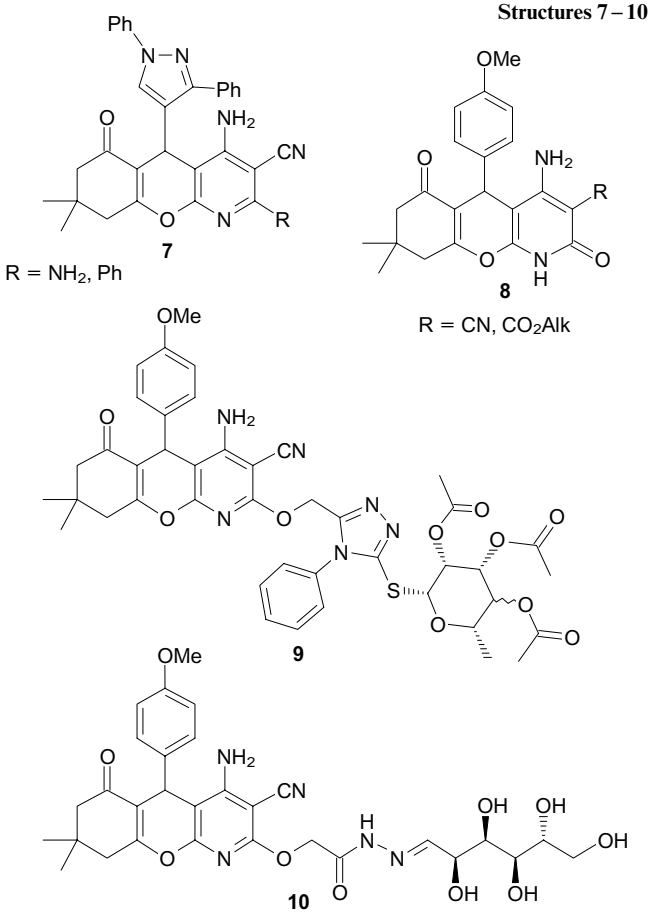
Less laborious procedure requiring no microwave irradiation is based on the multicomponent reaction between benzaldehydes, malononitrile and dimedone, taking place in the presence of triethylamine in boiling n-propanol.[32] However, the yields of the resulting products **3** are slightly decreased (down 70% – 85%).

Several representatives of 6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]pyridines show biological activity, most often antimicrobial one.[33 – 35] So, compounds **7** have antibacterial action, especially against gram-negative bacteria, and antifungal activity.[33] Chromeno[2,3-*b*]pyridines **8** – **10** well inhibit the growth of both gram-negative and gram-positive bacteria.[34, 35]

When the second carbonyl group is present in the aromatic aldehyde, the multicomponent reaction can be directed on each of them. Thus, the pseudo-five-component reaction produced bis-heterocyclic tetrahydrochromeno[2,3-*b*]pyridine-3-carbonitriles **11** and **12**, in which two parts of a molecule were tethered to each other by a bridging spacer (Scheme 2).[36] The reaction between bis-aldehydes, malononitrile, and dimedone proceeds in 5 h in boiling ethanol and furnishes products in 85% – 92% yields. For catalysis, a two-fold excess of piperidine (Pip) was used.

The mechanism of this process is similar to that of multicomponent transformations of compounds bearing one aldehyde functionality (see Scheme 1), except that the reaction proceeds on each carbonyl group of a bis-aldehyde. In the case of an aromatic aldehyde with a short bridge in the *ortho*-position to the carbonyl group, the reaction results in the formation of 2-oxochromeno[2,3-*b*]pyridine-3-carbonitriles **12**. In the authors' opinion, chromeno[2,3-*b*]pyridines **12** are formed *via* an imine hydrolysis (see intermediate **6** in Scheme 1), which occurs instead of the tautomeric transformation following the second cyclization, and the steric crowding of the molecule favours hydrolysis.

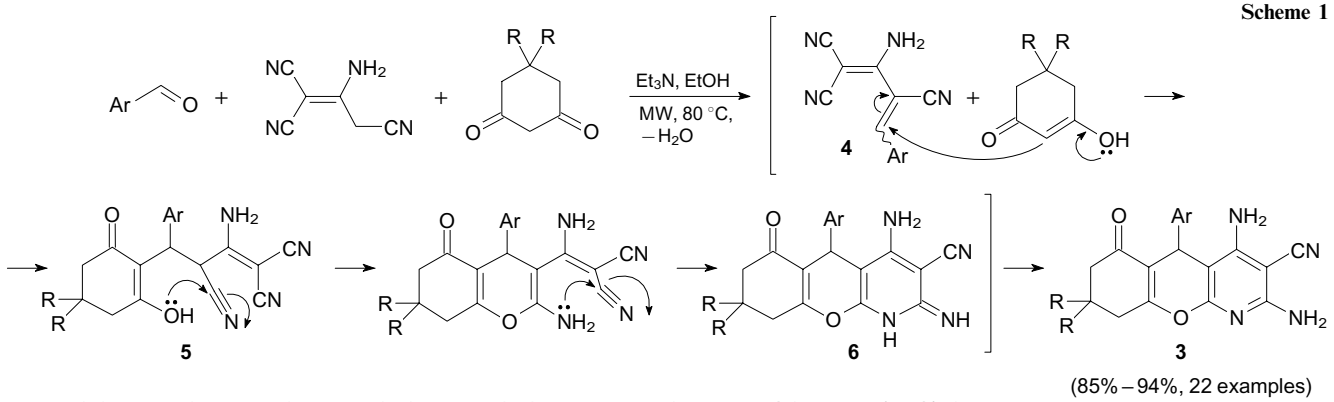
**Structures 7 – 10**




## 2.2. Reactions involving aldehydes, malononitrile dimer, and phenol derivatives

The hydroxyvinyl moiety of resorcinol and naphthols as well as carbazoles and indoles bearing the hydroxyl group is similar in structure to the enol tautomer of cyclohexane-1,3-dione. Such compounds enter cyclization reactions on the α-position to the hydroxyl group and the subsequent cyclization on the hydroxyl group itself.

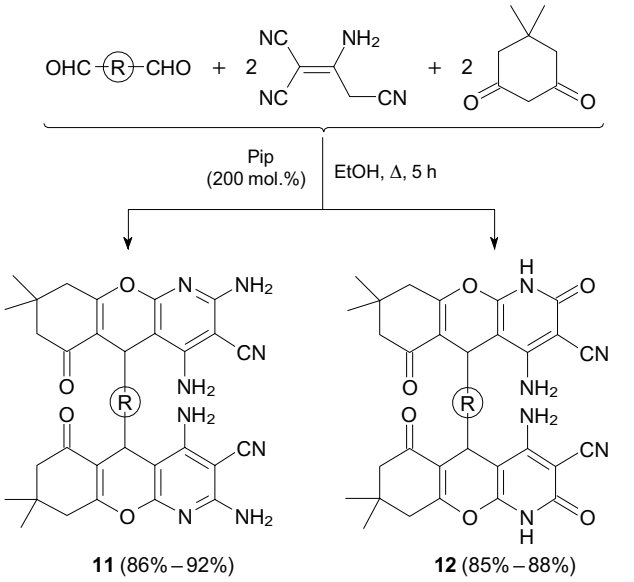
**Scheme 1**




(85% – 94%, 22 examples)

Ar = 4-$ClC_6H_4$, 4-$FC_6H_4$, 4-$BrC_6H_4$, 3,4-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 2,3-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-Th; R = H, Me; Th is thienyl

**Scheme 2**




R for **11**: $C_6H_4O(CH_2)_3OC_6H_4$ (*para*-isomer),
$C_6H_4O(CH_2)_4OC_6H_4$ (*ortho*-isomer),
5-$BrC_6H_3O(CH_2)_4O$(5-$BrC_6H_3$) (*ortho*-isomer),
$C_6H_4OCH_2C_6H_4CH_2OC_6H_4$ (*para*-isomer, *para*-isomer),
$C_6H_4OCH_2C_6H_4CH_2OC_6H_4$ (*para*-isomer, *ortho*-isomer);

R for **12**: $C_6H_4O(CH_2)_2OC_6H_4$ (*ortho*-isomer),
5-$BrC_6H_3O(CH_2)_2O$(5-$BrC_6H_3$) (*ortho*-isomer),
$C_6H_4O(CH_2)_3OC_6H_4$ (*ortho*-isomer)

Thus, the reaction of aliphatic aldehydes, malononitrile dimer, and resorcinol proceeds in an isopropanol – water (1 : 4 v/v) mixture at 40 °C.[37] Synthesis of 8-hydroxy-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **13** is accomplished in 4 h under catalysis of an equimolar amount of potassium hydroxide, the yields of the products are 37% – 65% (Scheme 3).

The similar reaction involving aromatic aldehydes and 2,3-dihydroxynaphthalene occurs in the absence of a solvent with less (10 mol.%) amount of a catalyst (guanidine hydrochloride) (see Scheme 3).[38] The process is completed in just 40 – 120 min on heating up to 100 °C; the yields of the resulting 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridine-10-carbonitriles **14** are 75% – 88%.

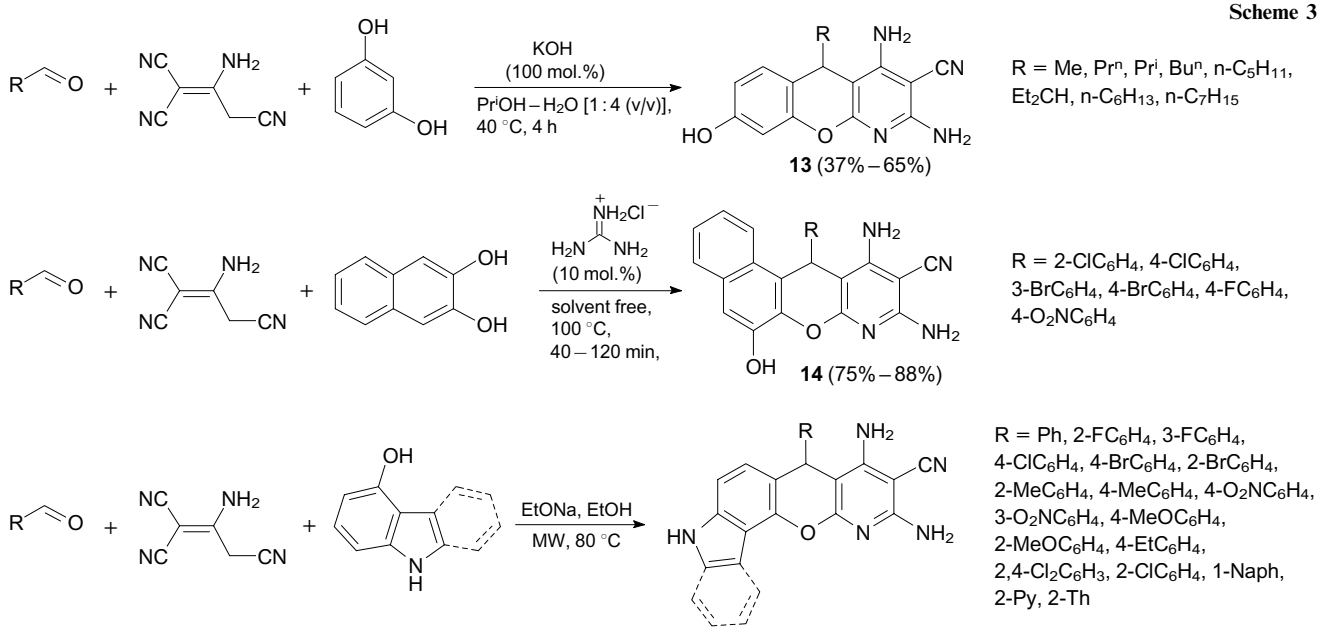
Reactions of this type also occur under microwave irradiation (see Scheme 3).[39] Thus, multicomponent transformation of benzaldehydes, malononitrile dimer, and carbazoles with OH group in the 5-position gives 5,8-dihydropyrido[3′,2′:5,6]pyrano[3,2-*c*]carbazoles **15** on simultaneous irradiating and heating under reflux in ethanol with sodium ethoxide. The same reaction with OH-indoles furnishes 3,6-dihydropyrido[3′,2′:5,6]pyrano[2,3-*e*]indoles **16**. Note that the yields of compounds **15** containing a carbazole moiety are slightly higher than those of compounds **16** with an indole moiety.

Despite the application of microwave irradiation and heating, this method uses an equimolar amount of a catalyst such as sodium ethoxide. On the other hand, apart from the difference in the reactivity of the hydroxyl group and the methylene fragment in the α-position in the transformations involving resorcinol and indoles, this method can be considered quite rapid since the reaction time for compounds **15** and **16** is 10 – 18 min, which is 2 – 20 times faster than for compounds **13** and **14**.

The sodium salt of malononitrile dimer reacts with aldehydes and 1-naphthol in boiling ethanol for 1 h (Scheme 4).[40] The yields of 7*H*-benzo[7,8]chromeno[2,3-*b*]-pyridine-9-carbonitriles **17** with aromatic substituents are 37% – 60%, while those of aliphatic derivatives are slightly lower — 12% – 62%.

Mechanisms of all the above processes are similar, therefore, they can be illustrated by an example of the Knoevenagel reaction between aldehydes, malononitrile dimer sodium salt, and 1-naphthol (see Scheme 4). In the first step, the Knoevenagel condensation of aldehyde and malononitrile dimer occurs with the elimination of a water

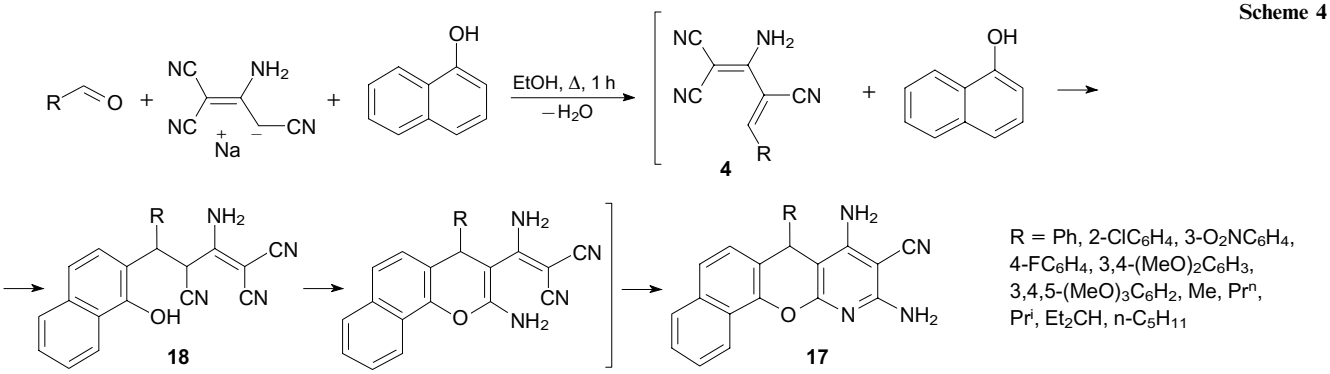
**Scheme 3**




**15** (carbazole derivatives, 75% – 85%),
**16** (indole derivatives, 67% – 85%)

Naph is naphthyl, Py is pyridyl

**Scheme 4**




molecule. Then, the electron-deficient adduct **4** enters the Michael reaction with 1-naphthol. The resulting intermediate **18** undergoes tautomeric transformations and the intramolecular Pinner cyclization to afford chromeno[2,3-*b*]pyridines **17**.

