SYNTHESIS OF 1,3,4-THIADIAZINES AND 1,3,4-OXADIAZINES

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Abstract - This review summarizes several methods for the synthesis of 1,3,4-thiadiazines and 1,3,4-oxadiazines reported in 1960s - 1990s.

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I. Introduction

The synthesis of 1,3,4-thiadiazine or 1,3,4-oxadiazine derivatives has been reported up to date by many research groups, and useful compounds have been found in some of the 1,3,4-thiadiazine or 1,3,4-oxadiazine derivatives with the natures of the phosphodiesterase inhibitor,¹ antimicrobial for plants,² and dyestuff,³ which have appeared in the patent literatures. Henceforward, the cooperative works of the synthetic chemists with other research groups would have continued to search for more useful and potent compounds. However, there have been few reviews or monographs⁴ summarizing various methods for the synthesis of the condensed and noncondensed 1,3,4-thiadiazines or 1,3,4-oxadiazines. Accordingly, a prompt publication would be desired concerning a review or monograph on the general synthesis of the 1,3,4-thiadiazine or 1,3,4-oxadiazine derivatives. In this review, we summarize the synthesis of the condensed and noncondensed 1,3,4-thiadiazine or 1,3,4-oxadiazine derivatives.

II. Synthesis of 1,3,4-Thiadiazines and 1,3,4-Oxadiazines

1. From the Reaction of α-Halogenomethyl Ketones or α-Bromo-α-cyanoacetyl Derivatives with Thiosemicarbazide

The reaction of ethyl 4-chloroacetoacetate (1) with thiosemicarbazide under heating in acetonitrile gave the 1,3,4-thiadiazine hydrochloride (2a), whose treatment with sodium bicarbonate afforded the enamine tautomer (2b) (Scheme 1).⁵ In this reaction, change of conditions such as solvent polarity, solvent acidity, and reaction temperature gave thiazole or thiazoline derivatives. Compound (2b) was converted into the various derivatives (3-6) under diverse reaction conditions shown in Scheme 2.⁵ Treatment of the hydrochloride (6) with sodium bicarbonate also provided the enamine tautomer (3). The reaction of the α-
bromo ketone (7) with thiosemicarbazide and then sodium bicarbonate gave the 1,3,4-thiadiazine (8), whose tautomerism between the 6H and 4H forms was supported by the NMR spectral data (Scheme 3).\(^6\) The methylenic proton (C₆-H₂) signal of the 6H form and the vinylic proton (C₆-H) signal of the 4H form were observed at 8 3.62 and 7.07 ppm.

The reaction of the α-bromo-α-cyanoacetyl derivatives (9) with 4-substituted thiosemicarbazides afforded the 2,5-diamino-1,3,4-thiadiazines (10) (Scheme 4).\(^7\) On the other hand, the reaction of compound (9, R = CONH₂) with 2,4-disubstituted thiosemicarbazides provided the 5-amino-2-imino-1,3,4-thiadiazines (11) (Scheme 5).\(^7\)
The reaction of 6-chloroquinoline-5,8-dione hydrochloride (12) with thiosemicarbazide or semicarbazide gave 2-amino-4H-1,3,4-thiadiazino[6,5-g]quinoline-5,10-dione (13) or 2-amino-4H-1,3,4-oxadiazino[6,5-g]quinoline-5,10-dione (14), respectively (Scheme 6).8 The
reaction of 2,3-dichloronaphthoquinone (15) with thiosemicarbazide afforded the naphtho[2,3-e][1,3,4]thiadiazine (16) (Scheme 7). 

