DOI 10.1007/s10593-024-03305-3
Chemistry of Heterocyclic Compounds **2024**, *60*(3/4), 124–126

HETEROCYCLES IN FOCUS

Approaches to the synthesis of thiazolo[3,2-*a*]pyridines (microreview)

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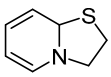
Published in Khimiya Geterotsiklicheskikh Soedinenii, 2024, *60*(3/4), 124–126

Submitted April 2, 2024
Accepted after revision May 23, 2024



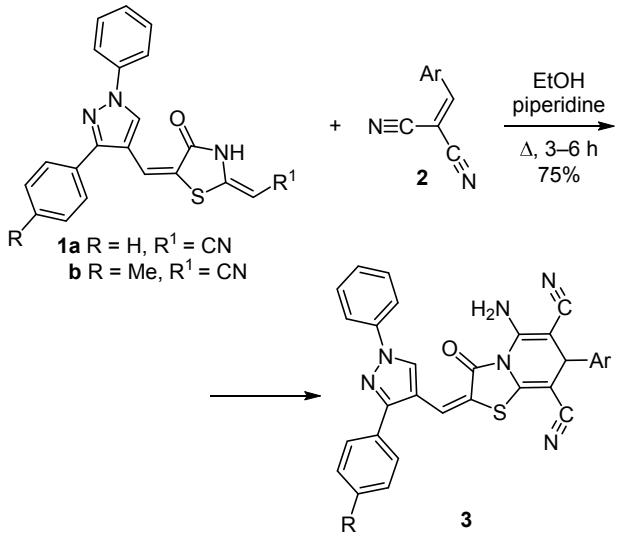
The present microreview provides a systematic and illustrative overview of the most typical methods for the synthesis of new thiazolo[3,2-*a*]pyridines. The material covers key works published since 2020.

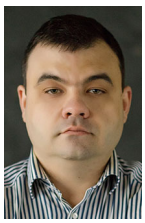
Introduction

Nitrogen-containing heterocycle pyridine occupies an important place in the field of medicinal chemistry. This privileged scaffold in the design of pharmaceutical drugs is one of the basic components of more than 7000 existing drug molecules with clinical applications.[1] Thiazole derivatives are no less interesting nitrogen-containing privileged heterocycles. Currently, there are 33 approved thiazole-containing drugs and more than 90 are at various stages of clinical trials.[2] The combination of pyridine and thiazole into one scaffold creates interesting condensed heterocyclic systems, known as thiazolopyridines, which are the subject of detailed research by many scientists around the world due to the wide range of their pharmacological activities.[3] Thiazolo[3,2-*a*]pyridines are one of the least accessible and poorly studied members of this class of organic compounds. The significant amount of data on the chemical and biological activity of this class of compounds allows us to consider them promising biologically active compounds. In recent years, antimicrobial,[4] apoptotic,[5] and antitumor[6] activities have been studied for this class of compounds with some success. It has been established that some representatives of this class of compounds are inhibitors of DNA gyrase[7] and SARS-Cov-2 glycoprotein.[8] These compounds also have many other useful properties – in particular, they are valuable functional organic materials.[9] The current paper summarizes literature data about the main synthetic approaches toward molecules containing thiazolo[3,2-*a*]pyridine.

Methods for the synthesis of thiazolo[3,2-*a*]pyridines

Recent advances in the chemistry of thiazolo[3,2-*a*]pyridines have become widespread, and many publications have been devoted to the methods of their synthesis. However, it should be noted that along with new approaches to the synthesis of compounds of this class, previously known approaches are also being successfully developed.[10] The search for new synthetic routes for this class of compounds led Mohamed et al. to a method based on the use of 4-oxothiazolidines **1a–d** as starting materials. In particular, the interaction of 2-(4-oxothiazolidin-2-ylidene)acetonitriles **1a**,**b** with 2-arylidenemalononitriles **2** in EtOH in the presence of a catalytic amount of piperidine allowed the authors to obtain 5-amino-7-aryl-3-oxo-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6,8-dicarbonitriles **3**.[7]