### 2.3. Reactions involving salicylaldehydes, malononitrile dimer, and five-membered heterocyclic CH-acids

In 2015, an active study of multicomponent reactions of salicylaldehydes, malononitrile dimer, and CH-acids began, with the focus being primarily on five-membered heterocyclic CH-acids.

The first publication in this field was the article[41] concerning the three-component synthesis of 5-isoxazolyl-5*H*-chromeno[2,3-*b*]pyridines **19a – g** from salicylaldehyde derivatives, malononitrile dimer, and 3-phenylisoxazol-5(4*H*)-one (Scheme 5). The reaction was carried out in boiling pyridine for 4 h with the product yields being 50% – 74%. In this process, pyridine acted both as a solvent and a catalyst.

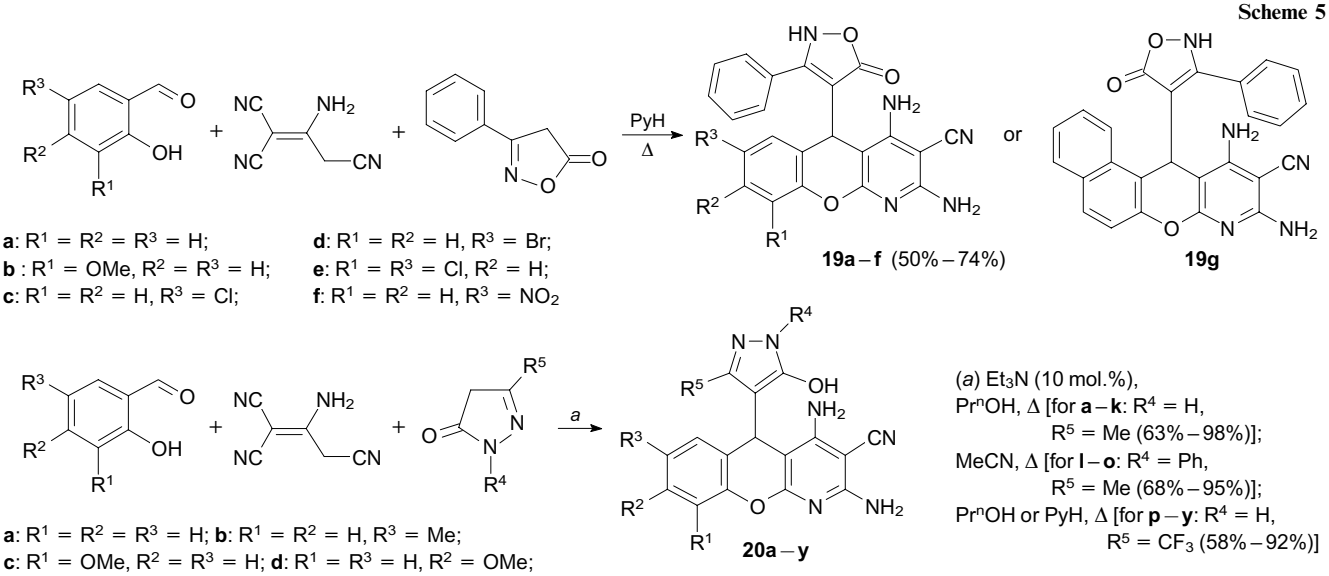
In 2018, various pyrazol-3-ones were introduced into a multicomponent reaction with salicylaldehydes and malononitrile dimer (see Scheme 5). Three-component transformation of salicylaldehydes, malononitrile dimer and 5-methylpyrazol-3-one was accomplished under catalysis with triethylamine (10 mol.%) in the minimum amount of boiling n-propanol for 1 h.[42,43] The authors called this method of carrying out the reaction 'on-solvent' — by analogy with 'on-water'-processes. The yields of 5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **20a – k** ($R^4$ = H, $R^5$ = Me) ranged from 63% to 98%.

The same reaction with 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (see Scheme 5) proceeds more effectively in the minimum amount of acetonitrile.[43] 5*H*-Chromeno[2,3-*b*]pyridine-3-carbonitriles **20l – o** were obtained in almost similar yields, which the authors attributed to the higher solubility of the starting pyrazolone in acetonitrile.

In the reaction of salicylaldehydes, malononitrile dimer, and trifluoromethyl derivative of pyrazolone ($R^4$ = H, $R^5$ = $CF_3$, see Scheme 5), chromeno[2,3-*b*]pyridines **20p – y** are formed.[44] The process was performed under catalysis with triethylamine and on heating under reflux in n-propanol for 4 h to give chromeno[2,3-*b*]pyridines **20p – y** in the yields from 58% to 92%. The same transformation being carried out in boiling pyridine afforded the products **20p – y** in 46% – 90% yields.

The considered methods for the synthesis of chromeno[2,3-*b*]pyridines **19**, **20** involve the use of simple equip-

**Scheme 5**




**a**: $R^1$ = $R^2$ = $R^3$ = H; **b**: $R^1$ = $R^2$ = H, $R^3$ = Me;
**c**: $R^1$ = OMe, $R^2$ = $R^3$ = H; **d**: $R^1$ = $R^3$ = H, $R^2$ = OMe;
**e**: $R^1$ = $R^3$ = H, $R^2$ = OH; **f**: $R^1$ = $R^3$ = H, $R^2$ = $NEt_2$;
**g**: $R^1$ = $R^2$ = H, $R^3$ = Cl; **h**: $R^1$ = $R^2$ = H, $R^3$ = Br; **i**: $R^1$ = $R^3$ = Cl, $R^2$ = H; **j**: $R^1$ = OMe, $R^2$ = H, $R^3$ = Br; **k**: $R^1$ = $R^2$ = H, $R^3$ = $NO_2$;
**l**: $R^1$ = $R^2$ = $R^3$ = H; **m**: $R^1$ = $R^3$ = H, $R^2$ = OMe; **n**: $R^1$ = $R^2$ = H, $R^3$ = Cl; **o**: $R^1$ = $R^2$ = H, $R^3$ = $NO_2$; **p**: $R^1$ = $R^2$ = $R^3$ = H;
**q**: $R^1$ = $R^2$ = H, $R^3$ = Me; **r**: $R^1$ = OMe, $R^2$ = $R^3$ = H; **s**: $R^2$ = OMe, $R^1$ = $R^3$ = H; **t**: $R^1$ = $R^2$ = H, $R^3$ = Cl; **u**: $R^1$ = $R^2$ = H, $R^3$ = Br;
**v**: $R^1$ = OMe, $R^2$ = H, $R^3$ = Br; **w**: $R^1$ = Cl, $R^2$ = H, $R^3$ = Cl; **y**: $R^1$ = I, $R^2$ = H, $R^3$ = I

ment; in most cases, the final compounds are formed as a precipitate directly during the reaction or after cooling the reaction mixture, they are isolated by filtration and do not require purification by chromatographic methods. However, the fact that pyridine is used as a solvent and catalyst in the synthesis of compounds **19** should encourage the development of more environmentally friendly methods corresponding to the 'green principles'.

### 2.4. Reactions involving salicylaldehydes, malononitrile dimer, and cyclic CH-acids containing more than 5 atoms in a ring

In continuation of the studies of the transformations discussed above, the reactions of six-membered heterocyclic CH-acids with salicylaldehydes and malononitrile dimer were investigated. Among heterocyclic acids studied, 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxy-6-methylpyridin-2(1*H*)-ones, and their bicyclic analogues such as 4-hydroxyquinolines, as well as 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid) can be mentioned (Scheme 6).

Heating the corresponding reactants under reflux in a pyridine – ethanol mixture (1 : 3 v/v) for 4 h furnishes chromeno[2,3-*b*]pyridines **21** (X = O) in moderate yields,[45] and when the oxygen atom is replaced with nitrogen in the CH-acid and the number of rings in this component is retained, 5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5*H*-chromeno[2,3-*b*]pyridines **22** are formed in higher yields.[46] It should be noted that, in the case of bicyclic CH-acids, the yields of products **22** remain almost at the same level, despite the 2-fold reduction in the reaction time.[47]

In this method, pyridine acts as both a catalyst and a co-solvent. The authors scaled the reaction by a factor of 10 (from 1 to 10 mmol), but did not reveal a significant change in the yields of chromeno[2,3-*b*]pyridines **22**.[46]

Structurally, kojic acid is a more complex heterocyclic moiety in comparison with other CH-acids. It comprises two OH groups and two vinyl moieties potentially capable of displaying CH-acidity. However, the multicomponent reaction of salicylaldehydes, malononitrile dimer, and kojic acid affords only one reaction product, namely, chromeno[2,3-*b*]pyridines **23** (see Scheme 6).[48] Compounds **23** are synthesized in boiling isopropanol for 2 h in the presence of 10 mol.% of potassium fluoride.

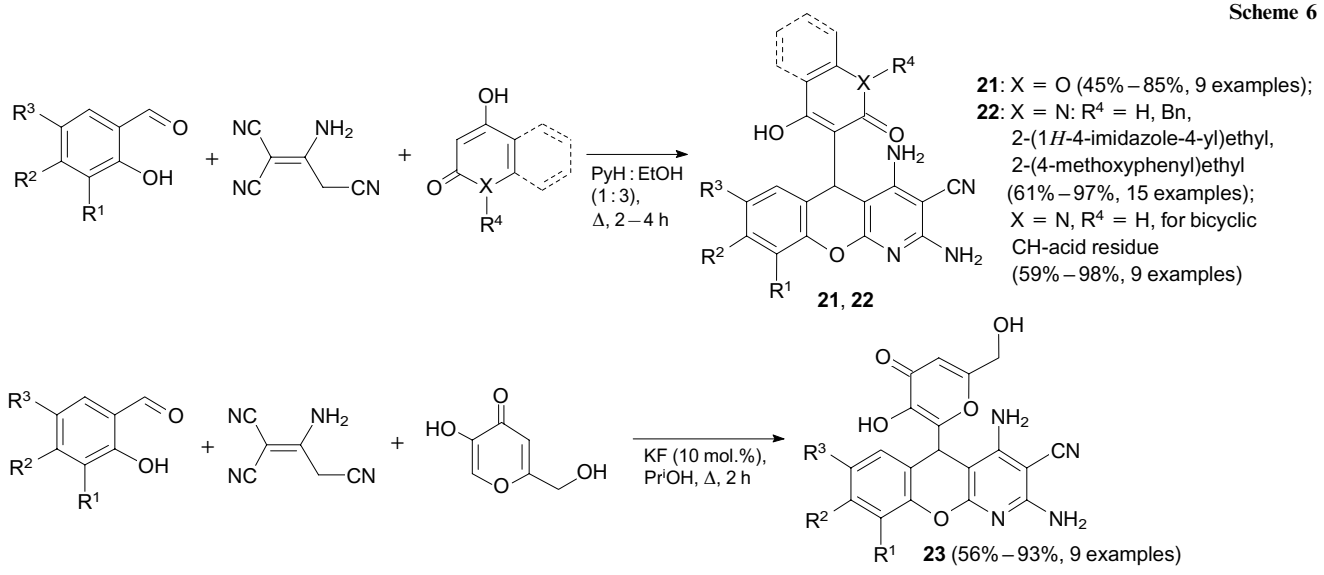
The mechanism of the transformations described in this Section was studied by the example of the reaction of salicylaldehyde, malononitrile dimer, and quinolinones using real-time NMR monitoring (Scheme 7).[47] In the first step, as a result of the Knoevenagel condensation of salicylaldehyde and malononitrile dimer, adduct **24** is formed, which cyclizes to chromene **25**.[47,49] Then, under the action of a base, the Michael addition of quinolinone to chromene **25** occurs, and it can proceed independently of the first step, for example, in a multistep process.[47] As a result of the Michael addition, anion **26** is formed, which successively undergoes tautomeric transformation, the Pinner cyclization, and final tautomerization to generate anion **27**. Protonation of anion **27** yields 5*H*-chromeno[2,3-*b*]pyridines **22**.

In contrast to the above reactions involving benzaldehyde, in the transformations of malononitrile dimer and 1,3-diketones, the phenolic hydroxyl group of salicylaldehyde is more prone to cyclization than the hydroxyl group of cyclohexane-1,3-dione in the enol form (see Scheme 1). For this reason, the multicomponent transformation of substituted salicylaldehydes, malononitrile dimer and cyclic 1,3-diketones proceeds with the formation of 5-(2-hydroxy-6-oxocyclohexyl)-5*H*-chromeno[2,3-*b*]pyridines **28a – l** (Scheme 8).[50] The reaction proceeds in refluxing acetonitrile in the presence of 10 mol.% triethylamine for 2 h. Under these conditions, chromeno[4,3-*b*]pyridines can also be synthesized.[51]

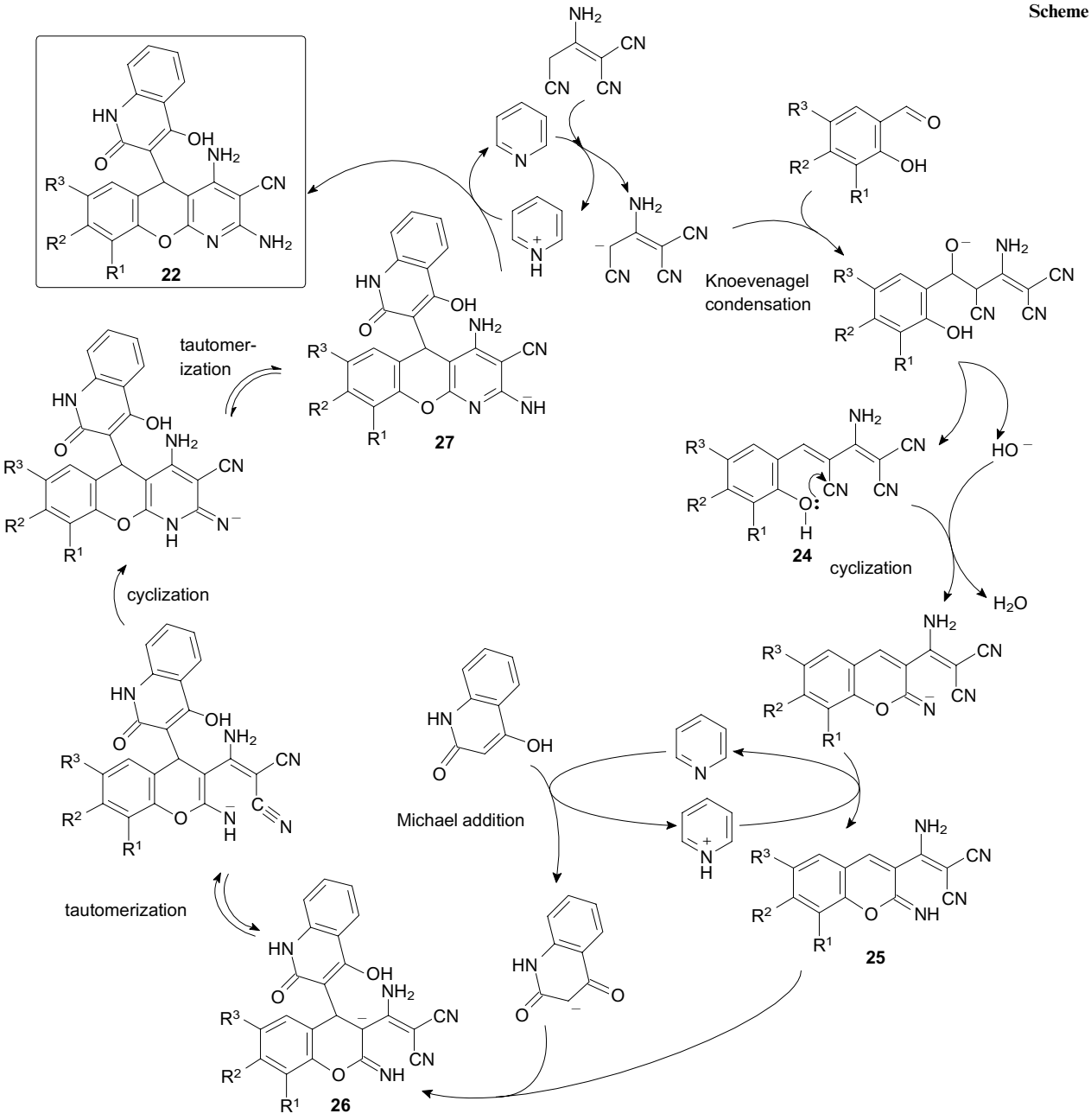
Theoretical evaluation of the inhibitory activity of 5*H*-chromeno[2,3-*b*]pyridines **28** against protein MK-2 has been performed.[52] In molecular modelling, 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridine-5-yl)malononitrile (**29a**), which has a known inhibitory activity against MK-2 protein, was chosen as a reference: its half maximal inhibitory concentration ($IC_{50}$) is 1.94 mol $L^{-1}$.[30] According to the modeling results, the calculated interaction energy of chromeno[2,3-*b*]pyridines **28e**,**g** with MK-2 is −8.93 and −10.00 kcal $mol^{-1}$, which is higher than the analogous parameter for the reference compound **29a** (−8.5 kcal $mol^{-1}$). Therefore, these chromeno[2,3-*b*]pyridines can be considered potential candidates for *in vitro* studies of their inhibitory activity.

