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ГЕТЕРОЦИКЛЫ В ФОКУСЕ

Химия гетероциклических соединений

Recent advances in the synthesis of thiazolo[4,5-*b*]pyridines. Part 2: Focus on thiazole annulation to pyridine ring (microreview)

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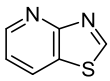
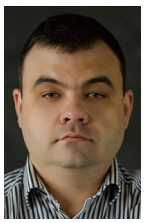


The present microreview provides access to recent advances in the synthetic approaches to novel thiazolo[4,5-*b*]-pyridines developed over the last years. This second part presents the overview and analysis of modern synthetic techniques for thiazolo[4,5-*b*]pyridine bicyclic scaffold construction starting from pyridine derivatives followed by thiazole heterocycle annulation.

Introduction

Pyridine-based heterocyclic derivatives make up one of the most significant classes of organic compounds and constitute an important part of modern-day drugs arsenal. The fraction of pyridine-containing compounds among approximately 1.5 thousand of the most commonly prescribed medicines has exceeded 10%.[2] It should be noted that condensed pyridine derivatives have attracted a considerable interest as shown in numerous studies in view of their multifaceted pharmacological effects and therapeutic applications. Such fused heteroatomic systems are often of much greater interest in terms of physiological action than related monocyclic compounds.[2] The appearance of qualitatively new properties of the annulated molecules, increasing possibilities for pharmacophore group alteration in different positions, as well as their ability to interact with a wider range of receptor targets may become the factors of crucial importance. Thiazolo[4,5-*b*]pyridines are among the most hardly accessible and insufficiently studied analogs within this class of organic compounds, and they are also biologically relevant purine bioisosteres.[3] They have been reported to possess a broad spectrum of pharmacological activities. Series of novel thiazolo[4,5-*b*]pyridines that exhibit high antioxidant,[4] antimicrobial,[5] herbicidal,[6] anti-inflammatory,[7] antifungal,[8] and antitumor[9] activities have been identified and developed in the recent years. It is worth mentioning that some representatives of this class have been also reported as histamine H3 receptor antagonists.[10]



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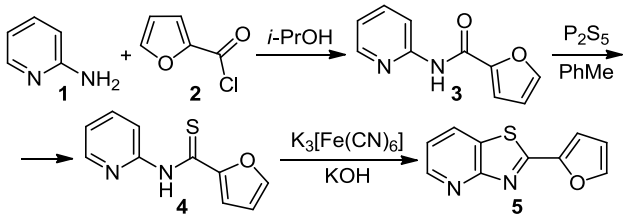
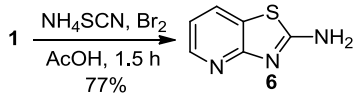
For Part 1, see.[1]

Thiazole annulation to pyridine ring

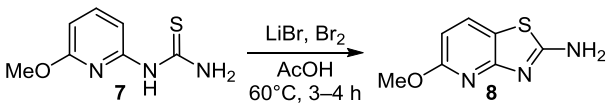
Thiazolopyridine system construction approaches starting from pyridine core containing functional groups amenable to cyclization into a fused thiazole ring are highlighted in quite numerous publications. Aleksandrov et al.[11] reported the acylation of pyridin-2-amine (**1**) with furan-2-carbonyl chloride (**2**) in propan-2-ol medium, which led to *N*-(pyridin-2-yl)furan-2-carboxamide (**3**). Further treatment of compound **3** with the excess of P_2S_5 in anhydrous toluene afforded the corresponding carbothioamide **4**. Its subsequent oxidation with potassium ferricyanide in an alkaline medium provided 2-(furan-2-yl)thiazolo[4,5-*b*]-pyridine (**5**).



