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HETEROCYCLES IN FOCUS

Synthesis of isoxazolo[5,4-*b*]pyridine derivatives (microreview)

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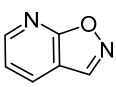


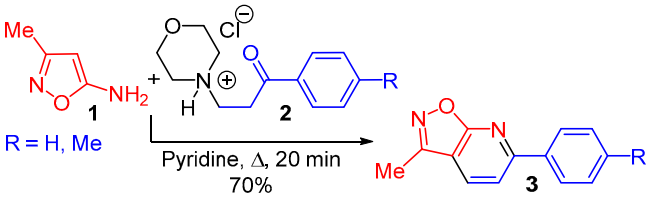
The microreview summarizes the data on heterocyclization methods leading to the formation of isoxazolo[5,4-*b*]-pyridines published over the last 5 years. The material is classified according to the method of constructing the isoxazolopyridine system.

Introduction

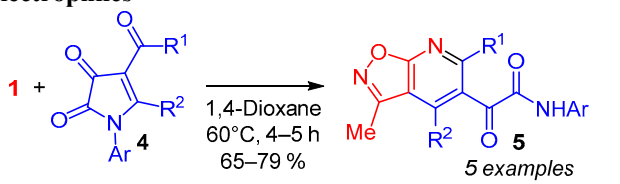
Substituted isoxazolo[5,4-*b*]pyridines and their condensed derivatives are compounds with high biological potential. They are characterized by a wide range of pharmacological activity, including antitumor activity.[1] The promising nature of this group of compounds is confirmed by the high potential of isoxazolo[5,4-*b*]pyridines in the field of agrochemistry: many derivatives have pronounced pesticidal activity and are also herbicide antidotes.[2] This microreview presents the most significant publications on the methods of synthesis of the isoxazolo[5,4-*b*]pyridine system over the 2016–2020 period.

Syntheses based on reactions of 5-aminoisoxazoles with 1,3-dielectrophiles

5-Amino-3-methylisoxazole (**1**) is the most accessible and versatile starting material for the preparation of isoxazolo-[5,4-*b*]pyridines. Review articles[3] considered earlier examples of the preparation of isoxazolopyridines based on heterocyclization reactions of 5-aminoisoxazole with 1,3-electrophilic agents. Among the newest approaches, a simple method for the preparation of substituted isoxazolopyridines from compound **1** and Mannich bases **2** in pyridine under reflux is notable.[4] The resulting products **3** exhibit antitumor activity.

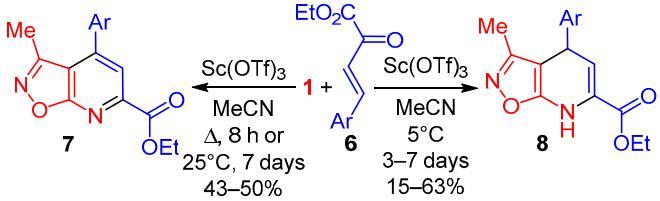


4-Acyl-1*H*-pyrrole-2,3-diones **4** undergo recycling upon treatment with isoxazole **1** to form α-ketoamides **5** in good yields.[5]



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

Functionalization of the isoxazolopyridine system at position 6 can be achieved by introducing isoxazole **1** into the reaction with keto esters **6**. Compounds **7** were obtained in moderate yields upon heating, while under milder conditions, partially hydrogenated analogs, for example, compounds **8**, can be isolated.[6]



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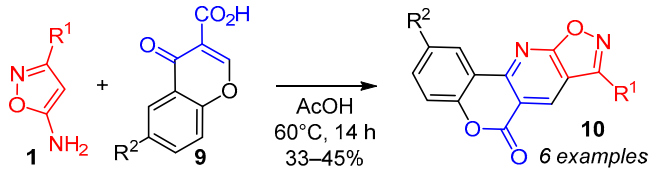
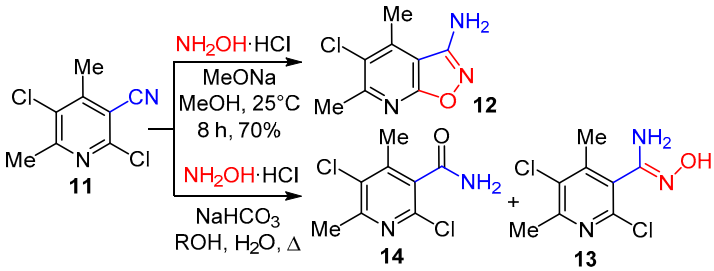
Syntheses based on reactions of 5-aminoisoxazoles with 1,3-dielectrophiles (continued)

