1,2,3-Dithiazole chemistry in heterocyclic synthesis

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Abstract
The chemistry of various 5H-1,2,3-dithiazoles is investigated with emphasis on assisted ring opening and ring closure reactions leading to new heterocycles. Thus on treatment with catalytic tetraalkylammonium iodide N-(2-chloropyrid-3-yl)- and N-(4-chloropyrid-3-yl)-4-chloro-1,2,3-dithiazol-5H-imines 19 and 20 give thiazolo[5,4-b]pyridine-2-carbonitrile 16 and thiazolo-[4,5-c]pyridine-2-carbonitrile 17 respectively. Similar treatment of bisdithiazoles 29 and 30 afford high yielding routes to 1,3,4-thiadiazole-2,5-dicarbonitrile 31 and thiazole-2,4,5-tricarbonitrile 32 respectively. N-(Pyrid-3-yl)-4-chloro-1,2,3-dithiazol-5H-imine 36 reacts with secondary alkylamines to give as main product pyrido[2,3-d]pyrimidines 37 and several minor byproducts including a deep green quinoidal 2,2'-bithiazole 40. Dithiazolylidenacetonitriles 43 react with either anhydrous HBr or tetraalkylammonium chloride to afford a series of 3-halo-4-substituted-isothiazole-5-carbonitriles 45 and 52 respectively. The reactions of dithiazoles 43 with tetraalkylammonium chloride are complicated owing to the formation of isothiazolo-pentathiepin-8-carbonitrile 53, isothiazolodithiin-4,5,7-tricarbonitrile 54, tetracyanothiophene 56 and an unidentified compound 55 whose possible structures are proposed. The mechanistic rationales for the formation of the identified products are proposed.

Keywords: Heterocycle, dithiazole, isothiazole, thiazole, acetylene

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Introduction

1,2,3-Dithiazole is one of the four possible dithiazole systems all of which are reported in the literature as cations. The salts are planar, $6\pi$ and therefore aromatic and can be adequately represented by three canonical forms where the charge (identifying the three most electrophilic sites) is distributed at C-5 or on either of the ring sulfur atoms (Scheme 1).

![Scheme 1](image)

Scheme 1

1,2,3-Dithiazolium salts are commonly prepared from substituted acetonitrile derivatives to afford the 5-substituted-4-chloro-1,2,3-dithiazolium chlorides $1,1,2$. One example has appeared in the literature where phenylacetoxime was treated with disulfur dichloride to afford the 5-chloro-4-phenyl-1,2,3-dithiazolium chloride $2$ and development of this route could provide access to 5-chloro-4-substituted-1,2,3-dithiazolium salts. $3,4$

Our interest focuses on the chemistry of the readily available 4,5-dichloro-1,2,3-dithiazolium chloride $3$ prepared from chloroacetonitrile and disulfur dichloride. $5$ Dithiazolium chloride $3$ on treatment with nucleophilic species affords neutral $5H$-dithiazoles $4$ (eg. treatment of dithiazolium $3$ with $H_2O$, aniline, diethyl malonate or $H_2S$ provides 1,2,3-dithiazolone $5$,
dithiazolimine 6, dithiazolylidene 7 and dithiazolethione 8 respectively in good yields (Scheme 2).\(^5\)

\[
\begin{array}{ccc}
\text{Cl} & \text{Cl} & \text{Cl} \\
\text{S} & \text{S} & \text{N} \\
\text{Cl}^{-} & + & \text{H}_{2}\text{X} \\
\end{array}
\xrightarrow{\text{Base}}
\begin{array}{c}
\text{X} \\
\text{S} & \text{S} & \text{N} \\
\end{array}
\]

Scheme 2

1,2,3-Dithiazoles have uses in both biological and material sciences: \(N\)-aryl-dithiazolimines show interesting antifungal,\(^6\) antibacterial,\(^7\) and herbicidal\(^8\) activities. A search for organic conductors based on neutral radicals has led to the preparation of two 1,2,3-dithiazolyl radicals \(^9\) and \(^10\) and also a tetrathiadiazafulvalene analogue \(^11\) has been prepared and studied.

