Chemistry of 1,3-thiazin-4-ones and their derivatives, 1995 – mid-2018

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Abstract
This review updates an earlier review published in 1996 by Ryabukhin, Korzhavina, and Suzdalev, which covered the literature through 1994. It deals with the synthesis and reactivity of 1,3-thiazin-4-ones and their derivatives. These include reduced compounds, 2-imino or 2-amino compounds, compounds with fused arenes or heterocycles, bridged compounds, and compounds combining various of these attributes.

Keywords: Thiazinones, benzothiazinones, heterocycles, synthesis, reactivity
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References
1. Introduction

Compounds with the 1,3-thiazin-4-one ring (Figure 1) have shown bioactivity in many areas, for example muscle relaxant,\textsuperscript{1} antitubercular,\textsuperscript{2,3} anticancer,\textsuperscript{4-6} CXC chemokine receptor 4 (CXCR4) antagonism,\textsuperscript{7} antimalarial,\textsuperscript{3} antibacterial,\textsuperscript{3,8} HIV-RT inhibition,\textsuperscript{9} antifungal,\textsuperscript{8} antiinflammatory,\textsuperscript{10} antioxidant,\textsuperscript{11} antihyperglycemic,\textsuperscript{12} and cardioprotection.\textsuperscript{13}

![Figure 1](image-url)

The only comprehensive review of 1,3-thiazin-4-ones and their derivatives was published by Ryabukhin, Korzhavina, and Suzdalev in 1996, covering chemistry through 1994.\textsuperscript{14} In this update, the literature from 1995-June 30, 2018 is reviewed. The reader is encouraged to read the original review as well for a comprehensive overview. As in the prior review, 1,3-thiazin-2,4-diones and 1,3-thiazin-2-thione-4-ones are excluded, but 2-imino or their 2-amino tautomers are included. The review is generally organized in the same manner as the earlier review. Synthesis of the ring system is grouped by commonality of the final structure. Reactions of the ring system are grouped by types of reaction.

2. Syntheses

2.1. 1,3-Thiazin-4-ones

2.1.1. 1,3-Thiazin-4-ones. Reaction of (Z)-2-cyano-3-sulfanyl-3-(phenylamino)acrylamide 1 with tetracyanoethylene 2 was found to yield 2,4-dicyano-6-anilino-1,3-thiazin-4-one 3 (Scheme 1).\textsuperscript{15} This was suggested to

![Scheme 1](image-url)
occur by attack of sulfur on the C=C of 2, followed by attack of the amide nitrogen on what becomes C2 of the heterocycle. Elimination of HCN then led to 3.

Thioamides 8 reacted with 3-bromopyruvoyl chloride 7 to give the 5-hydroxy-1,3-thiazin-4-ones 9 in a one-pot, two-step process (Scheme 2). The reaction was shown to proceed through compound 10, which could be converted into 9 with base.

Scheme 2

Oxidation of C2-phenylene bridged bis-2,3-dihydro-1,3-thiazin-4-one 11 with nitrobenzene provided the bis-1,3-thiazin-4-one 12 (Scheme 3).

Scheme 3

2.1.2. 2-Imino or 2-amino derivatives of 1,3-thiazin-4-ones. Arylazo cyanoacetate derivatives 13 were shown in two cases to undergo condensation reactions with thiourea 14 to produce the 2,6-diamino-5-azo-1,3-thiazin-4-ones 15 (Scheme 4).

Scheme 4
Similarly, substituted thiosemicarbazide 17 reacted with malonyl dichloride 16 to produce 2-imino-3-amino-6-hydroxy-1,3-thiazin-4-one 18 (Scheme 5). The text of the paper says triethylamine is involved, but the experimental procedure does not.\(^\text{20}\)

\[
\begin{align*}
\text{O} & \quad \text{Ph} \quad \text{Ph} \\
\text{HN} & \quad \text{N} \quad \text{Ph} \\
\text{HS} & \quad \text{N} \quad \text{N} \quad \text{Ph} \\
\text{Cl} & \quad \text{Cl} \\
16 & \quad 17 & \quad 18 \\
\end{align*}
\]

Scheme 5

The earlier review mentioned condensation of acetylenic esters with thioureas. It has since been reported that the reaction of acetylenic diesters 19 with dialkylthioureas 20 can be run with water as the solvent and triphenylphosphine as catalyst is a simple procedure (Scheme 6).\(^\text{21}\) There was no reaction without the catalyst.

\[
\begin{align*}
\text{CO}_2 & \quad \text{R}^1 \\
\text{CO}_2 & \quad \text{R}^1 \\
\equiv & \\
\text{S} & \quad \text{N} \\
\text{HN} & \quad \text{R}^2 \\
\text{S} & \quad \text{N} \\
\text{HN} & \quad \text{R}^2 \\
19 & \quad 20 & \quad 21 \\
\text{PPh}_3 & \quad \text{H}_2\text{O} \\
50 & \quad ^\circ\text{C} \\
\end{align*}
\]

Scheme 6

The 2-imino-1,3-thiazin-4-one 24 was the result of a dehydrogenation that occurred when the 2-imino-2,3-dihydro-1,3-thiazin-4-ones 22 (see Schemes 36 and 38 for preparation) were heated to 160 °C with phenacyl bromides 23 (Scheme 7).\(^\text{22}\) Similar reactions can be found in Schemes 18 and 87.

\[
\begin{align*}
\text{Ar}_1 & \quad \text{N} \quad \text{Ph} \\
\text{S} & \quad \text{N} \\
\text{Ar}_1 & \quad \text{N} \quad \text{Ph} \\
22 & \quad 23 & \quad 24 \\
\text{O} & \quad \text{Ph} \\
\text{Ar}_2 \quad \text{Br} & \quad \text{Ar}_2 \quad \text{COMe} \quad \text{HBr} \\
160 & \quad ^\circ\text{C} \\
\end{align*}
\]

Scheme 7
2.2. 1,3-Benzothiazin-4-ones
2.2.1. 1,3-Benzothiazin-4-ones. 2-Fluorobenzoyl chlorides 25 were converted to 2-fluoro-1-benzoyl isothiocyanates 26 by treatment with ammonium thiocyanate in a solvent at 40 °C. \( \text{NH}_4\text{Cl} \) was filtered off and the solution of 26 was combined with nucleophilic methylenes 27 to produce addition products 28. Treatment with triethylamine in refluxing toluene induced cyclization to 2-vinyl 1,3-benzothiazin-4-ones 29 (Scheme 8). The reaction appears to proceed by addition of the C-nucleophile to the isothiocyanate, and then intramolecular cyclization via nucleophilic aromatic substitution. When (pyridine-2-yl)acetonitrile 30 was used in place of 27, both steps took place in acetonitrile at room temperature (Scheme 9). Reactions of 27 with polyfluorinated analogs of 26 also in some cases needed triethylamine for the cyclization and in some cases didn't. Some other examples using \( N \)-nucleophiles are discussed in Section 2.2.2.

Scheme 8

Scheme 9
Methyl 2-sulfanylbenzoates 32, aryl nitriles 33 and triethylamine were heated to reflux in toluene to give products 34 (Scheme 10). This is a variant on the commonly used reaction of a 2-sulfanylbenzoic acid 35, one of which was also used, in pyridine (Scheme 11).