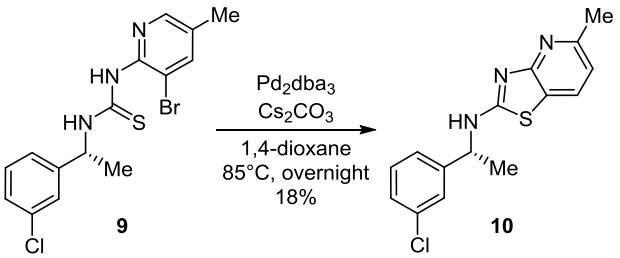
Another way of fused thiazolo[4,5-*b*]pyridine system construction starting from compound **1** exploited its condensation with ammonium thiocyanate in the presence of Br_2. The reaction proceeded in glacial acetic acid and allowed to obtain 2-aminothiazolo[4,5-*b*]pyridine (**6**).[12]



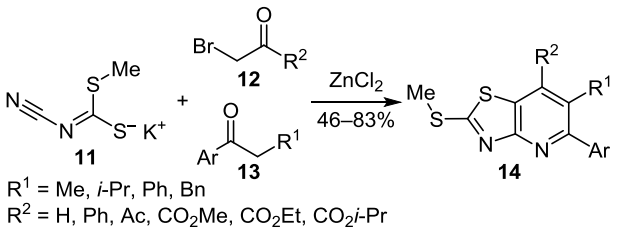
Gour et al. reported the efficient method for thiazolo[4,5-*b*]-pyridine synthesis based on 1-(6-methoxypyridin-2-yl)-thiourea (**7**) cyclization in the presence of LiBr and Br_2 in acetic acid resulting in the target 5-methoxythiazolo[4,5-*b*]-pyridin-2-amine (**8**).[13]



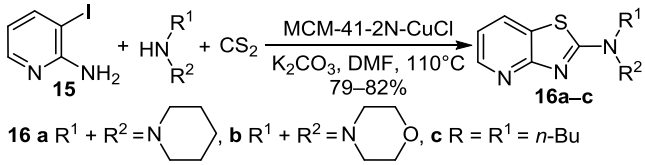
Other equally important synthetic protocol involved 1-(3-bromo-5-methylpyridin-2-yl)-3-[1-(3-chlorophenyl)ethyl]-thiourea (**9**) cyclization with dibenzalacetone palladium complex in dioxane in the presence of cesium carbonate which allowed to obtain aminothiazolo[4,5-*b*]pyridine derivative **10**.[14]

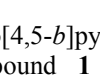


Snieckus and Gomes[15] reported three-component condensation of mercaptonitrile potassium salt **11**, appropriate α-bromo ketones **12**, and ketones **13** catalyzed by $ZnCl_2$. The proposed condensation led to 5,6,7-trisubstituted thiazolo[4,5-*b*]pyridines **14**.

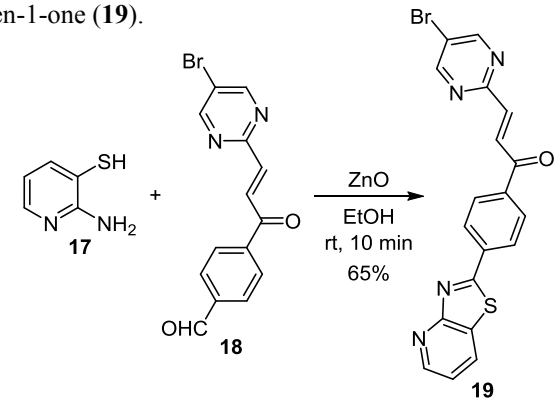


The heterogeneous copper-catalyzed cascade three-component reaction of 3-iodopyridin-2-amine (**15**), carbon disulfide, and various secondary amines was applied for the generation of 2-substituted thiazolo[4,5-*b*]pyridines **16a**–**c**.[16] The above-mentioned transformation was achieved in DMF at 110°C in the presence of 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper(I) complex [MCM-41-2N-CuCl] by using potassium carbonate as a base.

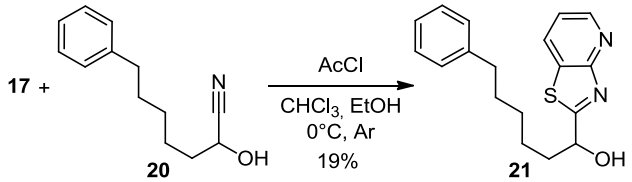


16 a $R^1 + R^2 =$  , **b** $R^1 + R^2 =$  , **c** R = R^1 = *n*-Bu

In order to afford novel thiazolo[4,5-*b*]pyridines, Koteswara Rao et al.[17] proposed a convenient preparation method based on stirrring of 2-aminopyridine-3-thiol (**17**) with 4-[(*E*)-3-(5-bromopyrimidin-2-yl)acryloyl]benzaldehyde (**18**) for 10 min in absolute ethanol medium at room temperature in the presence of zinc oxide nanoparticles. After completion of the reaction, as monitored by TLC, the solvent was evaporated under vacuum and the crude solid product was purified by column chromatography with EtOAc–hexane, 7:3. This approach allowed to obtain the target (*E*)-3-(5-bromopyrimidin-2-yl)-1-[4-(thiazolo[4,5-*b*]pyridin-2-yl)phenyl]prop-2-en-1-one (**19**).