Scheme 6

\[
\begin{align*}
\text{2,3-dichloronaphthoquinone (15)} & \rightarrow \text{naphtho}[2,3-e][1,3,4]\text{thiadiazine (16)} \\
\text{in Ethylene Glycol} & \rightarrow \text{naphtho}[2,3-e][1,3,4]\text{thiadiazine (16)} \\
\end{align*}
\]

Scheme 7

\[
\begin{align*}
\text{2,3-dichloronaphthoquinone (15)} & \rightarrow \text{naphtho}[2,3-e][1,3,4]\text{thiadiazine (16)} \\
\text{in EtOH} & \rightarrow \text{naphtho}[2,3-e][1,3,4]\text{thiadiazine (16)} \\
\end{align*}
\]

3. From the Reaction of (o-Halogenoheteroaryl)hydrazines with Isothiocyanates or Carbon Disulfide

The reaction of 2-chloro-3-hydrazinopyridine (17) with phenyl isothiocyanate gave the pyrido[3,2-e][1,3,4]thiadiazine (18) (Scheme 8). The reaction of 2-chloro-3-hydrazinopyrazine (19) with isothiocyanates afforded the adducts (20a-c), which were cyclized

Scheme 8

\[
\begin{align*}
\text{2-chloro-3-hydrazinopyridine (17)} & \rightarrow \text{pyrido}[3,2-e][1,3,4]\text{thiadiazine (18)} \\
\text{in MeOH} & \rightarrow \text{pyrido}[3,2-e][1,3,4]\text{thiadiazine (18)} \\
\end{align*}
\]
Scheme 9

\[
\begin{align*}
\text{19} & \xrightarrow{\text{RNCS}} \text{20a, 20b, [20c]} \\
\text{21a-c} & \xrightarrow{\text{MeO}_2\text{O}} \text{22a}
\end{align*}
\]

R : a COOEt, b CH₂COOEt, c Ph

Scheme 10

\[
\begin{align*}
\text{23a-c} & \xrightarrow{\text{MeO-NCS}} \text{24a-c}
\end{align*}
\]

R : a Me, b Ph, c CH₂Ph

Into the pyrazino[2,3-e][1,3,4]thiadiazines (21a-c), respectively (Scheme 9).\(^1\) Compound (21a) was methylated with N,N-dimethylformamide dimethyl acetal to provide the N-methyl carbamate (22a). The reaction of the 4-chloro-5-(1-methylhydrazino)pyridazin-3-ones (23a-c) with 2,2-dimethoxyethyl isothiocyanate in the presence of triethylamine produced the pyridazino[4,5-e][1,3,4]thiadiazin-8-ones (24a-c), which were further cyclized into the imidazo[2,1-b]pyridazino[4,5-e][1,3,4]thiadiazin-9-ones (25a-c), respectively (Scheme 10).\(^1\) Similarly, the 5-chloro-4-(1-methylhydrazino)pyridazin-3-one (26) was
converted into the pyridazino[4,5-e][1,3,4]thiadiazin-5-one (27), which was cyclized into the imidazo[2,1-b]pyridazino[4,5-e][1,3,4]thiadiazin-6-one (28) (Scheme 11). The reaction of compound (23a) with carbon disulfide/alkyl halide gave the 2-alkythiopyridazino[4,5-e][1,3,4]thiadiazin-8-ones (29a-d) (Scheme 12). The reaction of 3,4-dichloro-5-(1-methylhydrazino)-pyridazine (30) with carbon disulfide/methyl iodide gave the 2-methylthiopyridazino[4,5-e][1,3,4]thiadiazine (31), while the reaction of compound (30) with benzyl isothiocyanate afforded the adduct (32), whose reaction with sodium hydroxide provided the 2-benzylaminopyridazino[4,5-e][1,3,4]thiadiazine (33) (Scheme 13). The reaction of the 6-chloro-5-(1-methylhydrazino)pyridazin-3-one (34) with carbon disulfide/methyl iodide gave the 2-methylthiopyridazino[5,6-e][1,3,4]thiadiazin-6-one (35),
while the 2-benzylamino-pyridazino[5,6-e][1,3,4]thiadiazin-6-one (37) was produced from compound (34) via the adduct (36) (Scheme 14).\textsuperscript{13}