Scheme 10

Scheme 11

2.2.2. 2-Imino or 2-amino derivatives of 1,3-benzothiazin-4-ones. 2-Halo-1-isothiocyanates 38 condensed with amines 39 produced 2-amino-1,3-benzothiazin-4-ones 40 via nucleophilic aromatic substitution (Scheme 12). Examples where the halogen is fluorine\(^{25-28}\) or chlorine\(^{29}\) have been reported in recent years. In the example given (X = Cl) in the earlier review, the ring closure was performed using lithium hydride, but in the cases reported since it was done either with triethylamine or with no base at all.\(^{25-27,29}\) One example where X = F used sodium hydride in THF and DMF at 110 °C.\(^{28}\) The amine 39 may be a hydrazine,\(^{25}\) an amino-heterocycle,\(^{26}\) an aryl amine,\(^{28}\) or a cyclic amine.\(^{27,29}\)
It recently was demonstrated that by use of t-butyl sulfoxide as a sulfenic acid equivalent, 2-(t-butylsulfinyl)benzamide 42 reacted with isocyanobenzene 43 to produce the 2-anilino-compound 44 (Scheme 13). The pathway of the reaction began with thermolysis of 42 to give the sulfenic acid 45. Condensation of 45 with isocyanobenzene 43 led to carbocation 46 which was then attacked by the amide nitrogen to close the ring.

![Scheme 13]

2-Sulfanylbenzoic acid 47 reacted with cyanamides 48 in refluxing dioxane to yield the 1,3-benzothiazin-4-ones 49 (Scheme 14). In this case, attack of the thiol group of 47 on the nitriles 48 was presumed to give intermediates 50, which cyclized to give 49.

![Scheme 14]
Treatment of 2,3,4,5-tetrafluoro-1-benzoylisothiocyanate 51 with imidazolidine-2-thione 52 produced compound 53, which with triethylamine gave the cyclized 1,3-benzothiazin-4-one 54 (Scheme 15).\(^{32}\)

![Chemical structures and reaction scheme](image)

**Scheme 15**

Nucleophilic substitution was used to convert 2-methylthio-1,3-benzothiazin-4-ones 55 to 2-cycloamino compounds 57 (Scheme 16).

![Chemical structures and reaction scheme](image)

**Scheme 16**

2.3. Reduced 1,3-thiazin-4-ones

2.3.1. 2,3-Dihydro-1,3-thiazin-4-ones with an exocyclic C=C. Reaction of 1 with 2-dicyanomethyleneindane-1,3-dione 58 gave product 59 with an exocyclic C=C at C2 (Scheme 17).\(^{15}\) The reaction path was proposed to be similar to that in Scheme 1.

![Chemical structures and reaction scheme](image)

**Scheme 17**
The 2-methylidene-2,3-dihydro-1,3-thiazin-4-one 62 was the result of a dehydrogenation reaction that occurred when the 2-methylidene-2,3,5,6-tetrahydro-1,3-thiazin-4-one 60 (see Scheme 51 for synthesis) was heated to 150 °C with phenacyl bromide 61 (Scheme 18). Similar reactions are shown in Schemes 7 and 87.

**Scheme 18**

### 2.3.2. 2-Imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones with an exocyclic C=C.

The 2-bromoethyl-alkenoates 63 were found to react with thiourea 14 in aqueous acetone to give the isothiouonium intermediate 64. After a wash with dichloromethane, the aqueous layer was treated with sodium bicarbonate to give the 1,3-thiazin-4-one 65, with an exocyclic C=C at C5, and an amine at C2 (Scheme 19). A proposed mechanism involved nucleophilic attack of the sulfur to displace the bromine, giving the isothiouonium bromides 64. Treatment with base removed HBr and cyclization occurred with loss of methanol.

**Scheme 19**

### 2.3.3. 2,3-Dihydro-1,3-thiazin-4-ones.

In the earlier review, the only syntheses presented of this group were a few ring-expansion reactions. Since then, some other types of syntheses have been developed.

In one method, aryl isothiocyanates 66 were reacted with cyanoacetamide 67 under basic conditions to give the isolated products 68. These intermediates were then reacted with an aldehyde 69 and cyclized with p-toluenesulfonic acid (TsOH) catalyst at room temperature to give 5-cyano-6-arylamino-2,3-dihydro-1,3-thiazin-4-ones 70 (Scheme 20). This has also been done in one pot using aldehydes or acetone. The reaction was also performed with NaOH in DMF at room temperature, then acetic acid and acetone were added and the mixture was heated by microwave irradiation to 80 °C (Ar = Ph, 4-Cl-C₆H₄, 4-Br-C₆H₄; R = alkyl, aryl, heteroaryl; 84-93%).
In another method, 3-alkyl(aryl)amino-2-cyano-3-sulfanylacrylamides 1 reacted with aldehydes and ketones 71, with catalytic TsOH as above, to produce compounds 72 (Scheme 21).

Another version involved a single example of an aryl aldehyde and ethanol at reflux, without TsOH.

A variety of 2-spiro compounds 75 were synthesized in a two-step, one-pot procedure beginning with reaction of isothiocyanates 73 with cyanoacetamide 67 in DMF-catalyzed sodium hydroxide to produce 1. Addition of cyclic ketones 74 and acetic acid and then microwave irradiation gave the products 75 (Scheme 22).
2.3.4. 5,6-Dihydro-1,3-thiazin-4-ones. In one recent method, malononitrile 6 was reacted with dimedone 76 to produce derivative 78, which was refluxed in acetic acid with thioacetamide 79 in the presence of sodium acetate to form the 2-methyl-6-spiro-5,6-dihydro-1,3-thiazin-4-one compound 80 (Scheme 23).45

In a method involving an isothiocyanate, treatment of the crude unstable compound 81 with amines 82 produced thioureas 83. Intramolecular cyclization was accomplished with boron trifluoride to produce 5,6-dihydro-1,3-thiazin-4-ones 84 (Scheme 24).46

2.3.5. 2-Imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones. Many of the approaches to these compounds involve thioureas.
Sulfonylthioureas 86 reacted with ethyl 3-bromopropionate 85 in the presence of sodium acetate in refluxing ethanol\textsuperscript{47,56} or acetic acid\textsuperscript{56,57} to give the products 87 (Scheme 25). In two cases ethanol alone was used.\textsuperscript{58,59}

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {\textbf{85}};
    \node (b) at (0,-1) {\textbf{86}};
    \node (c) at (1,-1) {\textbf{87}};
    \node (d) at (1,0) {NaOAc};
    \node (e) at (1,-2) {EtOH reflux};
    \node (f) at (0,-2) {\textbf{R}^2};
    \node (g) at (0,-3) {\textbf{R}^1};
    \path (a) edge node {OEt} (b);
    \path (b) edge node {\scriptsize{\text{S=O}}} (c);
    \path (a) edge node {Br} (d);
    \path (d) edge node {\scriptsize{\text{H}}} (e);
    \path (b) edge node {\scriptsize{\text{O}}} (f);
    \path (f) edge node {\scriptsize{\text{H}}} (g);
    \path (g) edge node {\scriptsize{\text{N}}=\text{S}} (c);
\end{tikzpicture}
\end{center}

**Scheme 25**

This also worked when there was a carbonyl group in place of the sulfone (Scheme 26).\textsuperscript{60}