In 2017, 5*H*-chromeno[2,3-*b*]pyridines **28a**,**c – i**,**k – n** were synthesized *via* the pseudo-four-component reaction

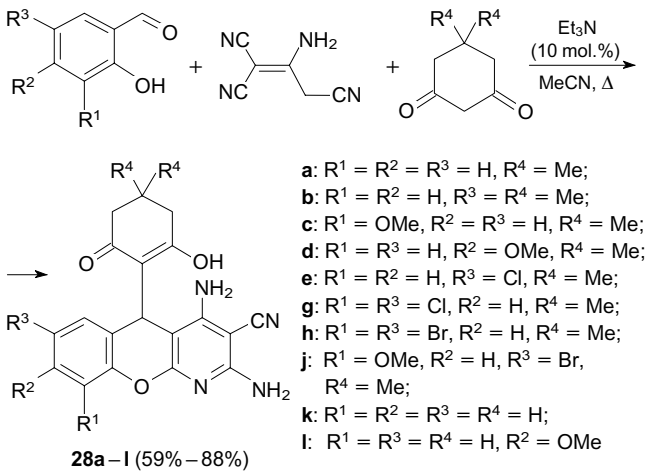
**Scheme 6**



**Scheme 7**



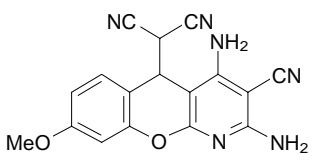

**Scheme 8**




**a**: $R^1 = R^2 = R^3 = H$, $R^4 = Me$;
**b**: $R^1 = R^2 = H$, $R^3 = R^4 = Me$;
**c**: $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = Me$;
**d**: $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = Me$;
**e**: $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = Me$;
**g**: $R^1 = R^3 = Cl$, $R^2 = H$, $R^4 = Me$;
**h**: $R^1 = R^3 = Br$, $R^2 = H$, $R^4 = Me$;
**j**: $R^1 = OMe$, $R^2 = H$, $R^3 = Br$, $R^4 = Me$;
**k**: $R^1 = R^2 = R^3 = R^4 = H$;
**l**: $R^1 = R^3 = R^4 = H$, $R^2 = OMe$

**28a – l** (59% – 88%)

**Structure 29a**

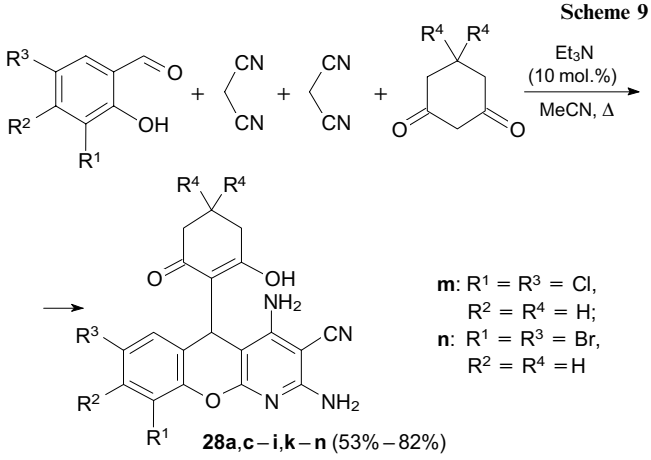


**29a**

between salicylaldehydes, malononitrile taken in the amount of 2 equiv., and cyclic 1,3-diketones (Scheme 9).[52] The process was carried out under the same conditions as in the case of malononitrile dimer, that is on heating under reflux in the presence of triethylamine in acetonitrile for 2 h; the yields ranged from 53% to 82%.

Similar multicomponent approach was applied to synthesize the above 5*H*-chromeno[2,3-*b*]pyridines **22** under reflux in pyridine (10 examples, 40% – 97% yields).[53]

**Scheme 9**




Thus, the use of two equivalents of malononitrile instead of malononitrile dimer in some cases leads to the same products with a slight decrease in their yields.

The mechanism of transformation of salicylaldehydes with the participation of malononitrile, taken in an amount of two equivalents, and cyclic CH-acids is common for pseudo-four-component reactions (see Scheme 13 in Section 2.5, instead of naphthol, the corresponding CH-acid enters the Michael reaction).

## 2.5. Reactions involving salicylaldehyde, malononitrile, and phenol derivatives

One of the interesting types of multicomponent reactions are pseudo-multicomponent transformations. In the course of such processes, the same reactant becomes part of different fragments of the final structure.

An example is the pseudo-four-component method for the preparation of chromeno[2,3-*b*]pyridines using two equivalents of malononitrile (Scheme 10). Accordingly, compounds **30**–**32** are formed in the reaction between substituted salicylaldehydes, malononitrile, taken in an amount of two equiv., and mono- and dihydroxy derivatives of naphthalene (see Scheme 10, conditions *a*).

Despite the significant steric crowding of the final products **30**–**32**, in the absence of solvent and catalyst the process is completed in 20–30 min. Nevertheless, its implementation requires heating to 110 °C, and the yields of the final compounds after purification using column chromatography are 80%–97%.[54]

The synthesis of compounds **30a**,**b**,**f** in n-propanol in the presence of triethylamine (conditions *b* in Scheme 10), providing similar yields of the products (92%–97%), has been reported. To carry out this process, irradiation in a microwave reactor at 300 W and temperature 150 °C is required.[55] Under the same conditions, the reaction with aminophenols takes place (yields 80%–92%, 9 examples).

The mechanism of these reactions considered by the example of the reaction between salicylaldehyde, malononitrile (2 equiv.), and 1-naphthol is illustrated in Scheme 11. In the authors' opinion,[55] the process begins with the Knoevenagel condensation of salicylaldehyde and malononitrile. Further, adduct **33a** undergoes subsequent cyclization to intermediate **34** (the Pinner reaction). Naphthol enters the Michael addition reaction with iminocoumarin **34** to give chromene **35**. Nucleophilic attack of the second malononitrile molecule at the cyano group of intermediate **35** and the subsequent Pinner intramolecular aminocyclization of nitrile **36** lead to the formation of chromeno[2,3-*b*]-pyridine **30a**.

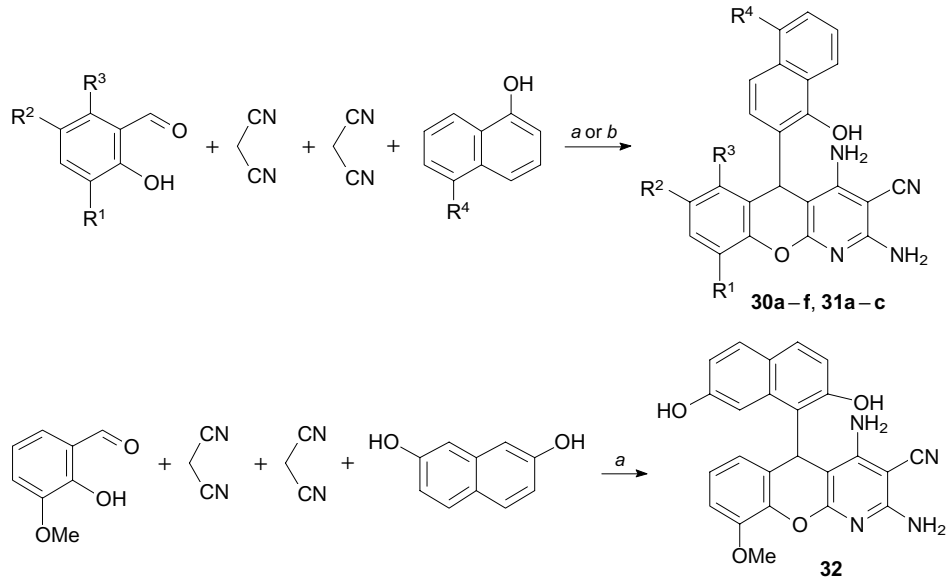
*In vitro* biological tests of chromeno[2,3-*b*]pyridines **30** have shown a high potential for the use of these compounds as anti-inflammatory agents ($IC_{50}$ = 6.9–65.7 mol $L^{-1}$, determined by NO release).[55] Compound **30a** proved to be the most active, being superior to ibuprofen, which is a well-known anti-inflammatory, analgesic and antipyretic drug, in activity during tests.[55]

## 2.6. Pseudo-four-component reactions involving salicylaldehydes and malononitrile

Chromeno[2,3-*b*]pyridines are formed as a result of multicomponent transformations involving only two starting compounds, namely, salicylaldehydes and malononitrile, and the structure of the product comprises three molecules of malononitrile.

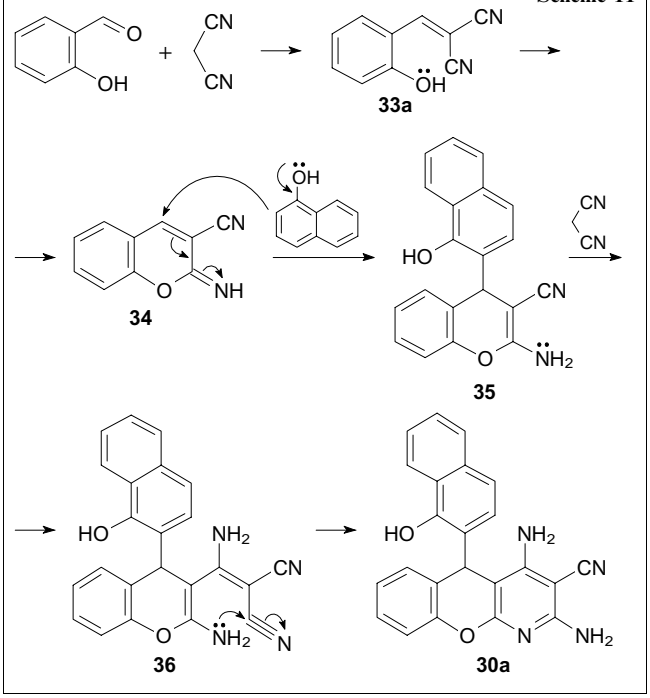
In 2014, pseudo-four-component electrochemical procedure was developed to obtain substituted chromeno[2,3-*b*]-pyridines **29b**–**h** (Scheme 12).[56] The advantage of the proposed method is the use of an undivided cell. The

**Scheme 10**

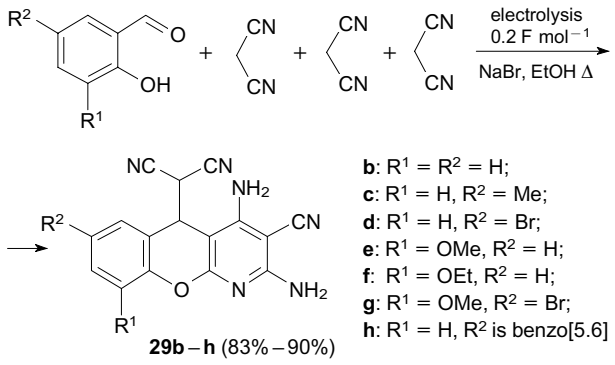



**30a**: $R^1 = R^2 = R^3 = R^4 = H$;
**30b**: $R^1$ = OMe, $R^2 = R^3 = R^4 = H$;
**30c**: $R^1$ = OH; $R^2 = R^3 = R^4 = H$;
**30d**: $R^1 = R^3 = R^4 = H$, $R^2$ = Br;
**30e**: $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$;
**30f**: $R^1 = R^4 = H$, $R^2 - R^3$ is benzo;
**31a**: $R^1 = R^2 = R^3 = H$, $R^4$ = OH;
**31b**: $R^1 = R^4$ = OH, $R^2 = R^3 = H$;
**31c**: $R^1 = R^3 = H$, $R^2$ = Br, $R^4$ = OH

**Scheme 11**



**Scheme 12**



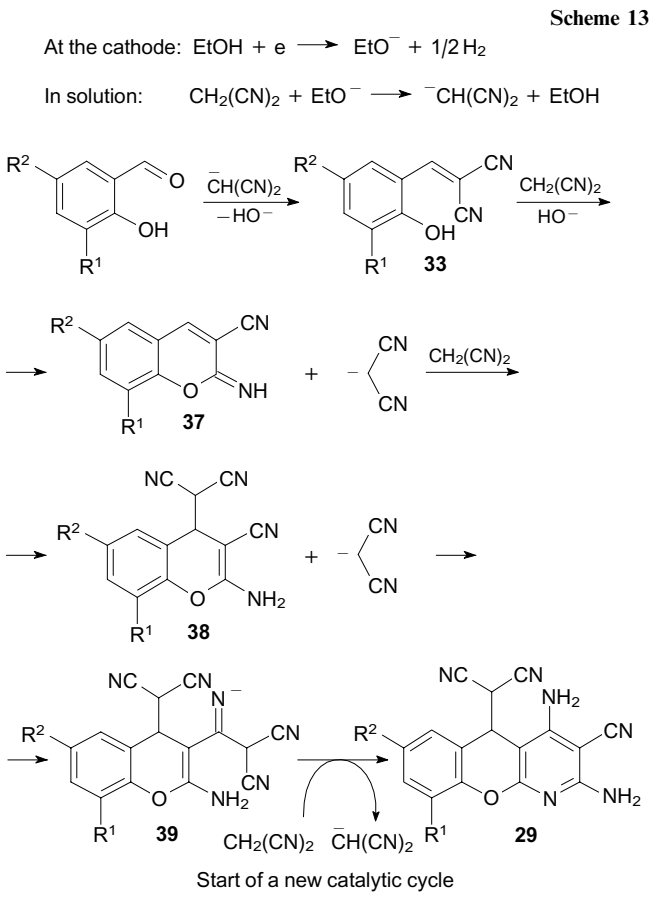
**b**: $R^1 = R^2 = H$;
**c**: $R^1 = H$, $R^2 = Me$;
**d**: $R^1 = H$, $R^2 = Br$;
**e**: $R^1 = OMe$, $R^2 = H$;
**f**: $R^1 = OEt$, $R^2 = H$;
**g**: $R^1 = OMe$, $R^2 = Br$;
**h**: $R^1 = H$, $R^2$ is benzo[5.6]

**29b–h** (83%–90%)

reaction proceeds in ethanol at an iron cathode and a graphite anode with an electric supply of 0.2 F $mol^{-1}$ with a current density of 5 mA $cm^{-2}$, and sodium bromide (10 mol.%) acts as a mediator.