\textbf{Scheme 13}

\begin{center}
\begin{tikzpicture}
\node (n1) at (0,0) {30};
\node (n2) at (2,0) {31};
\node (n3) at (0,-2) {32};
\node (n4) at (2,-2) {33};
\node (n5) at (0,-4) {35};
\node (n6) at (2,-4) {37};
\node (n7) at (1,-6) {36};
\node (n8) at (1,-2.5) {NaOH};
\node (n9) at (1,-1.5) {PhCH\textsubscript{2}NCS};
\node (n10) at (1,-3.5) {MeI};
\node (n11) at (1,-0.5) {CS\textsubscript{2}, NaOH};
\draw[->] (n1) -- (n2) node[midway, above] {(1) CS\textsubscript{2}, NaOH};
\draw[->] (n1) -- (n3) node[midway, above] {(2) MeI};
\draw[->] (n3) -- (n4) node[midway, above] {NaOH};
\draw[->] (n5) -- (n6) node[midway, above] {CS\textsubscript{2}, NaOH};
\draw[->] (n5) -- (n7) node[midway, above] {PhCH\textsubscript{2}NCS};
\draw[->] (n7) -- (n6) node[midway, above] {NaOH};
\end{tikzpicture}
\end{center}

\textbf{Scheme 14}

\textsuperscript{4} From the Reaction of 4-Aryl- or 4-Heteroarylthiosemicarbazides with Oxidizing Agents
The reaction of the 1-phenylthiosemicarbazides (38) with bromine gave the 1,3,4-benzothiadiazines (39) (Scheme 15). The reaction of the 5-(1-methylhydrazino)pyridazin-3-one (40) with alkyl or aryl isothiocyanates afforded the 1-(pyridazin-5-yl)thiosemicarbazides (41a-c), whose reaction with N-bromosuccinimide produced the pyridazino[4,5-e][1,3,4]thiadiazin-8-ones (42a-c), respectively (Scheme 16). The reaction of the 1,3-dialkyl-6-hydrazinouracils (43) with isothiocyanates or the reaction of the 1,3-dialkyl-6-chlorouracils (44) with thiosemicarbazide produced the 1-(1,3-dialkyluracil-6-yl)thiosemicarbazides (45), whose reaction with N-chlorosuccinimide gave the pyrimido[4,5-e][1,3,4]thiadiazines (46) (Scheme 17). The reaction of the 5-(1-methylhydrazino)pyridazin-3-one (47) with isothiocyanates afforded the 1-(pyridazin-5-yl)thiosemicarbazides (48a-d), whose reaction with diethyl azodicarboxylate provided the pyridazino[4,5-e][1,3,4]thiadiazin-8-ones (49a-d), respectively (Scheme 18).
The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide (50) with various isothiocyanates gave the 4-substituted 1-(quinoxalin-2-yl)thiosemicarbazides (51a-e) (Scheme 19). The reaction of compound (51a) with acetic anhydride effected cyclization to afford the 2-acetamido-1,3,4-thiadiazino[5,6-b]quinoxaline (52), and the reaction of compound (51a) with trifluoroacetic anhydride provided the 2-trifluoroacetamido-1,3,4-thiadiazino[5,6-b]quinoxaline (53) (Scheme 20). The trifluoro-acetyl group of compound (53) was easily hydrolyzed to give the 2-methylamino derivative (54), while the acetyl group of compound (52) was hardly eliminated. The reaction of compound (53) with
Scheme 19

\[
\begin{align*}
\text{Cl} & \text{N}^+ \text{H} & \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{H} & \text{Me} \\
50 & \text{RNCS} & \rightarrow & \text{Cl} & \text{N}^+ \text{H} & \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{H} & \text{Me} \\
& & & \text{51a-e} \\
R : & \text{a} \text{ Me}, \text{b} \text{ Ph}, \text{c} \text{ } \text{C}_6\text{H}_{4}4-\text{Cl}, \text{d} \text{ } \text{C}_6\text{H}_{4}4-\text{Br}, \text{e} \text{ CH}_2\text{Ph} \\
\end{align*}
\]