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {\textbf{85}};
    \node (b) at (0,-1) {\textbf{88}};
    \node (c) at (1,-1) {\textbf{89}};
    \node (d) at (1,0) {NaOAc};
    \node (e) at (1,-2) {EtOH reflux};
    \node (f) at (0,-2) {\textbf{R}^2};
    \node (g) at (0,-3) {\textbf{R}^1};
    \path (a) edge node {OEt} (b);
    \path (b) edge node {\scriptsize{\text{S=O}}} (c);
    \path (a) edge node {\scriptsize{\text{H}} (\text{O})} (d);
    \path (d) edge node {\scriptsize{\text{H}}} (e);
    \path (b) edge node {\scriptsize{\text{H}} (\text{O})} (f);
    \path (f) edge node {\scriptsize{\text{H}}} (g);
    \path (g) edge node {\scriptsize{\text{N}}=\text{O}} (c);
\end{tikzpicture}
\end{center}

**Scheme 26**

Reaction of thioureas 19 with ethyl 3-bromopropionate 85 was done just by refluxing in dioxane to give compounds 90 (Scheme 27).\textsuperscript{61-63} Refluxing ethanol has also been used.\textsuperscript{64}

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {\textbf{85}};
    \node (b) at (0,-1) {\textbf{19}};
    \node (c) at (1,-1) {\textbf{90}};
    \node (d) at (1,0) {\textbf{R}^2};
    \node (e) at (1,-2) {\textbf{R}^1};
    \path (a) edge node {OEt} (b);
    \path (b) edge node {\scriptsize{\text{H}} (\text{O})} (c);
    \path (a) edge node {\scriptsize{\text{H}} (\text{O})} (d);
    \path (d) edge node {\scriptsize{\text{H}}} (e);
    \path (b) edge node {\scriptsize{\text{H}} (\text{O})} (e);
    \path (e) edge node {\scriptsize{\text{N}}=\text{N}} (c);
    \node (f) at (0,-2) {dioxane reflux};
\end{tikzpicture}
\end{center}

**Scheme 27**

Reaction of 3-chloropropanoic acid 91 with thiosemicarbazones 92 under typical conditions (NaOAc, AcOH, Ac\textsubscript{2}O) gave yields of products 94 of 44-48\%, whereas use of the ionic liquid \textit{N}-methylpyridinium \textit{p}-toluenesulfonate 93 gave 74-75\% yields (Scheme 28).\textsuperscript{65} Dicyclohexylcarbodiimide (DCC) in THF at 0 °C has also been used in this type of reaction (55\%).\textsuperscript{66}
Scheme 28

3-Chloropropanoyl chloride 95 and potassium thiocyanate were refluxed in acetone and then 2,4-dimethylaniline 96 was added at room temperature to produce 2-imino-5,6-dihydro-1,3-thiazin-4-one 97 (Scheme 29). Use of 3-bromopropanoyl was discussed in the earlier review.

Scheme 29

Previously it had been reported that the known thermal reaction of methacroyl isothiocyanate 98 with isonicotinylhydrazide 99 led to the 2-hydrazide-1,4-diacyl-thiosemicarbazide 100, which when heated to 70 °C in 2-propanol gave compound 103 (65% from 100). It was then found that addition of a cyclic secondary amine base 101 promoted the intramolecular (conjugate-addition) cyclization of 100, making the reaction run faster, at lower temperature (30 °C) and in higher yield (82%) (Scheme 30). It was proposed by the authors that the base mediates formation of the thiol tautomeric form 102 of 100 to allow its cyclization.

Methacroyl isothiocyanate 98 was prepared in situ by reaction of KSCN with methacroyl chloride, and then treatment with morpholin-4-amine or adamantane-1-amine generated the thiourea 100, which then cyclized to the product as in Scheme 30.

Under the same conditions as the reaction shown in Scheme 23, replacement of thioacetamide 79 with thioureas 104 gave the 2-amino-5-cyano-6-spiro-5,6-dihydro-1,3-thiazin-4-ones 105 (Scheme 31).
A number of preparations involve conjugate addition of the thiourea derivative. A three-component reaction of a primary alkyl amine 82, phenylisothiocyanate 107, and 2-propenoyl chloride 106 in the presence of triethylamine produced the 2-amino compounds 108 (Scheme 32). The thiourea derivative was presumably formed in situ from the amine and the isothiocyanate. The reaction only gave the product in which the ring nitrogen bears the phenyl substituent.\(^7\)

\[
\text{O} + \text{N} + \text{RNH}_2 \xrightarrow{\text{Et}_3\text{N, CH}_3\text{CN}} \text{Ph}
\]

\[
\text{108}
\]

\(R = \text{alkyl} \) 83-86%
A three-component reaction of amines 109, isocyanates 73, and itaconic anhydride 110 gave 5-acetic acid products 111 (Scheme 33). A possible pathway involved initial attack of the amines 109 on the isothiocyanates 73 to give substituted thioureas 112, followed by attack of the sulfur on the exocyclic double bond in a conjugate addition to open the ring, then cyclization by the nitrogen attacking the ketene intermediates 113. 71

Scheme 33

A one-pot reaction, in the presence of ionic liquid catalyst [Bmim]Br 117, of 2-phenyl-1,3-oxazol-5-one 114 or 2-methyl-2-phenyl-1,3-oxathiolan-5-one 115 with aldehydes 116, followed by addition of thioureas 104 gave the 2,5-diamino-6-aryl-5,6-dihydro-1,3-thiazin-4-ones 120 or 2-amino-6-aryl-5-mercapto-5,6-dihydro-1,3-thiazin-4-ones 121 with high diastereoselectivity (Scheme 34). The proposed mechanism was a first step of condensation of the aldehydes 116 with the esters 114 or 115, then conjugate addition of the sulfur of thiol tautomeric form of thioureas 104 to give intermediate 122 or 123, and then an intramolecular cyclization to give the products 120 or 121. The ionic liquid 117 was said to hydrogen bond to the carbonyl oxygen, making the carbon more electrophilic (not shown in Scheme). 72

Cyclization via intramolecular conjugate addition has also been reported. Treatment of thiourea derivative 125 with sodium ethoxide in ethanol at room temperature led to the product 126, as the kinetic product resulting from attack of the thiolate anion on the alkene. 73,74 When the reaction was run at reflux, the thermodynamic product 124 resulting from attack by nitrogen was obtained (Scheme 35). 74 The room temperature reaction has been shown to work in other examples as well. 73,75-77
The same type of reaction was shown to be catalyzed by HCl in acetone (Scheme 36). The initial product was the HCl salt. Treatment with sodium bicarbonate or potassium bicarbonate removed the acid to give 128.硼 trifluoride also has been shown to catalyze this type of cyclization.79
In one particular case, this type of cyclization took place in refluxing acetone alone (Scheme 37).\(^{80}\)

A one-pot reaction was done in which thioureas 132 were reacted with 3-aryl-2-propenoyl chlorides 131 in acetone to give products 133 (Scheme 38).\(^{22}\) For R = H, the product was the HCl salt of 133. It was presumed that the N-acylation product was formed first, followed by cyclization as in the examples above.