This multicomponent electrochemical process starts with the formation of ethoxide anion at the cathode, deprotonating the malononitrile molecule, the anion of which, in turn, initiates further transformations (Scheme 13). The Knoevenagel condensation of salicylaldehyde with malononitrile anion results in the formation of adduct **33** and expulsion of hydroxide anion. The hydroxide anion initiates the Pinner's intramolecular cyclization of unsaturated adduct **33** to the anion of 4*H*-chromene **37**, which is involved in the subsequent deprotonation of the second malononitrile molecule. The resulting anion of malononitrile enters the Michael reaction with 4*H*-chromene **37** to generate anion of (4*H*-chromen-4-yl)malononitrile **38**. The latter is involved in the deprotonation of the third malononitrile molecule, which attacks the nitrile group of the pyran ring of (4*H*-chromene-4-yl)malononitrile **38**. This leads to anion **39**, which undergoes tautomeric transformations, cyclization and protonation, thereby affording chromeno[2,3-*b*]pyridine **29**. In the final step,

**Scheme 13**

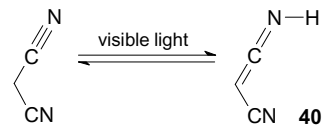


another malononitrile anion is formed, which initiates a new chain of transformations to give products **29**. The structure of chromeno[2,3-*b*]pyridines **29** was confirmed by the X-ray diffraction analysis data.[56]

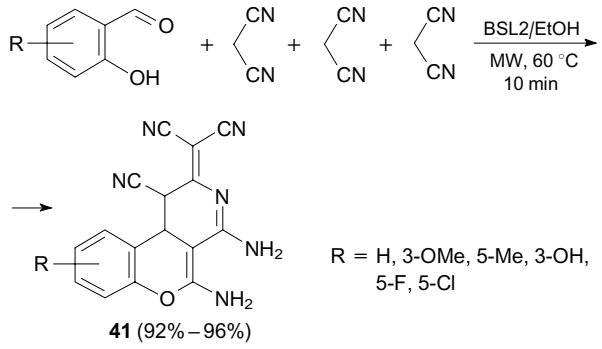
Subsequently, such pseudo-four-component synthesis of 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malononitriles **29** was carried out at room temperature in an ethanol–water (1 : 1 v/v) mixture under fluorescent lightning. The yields of the products were 88%–97%.[57] The mechanism of this transformation is similar to that of an electrochemical process (see Scheme 13), except that malononitrile is activated by visible light. According to the authors, light initiates a tautomeric transformation of the malononitrile molecule (Scheme 14), and 3-iminoacrylonitrile **40** participates in the 'domino' process.[57] Probably, in the course of the reverse tautomeric transformation of 3-iminoacrylonitrile (by analogy with enamines), the malononitrile anion is formed, which enters the reaction.

Microwave irradiation of salicylaldehyde and malononitrile, taken in an amount of 3 equiv., in the presence of *Bacillus subtilis* lipase (BSL2) changes the direction of cyclization, affording 2-(4,5-diamino-1-cyano-1,10*b*-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-yliden)malononitriles **41** (Scheme 15).[58] The reaction proceeds in ethanol at 60 °C for 10 min providing high yields of the products.

**Scheme 14**



**Scheme 15**




**41** (92% – 96%)

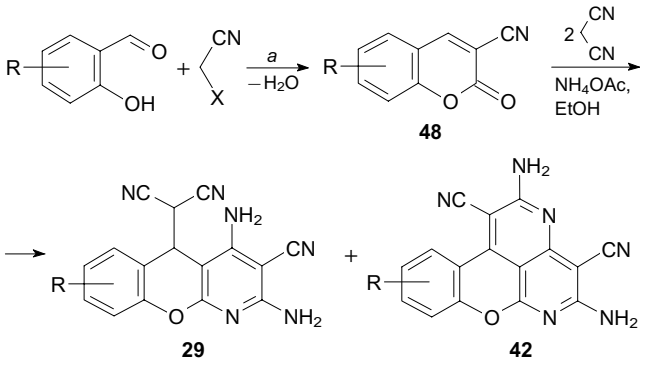
In contrast to the publication [56] presenting an electrochemical method of synthesis, in the cited study,[58] the structures of the obtained compounds were not confirmed by X-ray diffraction. The structures were proposed on the basis of spectral data, which turned out to be similar to those for chromene[2,3-*b*]pyridines **29** due to the presence of the same functional groups.

Heating salicylaldehyde and 3 equiv. of malononitrile under reflux in anhydrous ethanol or DMF in the presence of potassium *tert*-butoxide leads to additional cyclization, enabling the synthesis of chromeno[2,3-*b*]pyridine **42a** (Scheme 16).[59] The reaction proceeds in 30 min, and the yields of the product are 49% – 51%. This reaction, being the first example of the interaction between substituted salicylaldehyde and three-fold excess of malononitrile furnishing chromeno[2,3-*b*]pyridine, was studied in 1992. However, the structure of compound **42a** has been proposed only on the basis of IR-spectroscopy and mass spectrometry data.

The mechanism of formation of chromeno[2,3-*b*]pyridine **42a** (see Scheme 16) [59] is in many respects similar to that considered in Scheme 13. An exception is the step of activation, which takes place under the action of a base; the steps of the Knoevenagel condensation, the Michael addition, cyclization, and nucleophilic attack at the cyano group coincide (see the formation of intermediates **43** and **44**). Intermediate **45**, formed as a result of two successive nucleophilic attacks of amino groups on cyano groups, undergoes two intramolecular cyclizations to give first intermediate **46**, and then dihydrochromeno[4,3,2-*de*][1,6]-naphthyridin-1,4-dicarbonitrile **47**. Oxidation of the latter leads to elimination of the water molecule, aromatization and the formation of chromeno[4,3,2-*de*][1,6]naphthyridin-1,4-dicarbonitrile **42a**.

Mention should also be made of the method for the preparation of chromeno[2,3-*b*]pyridine **42a**, in which 2-oxo-2*H*-1-benzopyran-3-carbonitrile **48** and a two-fold excess of malononitrile were used as starting compounds (Scheme 17). Compound **48** was preliminarily synthesized from salicylaldehyde and cyanoacetate by condensation and cyclization, after which further transformations were carried out.

**Scheme 17**




(*a*) $NH_4OAc$, EtOH; X = $CO_2Et$, CN

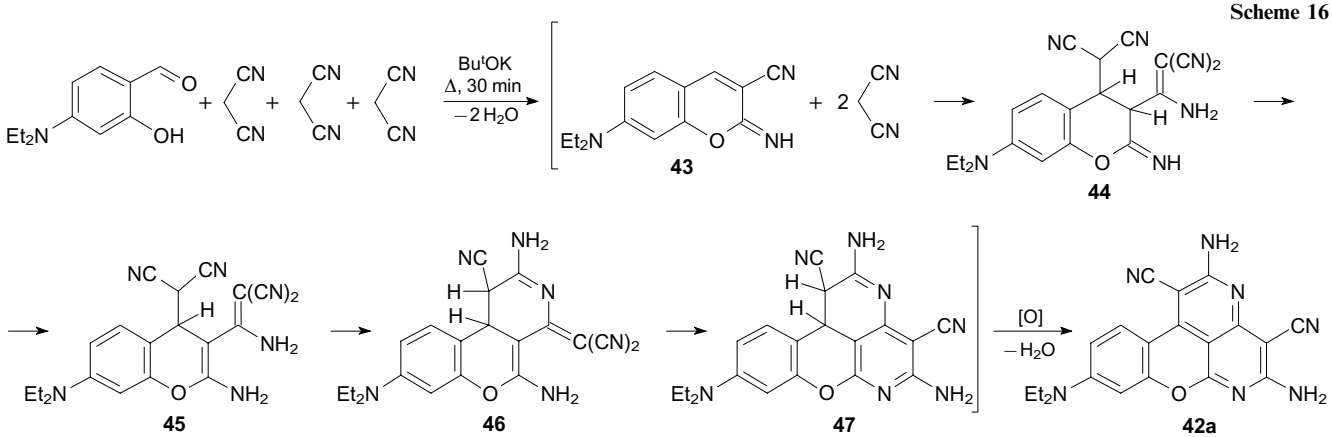
For the first time, the addition of two malononitrile molecules to intermediate **48** was carried out back in 1971 in the presence of ammonium acetate in ethanol.[60] As a result, an inseparable mixture was obtained, the components of which could not be identified at that time due to the lack of suitable spectral methods. But 25 years later, the composition of the mixture was identified: the reaction furnished tetra- and tricyclic chromeno[2,3-*b*]pyridines **42** and **29**.[61, 62]

Compound **42a** can be obtained using a six-fold excess of malononitrile under reflux with the corresponding aldehyde in DMF in the presence of 15% aqueous solution of KOH. However, this method cannot be considered effective due to the significant consumption of malononitrile and low product yields (8% – 24%).[59]

### 2.7. Pseudo-four-component reactions involving benzaldehydes, malononitrile, and 2-hydroxyacetophenones

Heterogeneous catalysts, particularly, nanocatalysts, are attracting increasing attention of synthetic chemists. As

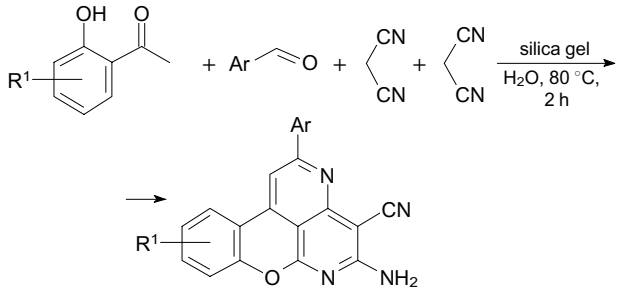
**Scheme 16**



noted above, their use makes it possible to simplify the work-up of the reaction mixture after the completion of the process, and to reuse the regenerated catalyst in the next synthesis.

A small amount of silica gel was introduced as a catalyst in the pseudo-four-component reaction between 2-hydroxyacetophenones, aromatic aldehydes, and malononitrile proceeding with the formation of 5-amino-2-arylchromeno[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles **49** (Scheme 18).[63] The process was carried out on heating at 80 °C in water for 2 h, the yields of the products were 62% – 81%.

**Scheme 18**




**49** (62% – 81%, 28 examples)

$R^1$ = H, 4-F, 4-Cl, 4-OH, 4-OMe, 5-Me, 5-OMe, benzo[5,6];
Ar = Ph, 4-$NCC_6H_4$, 4-$MeC_6H_4$, 4-$HOC_6H_4$, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2,3-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 3-$FC_6H_4$, 4-$FC_6H_4$, 2-$ClC_6H_4$, 3-$ClC_6H_4$, 4-$ClC_6H_4$, 2-$BrC_6H_4$, 3-$BrC_6H_4$, 4-$BrC_6H_4$, 4-$IC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-Py, 2-Th

Relying on the data from electrospray ionization mass spectrometry (ESI-MS), the authors proposed the following mechanism of the reaction (Scheme 19). The first step is aldol condensation of aldehyde and 2-hydroxyacetophenone, leading to intermediate **50**. Malononitrile condenses with the carbonyl group of intermediate **50** to form intermediate **51**, which, in turn, undergoes intramolecular cyclization to chromene **52**. At the next step, chromene **52** is attacked by another malononitrile molecule with the formation of intermediate **53**. The latter undergoes two intramolecular cyclizations and aromatization, accompanied by oxidation and elimination of water, which leads to 5-amino-2-arylchromeno[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles **49**.

The same reaction takes place upon catalysis with iron scale ($Fe_3O_4$) nanoparticles in water at 70 °C.[64] The reactants must be additionally exposed to microwave irradiation (400 W) for 25 min, then compounds **49** are formed in the yields of 80% – 88%.

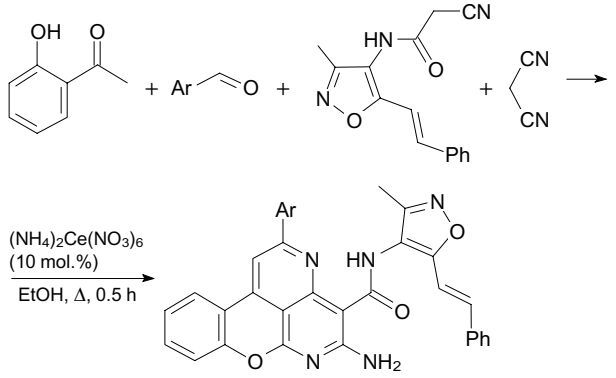
According to the authors, the combination of microwave irradiation with the use of a nanocatalyst makes the reaction highly efficient, and such side processes as decomposition or deactivation of the catalyst because of temperature exposure are not observed due to short irradiation.

Another catalyst for this transformation are supermagnetic nanoparticles. After the completion of the reaction, the nanoparticles are easily separated from the reaction mixture using an external magnet, and upon repeated use, no noticeable loss of their activity is observed. In the presence of γ-$Fe_2O_3$@$SiO_2$ nanoparticles with grafted γ-aminobutyric acid[65] in an aqueous medium on heating to 80 °C, the reaction proceeds in 45 – 60 min, the yields of the product reach 86% – 93%. Slightly less effective supermagnetic catalysts are $Fe_3O_4$@$SiO_2$ – $OB(OSO_3H)_2$ nanoparticles.[66] In this case, the reaction time is 60 – 100 min, and the yields are 73% – 96%. Both methods provide mild green reaction conditions and convenient isolation of the products.

When 1 equiv. of malononitrile is replaced with isoxazolylcyanacetamide, arylchromeno[4,3,2-*de*][1,6]naphthyridines **54** are formed in this reaction (Scheme 20).[67] The transformation takes place in boiling ethanol in 30 min to give products in 59% – 67% yields.

Functionalized 5-amino-2-arylchromeno[4,3,2-*de*][1,6]-naphthyridine-4-carbonitriles **49** obtained by the Suzuki cross-coupling reaction are promising as fluorescent dyes.

