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HETEROCYCLES IN FOCUS

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

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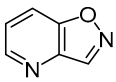


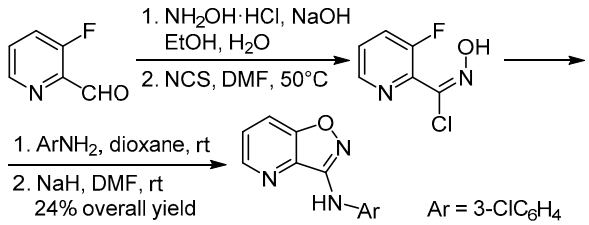
The most recent approaches toward isoxazolo[4,5-*b*]pyridine derivatives are discussed. The microreview covers the latest selected examples (2012–2022) on the synthesis of isoxazolo[4,5-*b*]pyridines *via* two main approaches: annulation of a pyridine ring to 4-aminoisoxazoles and isoxazole ring closure in functionalized pyridine derivatives. In addition, some special cases of the isoxazolo[4,5-*b*]pyridine system formation will be mentioned.

Introduction

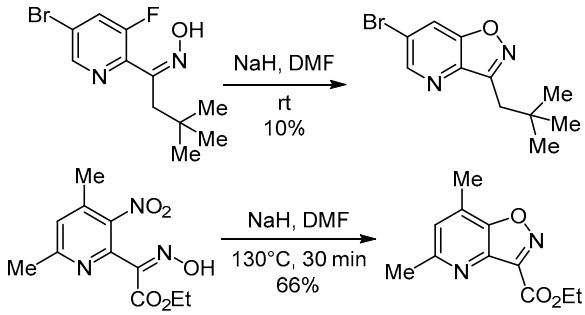
Isoxazolo[4,5-*b*]pyridines represent an interesting heterocyclic system which is not readily available to date. The overwhelming majority of these compounds are described in patents. However, there is a lack of methods for the synthesis of isoxazolo[4,5-*b*]pyridines in literature. At the same time isoxazolo[4,5-*b*]pyridines display a remarkable variety of biological activities[1] such as antibacterial,[2] anticancer,[3] and antiproliferative.[4] Isoxazolo[4,5-*b*]pyridine derivatives have also been studied as inhibitors of cytochrome P450 CYP17 which is responsible for the biosynthesis of precursors of both androgens and estrogen.[5]

Annulation of isoxazole ring to pyridines

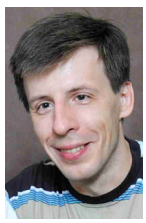
Intramolecular nucleophilic substitution of halogen or nitro group in pyridines with appropriate N–O nucleophile in position 2 is one of the most obvious approaches to isoxazolo[4,5-*b*]pyridine skeleton. For instance, reaction of (3-fluoropyridin-2-yl)carboximidoyl chloride with excess of aniline followed by intramolecular cyclization yielded 3-arylamino derivative.[6]



Similarly, 3-fluoro-[5,7] and 3-nitropyridines[8] bearing neighboring hydroxyimino group gave the corresponding isoxazolo[4,5-*b*]pyridines under the action of NaH in DMF.



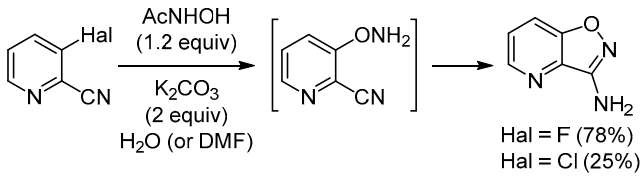
Vladislav V. Nikol'skiy was born in 1997 in Moscow, Russia. He graduated from the Moscow State University in 2021. Currently, he is a PhD student of the Laboratory of Aromatic Nitrogen Compounds at the N. D. Zelinsky Institute of Organic Chemistry. His research interests cover the chemistry of nitrogen heterocycles and nitroarenes, nucleophilic functionalization, and synthesis of polycyclic heteroarenes.