The bioactive compound 136 was synthesized by heating an acetic acid solution of N,N'-dimethylthiourea 135 with N-(4-chlorophenyl)maleimide 134 (Scheme 39).\(^{81}\)
Another novel reaction involving a ring-opening combined thiourea derivatives 138, 2,3-diphenyl-cyclopropenone 137, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give 139 (Scheme 40). The mechanism was proposed to begin with conjugate addition of the sulfur to the cyclopropenone to give intermediate 140. The strained ring then opened, producing intermediate 141, and then intramolecular attack of nitrogen on the ketene gave compound 142 which then was oxidized by DDQ to product 139. Compound 142 was isolated in a separate experiment and shown to undergo DDQ oxidation to provide 139.

2-Peptidylimino-2,3-dihydro-1,3-thiazin-4-ones 146 were synthesized from the corresponding 2-thiones 143 (Scheme 41). Treatment of 143 with diethyl sulfate gave isolable salts 144 with a stabilized carbocation. Treatment with dipeptides 145 (gly, gly or gly, L-alal) provided compounds 146.
2.3.6. 2,3-Dihydro-1,3-benzothiazin-4-ones. In the original review, it was stated that the most common method used for the synthesis of 2,3-dihydro-1,3-benzothiazinones 149 was the reaction of 2-sulfanylbenzamides with carbonyl compounds. Since then, however, the most widely used method has been the reaction of 2-sulfanylbenzoic acids 147 with imines 148, which can be prepared in situ (Scheme 42). In the prior review, this was mentioned as a way to prepare N-alkyl or N-amido 2,3-dihydro-1,3-benzothiazin-4-ones, by refluxing in a solvent. Thermal methods continue to be used. In recent examples, N-aryl and N-amido compounds were made in refluxing benzene, N-amido compounds were prepared in 1,4-dioxane at 100 °C or 130 °C, and N-alkyl compounds were synthesized in refluxing toluene. Sodium sulfate was used to remove water from the condensation reaction in refluxing dioxane to make one N-aryl compound in each of two reports. Another report shows Na$_2$SO$_4$ in the graphic, but this is not mentioned in the experimental, where it was stated that the reaction ran at room temperature. There is a claim in the literature that treatment of 2-sulfanylbenzoic acid with molecular sieves dehydrated it to give a thioketene intermediate, which reacted with N-benzylideneaniline to give 2,3-diphenyl-2,3-dihydro-1,3-benzothiazin-4-one. However, the $^1$H NMR data and melting point do not match those reported elsewhere which were confirmed by x-ray crystallography.

The reaction has also been catalyzed by TsOH in refluxing toluene (33-73%).

Scheme 42
Highly polarized imines 151 have been used to form 2,2-disubstituted-2,3-dihydro-1,3-benzothiazin-4-ones 152 at room temperature in THF (Scheme 43).\textsuperscript{96,97} Scheme 59 shows a similar reaction.

\begin{equation}
\begin{array}{ccc}
\text{47} & + & \begin{array}{c}
\text{151} \\
R^1 = \text{P(O)(OEt)}_2, \text{CO}_2\text{Me} \\
R^2 = \text{CF}_3, \text{CHF}_2
\end{array} \\
\text{THF} & \text{rt} & \text{152} \\
\end{array}
\end{equation}

Scheme 43

Microwaves have also been used in this type of reaction and they greatly increased the rate of the reaction (6-8 min vs. 10-13 h thermal) of exocyclic imines 153 in ethanol/acetic acid to give spiro compounds 154 (Scheme 44). Yields were also generally somewhat improved compared to thermal reactions without microwave irradiation (74-81% vs. 65-72%).\textsuperscript{98}

\begin{equation}
\begin{array}{ccc}
\text{47} & + & \begin{array}{c}
\text{153} \\
R^1 = \text{2-CF}_3, 3-\text{CF}_3 \\
R^2 = \text{H, 5-Me}
\end{array} \\
\text{MW} & \text{EtOH} & \text{AcOH} & \text{154} \\
\end{array}
\end{equation}

Scheme 44

DCC has been used to activate the acid in three-component reactions. The reaction of amines 155, aldehyde 156, and 2-sulfanylbenzoic acid 47 was run in refluxing toluene.\textsuperscript{99,100} In another case, an HCl salt of the amine was used. Sodium bicarbonate was included in the reaction to neutralize the HCl, with \textit{N,N-}dimethylaminopyridine (DMAP) as a promoter along with DCC (Scheme 45). The desired 2,3-dihydro-1,3-benzothiazin-4-one 157 was accompanied by 158, which did not include the amino ester.\textsuperscript{101}
Another reagent that has been used to activate the carboxylic acid is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P) \( \text{T3P} \) \( ^{159} \), with either pyridine at room temperature, \(^{92-94,102-105}\) or diisopropylethylamine (DIPEA) at 90 °C. \(^{106,107}\) The mechanism was proposed to begin with reaction of the acid with T3P \( \text{T3P} \) \(^{159}\) to give phosphate intermediate \( \text{160} \), then attack by the nitrogen on the activated carbonyl to give iminium ion \( \text{161} \), and then ring closure by attack of the sulfur to produce product \( \text{162} \) (Scheme 46). \(^{106}\) \( R^2 \) can be aryl (13-43%) \(^{92-94,102-105}\) or methyl (99%). \(^{106,107}\) \( R^1 \) is aryl in these examples, but also see Scheme 106 for cycloalkyl.

**Scheme 46**

Methyl 2-sulfanylbenzoate \( \text{163} \) was reacted with ammonia and acetophenone derivative \( \text{164} \) in methanol under microwave irradiation at 150 °C to give the 2-aryl-2-methyl-2,3-dihydro-1,3-benzothiazin-4-one \( \text{165} \) (Scheme 47). \(^{108}\)
Scheme 47

In the earlier review, the reaction of acetylenic esters with 2-sulfanylbenzamides was discussed. In a recent report, methyl propiolate 167 was reacted with 2-sulfanylbenzamides 166 in the presence of potassium phosphate in refluxing toluene to give products 168 in a one-pot procedure (Scheme 48). The first step was proposed to be 1,4-addition of the thiol to the terminal alkyne, and then the base catalyzed addition of the amide nitrogen to the alkene intermediate. Ester 167 could be replaced with an acetylenic ketone or amide, and could also be an internal alkyne.

Scheme 48

Photoisomerization of 1,2-benzothiazine 1,1-dioxides 169, including the non-steroidal anti-inflammatory drug (NSAID) piroxicam, has been shown to produce the 2,3-dihydro-1,3-benzothiazin-4-one compounds 170 (Scheme 49).