Scheme 20

\[
\begin{align*}
\text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
51a & \text{in Ac}_2\text{O} \text{ or } \text{Ac}_2\text{O} / \text{AcOH} & \rightarrow & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
& \text{(CF}_3\text{CO})_2\text{O} & \text{in Dioxane} & \rightarrow & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
53 & \text{NEt}_3 / \text{H}_2\text{O} & \text{in Dioxane} & \rightarrow & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
& \text{2 x MCPBA} & \rightarrow & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
55 & \text{PhNCO} & \text{or} & \text{CICH}_2\text{COCl} & \rightarrow & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
56a & (R = \text{NHPh}) & \text{NEt}_3 & \text{in Dioxane} & \rightarrow & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} & \text{Cl} & \text{N}^+ \text{Me} & \text{Me} \\
56b & (R = \text{CH}_2\text{Cl})
\end{align*}
\]

\textit{m}-chloroperbenzoic acid afforded the 1,1-dioxide (55), and the reaction of compound (54) with phenyl isocyanate or chloroacetyl chloride provided the ureido (56) or chloroacetyl
(56b) derivative. The reaction of compounds (51b-e) with trifluoroacetic anhydride gave various 2-trifluoroacetamido derivatives (57b-e), which were hydrolyzed to change into the arylamino and benzylamino derivatives (58b-e), respectively (Scheme 21). However, compounds (51b-e) were not converted into the 2-acetamido derivatives (59b-e).

Scheme 21

![Scheme 21](image)

R : b Ph, c C₆H₄-4-Cl, d C₆H₄-4-Br, e CH₂Ph

Chart 1

The cyclization of compounds (51) into the 1,3,4-thiadiazino[5,6-b]quinoxalines would proceed via an acylated intermediate A shown in Chart 1. On the other hand, the reaction of compound (50) with acetic anhydride would give an acetylated intermediate B, which is cyclized into the 2-methyl-1,3,4-oxadiazino[5,6-b]quinoxaline (61a) (Scheme 22).
However, the yield is low (23%) in this reaction. Accordingly, the 2-methyl (61a) or 2-trifluoromethyl (61b) derivative of 1,3,4-oxadiazino[5,6-b]quinoxaline was synthesized via the acetyl (60a) or trifluoroacetyl (60b) derivative [overall yield: (61a) (58%), (61b) (56%)]. Compound (61b) was further transformed into the 2-trifluoromethyl-1,3,4-thiadiazino[5,6-b]quinoxaline (63) via compound (62).

Scheme 22

The reaction of compound (50) with 2-fold molar amount of ethyl chloroglyoxalate gave the 1,3,4-oxadiazino[5,6-b]quinoxaline-2-carboxylate (64), whose reaction with hydrazine hydrate afforded the acyl hydrazide (65) (Scheme 23). The reaction of compound (65) with nitrous acid provided the acyl azide (66), whose reaction with water provided the 2- amino derivative (67). The reaction of the acyl azide (66) with amines or alcohols
produced the ureido (68) or carbamate (69) derivatives, while the reaction of the 2-amino derivative (67) with anhydrides gave the 2-acylamino derivatives (70).

Scheme 23

\[
\begin{align*}
\text{Pyridine} & \quad \text{in CHCl}_3 \\
\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} & \\
\text{HNO}_2 & \\
\text{H}_2\text{O} & \quad \text{in Dioxane} \\
\text{(R'CO)}_2\text{O} & \end{align*}
\]

\(R' = 4\text{-F, 3-F, 3-CF}_3; \ R'' = \text{Et, Bu, (CH}_2)_3\text{Cl}; \ R''' = \text{CF}_3, \text{Me, CH}_2\text{Cl}\)