Our interest in 1,2,3-dithiazole chemistry revolves around the construction of dithiazole systems that can be converted into new heterocyclic systems \textit{via} ring transformation. The majority of these ring transformations involve the initial preparation of a neutral dithiazole which supports a potentially nucleophilic side chain or substituent capable of attacking the electrophilic dithiazole at either S-1 (Path A) or at C-5 (Path B) with subsequent ring opening. Dithiazoles, however, can also be ring opened with the use of soft nucleophiles to afford the disulfide intermediate \(^12\) (Path C) (Scheme 3). This disulfide can be a source of both electrophilic and nucleophilic sulfur.
Scheme 3

Various dithiazolylidenes have been prepared specifically with these mechanistic possibilities in mind in order to broaden the capability of dithiazolium chloride 3 as a useful synthetic tool. Emphasis will be made on the \textit{in situ} generation of disulfides 12 endowed with electrophilic traps for nucleophilic sulfur (Path C).

1. Synthesis of thiazolopyridine-2-carbonitriles

Benzo[\textit{d}]thiazole-2-carbonitrile 13 can be prepared readily from the thermolysis of \textit{N}-phenyl-1,2,3-dithiazol-5\textit{H}-imine 6 in particular where the aryl substituent is electron rich.

Scheme 4
Where the aryl group is electron deficient the major product is the imidoyl chloride carbonitrile 14. The mechanism that has been proposed by Rees is shown in Scheme 4. To our knowledge no examples of the thermolysis of N-heteroaryl-1,2,3-dithiazol-5H-imines have appeared in the academic or patent literature.

Thermolysis of \( N \)-(pyrid-3-yl)-4-chloro-1,2,3-dithiazol-5H-imine 15 gave thiazolo[5,4-b]pyridine-2-carbonitrile 16 and thiazolo[4,5-c]pyridine-2-carbonitrile 17 in low yields as might be expected based on the mechanism to give benzothiazole 13. Repeating the reaction in the presence of a soft nucleophile benzyltriethylammonium iodide at 132 °C in chlorobenzene gave improved but still moderate yields of both isomers. Under these conditions the dithiazole ring is anticipated to suffer an assisted nucleophilic ring opening-ring closure (ANRORC)12 like mechanism involving the intermediate disulfide 18. The nucleophilic sulfur that is generated (S-1) is trapped at the electrophilic pyridyl C-2 and C-4 positions and a subsequent oxidation restores the aromaticity of the thiazolopyridine systems.

Introducing a chlorine substituent at either C-2 or at C-4 on the pyridyl ring was expected to assist in directing the ring closure and furthermore adjusts the oxidation level of the starting systems thus avoiding the need for oxidative rearomatisation. The 2-chloro and 4-chloro-derivatives 19 and 20 were readily prepared starting from the corresponding aminochloropyridines and dithiazolium chloride 3. Gratifyingly treatment with catalytic iodide (5 mol %) gave the expected single isomers in near quantitative yields.
Thermolysis of either the 2-chloro and 4-chloro-derivatives 19 and 20 did not yield regiospecific ring closures but mixtures of products were isolated adding further support to the ANRORC type mechanism proposed above.

We attempted to extrapolate the above success to the preparation of 3,1-benzothiazin-4-ones starting from the readily available methyl ester 21 where the electrophilic trap was now the carboxylate group. Initial thermolysis of the ester 21 gave some of the desired benzothiazinone 22 together with the benzothiazolecarbonitrile 23.
On treatment with various soft nucleophilies the major product was however the N-arylcyanothioformamide 24. This could be obtained in near quantitative yield with the use of catalytic benzyltriethylammonium iodide (5 mol%) providing a good route to this useful intermediate.

Interestingly Besson, Rees et al. reported a quantitative conversion of the iminocarboxylic acid 25 into benzothiazinone 22 on treatment with triphenylphosphine and proposed that the phosphonium salt byproducts help activate the carboxylic acid towards attack (cf. intermediate 26).13 In our case the methyl ester 21 on treatment with triphenylphosphine gave only a moderate yield of the cyanothioformamide 24.