The domino reaction of chromone-3-carboxylic acids **9** with 5-aminoisoxazoles **1** yielded a series of polynuclear heterocyclic compounds **10** exhibiting fluorescence and the ability to inhibit the activity of the enzyme ecto-5'-nucleotidase.[7]

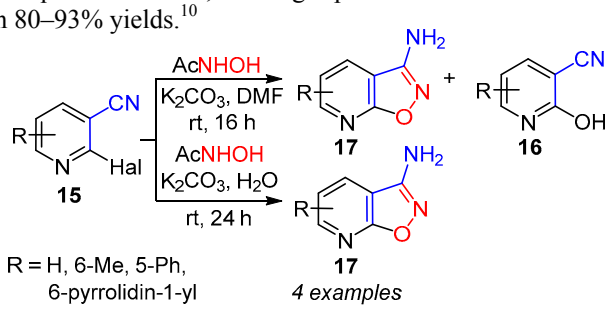


Syntheses based on hydroxylamine

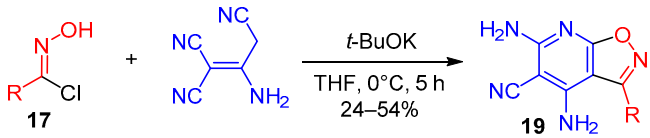
Condensation of hydroxylamine with the available 2-substituted nicotinonitriles is a convenient alternative to the above-considered aminoisoxazole-based methods.[8,9] Some of the limitations of this approach to the preparation of isoxazolo[5,4-*b*]pyridines include the difficult to predict dependence of the regiodirectivity of the reaction on the reaction conditions. Thus, nicotinonitrile **11** reacts with NH_2OH in anhydrous MeOH to form the target product **12**, whereas a mixture of the corresponding amidoxime **13** and nicotinamide **14** is formed in an aqueous ethanol solution.[8]



At the same time, the reaction of nicotinonitriles **15** with acetohydroxamic acid in DMF leads to, along with the expected isoxazolopyridines **17**, hydrolysis products **16**; in an aqueous medium, the target products **17** were obtained in 80–93% yields.[10]

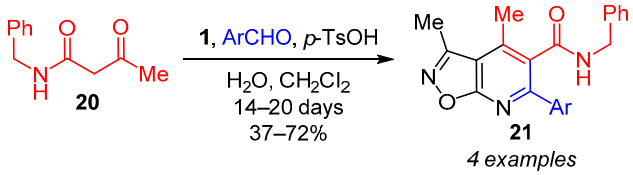


Isoxazolo[5,4-*b*]pyridines **19** were synthesized in low yields by the reaction of chloroximes **18** with malononitrile dimer in the presence of a strong base.[11]

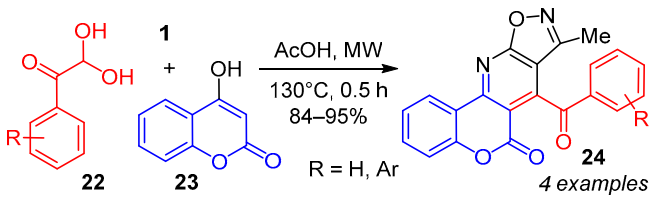


Multicomponent syntheses of isoxazolo[5,4-*b*]pyridines

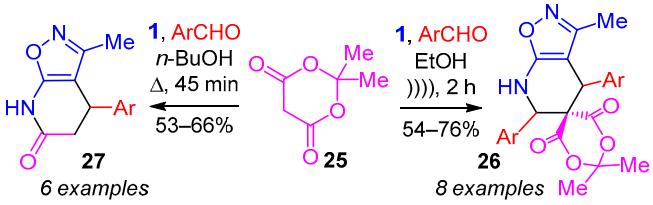
An analysis of various strategies for multicomponent synthesis of heterocyclic systems (including isoxazolo-[5,4-*b*]pyridines) based on the Michael and Hantzsch reactions is presented in reviews.[3b,12] In recent publications, multicomponent synthesis of isoxazolo[5,4-*b*]pyridines is represented by a wide range of examples, where the key reagent is 5-aminoisoxazole, whereas aldehydes, dicarbonyl compounds, isatins, etc. are used as the other heterocyclization components. Thus, the three-component reaction of isoxazole **1** with aromatic aldehydes and ketoamide **20** makes it possible to obtain isoxazolo[5,4-*b*]-pyridines **21** which exhibit antitumor activity.[13]