The reaction of compounds (69a,b) and (70a,b) with methyl iodide/1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) afforded the \(N_{10}\)-methyl derivatives (71a,b) and (72a,b), respectively (Scheme 24).\(^{21}\) The structure of the \(N_{10}\)-methyl derivatives (71a,b) and (72a,b) was supported by the NOE between the \(C_9\)-H and \(N_{10}\)-Me protons. The reaction of compound (69a) with \(N,N\)-dimethylformamide dimethyl acetal also resulted in the \(N_{10}\)-methylation to provide compound (71a). Moreover, compound (70a) was found to exist as the \(N_{10}\)-H form,
but not as the C2-NH form, from the NOE between the NH and C9-H protons. The N10-H form of compounds (69a,b) and (70a,b) and the N10-Me form of compounds (71a,b) and (72a,b) were also supported by the NMR spectral data in deuteriodimethyl sulfoxide (DMSO-d6) and in deuteriotrifluoroacetic acid (TFA-d4) (Chart 2). Especially, the
chemical shifts of the $C_{9a}$ and $C_{10a}$ carbons in DMSO-$d_6$ were similar to those in TFA-$d_1$. On the contrary, the $N_5$-deuteration was suggested in the 1,3,4-thiadiazino[5,6-$b$]quinoxalines (52) and (53) from the comparison of the carbon chemical shifts in DMSO-$d_6$ with those in TFA-$d_1$ (Chart 3). Namely, the $C_{4a}$ and $C_{5a}$ carbon chemical shifts were shielded in TFA-$d_1$ when compared with those in DMSO-$d_6$. On the other hand, the $C_{9a}$ and $C_{10a}$ carbon chemical shifts were deshielded in TFA-$d_1$ when compared with those in DMSO-$d_6$.

Chart 3

<table>
<thead>
<tr>
<th>Chemical Shift (δ ppm)</th>
<th>52</th>
<th>53</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{4a}$</td>
<td>144.9</td>
<td>143.8</td>
</tr>
<tr>
<td>$C_{5a}$</td>
<td>139.1</td>
<td>139.0</td>
</tr>
<tr>
<td>$C_{9a}$</td>
<td>130.0</td>
<td>130.5</td>
</tr>
<tr>
<td>$C_{10a}$</td>
<td>136.0</td>
<td>132.8</td>
</tr>
</tbody>
</table>

6. From the Reaction of Hydrazonyl Halides with Thioacetate or Acetate

The reaction of the 4,5-dichloropyridazin-3-ones (73a-d) with hydrazine and then benzaldehyde gave the hydrazone (74a-d), whose reaction with bromine afforded the hydrazonyl bromides (75a-d), respectively (Scheme 25). The reaction of compounds (75a-d) with potassium thioacetate provided the 4-acetylpyridazino[4,5-e][1,3,4]thiadiazines (76a-d), whose hydrolysis with concentrated hydrochloric acid/ethanol gave the pyridazino[4,5-e][1,3,4]thiadiazines (77a-d), respectively. The reaction of compound (77a) with methyl iodide afforded the 4,7-dimethyl derivative (78a). The reaction of the
hydrazonyl halides (79a-d) with sodium thioacetate provided the 1,3,4-benzothiadiazines (Scheme 25).

\[
\text{Scheme 25}
\]

\[
\begin{align*}
& \overset{\text{(1) NH}_2\text{NH}_2}{\text{R}} \overset{\text{(2) PhCHO}}{\text{N}} \overset{\text{(3) Br}_2}{\text{N}} \overset{\text{(4) AcSK}}{\text{Cl}} \overset{\text{(5) conc. HCl / EtOH}}{\text{Cl}} \overset{\text{(6) MeI}}{\text{Cl}} \\
\end{align*}
\]

\[
\text{73a-d} \rightarrow \text{74a-d} (X = H) \rightarrow \text{75a-d} (X = Br)
\]

(1) NH\textsubscript{2}NH\textsubscript{2} (2) PhCHO (3) Br\textsubscript{2} (4) AcSK (5) conc. HCl / EtOH (6) MeI

\[
\begin{align*}
& \overset{\text{R : a Me, b CH\textsubscript{2}Ph, c Ph, d H}}{\text{76a-d}} \overset{\text{(R' = Ac)}}{\text{(5)}} \rightarrow \text{77a-d} (R' = H) \\
& \overset{\text{(6)}}{\text{78a}} (R' = Me)
\end{align*}
\]

