FUSED 1,2,5-THIADIAZOLES AND SELENADIAZOLES

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Abstract -- Syntheses of aromatic and azaaromatic fused 1,2,5-thia- and selenadiazoles are described as well as the examples of their chemical reactivity are given.

I. INTRODUCTION
The present paper, a continuation of our review1, is dealing with heterocycles containing thiadiazole or selenadiazole ring condensed with aromatic system2. These compounds are interesting for their biological activity; they are used as drugs3-6, herbicides7,8 or radioprotective agents9,10. An attention ought to be paid to thia- and selenadiazoles fused with azaaromatic, especially pyrimidine ring, these compounds being analogs of purines and pteridines11-19. Fused thia- and selenadiazoles can be classified into two groups, according to the incorporated aromatic or azaaromatic system.

II. FUSED THIADIAZOLES
1 Syntheses
The parent compound of thiadiazoles condensed with aromatic ring is 2,1,3-benzothiadiazole, available from o-phenylenediamine in following reactions20-26:

\[
\begin{array}{c}
\text{NaHSO}_3, \text{SOCl}_2, S_2Cl_2, S_2Br_2, \\
\text{SO}_2 \text{ or TsNSO}
\end{array}
\]

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In an analogous manner thia diazoles containing azaromatic ring /pyridine, pyrimidine, pyrazine/ can be prepared and the appropriate o-diaminoheterocycles are used as starting materials\textsuperscript{27}.

In the reaction of o-phenylenediamine with thionyl chloride, the initially formed 2-amino-N-sulfinylaniline undergoes the intramolecular cyclization to give 1. Rearrangement of 1 and the following water elimination yields benzo thiadiazole\textsuperscript{28}.

The interaction of N-methyl-o-phenylenediamine instead of o-phenylenediamine with thionyl chloride gives rise to benzo thiadiazolium chloride\textsuperscript{29}:

In the transsulfinylation reaction of o-phenylenediamine with TsNSO, the first step results in 2-amino-N-sulfinylaniline, which at higher temperatures undergoes a disproportionation to benzo thiadiazole and o-phenylenediamine\textsuperscript{30}.
When 3,3'-diaminobenzidine was treated with sulfur dioxide in the DMF solution, 2 did not form, and the reaction resulted only in formation of 3. This compound can be used as starting material in syntheses of heterocyclic steroidal analogs.

Among fused thiadiazole azaaromatics the thiadiazolopyridines should be mentioned. Harts obtained the following chloro and hydroxy derivatives of thiadiazolopyridines:

\[ X = H, Cl, OH \]

As the synthetic route the reaction of suitable o-diaminopyridines with thionyl chloride was used.

An other synthetic approach to thiadiazolopyridines, involving the pyridine ring formation, was described by Mataka and coworkers. In this method, the 3,4-diaryl-1,2,5-thiadiazoles are treated with amines in the presence of DBU catalyst:
Fused thiadiazole systems, incorporating pyrimidine ring are interesting for their biological activity. These compounds are available from o-diaminopyrimidines in the reaction with thionyl chloride, sulfur dioxide or N-sulfinylaniline.\textsuperscript{16,28,31} In the preparation of chlorothiadiazolopyrimidines, as in the case of their pyridine analogs, the nucleophilic substitution of the chlorine atom can occur:\textsuperscript{33}

The use of N-sulfinylaniline in these syntheses is preferred over thionyl chloride because of the milder reaction conditions. In this way a series of substituted thiadiazolopyrimidines was obtained:\textsuperscript{33}

\[ X = \text{NH}_2, \text{NMe}_2, \text{NHCOCH}_3 \]
\[ Y = \text{H, Me, SH, SMe} \]
Carrying out reactions of o-diaminopyrimidines with N-sulfinylaniline derivatives, the influence of substituents on their reactivity was investigated. If N-sulfinylaniline is substituted by electron-donating groups, the electronegative character of sulfur atom, and in turn, its reactivity is decreased; therefore such N-sulfinylanilines can be used in the transsulfinylation reaction of very reactive o-diaminopyridines

In the syntheses carried out with N-sulfinylaniline, thiadiazolopyrimidines are formed in the disproportionation of the initially resulting 2-amino N-sulfinylanilines, e.g.:

\[
\begin{align*}
\text{HN} & \quad \text{Me} \\
\text{NN} & \quad \text{NN} \\
\text{NH} & \quad \text{NH} \\
\text{Me} & \quad \text{NSO} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{Me} \\
\text{NN} & \quad \text{NN} \\
\text{NH} & \quad \text{NH} \\
\text{NSO} & \\
\end{align*}
\]

There were synthesized numerous thiadiazoloheterocycles, incorporating pyrimidine ring, analogs of adenine, guanine, xanthine or theophylline, as well as hypoxanthines and mercaptopurines; for instance, the analog of theophylline was obtained in the reaction:

\[
\begin{align*}
\text{HN} & \quad \text{Me} \\
\text{O} & \quad \text{HN} \\
\text{Me} & \quad \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{NN} & \quad \text{NS} \\
\end{align*}
\]

The thio-derivatives of thiadiazolopyrimidines were produced in the following manner:
Among so far not much studied thiadiazoles fused with polyyclic systems there ought to be mentioned the indene derivative 5, obtained by Mataka and coworkers:

$$\text{C}_{6}\text{H}_{5}-\text{NSO}$$

Compounds of the type 6 were synthesized by Tashiro and coworkers by the action of tetrasulfur tetranitride on phenylacetylene:

$$\text{N}_4\text{S}_4$$

Danylec and Davis have carried out the following reactions:

$$\text{Me-SO}_2\text{-NSO}$$
Compound 7 can also be obtained by the amination of 8, followed by reduction and cyclization with thionyl chloride:

Benzotriothiadiazole has been described by Komin and Carmack:

The heptacyclic system 9 can be obtained in the following condensation reaction:
The synthesis of thiadiazoloquinolines was reported by Sharma and coworkers:\textsuperscript{12}

\[
\text{benzene} \xrightarrow{\text{SOC}_{\text{2}}} \text{thiadiazoloquinoline}
\]

To heterocycles containing thiadiazole ring can be included also the mesoionic compound 10 prepared by Masuda and coworkers:\textsuperscript{42}

\[
\text{SOC}_{\text{2}}, \text{S}_{\text{2}}\text{C}_{\text{2}} \text{or C}_{\text{6}}\text{H}_{\text{2}}-\text{NSO} \xrightarrow{\text{SOC}_{\text{2}}, \text{S}_{\text{2}}\text{C}_{\text{2}} \text{or C}_{\text{6}}\text{H}_{\text{2}}-\text{NSO}} \text{mesoionic compound 10}
\]

\section{Chemical reactivity}

The redox behaviour of benzothiadiazoles has been determined using mercury and platinum electrode.\textsuperscript{43}

The oxidation of aromatic fused thiadiazoles results in the formation of dicarboxylic acid, e.g.:\textsuperscript{44}

\[
\text{thiadiazole} \xrightarrow{\text{O}_{\text{3}} \text{or KMnO}_{\text{4}}} \text{dicarboxylic acid}
\]
In the reduction of fused aromatic thiadiazoles o-diamines are formed; an analogous reductive cleavage was observed in the case of thiadiazolopyridines and -pyrimidines; the action of hydrogen sulfide however gave rise to the thio derivative 11. These reactions are useful in the structure elucidation of condensed aromatic thiadiazoles.31,33

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2 \quad \text{Raney Ni} \\
\text{NH}_2 & \\
\text{N} & \quad \text{N} & \quad \text{S} \\
\end{align*}
\]

The interaction of 4-bromobenzothiadiazole with chlorosulfonic acid results in sulfochloride 12, which undergoes hydrolysis to give the sulfonic acid 13.44

\[
\begin{align*}
\text{Br} & \quad \text{ClSO}_2\text{H} \\
\text{N} & \quad \text{N} & \quad \text{S} \\
\end{align*}
\]

The quaternization reactions of benzothiadiazoles were examined by Davis and coworkers using dimethyl sulfate.45

To investigate the reactivity of benzothiadiazoles their electrophilic substitution was studied. As examples of this reaction, the nitration and halogenation were performed in the benzene and naphthalene thiadiazole series.6,19,21,44,46,47.
Positions of the electrophilic attack are:

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{S}
\end{align*}
\]

→ nitration

··· → halogenation

Nucleophilic substitution of the Br atom in bromobenzothiadiazoles was studied by Sharma.\textsuperscript{19,21,30}

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{X} & \quad \text{X} \\
\text{Br} & \quad \text{S}
\end{align*}
\]

\[X = \text{H, NO}_2\]

Thiadiazolopyridines undergo electrophilic substitution in a similar way as benzothiadiazoles. The thiadiazole ring for its electron-withdrawing properties makes the electrophilic substitution of the pyridine moiety difficult.\textsuperscript{30,31}

Positions of the electrophilic attack are:

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{S}
\end{align*}
\]

→ nitration

··· → halogenation
The nucleophilic substitution of halogen in halogenothiadiazolopyridines is a useful synthetic approach to derivatives of thia diazolopyridines. In the chlorothiadiazolo[3,4-b]pyridines the 6-Cl, and in the [3,4-c] isomers the 7-Cl atoms do not undergo nucleophilic substitution, as is summarized in the following scheme.

**Hydrolysis**

/ 5% AcOH, 2h, 100° /

![Reaction scheme for hydrolysis]

**Ammonolysis**

/ NH₃, 15h, 75° /

![Reaction scheme for ammonolysis]

Heating of 4-chlorothiadiazolo[3,4-b]pyridine with aniline in pyridine gives rise to amino- and anilino derivatives.
Aromatic and azaaromatic selenadiazoles are not so much studied as their sulfur analogs. Benzoselenadiazoles are formed in the reaction of o-phenylenediamines with selenious acid or diselenium dichloride\(^50\).

In a similar manner the substituted benzoselenadiazoles are obtained as follow\(^51,52\).

The reaction of o-diamines with selenious acid, resulting in fused selenadiazole systems can be useful as the photometric method of the selenium determination\(^53\).

When in the reaction with selenious acid, instead of o-phenylenediamine its N-methyl derivative is used, the benzoselenadiazolium chloride is formed\(^29\).
Pedersen treated 1,2-dioximes with diselenium dichloride to obtain in the first step N-oxides 14 and 15. The N-oxide 14 undergoes thermolysis to give benzoselenadiazole and benzooxadiazole, whereas in the photolysis only benzooxadiazole is formed. An other reaction of this kind proceeds as follows: An other reaction of this kind proceeds as follows:

\[
\begin{align*}
\text{N-oxide } 14 & \xrightarrow{\text{thermolysis}} \text{benzoselenadiazole} + \text{benzooxadiazole} \\
\text{o-Diaminopyridines reacted with selenious acid to give selenadiazolo-pyridines:} & \quad X = H, Cl, OH
\end{align*}
\]

An other reaction of this kind proceeds as follows: 54
In a similar way selenadiazoloquinolines 16 and 17 were synthesized\(^\text{12}\).

\[
\begin{align*}
16 & \quad \text{Se} \\
17 & \quad \text{Se}
\end{align*}
\]

The rates of quaternization of benzothiadiazoles were determined using dimethyl sulfate\(^\text{45}\).

REFERENCES


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