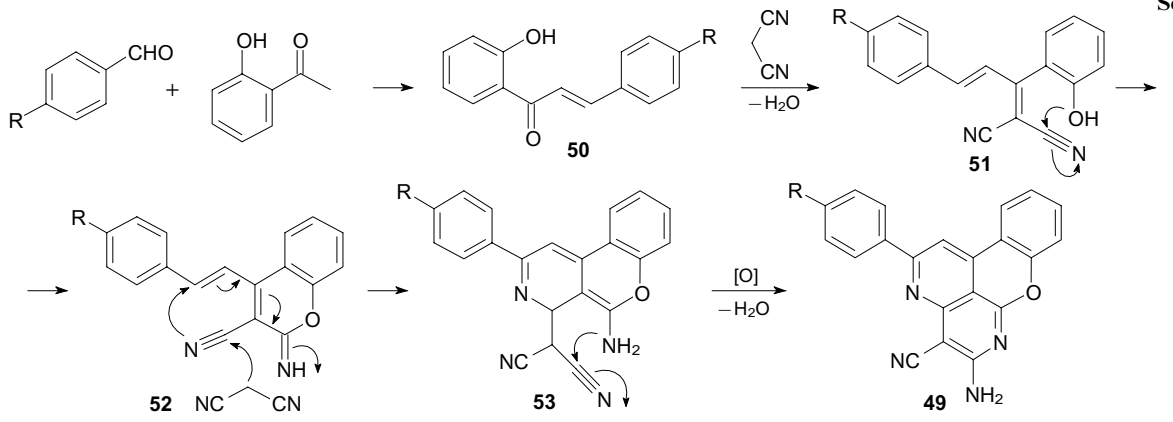
**Scheme 20**



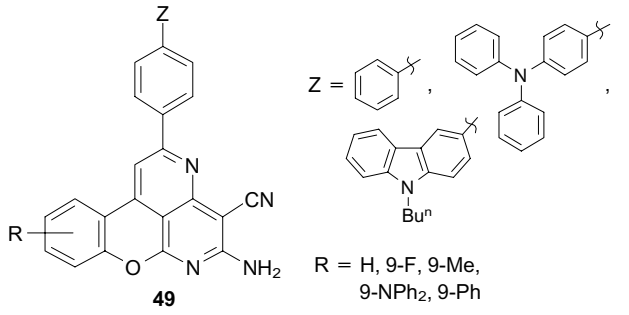

**54** (59% – 67%)

Ar = Ph, 2-$ClC_6H_4$, 2-$BrC_6H_4$, 4-$MeC_6H_4$, 2-$MeOC_6H_4$, 4-$HOC_6H_4$

**Scheme 19**



**Structures 49**




**49**

These compounds showed an intense blue-green fluorescence coupled with high quantum yields. Therefore, they are potential materials for OLED display applications.[68, 69] Below are examples of compounds **49** with high quantum fluorescence yields.

### 2.8. Reactions involving salicylaldehydes, homophthalonitriles, and various CH-acids

Multicomponent methods make it possible to create several new chemical bonds in one synthetic procedure. In some cases, the reactivity of the starting compounds is not high enough as to obtain the desired product by direct mixing of the reagents. Then, a one-pot approach is used, with the necessary reactants being added in a specific order.

One-pot synthesis of compounds **55** and **56** is performed in two steps (Scheme 21; the position of substituents in the substrate is indicated).[70] First, salicylaldehydes, homophthalonitrile, and ammonium acetate are heated in isopropyl alcohol to 150 °C in a sealed vessel of a microwave reactor for 10 min, then the second reactant and triethylamine are added to the reaction mixture and heating is continued for another 10 min. When nitromethane is added the second step, compounds **55**[70] are formed, and the introduction of indole or its azo derivatives gives products **56**.[71]

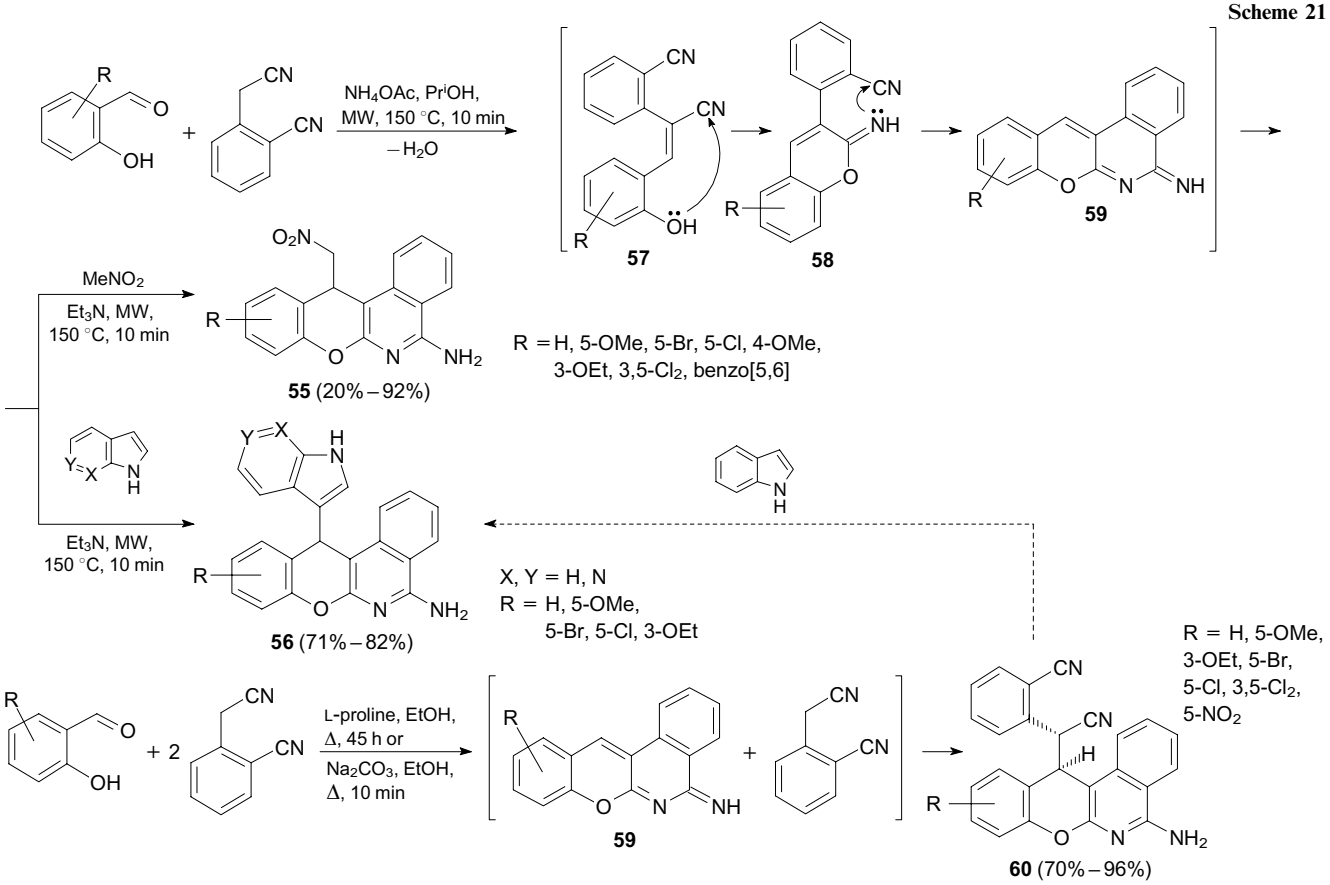
Carrying out the process under microwave irradiation can shorten the reaction time and increase the yield of target compounds. However, it should be noted that for this reaction, salicylaldehyde is taken in a threefold excess with respect to homophthalonitrile, ammonium acetate and indole are in a twofold excess, and nitromethane is in a tenfold excess. The products are isolated by chromatography or extraction.

The authors explain the low yields of some compounds. The low reactivity of 4-methoxysalicylaldehyde in the Knoevenagel condensation accounts for the 46% yield of product **55** bearing the corresponding substituent in the 9-position. Benzannulated analogue of compounds **55** — pentacyclic derivative based on 2-hydroxy-1-naphthaldehyde — was obtained in the lowest yield (20%) due to steric hindrances generated by the fused benzene ring.

The use of nitrovinyl derivative of salicylaldehyde does not lead to the formation of compound **55**, and the multicomponent transformation of salicylaldehyde, homophthalonitrile, and nitromethane catalyzed by ammonium acetate in an ethanol–water (3 : 1 v/v) mixture gives chromenoisoquinolinamine **55** (R = H) in a yield of as low as 18%. For this reason, a one-pot reaction is the optimal method.

The mechanism of one-pot transformation is shown in Scheme 21. Under the action of ammonium acetate, the Knoevenagel condensation of salicylaldehyde with homophthalonitrile occurs to form intermediate **57**, which under-

**Scheme 21**



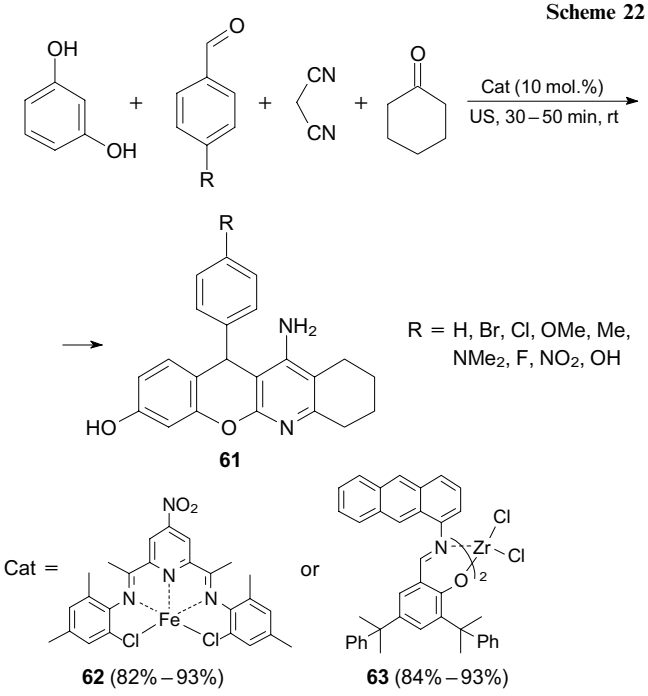
goes two successive intramolecular cyclizations furnishing intermediates **58** and **59**. In the next step, nitromethane introduced into the reaction mixture adds to intermediate **59** under the action of triethylamine to give compound **55**.[70]

In reactions with indole derivatives, as suggested by the authors, compound **56** (X = Y = CH) can be obtained both by the standard mechanism, governed by the order of addition of the reactants, and from isoquinolinamine **60** (see Scheme 21). Under the conditions of a three-component reaction, isoquinolinamine **60** reacts with an excess of indole affording compound **56** (X = Y = CH) in 75% yield.[71]

Pseudo-three-component reaction of salicylaldehyde with 2 equiv. of homophthalonitrile in ethanol in the presence of sodium carbonate leads to unsubstituted isoquinolinamine **60a** (R = H) in 96% yield (see Scheme 21).[71] The reaction is completed in just 10 min, and the product is formed in a diastereomeric ratio of 61 : 39. Carrying out this process with L-proline (30 mol.%) provides lower yield of compounds **60** (X = Y = CH) (70% – 93%) and diastereomer ratio > 93 : 7, but with a longer reaction time (45 h).[71]

The mechanism of this process virtually does not differ from that discussed above (see Scheme 21). The diastereomeric ratio is provided by L-proline-catalyzed addition of the second homophthalonitrile molecule to the tetracyclic imine **59**.

**Scheme 22**




US is ultrasonic irradiation

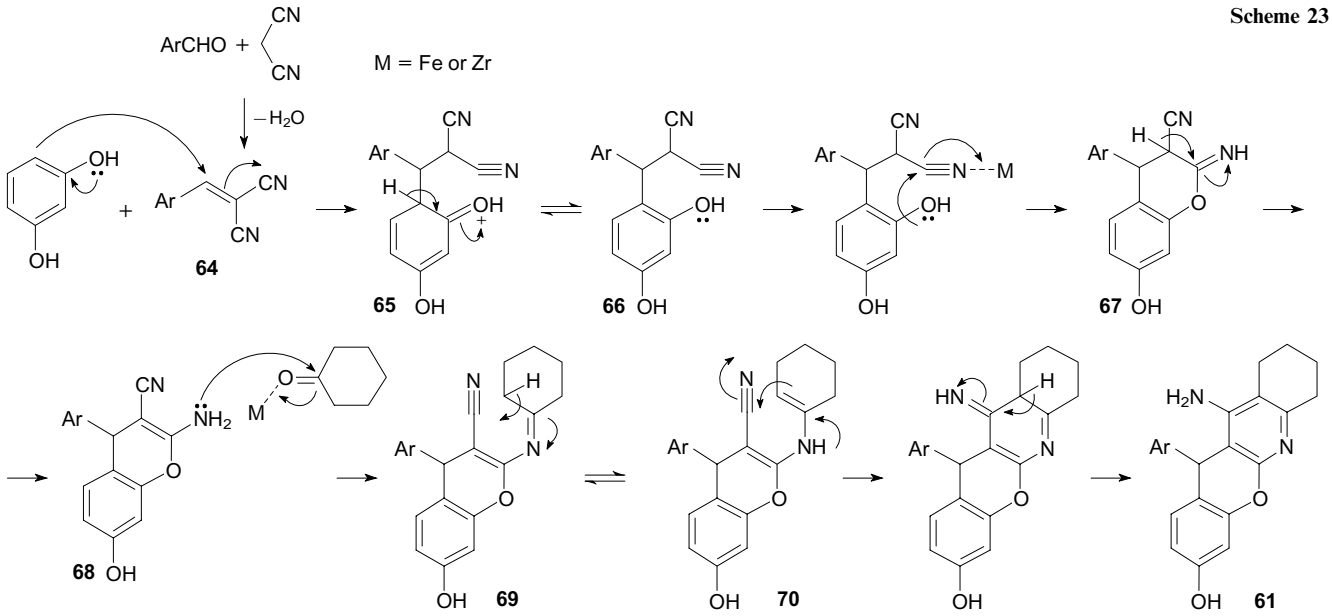
## 2.9. Other multicomponent routes to 5*H*-chromeno[2,3-*b*]pyridines

Some reactions are rather difficult to attribute to any type within the framework of our proposed classification. The following are the original multicomponent methods for the synthesis of 5-C-substituted chromeno[2,3-*b*]pyridines, which have no close analogues yet.

Thus, multicomponent transformation of resorcinol, (un)substitued benzaldehyde, malononitrile, and cyclohexanone furnishes 7*H*-chromeno[2,3-*b*]quinolin-3-ols **61** (Scheme 22). Optimal reaction conditions have been found under which solvent-free reactants were exposed to ultrasonic irradiation in the presence of metal complexes such as iron dichloride with bis(imino)pyridine ligand (**62**)[72] or bis[*N*-(3,5-dicumylsalicylidene)anthracylaminato]zirconium(IV) (**63**).[73] Both catalysts provide fairly high product yields (82% – 93%).

In the first step of this four-component process, the Knoevenagel condensation of benzaldehyde with malononitrile takes place (Scheme 23). C-Alkylation of the unsaturated product **64** with resorcinol generates cation **65**, which is deprotonated to intermediate **66**. Coordination interactions arise between the nitrile **66** and the metal ion of the catalyst, leading to the Pinner cyclization of this anion to give 2-iminochromene **67**. As a result of tautomeric transformations, 2-aminochromene **68** is formed from compound **67**. Cyclohexanone coordinated with the metal ion of the catalyst reacts with 2-aminochromene **68**. Subsequent cycli-

**Scheme 23**

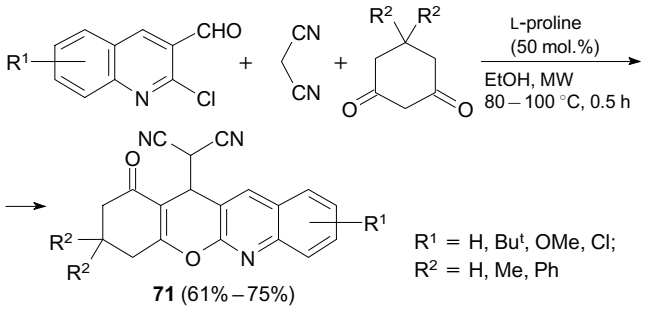


zation and tautomeric transformations proceed *via* the formation of intermediates **69**, **70** and afford product **61**.

