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HETEROCYCLES IN FOCUS

Recent progress in the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles (microreview)

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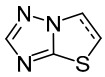


A summary of the most recent approaches toward synthesis of thiazolo[3,2-*b*][1,2,4]triazole system is reported. The microreview covers the latest selected examples on the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles *via* condensation, annulation of a multiple bond or thiirane ring, as well as C–H functionalization of thiazole moiety.

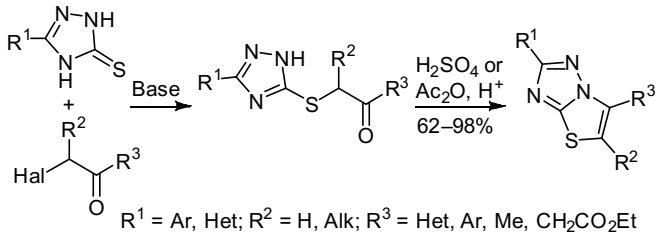
Introduction

Thiazolo[3,2-*b*][1,2,4]triazoles are highly attractive heterocyclic units because of their diverse biological activity.[1–13] They have shown anticancer,[7] antimicrobial,[2,5,6,8,12,13] analgesic,[4,9–11] antioxidant,[4] anti-inflammatory,[1,4,9–11] bronchodilatory,[5] anticonvulsant,[8] fungicide,[5,9,13] and G-quadruplex stabilizing activity.[3] Thus, development of efficient routes to construct novel thiazolo[3,2-*b*][1,2,4]-triazole derivatives is desirable. Modern synthetic approaches to thiazolo[3,2-*b*][1,2,4]triazoles can formally be divided into a few groups: condensation reactions, annulation of a multiple bond or thiirane ring, and *via* C–H functionalization of thiazole moiety.

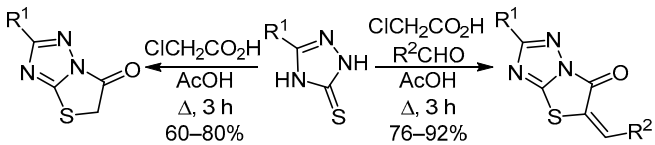
Condensation reactions to 1,2,4-triazole-3-thione/thiol

The condensation reaction of triazolethiones with α-halomethylcarbonyl compounds is the main method for the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles. This reaction can be performed in acetone at room temperature in the presence of a base (NaOAc, Na_2CO_3). The obtained thioethers can be transformed into the corresponding thiazolo[3,2-*b*][1,2,4]triazoles under the action of sulfuric acid or acetic anhydride in acidic medium.[1–5] The synthesis of thiazolo[3,2-*b*][1,2,4]triazoles proceeds *via* oxidative alkylation with acidic condensation and MW irradiation.[6]

Also 2-chloroacetic acid as the alkylating agent is used in the reaction of 1,2,4-triazole-3-thiones.[14–16] As a result the thiazolo[3,2-*b*][1,2,4]triazolones were obtained. If the (het)-arylcarbaldehyde is added to the reaction mixture, a variety of thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones with different 5-(het)arylidene substituents can be synthesized.[7–11,17]



R^1 = Ar, Het; R^2 = H, Alk; R^3 = Het, Ar, Me, CH_2CO_2Et



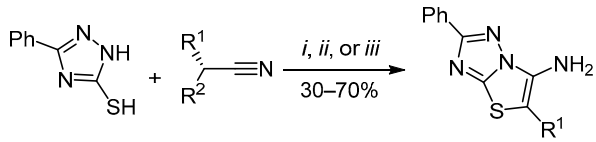
R^1 = Alk, Ar; R^2 = Ar, Het

Nataliya Korol was born in 1991 in Uzhhorod, Ukraine. She graduated from the Uzhhorod University, obtaining her Master of Science degree in organic chemistry in 2013. She is currently working toward her PhD under the supervision of Prof. M. Slivka. Her research interests focus on studying synthesis of functionalized and condensed triazoles, their reactivity and pharmacology of triazole-containing condensed systems.

Mikhailo Slivka was born in 1974 in Uzhhorod, Ukraine. He graduated with honors from the Uzhhorod University in 1996 and obtained his PhD in organic chemistry at the Institute of Organic Chemistry in Kyiv, in 2001. At present, he is Associate Professor and research group leader at the Uzhhorod University. His scientific interests include synthesis of functional and condensed heterocycles, investigations of their reactivity and application.