Scheme 49

1,3-Benzothiazin-4-ones 171 (see Section 2.2.1) were converted into 2,3-dihydro-1,3-benzothiazin-4-ones 172 by reduction of the C=N bond using sodium borohydride in ethanol (Scheme 50).
Scheme 50

2.3.7. 2,3,5,6-Tetrahydro-1,3-thiazin-4-ones with an exocyclic C=C. Condensation of thioamide 174 with 3-(4-nitrophenyl)-2-propenoyl chloride 173 was reported to produce the 2,3,5,6-tetrahydro-1,3-thiazin-4-one 60, with an exocyclic C=C double bond at C2, in a 1:1 mixture with lactam 175 (Scheme 51).\(^ {33}\) The 1,3-thiazin-4-one was only formed in this specific case; different products were obtained, depending on the substituents on the thioamide and the propenoyl chloride. The authors suggested that in the presence of K\(_2\)CO\(_3\) the nitrogen in 174 attacked the carbonyl in 173, giving an intermediate amide, which then converted to the two products. However, only one product was formed when phenylsulfonylthioamides 177 were reacted with 3-phenyl-2-propenoyl chloride 176 (Scheme 52).\(^ {111}\)

Scheme 51

Scheme 52

A different approach to a 2-alkylidene compound started with 2,4-dihydropyrazol-3-one 179, which had an active methylene which was deprotonated with sodium hydride and reacted with phenyl isothiocyanate 107 to yield the sodium salt of the enethiol form of thioamide 180. Addition of ethyl 3-bromopropanoate 85 to the reaction mixture yielded the product 181 (Scheme 53).\(^ {112}\)
In a similar vein, the active methylene in α-cyanoacetamides 182 was deprotonated with KOH and reacted with phenyl isothiocyanate 107, then acidified to give the isolated thioamide tautomers 183. Treatment with 3-chloropropanoyl chloride 95 and triethylamine afforded the 2-alkylidene products 184 (Scheme 54).

Ethyl 3-sulfanylpropanoate 185 reacted with malononitrile 6 with catalytic potassium carbonate in ethanol to give 186. Under thermal conditions the yield was only 3%, but with microwave irradiation, a 27% yield was achieved (Scheme 55).

2.3.8. 2,3,5,6-Tetrahydro-1,3-thiazin-4-ones. The most commonly used method for the preparation of 2,3,5,6-tetrahydro-1,3-thiazin-4-ones 189 has been the combination of a 3-sulfanylpropanoic acid 187 and an imine 188, which can be prepared in situ (Scheme 56).
Some compounds were prepared just by heating, as reported in the previous review. Usually this has been done in benzene or toluene. In a recent report, one example was carried out as a three-component reaction at 120 °C without a solvent. In one case, it was shown that at room temperature in toluene the product formed was the result of attack by the sulfur on the imine carbon. Upon heating to reflux, the amide bond formed (Scheme 57).

Pyridine was used as solvent for the reaction of 4-aminocoumarin with benzaldehyde and 3-sulfanylpropanoic acid (Scheme 58). The authors suggested imine formation was followed by conjugate addition of the sulfur and then amide formation. The role of pyridine was not commented on.
Highly polarized imines 151 have been used to form the 2,2-disubstituted-2,3,5,6-tetrahydro-1,3-thiazin-4-ones 197 at room temperature in benzene\(^6\) or ether (Scheme 59).\(^{37}\) Scheme 43 shows a similar reaction.

![Image of Scheme 59](attachment:image.png)

**Scheme 59**

More commonly, since the last review, a catalyst or promoter has been used. Many investigators have used reagents that activate the carboxylic acid to promote amide formation. These include carbodiimides DCC,\(^4,12,87,100,118-123\) diisopropylcarbodiimide (DIC),\(^124,125\) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC);\(^3,126,127\) thionyl chloride,\(^128\) \(N,N,N',N'\)-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU)/DIPEA,\(^129\) and T3P 159 with pyridine\(^93,130-132\) or DIPEA.\(^133\) Most of the reports used aldehydes, but two of them used ketones.\(^120,128\) T3P 159 has been shown to work with \(N\)-acetylcysteine as the thioacid.\(^93,117,133\)

Acid catalysis has also been used. Acids used include \(\text{ZnCl}_2\)\(^134\) and \(\text{TsOH}\).\(^135\) Trifluoroacetic acid has been used to catalyze a reaction using an oxime 198 instead of an imine (Scheme 60).\(^136\)

![Image of Scheme 60](attachment:image.png)

**Scheme 60**

The effect of ultrasound on three-component reactions has been investigated. In one study, reactions were carried out either in refluxing toluene, or at room temperature in toluene with ultrasound. Yields were somewhat lower with ultrasound (41-88\% vs. 41-97\%), but the reactions were substantially faster (25 min. vs. 19 h).\(^137\) Another group found optimal conditions for their reaction when a polyethylene glycol (PEG)-\(\text{OSO}_3\)\(^3\) catalyst was used in combination with ultrasound in water (Scheme 61). PEG-\(\text{OSO}_3\)\(^3\) acted as both an acid catalyst and a phase transfer catalyst.\(^138\) Reactions under these conditions ran to completion in 20-38 min. with 85-89\% yields.
Microwaves have also been used in this reaction and they greatly increased the rate (11-17 min. vs 13-20 h) and more modestly the yields (68-82% vs. 14-68%) in ethanol (Scheme 62). The MW reactions were run for only 2-4 min. in the acidic ionic liquid 1-methylimidazolium tetrafluoroborate ([MIM]BF₄) at 140 °C, giving excellent yields of spiro compounds 204 (90-97%). Alternatively, the reactions were run without solvent using acidic solid montmorillonite KSF as a support while irradiating (6-8 min., 75-93%).

Reaction of enones 205 with excess 3-sulfanylpropanoic acid 190 and ammonium carbonate gave addition of two equivalents of the acid, with one cyclizing with a nitrogen to give the 2,2-disubstituted-2,3,5,6-tetrahydro-1,3-thiazin-4-ones 206 (Scheme 63). No mechanism was proposed.
Reaction of 3-mercaptopropanamide 207 with aryl methyl ketones 208 with TsOH catalyst in refluxing toluene produced 2,2-disubstituted-2,3,5,6-tetrahydro-1,3-thiazin-4-ones 209 (Scheme 64).

\[
\begin{align*}
\text{CONH}_2 \quad \text{SH} & \quad \text{R} \quad \text{TsOH} \quad \text{toluene} \quad \text{reflux} \quad \text{CONH}_2 \quad \text{S} \\
\text{207} & \quad \text{208} & \quad \text{209} \\
\end{align*}
\]

\( \text{R} = 5\text{-pyrimidyl, 3-OCH}_3\text{-C}_6\text{H}_4 \)

**Scheme 64**

The reaction of thioamides 8 with ethyl acrylate 210 in the presence of boron trifluoride in toluene produced the 2-ethoxy-2-fluoroalkyl-2,3,5,6-tetrahydro-1,3-thiazin-4-ones 213. Presumably, the reaction initially produced the 5,6-dihydro compound 212, but addition of ethanol to the C=N unit gave 213 (Scheme 65).

\[
\begin{align*}
\text{COOEt} \quad \text{NH}_2 & \quad \text{S} \quad \text{R} \quad \text{BF}_3\cdot\text{OEt}_2 \quad \text{toluene} \quad \text{HO} \quad \text{OEt} \quad \text{EtOH} \quad \text{EtOH} \\
\text{210} & \quad \text{8} & \quad \text{211} & \quad \text{212} & \quad \text{213} \\
\end{align*}
\]

\( \text{R} = \text{C}_3\text{F}_7, \text{H(CF}_2)_2, \text{CF}_3 \)

\( \text{25-50\%} \)

**Scheme 65**

2.4. 1,3-Thiazin-4-ones with fused heterocycles

2.4.1. e-Fused 1,3-thiazin-4-ones. As part of a synthesis of the natural product cyclobrassinon, t-butoxycarbonyl (Boc)-activated isothiocyanate 214 was reacted with methanol in acetone to produce the monothiocarbamate 216. Addition of triethylamine to the reaction mixture induced cyclization by aromatic substitution of the indole chlorine atom to give the desired indole-fused 217 (Scheme 66). Other examples were also demonstrated in which methanol was replaced with ethanol or isopropanol (47-64% from 214).

\[
\begin{align*}
\text{Boc} \quad \text{Cl} \quad \text{C=SS} & \quad \text{ROH} \quad \text{Et}_3\text{N} \quad \text{acetone} \quad \text{215} \quad \text{216} \quad \text{217} \\
\text{214} & \quad \text{216} & \quad \text{R} = \text{Me, Et, i-Pr} \\
\end{align*}
\]

\( \text{47-64\% (2 steps)} \)

**Scheme 66**
From compounds 218, analogous to 216 but where the indole nitrogen bears an alkyl or alkoxy substituent rather than the activating Boc group, cyclization under known conditions such as NaH, LiH, Et₃N, NaOMe, and heat failed. Cyclization was ultimately achieved photochemically (Scheme 67). A similar reaction is shown in Scheme 73.