2. Synthesis of percyano thiazole and 1,3,4-thiadiazole

The 1,2,3-dithiazole ring can act as both a source of nucleophilic sulfur at S-1 and as electrophilic trap at the ring carbon C-5. On treatment with soft nucleophiles bisdithiazole systems such as 27 can therefore be considered as possible precursors to heterocyclic systems of type 28 (Scheme 5). Two bisdithiazoles of this type compound 2914 and compound 3015 have been reported in the literature and each could provide rapid routes to the corresponding percyano-1,3,4-thiadiazole 31 and percyanothiazole 32 respectively.
Scheme 5

Treatment of either bisdithiazole 29 or 30 with soft nucleophiles such as chloride, bromide or iodide gave the expected percyano-1,3,4-thiadiazole 31 and thiazole 32 systems respectively. These percyano heterocycles suffered hydrolysis during chromatographic isolation to afford a moderate quantity of the corresponding carboxamides 33 and 34 respectively.

Table 1. Transformation of bisdithiazole 29 into 1,3,4-thiadiazoles 31 and 33

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conditions</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BnEt3NI (1 equiv.)</td>
<td>Ar, PhCl, 132 °C, 40 min</td>
<td>79 19</td>
</tr>
<tr>
<td>BnEt3NI (0.25 equiv.)</td>
<td>Ar, PhCl, 132 °C, 6 h</td>
<td>76 18</td>
</tr>
<tr>
<td>Ph3P (5 equiv.)</td>
<td>CH2Cl2, 20 °C, 5 min</td>
<td>Trace 0</td>
</tr>
<tr>
<td>Ph3P – polymer bound (6 mol equiv.)</td>
<td>CH2Cl2, 20 °C, 10 min</td>
<td>69 0</td>
</tr>
</tbody>
</table>
Table 2. Transformation of bisdithiazole 30 into thiadiazoles 32 and 34

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conditions</th>
<th>Yields (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BnEt₃NI (1 equiv.)</td>
<td>Ar, PhCl, 132 °C, 15 min</td>
<td>70</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>BnEt₃NBr (0.5 equiv.)</td>
<td>Ar, PhCl, 132 °C, 15 min</td>
<td>68</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Ph₃P (5 equiv.)</td>
<td>CH₂Cl₂, 20 °C, 10 min</td>
<td>Trace</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ph₃P – polymer bound</td>
<td>CH₂Cl₂, 20 °C, 4h</td>
<td>76</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Chromatography could be avoided by using polymer bound triphenylphosphine as the soft nucleophile since the polymer resin could be separated by filtration to afford a clean solution of the desired percyano heterocycle. Recrystallisation of this gave pure product free of any impurities or carboxamide. Surprisingly free triphenylphosphine gave only traces of product.


The dithiazolimine 36 prepared from the available fully substituted 2-aminopyridine 35 gave on treatment with cyclic secondary amines the expected fully substituted pyrido[2,3-d]pyrimidines 37 in moderate to good yields together with minor quantities of the guanidine 38 and the 4-aminosubstituted dithiazolimine 39 (Scheme 6).
Scheme 6

We have shown that the guanidine 38 is a product of the reaction of pyrido[2,3-\(d\)]pyrimidine 37 with excess amine presumably by nucleophilic attack by \(R_2NH\) at the electrophilic pyrimidine C-2, with pyrimidine ring opening and release of \(R_2NH\) from C-4. Surprisingly when acyclic secondary amines such as diethylamine are used in the reaction of dithiazolimine 36 a new previously unobserved green colored byproduct 40 is observed in addition to the byproducts 37-39.

Due to very low solubility NMR or MS spectroscopic data were not obtainable and the structure was solved by single crystal X-ray crystallography to afford the unexpected quinoidal 2,2’-bithiazole 40.

Figure 1. X-Ray structure of 2,2’-bithiazole 40.

