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ГЕТЕРОЦИКЛЫ В ФОКУСЕ

Химия гетероциклических соединений

Recent advances in the synthesis of thiazolo[4,5-*b*]pyridines. Part 1: Focus on pyridine annulation to thiazole ring (microreview)

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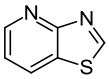
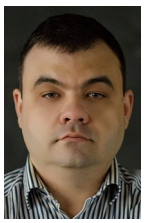


The present microreview systematizes recent advances in the synthetic approaches for novel thiazolo[4,5-*b*]-pyridines and summarizes pharmacological effects they were found to possess. In particular, modern synthetic techniques for thiazolo[4,5-*b*]pyridine bicyclic scaffold construction starting from thiazole or thiazolidine derivatives followed by pyridine annulation, which results in the target fused thiazolo[4,5-*b*]pyridines, are analyzed.

Introduction

Combination of two potentially bioactive heterocyclic moieties (thiazole[1] and pyridine[2]), both of the priority importance for medicinal chemists, into a single "matrix" may be considered as a systematic approach toward the discovery of drug-like molecules. The most important feature of the fused core scaffold prepared in this way is the presence of multiple reactive sites which enable its wide-range modifications leading to the series on novel polyfunctional analogs. Fused systems with thiazole core occupy a prominent place in medicinal chemistry due to their broad spectrum of pharmacological activities.[3] Thiazolo[4,5-*b*]pyridines[4] as purine bioisosteres incorporate the biologically relevant heterocyclic scaffold that has attracted special interest due to wide variety of their pharmacological effects in conjunction with the synthetic possibilities for the derivatives functionalization in various positions. The recent data published in the scientific literature cited a diversity of biological effects exhibited by fused thiazolo[4,5-*b*]pyridines. Some thiazolo[4,5-*b*]-pyridine derivatives were found to have high antioxidant,[5] herbicidal,[6] antimicrobial,[7,8] anti-inflammatory,[9] anti-tumor[10] activities.



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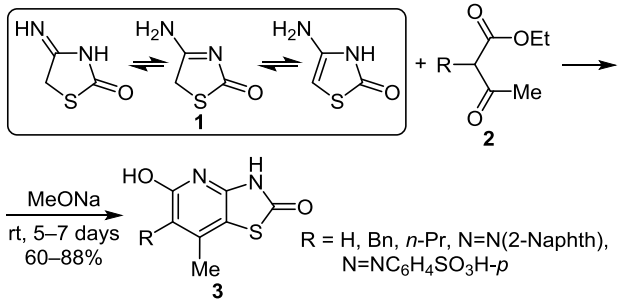
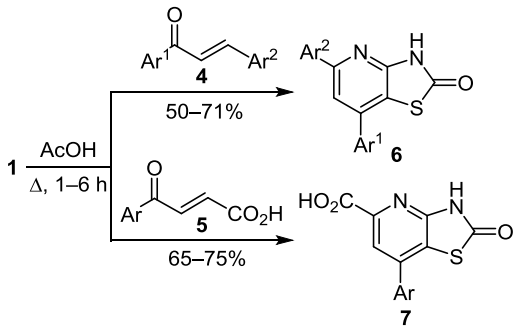
Pyridine annulation to thiazole ring

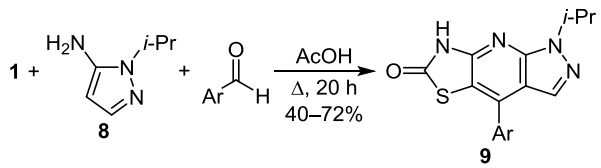
Among the numerous reported protocols for thiazolo[4,5-*b*]-pyridine construction, the most used synthetic routes are based on pyridine annulation to thiazole ring. Some of them explore 4-iminothiazolidones as precursors. They are characterized by the presence of three tautomeric forms of varying stability.[11] In particular, 4-iminothiazolidin-2-one (**1**) in the presence of MeONa reacts with β-dicarbonyl compounds **2** to afford the corresponding hardly accessible 6-*R*-5,7-disubstituted 3*H*-thiazolo[4,5-*b*]pyridin-2-ones **3**.[12]