(79a-d), respectively (Scheme 26),\textsuperscript{25} and the reaction of the hydrazonyl bromide (81) with sodium thioacetate similarly produced the naphtho[1,2-e][1,3,4]thiadiazine (82) (Scheme 27).\textsuperscript{25} The reaction mechanism is shown in Scheme 28.\textsuperscript{26,27} The reaction of the hydrazonyl bromides (83a-d) or (83e) with sodium acetate gave the acetyl group-migrated
products (84a-d) or 1,3,4-benzoxadiazine (84e), respectively (Scheme 29). The reaction of compounds (84a-c) with triethylamine/sodium hydroxide or the reaction of compound

Scheme 28

Scheme 29

84e 85d 85a-c

a Ar = 4-MeO-C₆H₄, X = Y = Br  
b Ar = 5-Br-Thienyl, X = Y = Br  
c Ar = 4-Cl-C₆H₄, X = Y = Br  
d Ar = Ph, X = F, Y = Br  
e Ar = Ph, X = Br, Y = NO₂
(84d) with triethylamine afforded the 1,3,4-benzoxadiazines (85a-c) or 4-acetyl derivative (85d), respectively.

7. By the Smiles Rearrangement

The reaction of the hydrazonyl bromides (86) with p-nitrophenol and triethylamine gave the hydrazonyl p-nitrophenyl ethers (87), whose boiling in triethylamine/ethanol effected the Smiles rearrangement to afford the acylhydrazides (88) (Scheme 30).28 Subsequent boiling of compounds (88) and sodium hydroxide/triethylamine in N,N-dimethylformamide provided the 4-(4-nitrophenyl)-1,3,4-benzoxadiazines (89). The 4-(2-nitrophenyl)-1,3,4-benzoxadiazine (92) was produced via the Smiles rearrangement of the hydrazonyl o-nitrophenyl ether to the arylhydrazide (91) (Scheme 31).29 The reaction of 2,4-dinitrofluorobenzene (93) with N-phenylbenzothiohydrazide or dithizone in triethylamine/acetonitrile gave the 1,3,4-benzothiadiazines (94) via the Smiles rearrangement.

Scheme 30

\[ \text{86 (8 Compounds)} \]
\[ \text{87 (8 Compounds)} \]
\[ \text{88 (8 Compounds)} \]
\[ \text{89 (5 Compounds)} \]
Scheme 31

(1) NEt₃ / Ethanol, (2) NaOH / NEt₃ / DMF

Scheme 32

(Scheme 32). The oxidation of compounds (94) with hydrogen peroxide afforded the 1,1-dioxides (95). The reaction of compounds (96, 98, and 100) with benzothiohydrazide and triethylamine provided the heterocycle-condensed 1,3,4-thiadiazines (97, 99, and 101), respectively, via the Smiles rearrangement (Scheme 33).

8. From the Reaction of 1-Halogeno-2-nitro- or 1,2-Dihalogenoaromatic Compounds with Acyl Hydrazide

The reaction of compound (93) with N'-phenylbenzohydrazide and triethylamine gave the 1,3,4-benzoxadiazine (102) via an intermediate C (Scheme 34). Similarly, the reaction of compounds (96, 104, 106, and 100) with N'-phenylbenzohydrazide and triethylamine
afforded the heterocycle-condensed 1,3,4-oxadiazines (103, 105, 107, and 108), respectively (Scheme 35).30

9. By the Ring Transformation

The reaction of the 1,3-oxathiolium salts (109) with phenylhydrazine or hydrazine hydrate resulted in ring transformation to give the 4,5-diphenyl-1,3,4-thiadiazines (110) or 5-phenyl-1,3,4-thiadiazines (111), respectively (Scheme 36).32,33 The reaction of the 3-amino-2-imino-2,3-dihydro[4,5-b]quinoxalines (112) with carbon disulfide effected ring transformation to afford the 2-mercapto-1,3,4-thiadiazino[5,6-b]quinoxalines (113),
Scheme 35

\[
\begin{align*}
\text{96} & \quad \text{PhCONHNHPh} \quad \text{NET}_3 \\
\rightarrow & \quad \text{103} \\
\text{104} & \quad \text{PhCONHNHPh} \quad \text{NET}_3 \\
\rightarrow & \quad \text{105} \\
\text{106} & \quad \text{PhCONHNHPh} \quad \text{NET}_3 \\
\rightarrow & \quad \text{107} \\
\text{100} & \quad \text{PhCONHNHPh} \quad \text{NET}_3 \\
\rightarrow & \quad \text{108}
\end{align*}
\]