As mentioned above, similar 5-C-substituted chromeno[2,3-*b*]quinolines exhibit neuroprotective activity,[29] and derivatives of cyclohexane-1,3-diones and chromeno[2,3-*b*]-quinolines *in vitro* showed a high inhibitory effect on the growth of HepG2 (human liver cancer cells) (see Section 2.4).[74]

In addition to salicylaldehydes, 2-chloroquinoline-3-carbaldehyde can be used in multicomponent reactions. This compound reacts with malononitrile and cyclohexane-1,3-dione to give 2-(1-oxo-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-12-yl)malononitriles **71** (Scheme 24).[74] The process is carried out with the addition of L-proline (50 mol.%) on heating to 80–100 °C and under microwave irradiation for 30 min. As a solvent, ethanol is preferable, but according to the patent information[74] the reaction also proceeds in DMF, tetrahydrofuran, toluene, ethylene glycol, *etc*.

**Scheme 24**

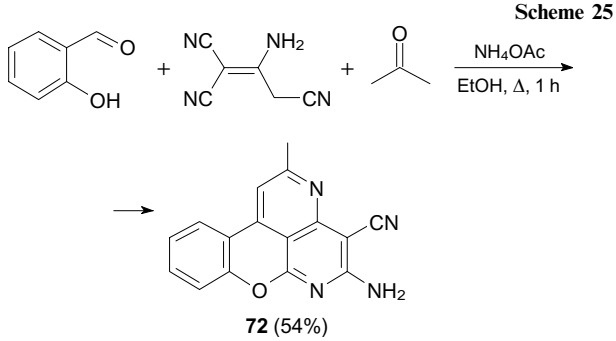



**71** (61%–75%)

At the end of this Section, it is worth mentioning the multicomponent reaction of salicylaldehyde, malononitrile dimer and acetone (Scheme 25).[75] It was carried out in 1988 under the classical conditions for the Hatzsch pyridine synthesis, which had been developed at the end of the 19th century.[76] In this process, acetone and ammonium acetate are present in the reaction mixture in a slight excess relative to other starting compounds, and as a result, 5-amino-2-methyl[l]benzopyrano[4,3,2-*de*][1,6]naphthyridine-4-carbonitrile (**72**) is formed. The yield of the product after heating under reflux in ethanol for 1 h is 54%.

Thus, interest in multicomponent, pseudo-multicomponent and one-pot processes, which produce 5-C-substituted chromeno[2,3-*b*]pyridines, persists over time. For the synthesis of some derivatives, methods developed more than 100 years ago are suitable; many transformations can be carried out by heating under reflux in ethanol and other solvents in the presence of a basic catalyst. For other reactions, various types of irradiation are used, allowing them to be accelerated and completed in a few minutes. Most of the processes affording chromeno[2,3-*b*]pyridines begin with condensation, and subsequent cyclizations and tautomeric transformations lead to the desired products. Interest in 5-C-substituted chromeno[2,3-*b*]pyridines is also supported by research focused on their potential applications in medicine.

**Scheme 25**



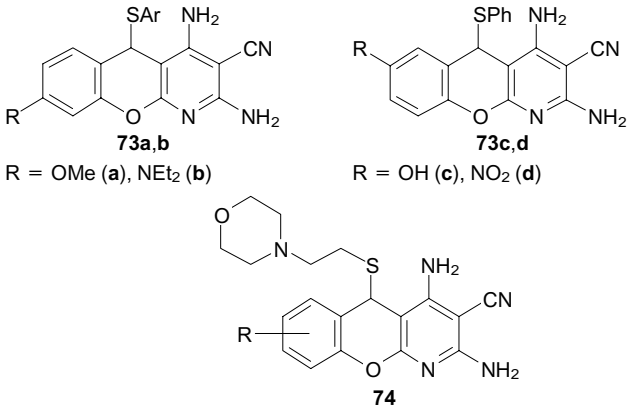

**72** (54%)

## 3. Synthesis of 5-S-substituted chromeno[2,3-*b*]pyridines

The most well-known methods for the synthesis of 5-S-substituted chromeno[2,3-*b*]pyridines are based on consecutive condensation and cyclization reactions, and the formation of the C–S bond at the 5-position occurs as a result of a nucleophilic attack of a thiol on the double bond formed in the multicomponent process. Reagents for such transformations are carbonyl derivatives in combination with malononitrile or its derivatives and sulfur compounds.

Some representatives of 5-S-substituted chromeno[2,3-*b*]pyridines possess biological activity. For instance, compounds **73a**,**b** displayed antiproliferative activity against melanoma and glioma cells,[77] as well as antifibrotic effect on liver cells.[78,79] In studies in rats and dogs, chromeno[2,3-*b*]pyridines **74** have shown gastric antisecretory activity.[80] Moreover, 5-(phenylthio)-5*H*-chromeno[2,3-*b*]-pyridines **73c**,**d** inhibit corrosion of low-carbon steel.[12]

**Structures 73, 74**




**73a**,**b**

R = OMe (**a**), $NEt_2$ (**b**)

**73c**,**d**

R = OH (**c**), $NO_2$ (**d**)

**74**

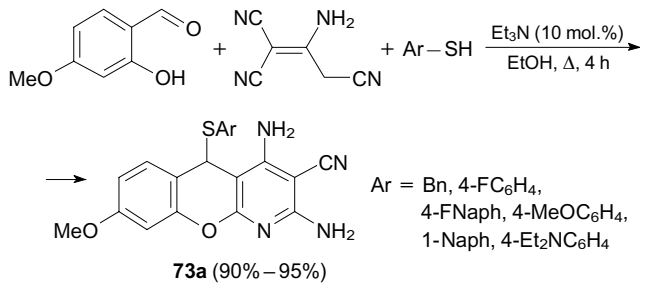
The most common catalysts for the synthesis of 5-S-chromeno[2,3-*b*]pyridines are amines, regardless of the reaction type. Thus, the multicomponent synthesis of chromeno[2,3-*b*]pyridine-3-carbonitriles **73a** from 4-methoxysalicylaldehyde, malononitrile dimer, and aromatic thiols proceeds in 4 h in boiling ethanol under catalysis with triethylamine (10 mol.%) providing the high yields of the products (Scheme 26).[77]

Triethylamine catalysis on heating under reflux in ethanol was also used for pseudo-four-component reactions of salicylaldehydes, 2 equiv.of malononitrile, and various thiols (Scheme 27).

For the first time this transformation was carried out by Russian scientists.[81,82] This triethylamine-catalyzed (7 mol.%) reaction took place within 3–3.5 h to give products in the yields from 50% to 86%.

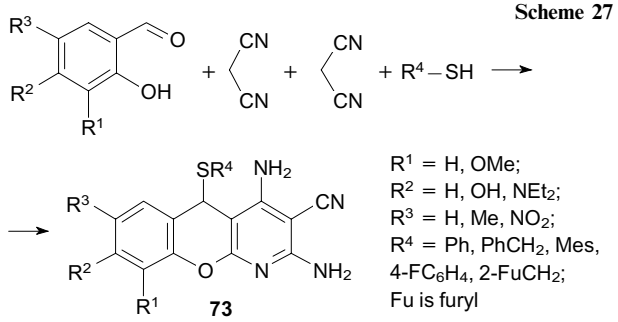
Later, other works on the synthesis of 5-alkyl(aryl)-thio-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **73** were

**Scheme 26**




**73a** (90%–95%)

**Scheme 27**

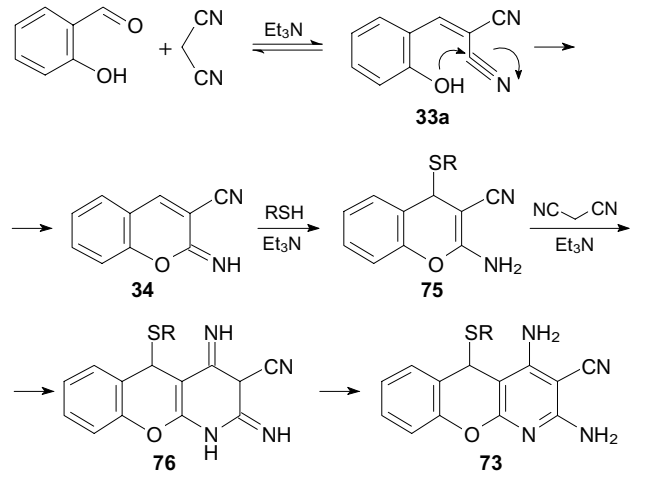



**73**

reported, wherein the authors made use of triethylamine–ethanol system, the yields ranging from 30% to 93% (see Scheme 27).[12,77–79,83] These studies were focused on useful applications of the obtained compounds. As a catalyst for the above reaction, pyridine (20 mol.%) was also used.[84] In this case, heating under reflux lasts 3–5 h, and the yield of chromeno[2,3-*b*]pyridines **73** is 45%–76%.

As mentioned above, in the first step of such transformations, the Knoevenagel condensation occurs (Scheme 28).[81] Prior to the step of imine **34** formation, the reaction mechanism is similar to that of the synthesis of 5-C-substituted chromeno[2,3-*b*]pyridines, *e.g.*, compounds **29**–**31** (see Section 2.5). Imine **34** is a Michael acceptor and in turn reacts with a strong nucleophile, that is, a thiol, to produce a stable chromene **75**. Under the action of triethylamine, another malononitrile molecule adds to chromene **75**, initializing the subsequent intramolecular cyclization and aromatization of intermediate **76** to form chromeno[2,3-*b*]pyridine **73**.

**Scheme 28**




More environmentally friendly approaches have also been proposed for the multicomponent transformation of salicylaldehydes, malononitrile, and thiols into chromeno[2,3-*b*]pyridines **73**. For example, such reaction is completed within 2.5–4 h under catalysis with potassium carbonate (20 mol.%) in a boiling ethanol–water (1 : 1 v/v) mixture providing 60%–92% yields of the product.[85] At the same time, at the beginning of the process, there is only 1 equiv. of malononitrile in a flask, the second one is added 30 min later.

The pseudo-four-component reaction of salicylaldehydes, malononitrile and thiols was carried out on heating under reflux in ethanol using 10 mol.% of the borax natural mineral (borax, $Na_2B_4O_7$)[86] or chitosan functionalized with citric acid as a catalyst.[87] Chitosan is a biopolymer with catalytic properties, its modification with citric acid increases the catalytic activity. Both catalysts provide the yields of the products in the range of 84%–94%, the reaction time is 30–45 min.

5-Alkyl(aryl)thio-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **73** were synthesized from salicylaldehydes, malononitrile, and thiols in boiling ethanol in the presence of nanoparticles.[88–90] The advantage of carrying out reactions on nanoparticles is that they are easily separated from the reaction mixture, after which they can be easily purified and reused.

Zirconium pyrophosphate ($ZrP_2O_7$) nanoparticles exhibit significant activity due to the high surface area to volume ratio. However, as they are used, a slow loss of their activity is observed, since in the fifth cycle of application of $ZrP_2O_7$ nanoparticles (5 mol%), the yield of unsubstituted 5-phenylthio-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile decreases from 91% to 85%.[88] The use of nanoparticles of tin oxide SnO (6 mol.%) requires further purification of 5-thio-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **73** using DMF.[89] To carry out this reaction in an ethanol–water (1 : 1 v/v) mixture, catalysis by $Fe_3O_4@SiO_2-NH_2$ nanoparticles (0.1 g per 1.5 mmol of salicylaldehyde) is also used.[90] The reaction time in the presence of the said particles is from 40 min to 1.5 h, the product yields range from 80% to 90%; in the case of $Fe_3O_4@SiO_2-NH_2$ the yield reaches 97%.[90]

The mechanism of reactions catalyzed by nanoparticles differs from that of the base-catalyzed process only by the activation step. In the first step, coordination bonds are formed by analogy with the action of Lewis acids, which triggers the subsequent steps of the Knoevenagel condensation, nucleophilic addition and cyclization (Fig. 1).

Catalysis of the reaction between salicylaldehyde, malononitrile, and thiol with piperidine at room temperature leads to chromenes **77** rather than to chromene[2,3-*b*]pyridines **73** (Scheme 29).[84] The authors note that by varying the temperature, it is possible to control the order in which the reactants enter the process and to obtain the desired product, namely, compound **73** or **77**. In this case, the

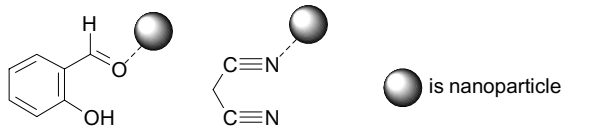
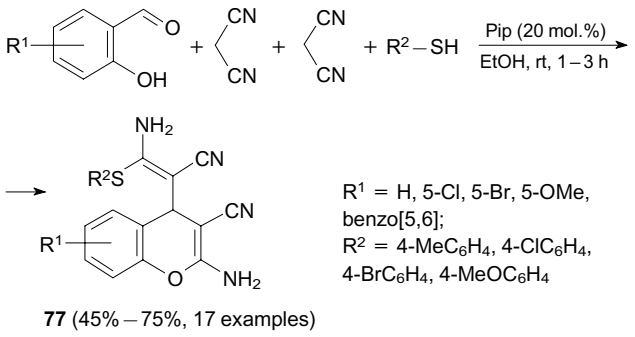


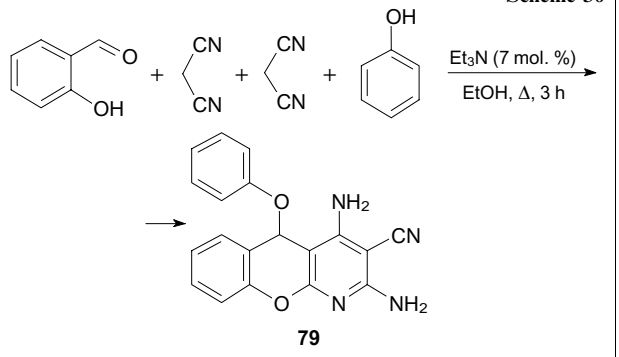

**Figure 1.** Coordinate bonds formed by nanoparticles with molecules of salicylaldehyde and malononitrile.

**Scheme 29**




**77** (45%–75%, 17 examples)

**Scheme 30**




**79**

reaction pathway is probably determined by either kinetic or thermodynamic control.

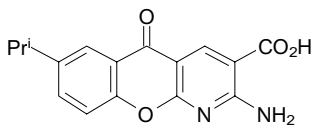
Therefore, multicomponent synthesis of 5-S-chromeno[2,3-*b*]pyridines is largely similar to the reactions yielding 5-C-substituted analogues. Many transformations are carried out by refluxing the reactants in ethanol or ethanol-based mixture of solvents and by catalysis with triethylamine or other amines; they usually proceed within several hours. It is worth noting that nanocatalysts are also used in such processes, which have the advantages of heterogeneous catalysis and lead to products in high yields.