Scheme 67

When α-arylhydrazonomalononitriles 221 were combined with 2-keto-3-sulfonylcinchonic acid derivatives 220, the reactions were run in refluxing acetic acid. It was suggested that the sulfur attacked one of the nitrile groups to give thioamide intermediates 222, which cyclized to form products 223 (Scheme 68).

Scheme 68

Methyl 2-sulfanylpyridine-3-carboxylate 224 has been reacted with aryl nitriles 33 in the presence of pyridine to give two 1,3-pyridothiazin-4-ones 225 in poor yield (Scheme 69). This is similar to the 1,3-benzothiazin-4-one preparations in Scheme 10.
2.4.2. e-Fused 2-imino or 2-amino derivatives of 1,3-thiazin-4-ones. To prepare 2-imino-1,3-pyridothiazin-4-one 231, 4-chloropyridine-3-carboxylic acid 226 was converted into the acid chloride 227, which was reacted with ammonium thiocyanate to give the isothiocyanate 228. Treatment with \( N \)-methyl-\( N \)-(4-chlorophenyl)amine 229 gave the substituted thiourea 230 and cyclization took place in the room temperature acetone solution (Scheme 70). This is similar to prior art using 2-chloropyridine-3-carboxylic acid.

![Scheme 70](image)

Scheme 70

![Scheme 71](image)

Scheme 71
Starting with 3-fluoropyridine-4-carboxylic acid 232, the cyclization step was performed using sodium hydride in DMF and THF at 110 °C. This also succeeded starting with 3-chlorothiophene-2-carboxylic acid 235 (Scheme 71). \(^{28}\)

In chemistry similar to Scheme 66, amines were added to indole isothiocyanate 214, yielding monothiocarbamates 238. Cyclization of the Boc-activated compound took place with addition of triethylamine in refluxing acetone to give indole-fused products 239 (Scheme 72). \(^{145}\)

![Scheme 72](image)

As in Scheme 67, cyclization of compound 242 under known conditions such as NaH, LiH, Et\(_3\)N, NaOMe, and heat failed. Cyclization was again achieved photochemically (Scheme 73). \(^{145}\)

![Scheme 73](image)

Instead of conversion of 2-chloropyridine-3-carboxylic acid chloride 244 into the isothiocyanate, the amides 245 were first formed. Then reaction with sodium hydride and an aromatic isothiocyanate 246 in DMF directly gave the 1,3-pyridothiazin-4-ones 247. The mechanism was proposed to go through the thiourea derivatives 248 (Scheme 74). \(^{147}\)
Scheme 74

2-Sulfanylpicolinic acid 224 was reacted with the N-cyanoacetamide 249 in N,N-dimethylacetamide (DMAC) at 100 °C to yield the 1,3-pyridothiazin-4-one 250 in low yield (Scheme 75). In this case, a thiourea intermediate was presumed to form from attack of the thiol of 224 on the nitrile of 249 to give intermediate 251, which cyclized to give 250. This only worked with 249; less electrophilic cyanamides did not react with the thiol of 224, which was less nucleophilic than in 2-sulfanylbenzoic acid 47.31

Scheme 75

2.4.3. e-Fused 2,3-dihydro-1,3-thiazin-4-ones. 2-Keto-3-sulfanylcinchonic acid derivatives 252 reacted with diaryl aldimines 253 in refluxing toluene to give products 254 (Scheme 76).146
Scheme 76

T3P 159 has been used to synthesize 2,3-dihydro-1,3-pyridothiazin-4-one 256 by the reaction of 2-sulfanylpyridine-3-carboxylic acid 224 with N-benzylideneaniline 255 (Scheme 77). This is analogous to reactions to prepare 2,3-dihydro-1,3-benzothiazin-4-ones and 2,3,5,6-tetrahydro-1,3-thiazin-4-ones (see Sections 2.3.6 and 2.3.8).

Scheme 77

Zeolite-supported acidic ionic liquid ZSM-5-([MIM]⁺BF₄⁻) and sonication were used in a three-component reaction to give 2-spiro-2,3-dihydro-1,3-pyridothiazin-4-ones 258 (Scheme 78). It was proposed that the reaction mechanism involved diradical intermediates.

Scheme 78
Microwaves were used in a similar three-component reaction (Scheme 79). Under thermal conditions (DMF, 140 °C, 8 h), there was no reaction between the imine 260 and 2-sulfanylpyridine-3-carboxylic acid 224.

Scheme 79

A novel two-step process was used in the preparation of 2,3-dihydro-1,3-pyridothiazin-4-one 265 (Scheme 80). In the first step, cyclic alkene 262 was reacted with monothiomalonodiamide 263 under basic conditions to yield cyclic thioamide 264. Treatment with acetone and catalytic conc. HCl yielded 265. The authors suggested that 262 underwent an Sn2 reaction in which the α-carbon of monothiomalonodiamide 263 displaced morpholine, then cyclization by nucleophilic attack of the thioamide nitrogen on the ketone gave 265.

Scheme 80

2,3-Dihydro-1,3-pyridothiazin-4-one 267 was prepared by a Schmidt rearrangement when compound 266 was treated with sodium azide and catalytic sulfuric acid in refluxing DMF (Scheme 81).
2.4.4. e-Fused 2-imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones. A novel four-component coupling strategy for preparation of thiosugar-fused 5,6-dihydro-1,3-thiazin-4-ones 270 has been reported. In the reaction, a sugar 268, masked sulfanylacetic acid equivalent 115, an amine 82, and the ionic liquid [bmim]SCN 269 were stirred with a few drops of water (Scheme 82, stereochemistry not shown for simplicity). A possible pathway involved a) tandem Knoevenagel-hydrothiocyanation of 268 by 115 and thiocyanate ion to give nitrile intermediates 271; b) attack by the amine 82 to give intermediate 272; c) intramolecular attack by nitrogen on the carbonyl leading to loss of acetophenone and formation of the 1,3-thiazin-4-one ring 273; d) rings closure by cyclodehydration to yield the cyclic thioethers 270.

Scheme 82

Recently, a similar reaction was reported, except 115 was replaced with a nitrogen-containing ring, compound 114 (Scheme 83).