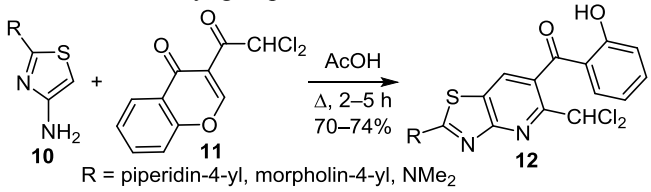
One more challenging synthetic approach is based on the involvement of compound **1** into reactions with chalcones **4** or 2-oxo-4-phenylbut-3-enoic acid and its derivatives **5**. Thus, Lozynskyi et al. reported the synthesis of 5,7-diaryl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones **6** and 2-oxo-7-phenyl-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acids **7**.[13]



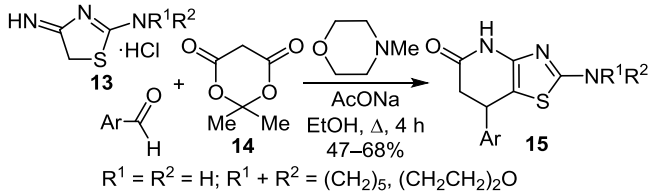
Krylov in his PhD thesis and also in the work with Komogortsev and coauthors[14] described the interaction of compound **1** with the appropriate aldehydes and a few substituted 5-aminopyrazoles **8** that proceeded in the boiling acetic acid medium affording corresponding heterocyclic systems **9** bearing thiazolo[4,5-*b*]pyridine scaffold in high yields.



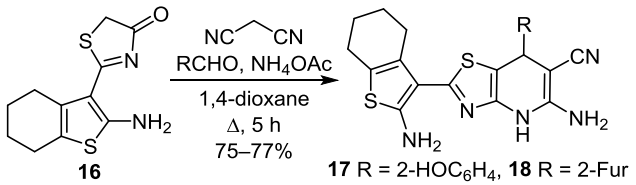
Domino reactions of heterocyclic enamines with chromone derivatives provide a beneficial synthetic technique leading to a wide variety of annulated heterocyclic systems. The interaction of 2-substituted thiazol-4-ylamines **10** with 3-(2,2-dichloroacetyl)-4*H*-chromen-4-one (**11**) allowed to obtain 2-substituted [5-(dichloromethyl)thiazolo[4,5-*b*]pyridin-6-yl](2-hydroxyphenyl)methanones **12**.[15] The reaction was accomplished through the conjugate addition of the carbon atom of compound **10** to carbon C-2 of the chromone followed by the ring cleavage and recyclization *via* the chromone carbonyl group.



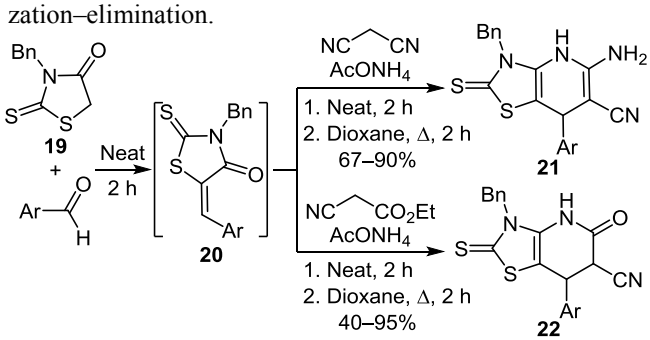
Kartsev et al.[8] showcased a three-component condensation of 2-aminothiazole derivative **13**, appropriate aldehydes, and Meldrum's acid (**14**). The best reaction conditions to obtain 6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones **15**, bearing unsubstituted or tertiary amino group at the C-2 atom of the thiazole ring, were achieved with a slight excess of AcONa and a catalytic amount of *N*-methyl-morpholine.