## 4. Synthesis of 5-O-substituted chromeno[2,3-*b*]pyridines

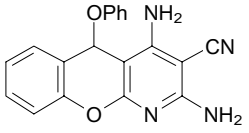
The best known compound of the class of 5-O-substituted chromeno[2,3-*b*]pyridines is the drug Amlexanox [trade name Aphthasol (**78**)]. Obtained at the end of the 20th century,[91] Amlexanox exhibits anti-inflammatory, antiallergic and immunomodulatory properties, it is also used to treat recurrent aphthous ulcers on the mucous membranes and other inflammatory conditions.[92] This drug is effective in the treatment of type 2 diabetes and obesity.[93]

Another practically useful compound of this class is 5-phenoxy-5*H*-chromeno[2,3-*b*]pyridine (**79**), which, when placed on the surface of low-carbon steel, prevents its corrosion even in a 15% hydrochloric acid solution.[83]

**Structures 78, 79**




**78** (Amlexanox)



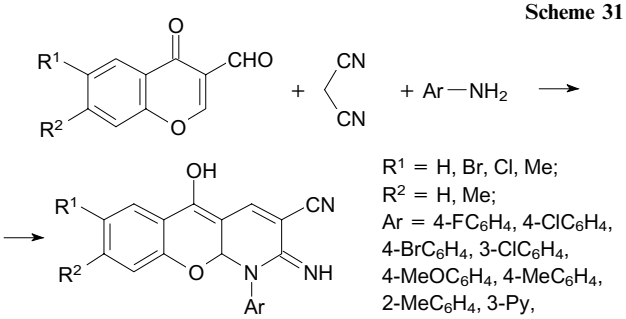

**79**

There are three multicomponent methods to obtain 5-O-substituted chromeno[2,3-*b*]pyridines reported in the literature. The closest to the processes discussed above is the transformation involving salicylaldehyde, malononitrile, and phenol, in which chromene[2,3-*b*]pyridine **79** is formed (Scheme 30). The reaction is carried out under conditions similar to the synthesis of other substituted chromeno[2,3-*b*]pyridines, that is, by heating with triethylamine under reflux in ethanol for 3 h.[83] The authors[83] focused their attention on studying the ability of such compounds to inhibit corrosion and described an example of the synthesis of only one product, which complicates the assessment of the effectiveness of this method.

The mechanisms of formation of 2,4-diamino-5-phenoxy-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**79**) and 2,4-diamino-5-phenylthio-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **73** with the unsubstituted benzene ring are similar (see Scheme 28).

Eco-friendly multicomponent synthesis of 5-hydroxychromeno[2,3-*b*]pyridines **80** from 3-formylchromones, malononitrile, and aromatic amines was carried out in two ways: on stirring in a reaction vessel without a solvent for 10–20 min or by grinding in a mortar for 5–10 min in the absence of solvent, catalyst and heating (Scheme 31).[94] The yields of compounds **80** turned out to be rather high.

**Scheme 31**



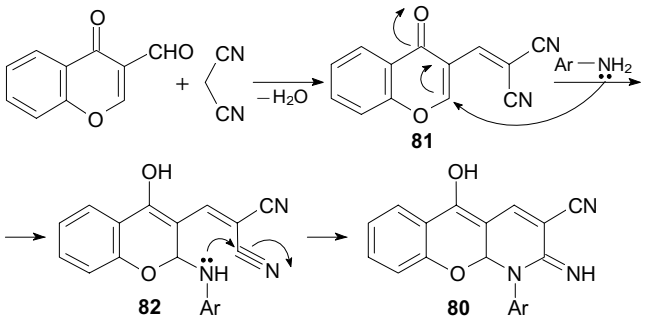

**80** (90%–96%, 18 examples)

The reaction begins with the Knoevenagel condensation of 3-formylchromone with malononitrile (Scheme 32). The electron-deficient intermediate **81** formed during condensation undergoes the Michael addition of an aromatic amine. Subsequent intramolecular nucleophilic attack and cyclization lead to the conversion of intermediate **82** to chromeno[2,3-*b*]pyridine **80**.

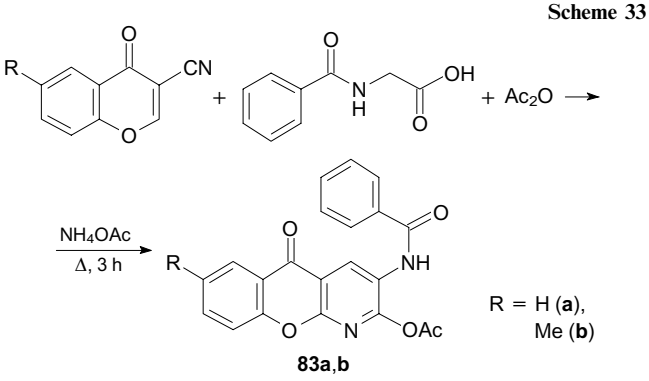
The first example of the multicomponent synthesis of 5-O-substituted chromeno[2,3-*b*]pyridines was the reaction between substituted 4-oxo-4*H*-1-benzopyran-3-carbonitriles, *N*-benzoylglycine, acetic anhydride, and ammonium acetate (Scheme 33).[95] In this case acetic anhydride acts both as a reagent and a solvent. Compounds **83a**,**b** are formed on heating under reflux for 3 h; their yields are 59% and 62% respectively.

The basic hydrolysis of 3-benzamido-5-oxo-5*H*-chromeno[2,3-*b*]-pyridine-2-yl acetates **83a**,**b** in ethanol proceeds to give the corresponding 3-amino-2-hydroxy-5*H*-chromeno[2,3-*b*]pyridin-5-ones **84a**,**b** (Scheme 34).

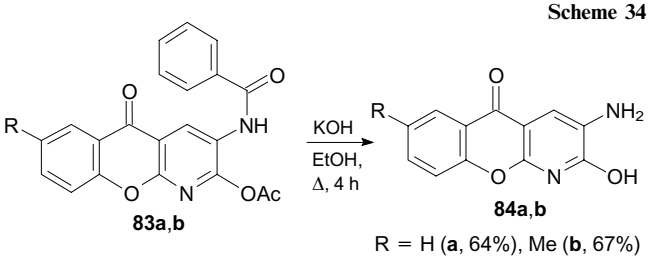
**Scheme 32**




**Scheme 33**




**Scheme 34**




Currently, a few examples of the synthesis of 5-O-substitutes chromeno[2,3-*b*]pyridines have been described. However, comparing the methods for the preparation of compounds **73** and **79**, it should be assumed that some approaches towards 5-S-substituted chromeno[2,3-*b*]pyridines can also be used for 5-O-substituted compounds.

## 5. Synthesis of 5-N-substituted chromeno[2,3-*b*]pyridines

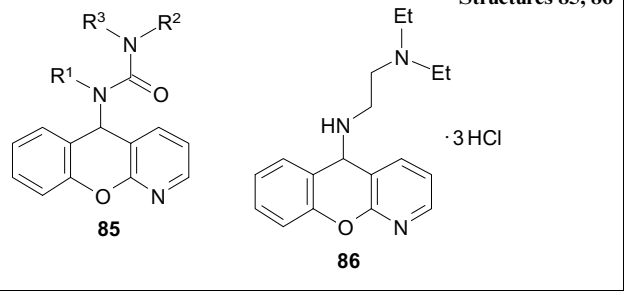
Among 5-aminochromeno[2,3-*b*]pyridines, compounds with various biological activities have been reported. For example, derivatives **85** showed gastric antisecretory activity in animal models.[96]

5-Diamino-substituted chromeno[2,3-*b*]pyridine trihydrochloride **86** suppresses stress-induced gastric ulcer in rodents, and also acts on muscarinic cholinergic receptors, inhibiting their action, and can be used as a spasmolytic agent.[97] 5-N-Derivatives of chromeno[2,3-*b*]pyridines inhibit proliferation of breast cancer cell lines.[98]

At present, one three-component and one pseudo-three-component reactions are described giving rise to 5-N-substituted chromeno[2,3-*b*]pyridines.

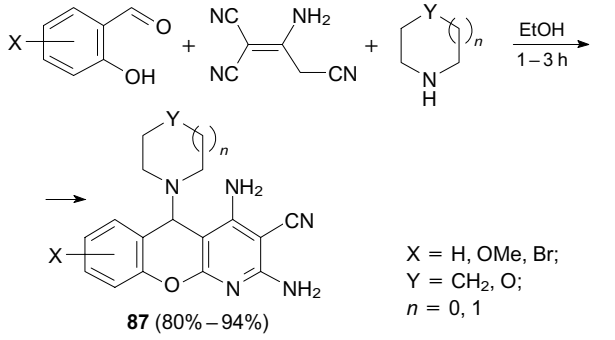
The multicomponent synthesis of 5*H*-chromeno[2,3-*b*]-pyridines **87** substituted at the 5-position with fragments of

**Structures 85, 86**




cyclic amines such as piperidine, pyrrolidine, and morpholine has been carried out starting from salicylaldehydes, malononitrile dimer, and the corresponding amines (Scheme 35).[99] This reaction takes place in ethanol at room temperature within 1 – 3 h.

**Scheme 35**



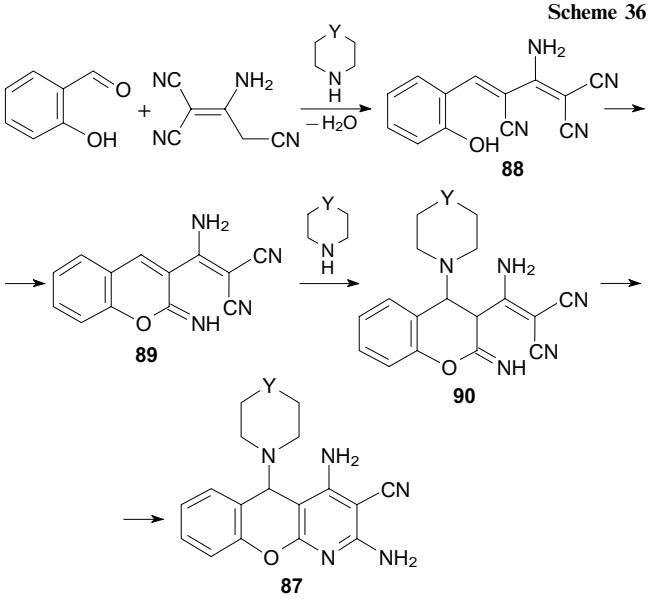

According to the authors, the presence of electron-withdrawing substituents in salicylaldehyde increases the yield of products, while replacing piperidine with morpholine reduces it. The least efficient is the conversion of pyrrolidine since its use affords the corresponding 5*H*-chromeno[2,3-*b*]-pyridines **87** in the lowest yield.

For this process, a mechanism has been described that includes the formation of an iminium ion from salicylaldehyde and a secondary amine.[99] However, based on the materials of the present review, the most probable process is that in which adduct **88** is first generated *via* condensation of salicylaldehyde and malononitrile dimer (Scheme 36). Further, it undergoes the intramolecular Pinner cyclization to intermediate **89** and the Michael addition. The formed chromene **90** cyclizes and aromatizes thereby furnishing 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **87**.

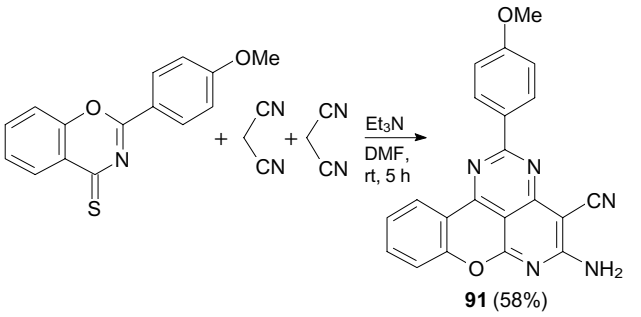
5-Amino-2-(4-methoxyphenyl)-7-oxa-1,3,6-triazabenzo[*de*]-anthracene-4-carbonitrile **91** is obtained through a pseudo-three-component reaction of 2-(4-methoxyphenyl)-4*H*-benzo[*e*][1,3]oxazine-4-thione with an excess of malononitrile in DMF under catalysis with triethylamine (Scheme 37).[100]

Compound **91** contains a chromeno[2,3-*b*]pyridine moiety and is formed by the addition of malononitrile dimer to benzo[*e*][1,3]oxazine-4-thione. Malononitrile dimer is generated directly in the reaction mixture from two molecules of malononitrile (Scheme 38). Subsequent intramolecular attack of an amino group in intermediate **92** and intramolecular attack of the oxygen atom in pyrimidine **93** yield chromene **94**. In the final step, the cyclization of chromene **94** is accompanied by the formation of product **91**.

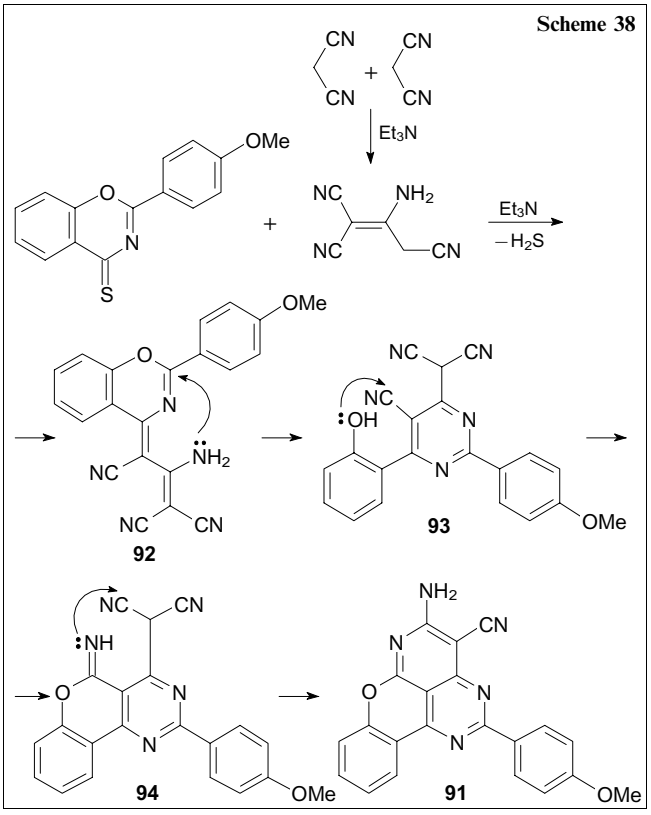
**Scheme 36**



**Scheme 37**



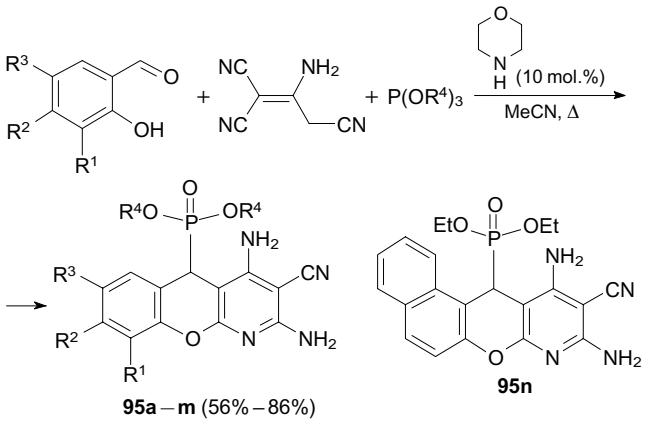
**Scheme 38**



## 6. Synthesis of 5-P-substituted chromeno[2,3-*b*]pyridines

The only representatives of this class of compounds at present are 5-(dialkoxyphosphoryl)-5*H*-chromeno[2,3-*b*]-pyridines **95** synthesized *via* a three-component transformation of salicylaldehydes, malononitrile dimer, and trialkyl phosphites (Scheme 39).[101] On one of their functional groups, compounds **95** are phosphonates, the derivatives of which have herbicidal[102] and antiproliferative[103] activities, as well as anti-inflammatory[104] and antibacterial properties.[105]