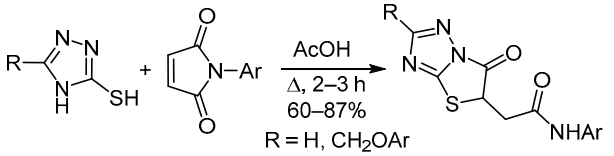
Annulation of a multiple bond or thiirane ring

5-Phenyl-1,2,4-triazole-3-thiol was treated with a variety of cyano compounds containing active methylene group in boiling acetic acid in the presence of sulfuric acid to give the corresponding 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*]-[1,2,4]triazoles in moderate yields.[12,18]



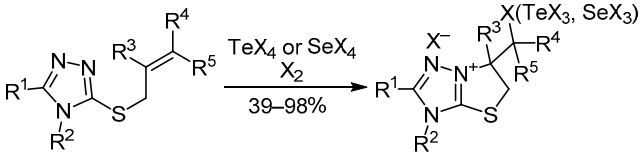
i: AcOH, H^+, Δ, 3 h; *ii*: KOH, H_2O, rt; *iii*: *t*-BuOK, *t*-BuOH, Δ, 6–8 h
R^1 = H, CN, $CONH_2$, CO_2Et; R^2 = Br, H

Reaction of mercaptotriazoles with various *N*-arylmaleimides in acetic acid medium yielded *N*-aryl-2-(6-oxo-5,6-dihydro[1,3]thiazolo[3,2-*b*][1,2,4]triazol-5-yl)acetamides.[7,13] From the structure–biological activity relationship of the obtained compounds it appears that the presence of groups like Cl or F at position 4 of both the phenyl rings resulted in considerable increasing of their activity.



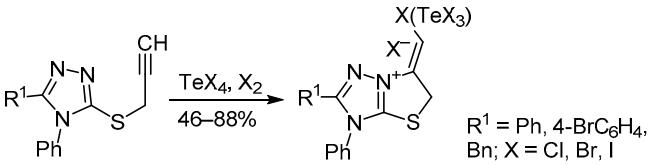
R = H, CH_2OAr

A regioselective method for the preparation of 5,6-dihydro-[1,3]thiazolo[3,2-*b*][1,2,4]triazolium salts *via* electrophilic heterocyclization of 3-alkenylsulfanyl-4*H*-1,2,4-triazoles was reported.[14,19–21] This cyclization was carried out in acetic acid medium at room temperature. The title thiazolo-triazolium salts may be used for the preparation of vinyl polyfunctional derivatives of symmetrical triazoles.[19]



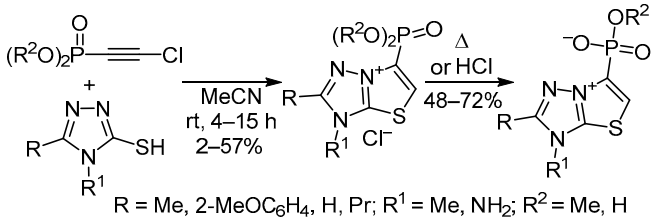
R^1 = Ar, Bn; R^2 = Ph, Me; R^3, R^4, R^5 = H, Me; X = Cl, Br, I

Unsaturated derivatives of thiazolo[3,2-*b*][1,2,4]triazolium salts can be produced *via* the same technique from propargyl thioethers of 4*H*-1,2,4-triazole.[22]



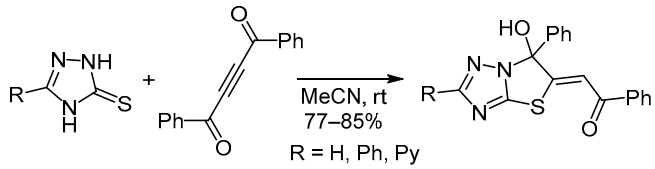
R^1 = Ph, 4-BrC_6H_4, Bn; X = Cl, Br, I

Reaction of dialkyl 1-chloroacetylene-2-phosphonate with 4-amino-5-methyl-1*H*-1,2,4-triazole-3-thiol proceeds readily under mild conditions affording in high selectivity 6-(dialkoxyphosphoryl)-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ylium chlorides. Prolonged exposure of the obtained intermediate to water or heating in a polar solvent at 50–70°C resulted in cleavage of one alkyl group of the dialkoxyphosphoryl fragment with the formation of a zwitterionic structure.[23]



R = Me, 2-$MeOC_6H_4$, H, Pr; R^1 = Me, NH_2; R^2 = Me, H

Functionalized thiazolo[3,2-*b*]triazoles were obtained by the reaction of dibenzoylacetylene and 1,2,4-triazole-3-thiones with excellent yields without the use of catalyst.[24]