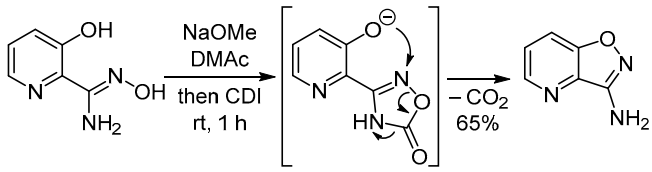
Alexey M. Starosotnikov was born in 1978 in Moscow, Russia. He graduated from the D. Mendeleev University of Chemical Technology (Higher Chemical College of the Russian Academy of Sciences) in 2000. He obtained his PhD (2003) and Doctor of Science degrees (2016) at the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. At present he is research group leader at this Institute. His research interests include chemistry of nitrogen heterocycles and aromatic nitro compounds, as well as pericyclic reactivity of aromatic systems.

Annulation of isoxazole ring to pyridines (continued)

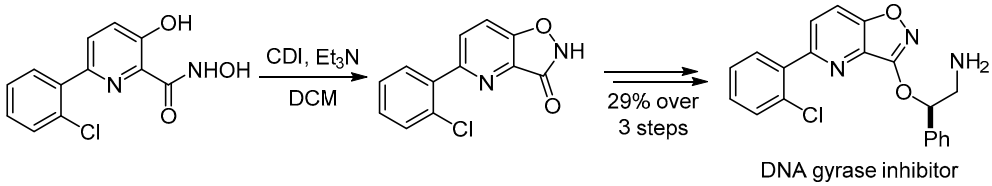
Synthesis of 3-aminoisoxazolo[4,5-*b*]pyridines has been described in a number of recent publications.[9,10] 3-Halogenated 2-cyanopyridines were used as starting materials which on reaction with *N*-hydroxyacetamide in basic media underwent successive substitution of halogen followed by cyclization of the isoxazole ring. *t*-BuOK–DMF system was also used for the cyclization, the yields were 62–71%[11].



Another example of the synthesis of 3-aminoisoxazolo[4,5-*b*]-pyridines was reported on the basis of 3-hydroxypyridine derivative.[12] The authors proposed that reaction of amidoxime with CDI afforded intermediate oxadiazolone which then underwent N–O bond formation with loss of carbon dioxide.



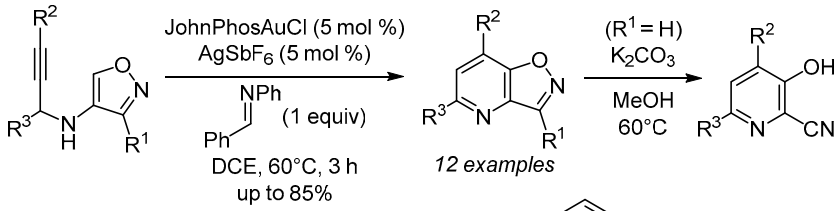
Stavenger and coworkers designed a series of heterocyclic antibacterials that allosterically inhibit DNA gyrase.[2] One of the target compounds incorporated isoxazolo[4,5-*b*]-pyridine core that was assembled on the basis of a pyridine precursor. Annulation of isoxazole ring was accomplished by CDI-mediated cyclization of *N*,3-dihydroxypyridine-carboxamide affording isoxazolo[4,5-*b*]pyridin-3(2*H*)-one in moderate yield.



DNA gyrase inhibitor

Annulation of a pyridine ring to isoxazole core

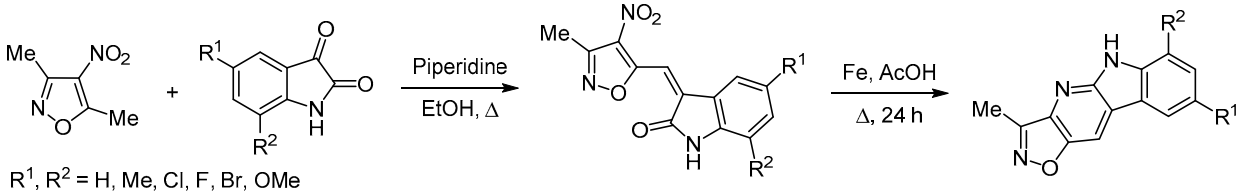
An efficient synthesis of isoxazolo[4,5-*b*]pyridines by Au(I)-catalyzed intramolecular S_EAr reaction of 4-(propargylamino)isoxazoles was reported by Nakamura and coworkers.[13] The authors demonstrated the first example of electrophilic substitution reaction at position 5 of isoxazole.



