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Tetrazolethiones: synthesis and S-functionalization reactions (microreview)

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N-NH This review presents current data (2007–2015) on the methods of synthesis of tetrazole-5-thiones and their V_N S-functionalization.

Introduction =

In the last decade, tetrazoles have attracted the attention of chemists thanks to a variety of applications in medicine,¹ agriculture,² as well as energetic materials³ and ligands to produce stable complexes.⁴ Tetrazole-5-thiones are of particular interest. The presence of an additional reaction center (sulfur atom) in the structure of tetrazole-5-thiones makes them suitable synthons for accessing a number of novel compounds and materials. Thus, heterocyclic sulfones, obtained by oxidation of tetrazolyl sulfides, are



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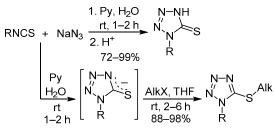


Dmitry Gymnanovich Kim was born in 1948 in Pskent, Uzbekistan. He graduated from the Faculty of Chemistry of the Irkutsk State University (ISU) in 1972, from 1972 to 1975, he studied in graduate school at A. E. Favorsky Irkutsk Institute of Organic Chemistry. In 1977 he defended his candidate thesis (ISU), while in 2004 his doctoral thesis (Ural State Technical University). Currently he is head of the Department of organic chemistry, SUSU, D.Sci., Professor. His research interests include chemistry of heterocyclic compounds, halocyclization reactions. He is the author of 170 publications, including 4 reviews in Chemistry of Heterocyclic Compounds. widely used in modern synthetic organic chemistry for the selective and efficient olefination of aldehydes by the Julia–Kocienski method.⁵ For example, using 1-(*tert*-butyl)-tetrazolyl sulfone in reactions of this type affords Z-tri-substituted alkenes with high efficiency, avoiding the separation of diastereomers.^{5b} Whereas chemistry of tetrazoles as a whole has been the focus of literature reviews,⁶ tetrazolethiones have not yet found detailed coverage in review literature.

Synthesis of tetrazole-5-thiones

The traditional approach to the synthesis of tetrazolethiones, first proposed by Lieber et al. in 1957,⁷ is based on the reaction of isothiocyanates with NaN₃ in water or ethanol. Significant disadvantages of this method are the limited number of suitable isothiocyanates, severe reaction conditions (heating for 4–8 h), and low yields.

The use of pyridine as the base in this reaction leads to the completion of the process already after 2 h at room temperature to give 1-substituted 1*H*-tetrazole-5-thiones in 72–99% yields.⁸ Also provided is a convenient and efficient one-pot method for the synthesis of 1-substituted 5-alkylsulfanyl-1*H*-tetrazoles from isothiocyanates and NaN₃ followed by addition of alkyl halides.



 $\begin{array}{l} {\sf R} = {\sf Et, All, n}{\sf .Pr, n}{\sf .Bu, Cy, Ph, Bn, (CH_2)_2Ph, 4}{\sf .MeC_6H_4, \\ {\sf 4}{\sf .ClC_6H_4; Alk} = {\sf Me, C_6H_{13}, (CH_2)_2Ph, (CH_2)_3Ph} \end{array}$

Synthesis of tetrazole-5-thiones (continued) :

Substitution of isothiocyanates with arylthiocyanates in the reaction with NaN₃ allows for an easy one-step synthesis of *S*-aryl derivatives of 1*H*-tetrazole-5-thiones. Thus, 2-amino-4,6-dimethoxy-5-(1*H*-tetrazol-5-ylsulfanyl)pyrimidine was obtained by reacting thiocyanatopyrimidine with NaN₃ in the presence of NH₄Cl in DMF.⁹

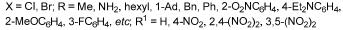
Haidar et al. have developed a new technique for the Me_2N synthesis of 1-aryl(alkyl)-1*H*-tetrazole-5-thiones from tetramethylthiuram disulfide *via* isolation of intermediate S-substituted 1,1-dimethylthiourea.¹⁰