**Scheme 39**



**a**: $R^1 = R^2 = R^3 = H$, $R^4 = Et$; **b**: $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Et$; **c**: $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = Et$; **d**: $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = Et$; **e**: $R^1 = R^3 = H$, $R^2 = NEt_2$, $R^4 = Et$; **f**: $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = Et$; **g**: $R^1 = R^2 = H$, $R^3 = Br$, $R^4 = Et$; **h**: $R^1 = R^3 = Cl$, $R^2 = H$, $R^4 = Et$; **i**: $R^1 = OMe$, $R^2 = H$, $R^3 = Br$, $R^4 = Et$; **j**: $R^1 = R^2 = R^3 = H$, $R^4 = Me$; **k**: $R^1 = R^3 =$ H, $R^2 = OH$, $R^4 = Me$; **l**: $R^1 = R^2 = H$, $R^3 = Br$, $R^4 = Me$; **m**: $R^1 = OMe$, $R^2 = H$, $R^3 = Br$, $R^4 = Me$

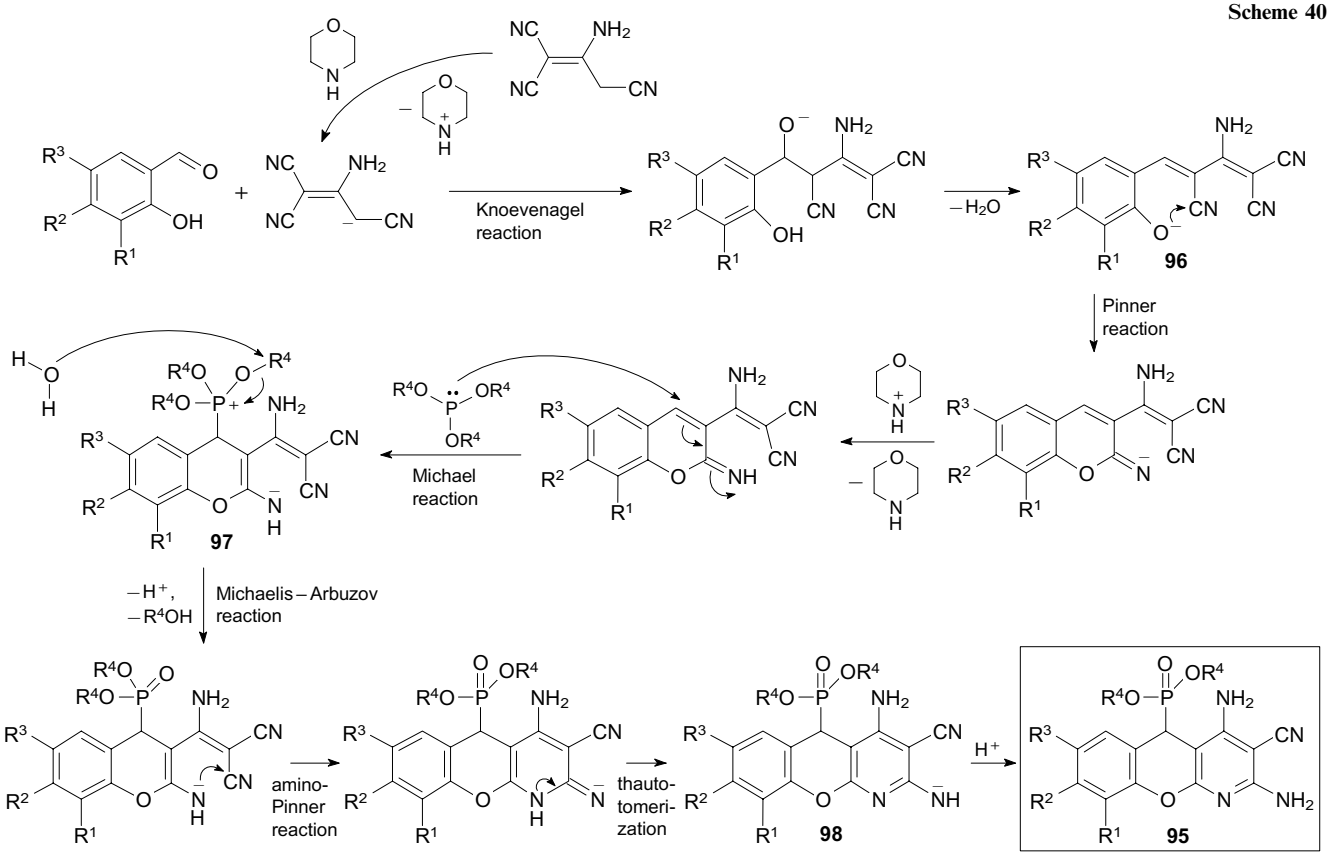
The multicomponent reaction of salicylaldehydes, malononitrile dimer, and trialkyl phosphites catalyzed by morpholine (10 mol.%) in boiling acetonitrile affords in 4 h 5-P-substituted 5*H*-chromeno[2,3-*b*]pyridines **95a**–**n**.[101] The implementation of this transformation in alcohols is limited by the side transesterification of alkoxy groups.

The mechanism of formation of 5-(dialkoxyphosphoryl)-5*H*-chromeno[2,3-*b*]pyridines **95** is shown in Scheme 40. Under the action of morpholine, the Knoevenagel condensation of malononitrile dimer with salicylaldehyde occurs, yielding adduct **96**. Unsaturated adduct **96** undergoes the intramolecular Pinner cyclization to imine. Further, as a result of the Michael addition of trialkyl phosphite, bipolar ion **97** is formed, which successively enters the Michaelis–Arbuzov reaction, the amino-Pinner reaction, and then isomerizes into anion **98**. Protonation of anion **98** affords chromene[2,3-*b*]pyridine **95**.

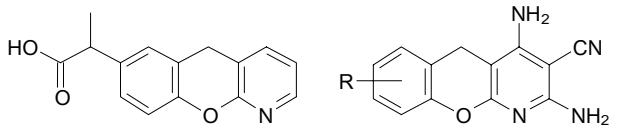
## 7. Synthesis of chromeno[2,3-*b*]pyridines with the unsubstituted 5-position

One of the most well-known representatives of this class is Pranoprofen (**99**), a drug used in some acute inflammatory processes in the eyes, as well as in postoperative ocular therapy.[106]

**Scheme 40**




**Structures 99, 100**



**99** (Pranoprofen)

**100**

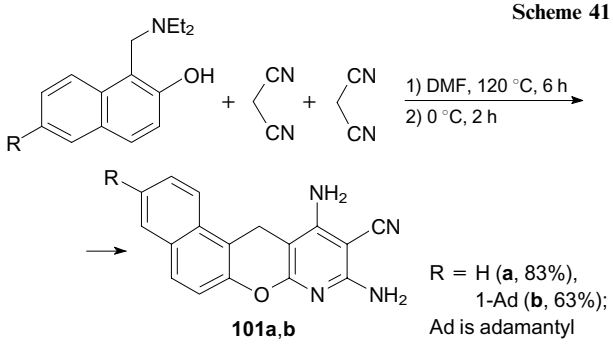
R = H, OH, $NH_2$, Me

Chromeno[2,3-*b*]pyridines **100** exhibit inhibitory properties against mitogen-activated protein kinase MK-2 and suppress the expression of tumour necrosis factor TNF-α, which is important in the treatment of inflammatory diseases such as psoriasis and rheumatoid arthritis.[30]

12*H*-Benzo[5,6]chromeno[2,3-*b*]pyridines **101a**,**b** are formed *via* the pseudo-three-component reaction from Mannich bases [2-hydroxy-1-(diethylaminomethyl)naphthalenes] and malononitrile in DMF (Scheme 41).[107] For the reaction to proceed, heating of the reaction mixture to 120 °C for 6 h followed by keeping it for 2 h at 0 °C is required.

Synthesis of 5-unsubstituted 5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **100a**–**c** was also carried out using (2-hydroxyphenyl)methyl-substituted quaternary ammonium salts and 2 equiv. of malononitrile (Scheme 42).[108] This reaction occurs under milder conditions such as heating under reflux in ethanol for 4 h; after heating the reaction mass should be kept at 10 °C. Sodium hydroxide, taken in an equimolar amount, acts as a catalyst. Despite a 10-fold excess of malononitrile, the yields of the target chromeno[2,3-*b*]pyridines **100a**–**c** were relatively low (30%–51%).

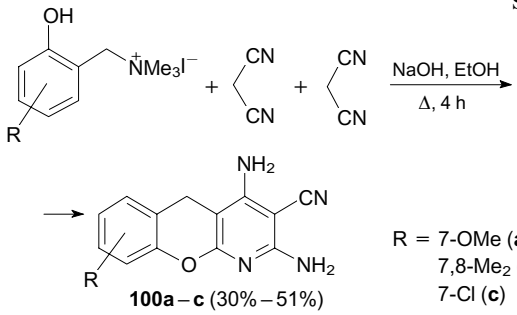
**Scheme 41**




**101a**,**b**

R = H (**a**, 83%),
1-Ad (**b**, 63%);
Ad is adamantyl

**Scheme 42**

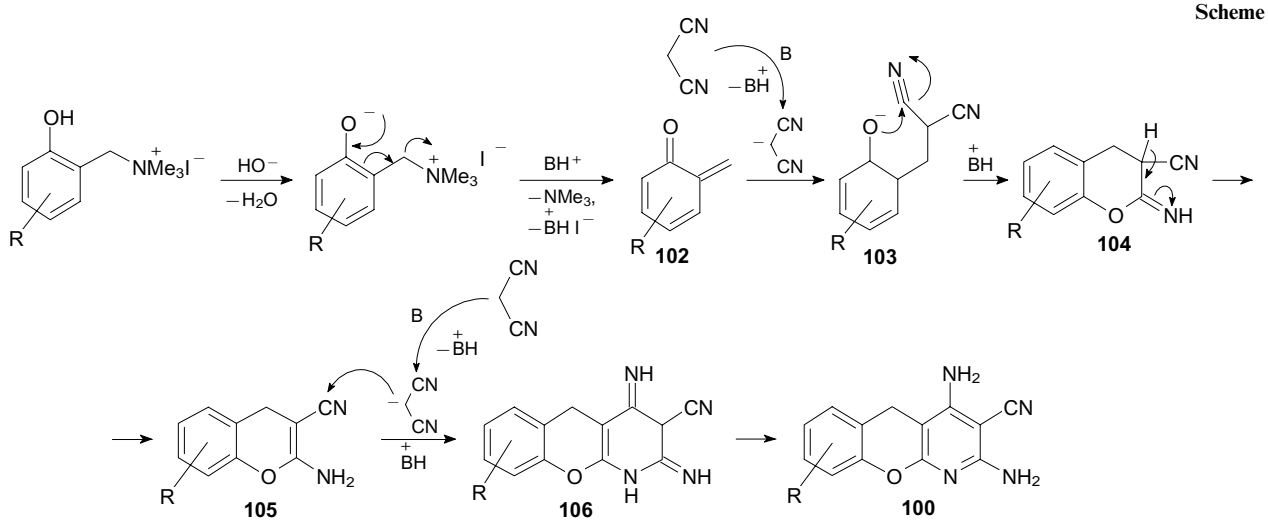



**100a**–**c** (30%–51%)

R = 7-OMe (**a**),
7,8-$Me_2$ (**b**),
7-Cl (**c**)

The authors suggest that the synthesis of chromeno[2,3-*b*]pyridines **100** (Scheme 43) proceeds *via* the intermediate **102** generated through the thermal decomposition of the quaternary ammonium salt. Then the malononitrile anion enters the Michael addition with intermediate **102** to form the anion of 2-hydroxybenzylmalononitrile **103**. Sub-

**Scheme 43**



sequent intramolecular nucleophilic attack of the hydroxyl group on the cyano group and cyclization of anion **103** (the Pinner reaction) give imine **104** after aromatization. Imine **104** undergoes tautomeric transformations into 2-amino-4*H*-chromene-3-carbonitrile **105**, to which the second equivalent of malononitrile is added. Further intramolecular nucleophilic attacks, cyclizations, and aromatizations through the formation of imine **106** afford chromeno[2,3-*b*]-pyridine **100**.

## 8. Conclusion

In recent years, methods of multicomponent, pseudo-multicomponent and one-pot design of various chromene[2,3-*b*]-pyridine systems have been actively developed. A significant part of the works in this field covers the preparation of 5-C- and 5-S-substituted compounds. The first method for the synthesis of 5-P-substituted chromeno[2,3-*b*]pyridines was elaborated, convenient and available approaches to obtain 5-C-substituted chromeno[2,3-*b*]pyridines were found, including electrochemical one.

The pyridine ring in chromeno[2,3-*b*]pyridine systems in most cases is formed from malononitrile or its dimer.[109] Other reagents forming the chromene[2,3-*b*]pyridine moiety or its substituents are very diverse.

Multicomponent procedures to obtain 5-S-, 5-P-, and even 5-N-derivatives of chromeno[2,3-*b*]pyridine are in many aspects similar to analogous reactions furnishing their 5-C-substituted analogues. Most of the formation processes of chromeno[2,3-*b*]pyridines begin with condensation, and subsequent cyclizations and tautomeric transformations give the target products.

The main and most common approach to chromeno[2,3-*b*]pyridines is the Hantzsch pyridine synthesis where reactions are carried out on heating the reactants under reflux in alcohols for several hours with addition of a basic catalyst, usually an amine. Of course, this method cannot be effective for the formation of any chromeno[2,3-*b*]pyridine system. Moreover, the need to use an equimolar amount of a catalyst and an excess of starting compounds, which sometimes reaches twofold values, as well as purification of products by column chromatography should be attributed to the drawbacks of known synthetic approaches.

Nanocatalysts have the benefits of heterogeneous catalysis and often lead to products in high yields. The possibility to easily separate supermagnetic iron particles and reuse them is undoubtedly an advantage of the method. However, the laborious synthesis of nanocatalysts, taking into account the gradual decrease in their catalytic activity is more costly in terms of the consumed resources than the synthesis of chromeno[2,3-*b*]pyridines without a nanocatalyst and is impractical for single examples.

Equally important is the use of various types of radiation, such as microwave and ultrasonic. Their use helps to accelerate the process and complete it in a few minutes with high product yields. At the same time, such activation is not generally a substitute for the use of high temperatures and, during scale-up, can lead to significant energy and material costs.

Therefore, further studies are to be expected on the preparation of novel chromeno[2,3-*b*]pyridines, in particular 5-N-, 5-O- and 5-P-substituted, which are currently underinvestigated. The best result of such work would be the formation of a common approach to the effective synthesis of chromeno[2,3-*b*]pyridines that would be based on environmental principles and would not require the use of sophisticated equipment and additional purification of the isolated products. The appearance of works devoted to the use of nanocatalysts and other catalytic methods is very likely. Such methods will only be meaningful if the catalysts are stable when reused.

The practical significance of chromeno[2,3-*b*]pyridine systems is mainly focused on their pharmacological activity. In addition, the researchers envisage the application of these compounds in OLED technology and in corrosion control.

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