This is the first time such a product type has been observed in 1,2,3-dithiazole chemistry, which raises new questions about the possibilities of the use of 1,2,3-dithiazoles in synthesis. A possible precursor to this compound is the 4-aminosubstituted dithiazolimine 39 which could
have been cleaved to afford the ring opened intermediate 41. These intermediates have been prepared starting from the 4-aminosubstituted dithiazolimines by Kim using alkali bases in alcohol.\textsuperscript{16} The two central carbons forming C-2 of the thiazole rings are presumed to be derived from the solvent CH\textsubscript{2}Cl\textsubscript{2}. However, attempts to improve the yield of the 2,2’-bithiazole 40 by replacing the solvent with different sources of carbon such at CHCl\textsubscript{3}, CCl\textsubscript{4}, CH\textsubscript{2}ClBr, CH\textsubscript{2}CII, CH\textsubscript{2}Br\textsubscript{2}, and CHBr\textsubscript{3} gave very similar reaction mixtures but surprisingly no trace of the green product, though formation of the green product 40 in the presence of CH\textsubscript{2}Cl\textsubscript{2} was reproducible.

The formation of the pyrido[2,3-\textit{d}]pyrimidine 37 from dithiazoline 36 is in itself mechanistically interesting as two possible pathways can be envisaged. In the first (Path A) the nitrile group neighbouring the dithiazolimine is initially attacked by the amine and cyclises onto the dithiazole C-5 carbon which instigates opening of the dithiazole ring. A second possibility (Path B) involves attack by the amine at the dithiazole ring sulfur S-2 to afford the disulfide intermediate 42 which then suffers ring closure to afford either the 4-aminodithiazolimine 39 or the pyrido[2,3-\textit{d}]pyrimidine 37 depending on which nitrile is attacked preferably by the incoming amine (Scheme 7). Further studies are needed to determine which is the predominant mechanism.

\begin{center}
\includegraphics{image.png}
\end{center}

\textbf{Scheme 7}
4. Chemistry of dithiazolylidenacetonitriles 43: Formation of isothiazoles

An example where more extensive studies have provided insight into the ring opening mechanisms of dithiazoles is the chemistry of dithiazolylidenacetonitriles 43.\textsuperscript{17-19} Treatment of dithiazoles 43 with anhydrous HBr afforded the 3-bromoisothiazoles 45 in moderate to good yields. However, with the dithiazolylidenemalononitrile 43 (X = CN) the analogous treatment with anhydrous HCl gives only a trace of the expected isothiazole 44.\textsuperscript{19} Here we argue that the reaction mechanism proceeds by formation of the imidoyl bromide 46 which then cyclises onto the dithiazole ring sulfur S-1. Anhydrous HCl being a weaker acid than HBr is unable to drive this transformation.

Earlier work on dithiazolylidenemalononitrile 43 (X = CN) showed clearly that catalytic chloride (BnEt\textsubscript{3}NCl 10 mol %) was sufficient to convert the dithiazole 43 (X = CN) into 3-chloroisothiazoledicarbonitrile 44 almost quantitatively. Treatment of dithiazolylidenemalononitrile 43 (X = CN) with secondary amines such as morpholine also afforded the 3-morpholinoisothiazoledicarbonitrile 47 although in moderate yield (60%).\textsuperscript{17}
Scheme 8

An alternative mechanism was proposed involving the disulfide 48. Nucleophilic attack on the ring sulfur at S-2 generates the disulfide 48 which can then recyclise to afford the isothiazole 44 (Scheme 8).

Scheme 9

During the investigation of this reaction mechanism two unexpected 3H-pyrroles were isolated.\textsuperscript{18} The first, a deep blue colored 3H-pyrrole 49 whose structure was determined by single crystal X-ray crystallography, was from the reaction of triphenylphosphine with
dithiazolylidenemalononitrile 43 (X = CN). The second, on treatment of the dithiazole 43 (X = CN) with excess morpholine, was the orange colored 3H-pyrrole 50.