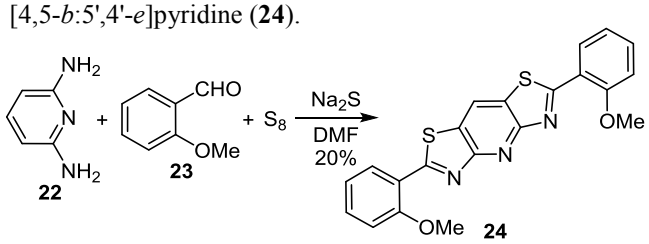


Janssen et al.[18] in their study treated an equimolar mixture of 2-aminopyridine-3-thiol (**17**) and 2-hydroxy-7-phenylheptanenitrile (**20**) in dry ethanol and dry chloroform with acetyl chloride added dropwise at 0°C under argon. The reaction produced 1-(thiazolo[4,5-*b*]pyridin-2-yl)-6-phenylhexan-1-ol (**21**).

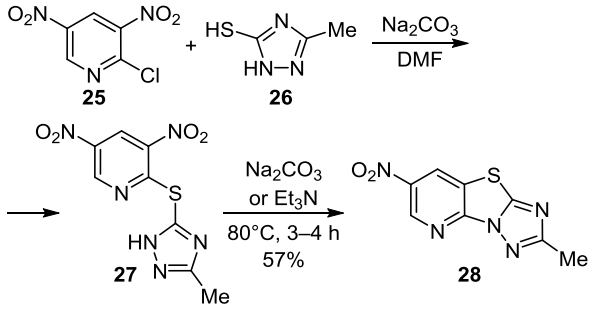


Thiazole annulation to pyridine ring (continued)

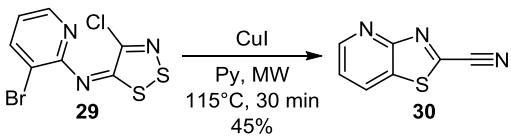
Darabi et al.[19] treated 2,6-diaminopyridine (**22**) with 2-methoxybenzaldehyde (**23**) and elemental sulfur. The mentioned interaction proceeded in anhydrous DMF in the presence of Na_2S and lead to 2,6-bis(2-methoxyphenyl)dithiazolo[4,5-*b*:5',4'-*e*]pyridine (**24**).



The two-stage method for the synthesis of fused thiazolo[4,5-*b*]pyridines was described by Starosotnikov et al.[20] First, the interaction of 2-chloro-3,5-dinitropyridine (**25**) with 3-methyl-1,2,4-triazole-5-thiol (**26**) in the presence of sodium carbonate led to the formation of 2-[(3-methyl-1*H*-1,2,4-triazol-5-yl)sulfanyl]-3,5-dinitropyridine (**27**). Compound **27** was then heated with Na_2CO_3 or Et_3N (1 equiv), which resulted in 2-methyl-7-nitro[1,2,4]triazolo[5',1':2,3]thiazolo[4,5-*b*]pyridine (**28**) obtaining.



Deau et al.[21] proposed efficient microwave-assisted synthesis of thiazolo[4,5-*b*]pyridine-2-carbonitriles **30**. A solution of 3-bromo-*N*-[4-chloro-5*H*-1,2,3-dithiazol-5-ylidene]pyridin-2-amine (**29**) in the presence of copper iodide in dry pyridine was heated under microwave irradiation (400 W) at 115°C for 30 min at atmospheric pressure.



Conclusion

Thus, it has been shown that recently reported advances in the development of synthetic protocols for thiazolo[4,5-*b*]-pyridines starting from pyridine derivatives with further thiazole cycle annulation offer a variety of methods based on two- or three-component reactions as well as intramolecular cylization.

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