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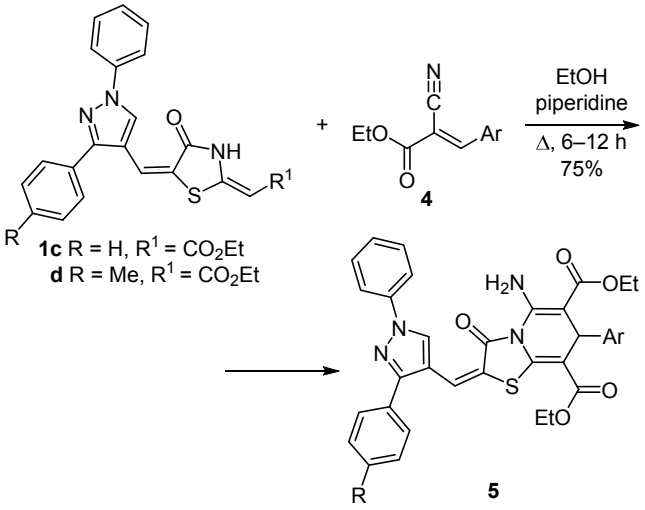
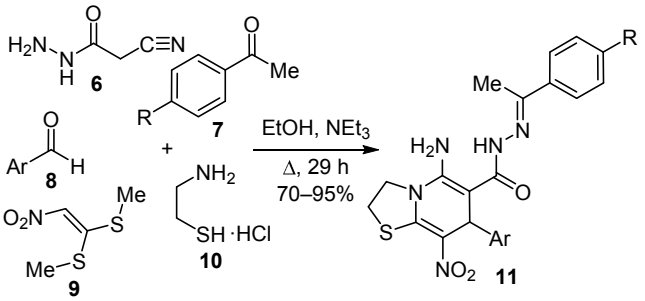
Methods for the synthesis of thiazolo[3,2-*a*]pyridines (continued)

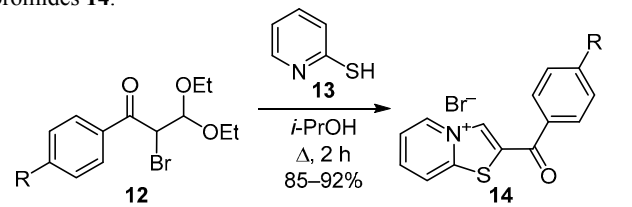
Similarly, the reaction of ethyl 2-(4-oxothiazolidin-2-ylidene)-acetate derivatives **1c**,**d** with ethyl 3-aryl-2-cyanoacrylate derivatives **4** under the same reaction conditions led to the corresponding diethyl 5-amino-7-aryl-3-oxo-3,7-dihydro-2*H*-thiazolo-[3,2-*a*]pyridine-6,8-dicarboxylates **5**.[7]



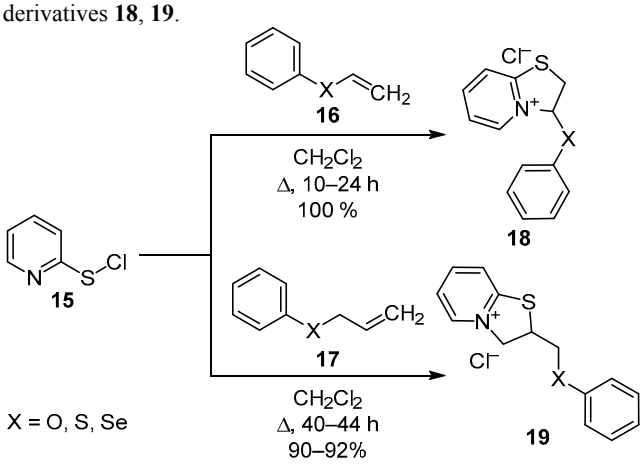
In the search for methods for the synthesis of thiazolo[3,2-*a*]pyridines, Razavi et al. developed a five-component cascade reaction based on the use of cyanoacetohydrazide (**6**), acetophenone derivatives **7**, aromatic aldehydes **8**, 1,1-bis(methylsulfanyl)-2-nitroethylene (**9**), and cysteamine hydrochloride (**10**). The above-mentioned transformation was achieved in EtOH in the presence of NEt_3 and allowed the authors to obtain 5-amino-7-aryl-*N*'-(1-aryl-ethylidene)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbo-hydrazides **11**.[11]