Scheme 83
2.4.5. \textit{b-}Fused 2-imino or 2-amino derivatives of 1,3-thiazin-4-ones. The reaction of cyclic thioureas 276 with gem-cyanoester epoxides 275 delivered the \textit{b-}fused 1,3-thiazin-4-ones 277 (Scheme 84).\textsuperscript{155} It was proposed that the reaction began with regioselective attack by sulfur on the epoxide, followed by elimination of HCN, and finally intramolecular nucleophilic acyl substitution.

\begin{center}
\begin{tikzpicture}
\node [align=center] (a) at (0,0) {\begin{minipage}{0.4\textwidth}
\begin{align*}
\text{275} \quad \text{276} \quad \text{277} \quad \text{278} \quad \text{279}
\end{align*}
\end{minipage}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 84}

The \textit{b-}fused triazolo-1,3-thiazin-4-ones 282 were prepared using conjugate addition to acetylenic esters 280 (Scheme 85).\textsuperscript{156}

\begin{center}
\begin{tikzpicture}
\node [align=center] (a) at (0,0) {\begin{minipage}{0.4\textwidth}
\begin{align*}
\text{280} \quad \text{281} \quad \text{282}
\end{align*}
\end{minipage}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 85}

\textit{b-}Fused imidazo-1,3-thiazin-4-ones 285 were synthesized by a palladium-catalyzed tandem amino-carbonylation-cyclization reaction (Scheme 86). Imidazoles 283 were treated with PdI\textsubscript{2}/KI/CO/O\textsubscript{2} (air)/R\textsubscript{2}NH/CH\textsubscript{3}CN at 100 °C. It was proposed that in the first step, the terminal alkyne was aminocarbonylated to produce the alkynyl amide intermediates 284. This then went through a second catalytic cycle that effected cyclocarbonylation to 285.\textsuperscript{157} Two carbon monoxides became incorporated into the molecule. The oxygen served to oxidize Pd(0) to Pd(III) in the first catalytic cycle.
Heating \( \beta \)-fused triazolo-5,6-dihydro-1,3-thiazin-4-ones 286 (see Scheme 118 for preparation of similar) to 200 °C with an aryl bromomethyl ketone 23 caused dehydrogenation to give the 1,3-thiazin-4-ones 287 (Scheme 87).\(^{158}\) This is similar to the reactions in Schemes 7 and 18.

\[
\text{286} \xrightarrow{\text{Ar}^2\text{COBr} \text{200 °C}} \text{287}
\]

\(\text{Ar}^1 = \text{Ph}, 4-\text{Cl-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4\)

\(\text{Ar}^2 = \text{Ph}, 4-\text{Cl-C}_6\text{H}_4\)

33-37%

\textbf{Scheme 87}

\textbf{2.4.6.} \( \beta \)-Fused 2-imino or 2-amino derivatives of 1,3-benzothiazin-4-ones. 2,3,4,5-Tetrafluoro-1-benzoyl chloride 25 has been used in reactions with cyclic thioureas 288 and 52 to obtain benzimidazo- and imidazo-products, 289 and 290, respectively (Scheme 88).\(^{159}\)

\[
\text{25} + \text{288} \xrightarrow{\text{toluene reflux}} \text{289}
\]

\(R = \text{H, F, Cl, Me}\)

67-94%

\[
\text{25} + \text{52} \xrightarrow{\text{pyridine, 80 °C}} \text{290}
\]

67%
Alternatively, 2-fluoro-1-benzoyl isothiocyanate 26 was reacted with cyclic thiourea 291 (Scheme 86). Evidently, the NCS moiety behaved as a leaving group in this case.\(^{32}\)

\[
\begin{align*}
\text{F} & \hspace{1cm} \text{F} & \hspace{1cm} \text{N=C=S} & \hspace{1cm} \text{CH}_3\text{CN} & \hspace{1cm} \text{reflux} & \hspace{1cm} \text{F} & \hspace{1cm} \text{F} \\
\text{26} & & & & & \text{292} & \text{90%} \\
\end{align*}
\]

Scheme 89

\(b\)-Fused imidazolo- and benzimidazolo-1,3-benzothiazin-4-ones 296 and 298 were synthesized in a two-step process (Scheme 90). First, cyclic thioureas 294/291 were reacted with 2-iodobenzoyl chloride 293 in the presence of Cul/TBAB/Cs\(_2\)CO\(_3\)/DMF at 130 °C. This gave the sulfides 295/297, which were cyclized by treatment with EDC.\(^{160}\)

\[
\begin{align*}
\text{293} & \hspace{1cm} \text{294} & \hspace{1cm} \text{DMF} & \hspace{1cm} 130 \degree \text{C} & \hspace{1cm} \text{295} & \hspace{1cm} \text{EDC} & \hspace{1cm} \text{296} & \text{66\%} \\
\text{293} & \hspace{1cm} \text{291} & \hspace{1cm} \text{DMF} & \hspace{1cm} 130 \degree \text{C} & \hspace{1cm} \text{297} & \hspace{1cm} \text{EDC} & \hspace{1cm} \text{298} & \text{65\%} \\
\end{align*}
\]

Scheme 90

In a similar reaction, 2-halo-1-benzoyl chlorides 299 were converted in a cascade reaction to the \(b\)-fused imidazole/benzimidazole products 301/302 (Scheme 91).\(^{161}\) The halogen could be Cl, Br, or I. 1,10-Phenanthroline 300 was used as a ligand.
Scheme 91

Methyl 2-iodobenzoates 303 reacted with a wide range of cyclic thioureas 304 in a similar copper-catalyzed cyclization to give 5, 6, and 7-membered b-fused rings 305 (Scheme 92).\(^{162}\)

Scheme 92

Under similar conditions, 2-iodobenzoic acid 306 was coupled with cyclic thioureas 307 (Scheme 93).\(^{163}\)
The same type of reaction, but catalyzed by FeCl₃, has been used to prepare b-fused benzimidazole, imidazole, and triazole compounds \(301/311\) (Scheme 94).\(^{164}\)

\[
\begin{align*}
\text{R} & \quad \text{FeCl}_3 \quad \text{Cs}_2\text{CO}_3 \quad \text{DMF} \quad 110 \ ^\circ \text{C,} \\
\text{then} & \quad \mathrm{AcOH} \quad 110 \ ^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{309} & \quad + \quad \text{291} \\
\text{then} & \quad \text{AcOH} \quad 110 \ ^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{FeCl}_3 \quad \text{Cs}_2\text{CO}_3 \quad \text{DMF} \quad 110 \ ^\circ \text{C,} \\
\text{then} & \quad \mathrm{AcOH} \quad 110 \ ^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{309} & \quad + \quad \text{310} \\
\text{then} & \quad \text{AcOH} \quad 110 \ ^\circ \text{C}
\end{align*}
\]

Scheme 94

Copper acetate has been used to promote the reaction of cyclic thioureas \(291/314\) with benzamides \(312/315\) to give the benzimidazole and imidazole compounds \(301/315\) (Scheme 95). The reaction was proposed to involve coordination of the sulfur, then bidentate coordination of the imidazole, oxidation from Cu(II) to Cu(III) by Cu(OAc)\(_2\), insertion of Cu into the Ar-H bond, reductive elimination and finally ring closure by nucleophilic acyl substitution (Scheme 96).\(^{165}\)

\[
\begin{align*}
\text{R} & \quad \text{Cu(OAc)}_2 \\
\text{then} & \quad \text{DMSO} \quad 130 \ ^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{312} & \quad + \quad \text{291} \\
\text{then} & \quad \text{DMSO} \quad 130 \ ^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{313} & \quad + \quad \text{314} \\
\text{then} & \quad \text{DMSO} \quad 130 \ ^\circ \text{C}
\end{align*}
\]

Scheme 95
2.4.7. \textit{b}-Fused 2,3-dihydro-1,3-benzothiazin-4-ones with an exocyclic C=C. 2-Sulfanylbenzoic acids 147 have been reacted with imines generated \textit{in situ} by a tandem Staudinger/aza-Wittig reaction of sugars with an azide group, as in Scheme 107. When 322 was used, however, the unexpected product 323 was formed, in which an elimination had occurred to give an exocyclic C=C at C2 (Scheme 97).\textsuperscript{166} The reaction may go through a different mechanism altogether than what is shown in Scheme 107.\textsuperscript{166}
Hydrolysis of 4-imino compound 324 gave the 4-oxo-triazole compound 325 (Scheme 98).\(^{167}\)

The likely pathway\(^ {169}\) involved *in situ* formation of the sulfonium ion 328.