Condensation of arylglyoxal hydrate **22**, 4-hydroxy-coumarin (**23**), and isoxazole **1** under the conditions of microwave activation leads to the formation of annulated isoxazolo[5,4-*b*]pyridines **24** in high yields.[14]

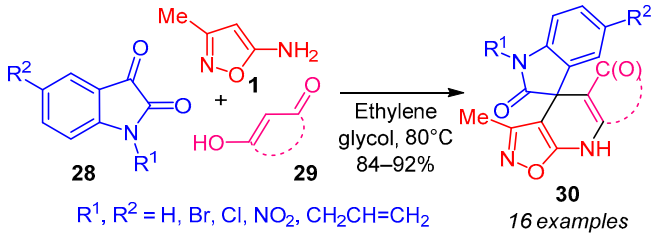


A detailed analysis of the three-component reaction of 5-amino-3-methylisoxazole (**1**) with aromatic aldehydes and Meldrum's acid (**25**) is presented in a study.[15] It was shown that under irradiation by ultrasound in EtOH, the reaction leads to the formation of spirocycles **26**, while during reflux in *n*-BuOH, the products are compounds **27**. According to the authors of the study,[15] compounds **26** are the reaction products formed under kinetic control, while compounds **27** are formed under thermodynamic control conditions. The yields of spirocycles **26** predictably increase when 2 equiv of the aldehyde is used.

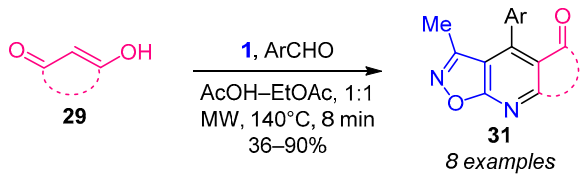


Multicomponent syntheses of isoxazolo[5,4-*b*]pyridines (continued)

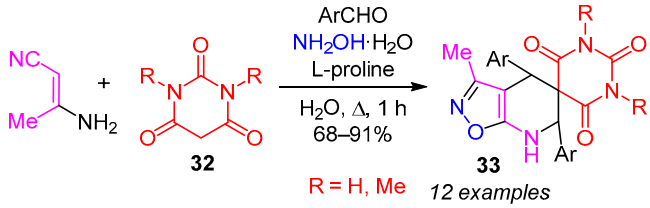
Isatins are often used for the synthesis of spiroisoxazolo-[5,4-*b*]pyridines *via* multicomponent reactions.[16–18] Thus, the three-component condensation of 5-amino-3-methylisoxazole (**1**), isatins **28**, and cyclic 1,3-dicarbonyl compounds **29** produced a series of isoxazolo[5,4-*b*]pyridines **30** exhibiting antitumor effects.[16]



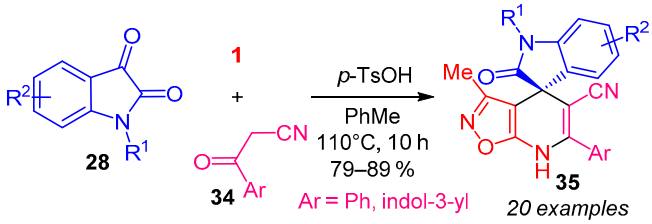
The reaction of enolizable cyclic 1,3-diketones **29** with isoxazole **1** and aromatic aldehydes under the conditions of brief microwave irradiation leads to the formation of annulated isoxazolo[5,4-*b*]pyridines **31** with changing yields.[19]



A pseudo-five-component domino reaction with the participation of acetonitrile dimer, hydroxylamine hydrochloride, aldehydes, and barbituric acids **32** leading to spirocycles **33** in high yields was described.[20] The formation of the key component (5-amino-3-methylisoxazole (**1**)) occurred *in situ* by condensation of acetonitrile dimer with hydroxylamine. It is noted that the reaction is regioselective and is not accompanied by the formation of the [3,4-*b*]-isomers.



Instead of 1,3-dicarbonyl compounds, other active metylene reagents can be used in condensation with isoxazole **1** and carbonyl components. Thus, β-ketonitriles **34** react with isatins **28** and isoxazole **1** to form spirocyclic isoxazolopyridines **35**.[21] It is noted that the maximum yields of products **35** (up to 89%) are achieved with prolonged heating of the reagents in PhMe under reflux in the presence of an acid catalyst.



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