Scheme 36

\[
\begin{align*}
\text{109} & \quad \text{PhNHNH}_2 \\
\rightarrow & \quad \text{110} \\
\text{109} & \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \\
\rightarrow & \quad \text{111}
\end{align*}
\]
Scheme 37

\[
\begin{align*}
\text{N} & \quad \text{Pyridine} \\
\text{I} & \quad \text{or} \\
\text{I} & \quad \text{NaOH/DMF}
\end{align*}
\]

\[
R = \text{H, Me, NO}_2
\]

(Scheme 37).\textsuperscript{34,35} The 2-mercapto and 2-thione tautomers are shown in the original paper,\textsuperscript{34} but there is no description for detailed spectral data.

10. From the Reaction of \(N\)-Iminophosphorane with Isothiocyanates or Isocyanates

The reaction of 1-amino-3-phenyl-2-thioxo-4-imidazolidin-4-one (114) with triphenylphosphine dibromide gave the iminophosphorane (115), whose reaction with various isothiocyanates afforded the imidazo[1,5-\(d\)][1,3,4]thiadiazines (116) via intermediates D

Scheme 38

\[
\begin{align*}
\text{R} & \quad \text{Me, Ph, CH}_2\text{Ph, C}_6\text{H}_4\text{-4-Me, C}_6\text{H}_4\text{-4-OMe, C}_6\text{H}_4\text{-4-F}
\end{align*}
\]
When isocyanates were used in place of isothiocyanates in the above reaction, the imidazo[1,5-d][1,3,4]oxadiazines (117) were obtained from the iminophosphorane (115) (Scheme 39).\\n
**Scheme 39**

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{S} \\
\text{N} \quad \text{= PPh}_3 \\
115 & \quad \xrightarrow{2 \times \text{RNCO}} \\
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{S} \\
\text{N} \quad \text{= H} \\
117 & \\
\end{align*}
\]

\[R = \text{C}_3\text{H}_7, \text{Ph, CH}_2\text{Ph, C}_6\text{H}_4-4-\text{Me, C}_6\text{H}_4-4-\text{OMe, C}_6\text{H}_4-4-\text{F}\]

III. Ring Contraction of Condensed 1,3,4-Thiadiazines through Sulfur Extrusion

When a solution of compounds (29a-d) in N,N-dimethylformamide or toluene was refluxed, the pyrazolo[3,4-d]pyridazin-4-ones (118a-d) were produced via an intermediate F accompanying with sulfur extrusion (Scheme 40). The reaction proceeded so rapidly in N,N-dimethylformamide (within 1 hour) in comparison with that in toluene (12 hours). Similarly, compounds (42a-c) were converted into the pyrazolo[3,4-d]pyridazin-4-ones (119a-c), respectively (Scheme 41). The reaction of compounds (76a-d or 77a-d) in methanolic potassium hydroxide gave the pyrazolo[3,4-d]pyridazin-4-ones (120a-d), respec-

**Scheme 40**

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{N} & \quad \text{S} \\
\text{N} & \quad \text{N} \\
\text{Me} & \quad \xrightarrow{\text{Reflux in DMF} \quad \text{or in Toluene}} \\
\text{Me} & \quad \text{O} \\
\text{N} & \quad \text{S} \\
\text{N} & \quad \text{N} \\
\text{Me} & \quad \xrightarrow{-S} \\
\end{align*}
\]

\[R : \text{a Me, b CH}_2\text{Ph, c CH}_2\text{COPh, d CH}_2\text{COOEt}\]
Scheme 41

\[
\text{Reflux in DMF} \quad \text{- S} \quad \text{Me} \quad \text{N} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{Me} \quad \text{NHR} \quad \text{NHR}
\]

\[
42a-c \quad \text{Me, Ph, } \text{CH}_{2}\text{Ph}
\]