In light of difficulties in displacing the 4-chloro substituent of neutral 5H-1,2,3-dithiazoles a rational mechanism for the formation of these 3H-pyrroles 49 and 50 required the involvement of the ring opened disulfide [cf. the proposed mechanism of the bismorpholino-3H-pyrrole 50 (Scheme 9)]. As such the dithiazolylidenemalononitrile 43 (X = CN) can ring open to afford an intermediate disulfide 51 that could afford isothiazoles, 3H-pyrroles and even (although this has not been observed yet) 1,2,3-dithiazole ring systems depending on the cyclisation modes of the tricyanovinyl group (Scheme 10).

Scheme 10

In order to investigate the reaction further, a series of substituted dithiazolyliden-acetonitriles was prepared and treated with benzyltriethylammonium chloride. Unfortunately for the halo and non-substituted acetonitrile derivatives 43 (X = H, Cl, or Br) the geometry of the attached nitrile group has not been determined (ie. cis or trans with respect to the dithiazole ring sulfur) but in each case only one isomer was observed by NMR and by chromatography. Owing to a strong non-bonding interaction between the ester carbonyl group with the dithiazole ring sulfur S-1 the ethyl carboxylate 43 (X = CO₂Et) is known to have a trans geometry for the nitrile group and the ring sulfur,¹⁰ however, this system was unreactive to halide.
The acetonitrile derivatives 43 (X = H, Cl, or Br) gave surprisingly complex reaction mixtures. At best 3,4-dichloroisothiazolecarbonitrile 52 (Y = Cl) could be obtained in a respectable yield (63 %), but it was clear that halide exchange was proceeding from the bromoacetonitrile derivative.

Analysis of the complex mixtures from the reaction of dithiazoles 43 (X = H, Cl or Br) and tetraalkylammonium chloride revealed the presence of several unexpected compounds, the isothiazolopentathiepin-8-carbonitrile 53, the isothiazolodithiin-4,5,7-tricarbonitrile 54, an unidentified purple compound 55 and tetracyanothiophene 56. The isothiazolopentathiepin 53 is known to react with dicyanoacetylene to give dithiin 54 and traces of tetracyanothiophene 56. These unusual products 53 – 56 are formally composed of one or two units of dicyanoacetylene and sulfur. As such the possibility that dithiazolyldenacetonitrile 43 (X = H) could be unzipped by deprotonation to afford dicyanoacetylene, diatomic sulfur and HCl was investigated.
Treatment of the dithiazolylidenacetonitrile 43 (X = H) with sterically hindered ethyldiisopropylamine (Hünigs base) gave the compounds 53 – 56 but no trace of the monocyclic isothiazole 52.

\[
\begin{array}{c}
\text{Cl} & \text{H} & \text{CN} \\
\text{N} & \text{S} & \text{S} \\
\end{array}
\xrightarrow{	ext{EtPr}_2\text{N (1 equiv.)}}
\text{CH}_2\text{Cl}_2, 45 ^\circ \text{C}, 55 \text{ min.} \\
53 \ (7 \%) & + & 54 \ (34 \%) & + & 55 \ (4.5 \%) & + & 56 \ (\text{Trace}) \\
\end{array}
\]

43 (X = H)

The unknown purple colored compound 55 is unstable on silica and hydrolyses during chromatographic isolation to afford a stable purple colored carboxamide 57. Neither compounds 55 and 57 have been identified but each show eight separate carbon resonances in the C-13 NMR and both show the presence of nitriles in the IR spectra. The molecular formulae have been deduced from mass spectrometry (55 C₈N₄S₃ and 57 C₈H₂N₄OS₃). Compound 55 formally contains two units of dicyanoacetylene and three sulfur atoms. The highly colored nature of the compound 55 leads to at least four possible structures (Scheme 11) that presumably could arise from a 4 component 10π cycloaddition between two equivalents of diatomic sulfur and two equivalents of dicyanoacetylene to give a fused seven-five heterocycle that then suffers ring contraction through loss of one sulfur atom to give the proposed six-five system. The identity of the purple compounds is being investigated.

Scheme 11

This chemistry looks promising as a possible new route to both pentathiepins and to new methods for the \textit{in situ} generation of acetylene derivatives. Understanding the mechanisms leading to the formation of these unexpected products will aid in the design of 1,2,3-dithiazoles which can be used to build new heterocyclic compounds.
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