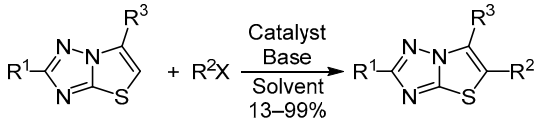
R = H, Ph, Py

Interaction between 3,5-dibromo-1-(thiiran-2-ylmethyl)-1,2,4-triazole and secondary amines leads to opening of the thiirane ring with formation of 1-(3-amino-2-mercapto-propyl)-3,5-dibromo-1,2,4-triazole. Further cyclization of the intermediate under reflux in ethanol for 3 h gives 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazoles. 2-Bromo-5-(piperidin-1-ylmethyl)-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole can also be obtained in 83% yield in the KOH-mediated reaction of 3,5-dibromo-1,2,4-triazole with 1-(thiiran-2-ylmethyl)piperidine.[25]

NRR^1 = BnNH, CyNH, $(Et)_2N$, piperidin-1-yl, azepan-1-yl, PhNH, 4-$EtO_2CC_6H_4NH$

Functionalization of thiazole moiety at the C-5 atom

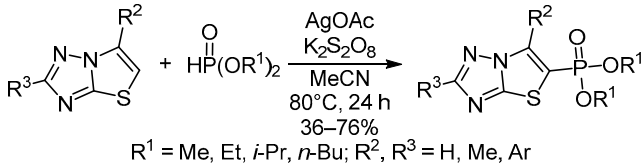
An efficient Pd-, Cs-, Ru-, Cu-catalyzed direct C-5 arylation of thiazolo[3,2-*b*][1,2,4]triazoles with aryl halides[26–30] or arylsulfonic acid sodium salt[31] was developed under different conditions. These methodologies were successfully applied for the synthesis of 5-substituted thiazolo[3,2-*b*]-[1,2,4]triazoles generally in good yields.



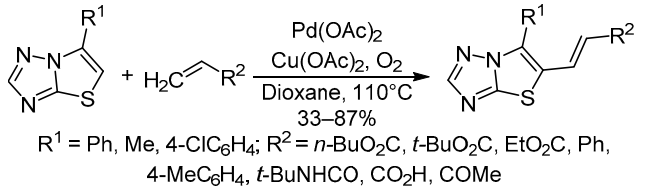
R^1 = H, Alk, Ar; R^2 = Ar, Het; R^3 = Ph, 4-BrC_6H_4, 4-MeC_6H_4, Me; X = Br, I, SO_2Na

Functionalization of thiazole moiety at the C-5 atom (continued)

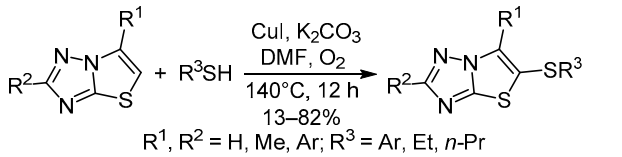
Silver-catalyzed direct regioselective phosphonation of thiazolo[3,2-*b*][1,2,4]triazoles with dialkyl phosphites was reported and the reaction mechanism was discussed in detail.[32]



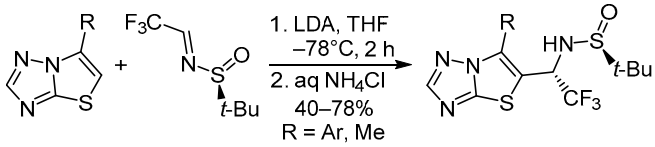
An efficient and regioselective palladium-catalyzed oxidative cross-coupling reaction between 2,5-unsubstituted thiazolo[3,2-*b*][1,2,4]triazoles and alkenes has been developed providing easy access to functionalized 5-alkenyl-substituted thiazolo[3,2-*b*][1,2,4]triazole derivatives.[33]



A simple and regioselective strategy has been developed to obtain a variety of 5-sulfanylated thiazolo[3,2-*b*][1,2,4]-triazoles *via* direct CuI-catalyzed sulfanylation with thiols.[34]



The reaction between C-5-lithiated thiazolo[3,2-*b*][1,2,4]-triazoles and enantiomerically pure (*S,S*)-*N*-*tert*-butane-sulfinyl-3,3,3-trifluoroacetaldimine leads to the formation of thiazolo[3,2-*b*][1,2,4]triazoles with a chiral (trifluoro)-ethylamine group at position 5.[35,36]



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