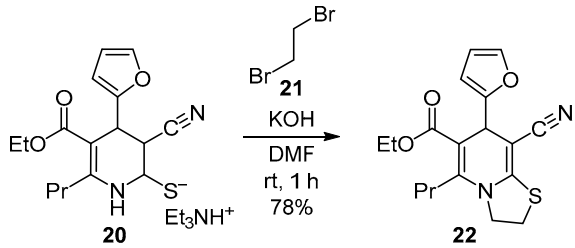
Another interesting method for closing the thiazolo[3,2-*a*]pyridine ring is the method proposed by Guseynov et al., which consists of the interaction of 1-aryl-2-bromo-3,3-diethoxypropan-1-ones **12** with pyridine-2-thiol (**13**) in dry *i*-PrOH. This transformation leads to the synthesis of 2-aroylthiazolo[3,2-*a*]pyridin-4-ium bromides **14**.[12]



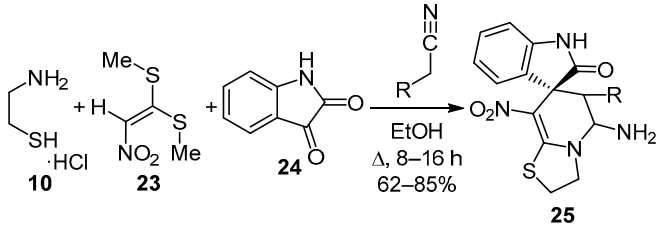
The annulation of sulfenyl chloride **15** with phenyl vinyl chalco-genides **16** and allyl phenyl chalcogenides **17** is presented in the work of Potapov et al.[13] These reactions proceeded regio-selectively, but with different regiochemical outcomes. In particular, the addition of the sulfur atom to vinyl chalcogenides occurred at the terminal atom of the double bond, while the formation of addition products in the case of allyl chalcogenides occurred against the Markovnikov rule. The presented transformations were carried out in CH_2Cl_2. Based on these reactions, the authors developed efficient one-pot methods for the synthesis of 2- and 3-substituted [1,3]thiazolo[3,2-*a*]pyridinium derivatives **18**, **19**.



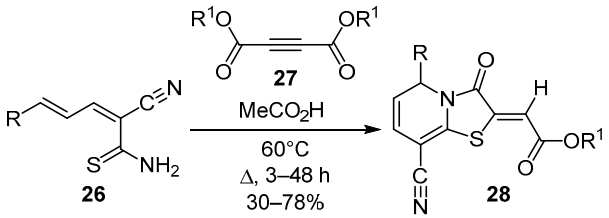
Kalashnik and Dyachenko[14] proposed a method for obtaining thiazolo[3,2-*a*]pyridines, which consists of the interaction of triethylammonium 3-cyano-5-ethoxy-4-(furan-2-yl)-6-propylcarbonyl-1,4-dihydropyridine-2-thiolate (**20**) with 1,2-dibromoethane (**21**) in DMF to form ethyl 8-cyano-7-(furan-2-yl)-5-propyl-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (**22**).



Nasri et al.[15] described a sequential multicomponent reaction of cysteamine hydrochloride (**10**), nitroketenedithioacetals **23**, isatin (**24**), and various CH acids. This method provides access to new functionalized spirooxindoles fused with thiazolopyridine **25**.

