Synthesis of Isothiazoles and Nitroisothiazoles

Isothiazole, the sulphur analogue of isoxazole, is relatively a new ring system. Adams and Slack first published the report on mononuclear isothiazoles in 1956.\textsuperscript{214} The chemistry of isothiazole has been reviewed by Adams and Wooldridge in 1965\textsuperscript{215} and by Wooldridge in 1970.\textsuperscript{216} The subject has been reviewed periodically by Kurzer\textsuperscript{217-220} and Davis.\textsuperscript{221} A comprehensive account on the chemistry of isothiazoles has been reported by Campbell.\textsuperscript{222}

Only a few nitroisothiazoles have been reported in the literature. They have been prepared through the nitration of preformed isothiazoles. These nitroisothiazoles have been prepared in high yields by nitration with concentrated sulfuric and fuming nitric acid or sulfuric acid and potassium nitrate.\textsuperscript{223-225}

5-Acylamido-3-methylisothiazole has been nitrated with concentrated sulfuric acid-fuming nitric acid to yield
4-nitroisothiazole (328). The presence of 5-acylamido, 3-or 5-alkyl, and 5-halogeno groups do not interfere during the nitration of isothiazole, but 5-aminoisothiazole undergoes nitration to give 5-nitramino derivatives.

A few 4-nitroisothiazolines have been prepared through the oxidative cyclization of thioamide (230), obtained by the condensation of nitroketeneaminals (329) with isothiocyanates. Bromine in ethyl acetate has been utilized as the oxidising agent to yield nitroisothiazoline (229) via N-S bond formation.
Recently, the direct formation of isothiazolines, even in the absence of the added oxidising agents, is reported in some of the reaction of acyl isothiocyanates with nitroketene S,N-acetals and nitroketene aminals.\(^{226}\)

The general method for the synthesis of 5-substituted aminoisothiazoles (330) reported by Goerdeler et al. involves the oxidative cyclization of the C-adduct of primary enamines with isothiocyanates (331).\(^{227-231}\)
A variety of 4-functionalized isothiazoles, such as 4-cyano, 4-acetyl, 4-carbethoxy isothiazoles with alkylamino and arylamino substituent at the 5-position have been synthesized by such an approach using appropriate enamine-isothiocyanate adduct ($R_2 = \text{CN, COOEt, COOR}$).

The synthesis of 4-nitroisothiazoles ($R_2 = \text{NO}_2$) by this approach, though attractive, is limited in scope because of the inaccessibility of the primary nitroenamines (332) and their C-adducts with isothiocyanates.

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\begin{align*}
\text{O}_2\text{N} & \quad \text{R} \\
\text{NH}_2
\end{align*}
\]

Hartke and Co-workers have synthesized a few 3-aminoisothiazoles by the reaction of $\beta$-mercaptoacrylonitrile with chloramine or hydroxylamine-O-sulfonic acid. The reaction possibly involves the initial S-N bond formation to yield the sulfenamides (333) which undergo intramolecular cyclization to the 3-aminoisothiazoles (334).
This method has been applied to the cyclization of thioacyl derivatives of malononitrile, ethyl cyanoacetate and diethylcyanomethanephosphonate to obtain 4-cyano, 4-carbethoxy, and 4-diethylphosphono-3-aminoisothiazoles (335), (336) and (337).
Similarly, amination of 2-mercapto-3-cyanopyridine has been employed by Gewald and co-workers for the synthesis of 3-aminoisothiazolopyridines (338).235

Recently, 2-mercapto-3-formylquinoline (339) and 2-mercapto-3-acetylthiophene (340) has been cyclized to isothiazolo[5,4-b]quinoline (341)236 and thieno[2,3-d]isothiazole (342)237 employing chloramine.
Similarly, 5-arylisothiazoles (343) have been prepared by the cyclization of aryl 2-dimethylaminovinylthio-ketones (344) with hydroxylamine-o-sulfonic acid.\(^{238}\)

![Chemical Structures](image)

Enethiolizable monothio\(\beta\)-dicarbonyl derivatives, such as thioamide derivatives (345) derived from the condensation of phenyl isothiocyanate with active \(\alpha\)-methylene ketones, have been cyclized with chloramine to yield 4-substituted-5-aminoisothiazoles (346).\(^{239}\)