The developed method was applied to the construction of isoxazolo[4,5-*b*]pyridine fused with naphthalene *via* tandem cyclization of a diyne.[13]

Equimolar amount of *N*-phenylbenzaldimine was used as hydrogen acceptor. Later the same authors showed that base-labile 3-unsubstituted derivatives (R^1 = H) can be converted to the corresponding 2-cyano-3-hydroxypyridines under mild conditions (K_2CO_3, MeOH, 60°C).[14]

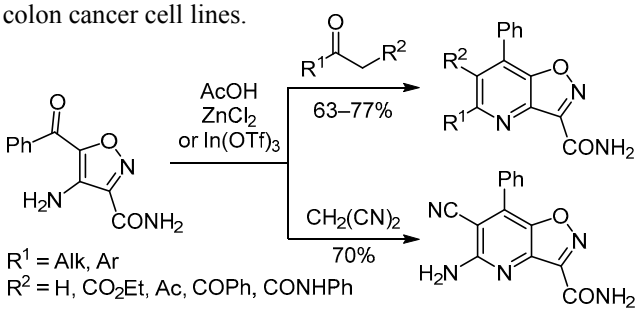
A series of polyheteroaromatic compounds incorporating isoxazolo[4,5-*b*]pyridine core were synthesized by the reaction of 3,5-dimethyl-4-nitroisoxazole with substituted isatins.[15] This one-pot process includes condensation of the isatin carbonyl group with isoxazole 5-methyl group, followed by reduction of the nitro group and subsequent pyridine ring closure. The yields were not reported. The resulting novel isoxazolo[5',4':5,6]pyrido[2,3-*b*]indoles showed potential *in vitro* and *in vivo* activity on human cancer cell lines. However, the mechanism of action needs to be clarified. Synthesis and biological evaluation of similar polycyclic derivatives containing 1,2,3-triazole moiety was also reported.[16]



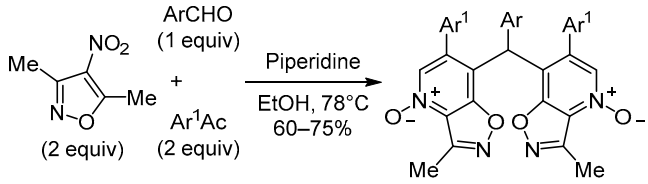
R^1, R^2 = H, Me, Cl, F, Br, OMe

Annulation of a pyridine ring to isoxazole core (continued)

Polyfunctional isoxazolo[4,5-*b*]pyridines were synthesized in moderate yields by $ZnCl_2$-catalyzed reactions of 4-aminoisoxazole with malononitrile, mono- and 1,3-dicarbonyl compounds.[4,17] The same reactions when carried out under microwave irradiation resulted in higher yields (70–86%) in considerably reduced reaction time. Some of the synthesized compounds showed high cytotoxic effect *in vitro* against colon cancer cell lines.



Rajanarendar and coworkers proposed a simple and efficient multicomponent protocol for the synthesis of bis-isoxazolo[4,5-*b*]pyridine bis-*N*-oxides starting from commercially available 3,5-dimethyl-4-nitroisoxazole, aromatic aldehydes, and acetophenones.[3] A stepwise synthesis was also studied, and the products were identical to those obtained in one-pot manner. One of the products (Ar, Ar^1 = Ph) possessed remarkable *in vitro* anticancer activity against human cancer cell lines and *in vivo* anticancer activity on EAC-bearing mice.



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