A multicomponent reaction between 2-(2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)thiazol-4(5*H*)-one (**16**), malononitrile, and furfural or salicylic aldehyde in 1,4-dioxane, described by Abdallah et al.,[16] afforded the corresponding 7-substituted 5-amino-2-(2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)-4,7-dihydrothiazolo[4,5-*b*]-pyridine-6-carbonitriles **17**, **18**.

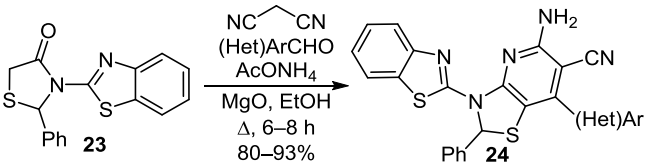


Another suggested route[17] to yield thiazolo[4,5-*b*]pyridines **21**, **22** comprised a one-pot Michael addition and cyclo-elimination cascade. In the first step, a Knoevenagel reaction of 3-benzyl-4-thiazolidine-2-thione (**19**) with aromatic aldehydes led to the formation of α,β-unsaturated ketone intermediate **20**, which, in turn, acted as the Michael acceptor, while carbanion, formed from malononitrile or ethyl cyanoacetate acted as the Michael donor. The resulting Michael adducts underwent intramolecular cyclization–elimination.

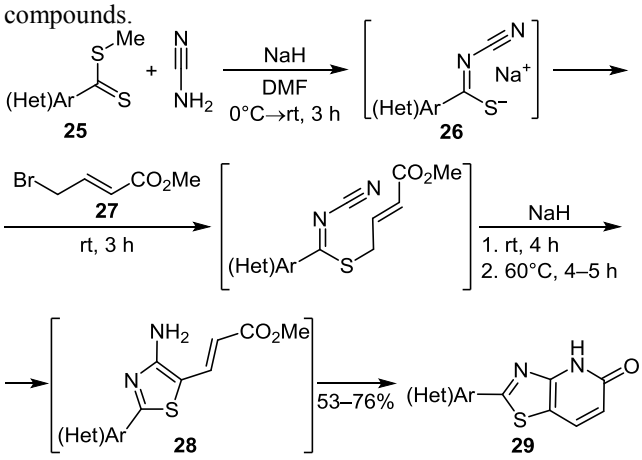


Pyridine annulation to thiazole ring (continued)

An environmentally friendly and highly efficient multi-component one-pot method has been developed by Gandhi et al.[18] for the synthesis of 5-amino-7-(het)aryl-3-(benzothiazol-2-yl)-2-phenyl-2,3-dihydrothiazolo[4,5-*b*]pyridine-6-carbonitriles **24** through the Knoevenagel condensation of thiazolidinone **23** with aldehydes and the subsequent Michael conjugate addition. Magnesium oxide was utilized as a green, low-cost, mild, and efficient heterogeneous base catalyst.



Kumar and Ila[19] proposed a synthetic approach to thiazolo-[4,5-*b*]pyridines preparation based on interaction of *N*-cyano-thioimidate salt **26** (preliminary obtained by the reaction of cyanamide with dithioester **25** in the presence of NaH) with methyl bromocrotonate (**27**) in the presence of NaH. The reaction mixture was stirred for 4 h in order to afford the corresponding 3-(4-aminothiazol-5-yl)acrylate **28**, while it was also reported that the increase of the reaction time to 4–5 h and heating of the reaction mixture led to the corresponding 2-substituted thiazolo[4,5-*b*]pyridin-5(4*H*)-ones **29** as the result of *in situ* intramolecular cyclization of acrylate **28**. Thus, the wide synthetic capabilities of this class of compounds and their high pharmacological potential are the indisputable justification for systematic studies of these compounds.



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