An alternative method of preparing tetrazolethiones involves the use of tetrazol-5-ones as precursors. A series of 1-substituted 4-methyl-1*H*-tetrazole-5-thiones was obtained by the action of P_2S_5 on the corresponding 4-methyl-1*H*-tetrazol-5-ones.¹¹ Lawesson's reagent is also used as a thiocarbonylating agent in such reactions.¹²



It is known that tetrazolethiones are ambident nucleophiles. However, in alkylation reactions with different alkyl halides they act solely as S-nucleophiles.^{1b,13} Thus, a series of 1-alkyl/aryl-5-benzylsulfanyl-1*H*-tetrazoles was synthesized *via* a reaction of 1-substituted 1*H*-tetrazole-5-thiones with the corresponding benzyl halides under phase-transfer catalysis conditions or in acetonitrile in the presence of Et₃N.^{1b}



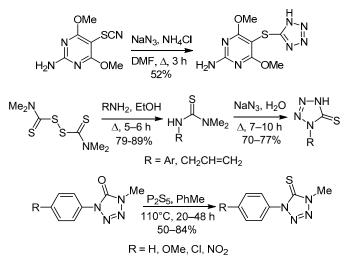


The reaction of *N*-boryltetrazolethione with benzyl bromides by heating in acetonitrile similarly proceeds regiospecifically to form the S-alkylation products.^{13b}

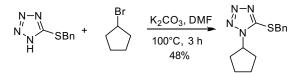


Arylation

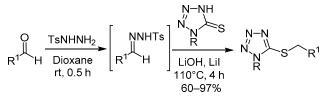
Methods for the synthesis of 9-alkyl-6-(1-methyl-1*H*-tetrazol-5-ylsulfanyl)-9*H*-purines¹⁶ and 2-ethoxy-3,5,6-trifluoro-4-(1-methyl-1*H*-tetrazol-5-ylsulfanyl)pyridine¹⁷ have been



Only further alkylation of 5-aryl/benzylsulfanyl-1*H*-tetrazoles with alkyl halides leads to the corresponding *N*-derivatives.^{9,14} 5-Benzylsulfanyl-1-cyclopentyl-1*H*-tetrazole was synthesized by the action of cyclopentyl bromide on benzyl-sulfanyltetrazole by heating in DMF in the presence of K_2CO_3 .¹⁴

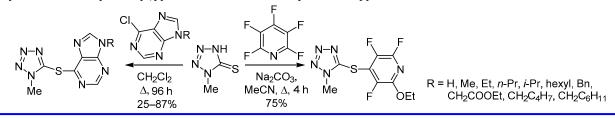


A fundamentally new, simple, convenient one-pot method for the synthesis of alkyl(1*H*-tetrazol-5-yl)thioethers has been developed, comprising condensation of aldehydes with *N*-tosylhydrazine to produce tosylhydrazones, which are then used *in situ* in reactions with 1*H*-tetrazole-5-thiones.¹⁵



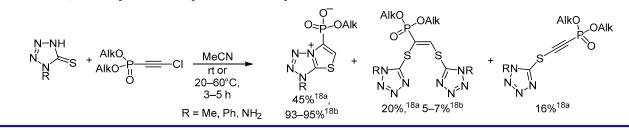
R = Me, Ph, t-Bu; R^1 = Et, Ph, (CH₂)₂Ph, 2-furyl, (CH₂)₄N(Bn)(R²)

proposed based on the reaction of 1-methyl-1*H*-tetrazol-5-thione with respectively 9-alkyl-6-chloro-9*H*-purines or pentafluoropyridine.



Reactions with chloroethynylphosphonates

The reaction of 1-substituted 1*H*-tetrazole-5-thiones with an equimolar amount of dialkyl chloroethynylphosphonates in acetonitrile proceeds ambiguously. According to ¹H, ¹³C, and ³¹P NMR, the major reaction product is the cyclic thiazolotetrazole zwitterion, whereas the phosphonate and thioethynylphosphonate are formed in negligible amounts.¹⁸



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