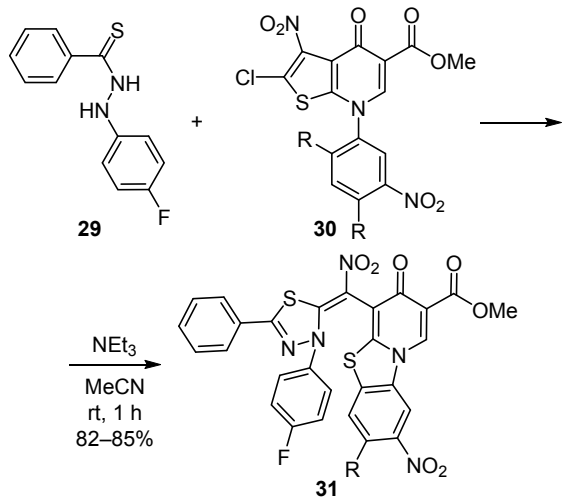


The construction of the thiazolo[3,2-*a*]pyridine ring can also be accomplished by the reaction of penta-2,4-dienthioamides **26** with acetylenedicarboxylic acid or its derivatives **27** in AcOH. The proposed method allowed the authors to obtain target 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridines **28**.[16]



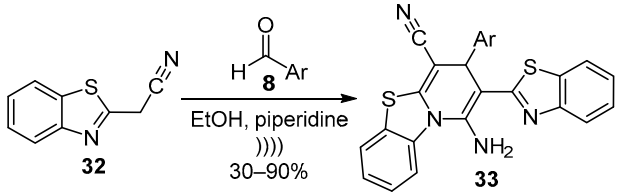
Methods for the synthesis of thiazolo[3,2-*a*]pyridines (continued)

Abadleh et al.[17] developed a method for the synthesis of thiazolo-[3,2-*a*]pyridines, which involved the reaction of *N*'-(4-fluoro-phenyl)hydrazide of thiobenzoic acid (**29**) with 2,4-dihalogen-substituted methyl 2-chloro-3-nitro-5-nitrophenyl-4-oxo-4,7-di-hydrothieno[2,3-*b*]pyridine-5-carboxylates **30**. The reaction was carried out in MeCN using NEt_3 as a catalyst. This transformation allowed to obtain (*Z*)-methyl-7-halogen-substituted 4-{3-(4-fluoro-phenyl)-5-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene](nitro)methyl}-8-nitro-3-oxo-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-2-carboxylates **31**.



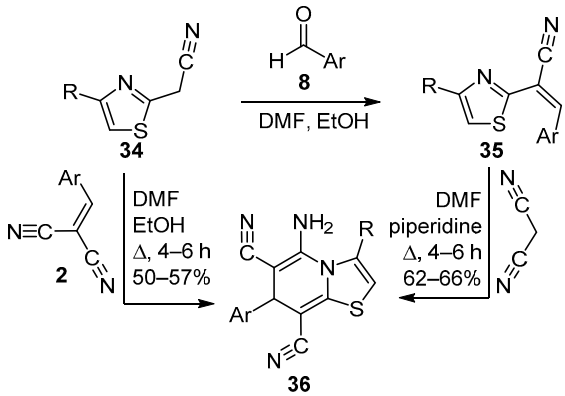
29 **30** **31**

Shirani et al.[18] proposed an interesting approach for the synthesis of 1-amino-3-aryl-2-(1,3-benzothiazol-2-yl)-3-hydrobenzo[4,5]-thiazolo[3,2-*a*]pyridine-4-carbonitriles **33**, which involved the reaction of 2-(1,3-benzothiazol-2-yl)acetonitrile (**32**) with aldehydes **8**. This transformation takes place in EtOH in the presence of piperidine as a catalyst under ultrasonic irradiation at room temperature, which provides several advantages, including shorter reaction time, cleaner reaction, and high yields.



32 **33**

In order to afford novel thiazolo[3,2-*a*]pyridines, Raslan and Sayed[19] proposed two methods for the synthesis of this class of compounds using 2-(thiazol-2-yl)acetonitriles **34** as a starting material. The first method is a two-step process. In particular, at the first stage, compound **34** reacted with aromatic aldehydes **8**, which allowed to obtain the corresponding (*Z*)-3-aryl-2-(thiazol-2-yl)acrylonitriles **35**. Further reaction of these compounds with malononitrile led to 5-amino-7-aryl-7*H*-thiazolo[3,2-*a*]pyridine-6,8-dicarbonitriles **36**. In contrast to the previous method, another method involved the reaction of compound **34** with arylidene-malononitrile derivatives **2** in the presence of a catalytic amount of piperidine. This transformation led to the same compounds **36** in one step.



34 **35** **2** **36**

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