Scheme 42

\[
\text{KOH/MeOH} \quad \text{- S} \quad \text{Ph} \quad \text{R} \quad \text{N} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{H}
\]

\[
76a-d \quad \text{(R' = Ac)} \quad 120a-d
\]

\[
77a-d \quad \text{(R' = H)}
\]

\[
\text{Reflux in DMF} \quad \text{- S} \quad \text{Ph} \quad \text{R} \quad \text{N} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{Me} \quad \text{NHR}
\]

\[
78a \quad \text{Me, CH}_{2}\text{Ph, Ph}
\]

\[
121a \quad \text{CH}_{2}\text{Ph, Ph, H}
\]

Scheme 43

\[
\text{Reflux in DMF} \quad \text{- S} \quad \text{R} \quad \text{N} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{H}
\]

\[
46 \quad \text{(14 Compounds)} \quad 122 \quad \text{(14 Compounds)}
\]
tively. In the case of the N$_1$-acetyl derivative (76a-d), the reaction was carried out under reflux. On the other hand, reflux of compound (78a) in N,N-dimethylformamide afforded compound (121a) (Scheme 42).$^{23,24}$ The reaction of the pyrimido[4,5-e][1,3,4]thiadiazine-6,8-diones (46) under reflux in N,N-dimethylformamide resulted in desulfurization to provide the pyrazolo[3,4-d]pyrimidine-4,6-diones (122) (Scheme 43).$^{15}$

Chart 4

Scheme 44

Thus, the sulfur extrusion easily takes place in the condensed 1,3,4-thiadiazines (29, 42,
46, 76, 77, and 78) having the β-amino-α-thioenone moiety (Chart 4), while the N₄-proton is necessary for the ring contraction of the pyrimido[4,5-e][1,3,4]thiadiazine-6,8-diones (46) into the pyrazolo[3,4-d]pyrimidine-4,6-diones (122). However, strong reaction conditions are required for the desulfurization of the 8-substituted pyridazino[4,5-e][1,3,4]thiadiazines (123a-f) into the pyrazolo[3,4-d]pyridazines (124a-f) (Scheme 44), presumably due to the lack of the β-amino-α-thioenone function. Compounds (35 and 37) (Scheme 14) possessing the β-aminoenone (but not β-amino-α-thioenone) moiety are inert for the above sulfur extrusion.

IV. Biologically Active 1,3,4-Thiadiazines and 1,3,4-Oxadiazines

The 1,3,4-thiadiazino[6,5-g]quinoline (13) and 1,3,4-oxadiazino[6,5-g]quinoline (14) (Chart 5) showed a remarkable activity against Micrococcus roseus, but these compounds exhibited no activity against Pseudomonas aeruginosa, Klebsiella pneumoniae, and Serratia sp. The 1,3,4-thiadiazino[5,6-b]quinoxalines (52 and 53) and 1,3,4-oxadiazino[5,6-b]quinoxalines (52 and 53) and 1,3,4-oxadiazino[5,6-b]quinoxalines...
xaline (61a) showed an excellent activity against *Sphaerotheca fuliginea.*\(^{37}\) The pyrimido[4,5-e][1,3,4]thiadiazines (46)\(^{15}\) were reported to be useful as hypotensive, diuretic, antiinflammatory, and antigastric ulcer agents,\(^{1}\) and the phosphodiesterase 50% inhibitory concentrations of compounds (46) were 10-112 \(\mu\)M (theophylline, 143 \(\mu\)M). The 1,3,4-benzothiadiazines (39)\(^{14}\) were developed as plant disease-controlling agents, and these compounds completely prevented rice seedling from infection with *Pyricularia oryzae.*\(^2\) The pyridazino[4,5-e][1,3,4]thiadiazines (77a-d) had a herbicidal activity.\(^{13,38}\) Especially, compound (77a) (\(R = Me\)) at 50 \(g/l\) are controlled *Digitaria sanguinalis, Cyperus microiria, Amaranthus, Portulaca oleracea, Calinsoga ciliata,* and *Brassica* in rice by above 90%.\(^{13,38}\)

REFERENCES


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