---

**Scheme 97**

**Scheme 98**

**Scheme 99**
Intramolecular cyclization of dimethyl indole-2,3-bis-(2-sulfanylbenzoate) 329 provided indole-fused 1,3-benzothiazin-4-one 330 (Scheme 100). This was carried out neat at 200 °C. A similar reaction is shown in Scheme 125.

![Chemical structure](image)

**Scheme 100**

The reaction of 2 equivalents methyl 2-sulfanylbenzoate 163 with 1 equivalent 1,1,2,2-tetracyanoethane 331 under basic conditions gave the tricyclic b-fused-pyrrolo product 334 (Scheme 101). The authors expected the reaction to stop at compound 332 but instead two consecutive cyclizations followed.

![Chemical structure](image)

**Scheme 101**

In an intentional double cyclization reaction, gem-dibromovinyl compound 335 was treated with catalytic Cu₂O, 1,2-dimethylethanediamine (DMEDA) as the ligand, and K₂CO₃ in toluene at 70 °C. The tetracyclic b-fused indolo product 327 was obtained (Scheme 102). A proposed mechanism involved bidentate coordination to copper, insertion into a vinyl C-Br bond, elimination of HBr to give a cyclic copper intermediate.
and then elimination of Cu to give N-vinylation. The process then essentially repeated itself, ending in S-vinylation.  

Scheme 102

2.4.8. *b*-Fused 2,3-dihydro-1,3-benzothiazin-4-ones. A three-component reaction of 5-nitro-2-fluorobenzoyl chloride 342, NaSH, and five- or six-membered cyclic imines 343 containing another heteroatom (O or S) in the ring gave a number of *b*-fused 2,3-dihydro-1,3-benzothiazin-4-ones 344 (Scheme 103).
Thionyl chloride has been used to generate the acid chloride. The acid chlorides 345 were prepared and used crude with imine 346 to give the pentacyclic products 347 (Scheme 104).5

Scheme 104

*b*-Fused oxazolo-2,3-dihydro-1,3-benzothiazin-4-ones 349 were prepared by heating 2,5-dihydroxazoles 348 with 2-sulfanylbenzoic acid 47 in toluene (Scheme 105).174

Scheme 105

T3P 159 has also been used to prepare a variety of *b*-fused 1,3-benzothiazin-4-ones 351 (Scheme 106).106,107

Scheme 106
2-Sulfanylbenzoic acid 47 has also been reacted with imines generated *in situ* by a tandem Staudinger/aza-Wittig reaction of sugars with an azide group (352). The three reactions were performed in one pot with microwave irradiation of the toluene solution at 100 °C (an example is shown in Scheme 107). The sequence was presumed to begin with reaction of triphenylphosphine with the azide functional group of the sugar 355 to give iminophosphorane 353. The aldehyde form 354 of the sugar then underwent an intramolecular aza-Wittig reaction to give the cyclic imine 355. 2-sulfanylbenzoic acid 47 was then added and microwaved again to form b-carbohydrate-fused 2,3-benzothiazin-4-one 356. In other examples, the carboxylic acid activator DCC was also added in the last step. Similar reactions are in Schemes 108, 131, and 140.

**Scheme 107**

When pyrrolidine azide 357 was used, the products were 359. The three reactions were done in one pot with microwave irradiation of the toluene solution at 80 °C (Scheme 108) to give 358. 2-Sulfanylbenzoic acids 147 and DCC were then added and irradiated with microwaves again to form 359. The reaction pathway was presumably the same as in Scheme 107. Similar examples can be found in Schemes 107, 131, and 140.

In a carbodiimide-promoted reaction with an unusual dearomatization of pyridine, 1-ethyl-3-(3-dimethylamino propyl) carbodiimide hydrochloride (EDCI) 361 was used to form pentacyclic structure 362 (Scheme 109). The pathway proposed was activation of the carboxylic acid by EDCI 361, then attack by the pyridine nitrogen to give the iminium ion intermediate 364. Attack by sulfur gave the heterocycle 362 with loss of the aromaticity of the pyridine ring.
A novel method recently reported used 2-iodobenzamides and potassium sulfide to construct tetracyclic systems (Scheme 110). The reaction was catalyzed by copper(II) acetate with tetramethylene-diamine (TMEDA) as ligand and run in N-methylpyrrolidone (NMP) at 120 °C. The reaction performed better in air than in oxygen or nitrogen atmosphere. The proposed pathway was copper-catalyzed coupling of the sulfide, followed by single-electron transfer redox step to give iminium ion, and then finally nucleophilic attack by sulfur to close the ring.
2.4.9. **b-Fused 2-imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones.** A common strategy for *b*-fused heterocycles 371 has been condensation of a cyclic thiourea 370 with a 3-halopropionic acid 369, where the halide is bromine 179-200 or chlorine 201-205 (Scheme 111). In one case, instead of NaOAc/ Ac₂O/ AcOH/reflux (52%), ionic liquid *N*-methylpyridinium tosylate was used at 100-110 °C (68%). 205 The bromide has also been used with NaOEt/KI/ DMF/reflux followed by Ac₂O/pyridine. 206

Similarly, 3-chloropropanoyl chloride 95 with potassium carbonate, acetonitrile, and phase transfer catalyst tetrabutyl ammonium bromide (TBAB) was reacted with a cyclic thiourea 372 at room temperature to give benzimidazole 373 (Scheme 112). 207 3-Bromopropanoyl chloride 374 with K₂CO₃ in DMF at 120 °C has similarly been used to yield pyrimidines 376 (Scheme 113). 208
Reaction of cyclic thiourea 378 with malonic acid 377 and acetyl chloride 379 in DMF gave the 6-oxo-b-fused compound 380 by condensation of both malonic acid groups (Scheme 114). There was a C=O at C6 of 380. The paper does not comment on the reaction.

Malonyl dichloride 16 was used in a similar fashion (Scheme 115).
Triazole 383 was cyclized by treatment with acetic anhydride and pyridine (Scheme 116).\(^\text{(211)}\)

\[
\begin{align*}
\text{HO-} & \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{H} \\
383 & \quad \text{Ac}_2\text{O} \quad \text{pyridine} \\
\text{reflux} & \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{H} \\
384 & \quad 62\%
\end{align*}
\]

**Scheme 116**

Cyclic thiourea 385 has been reacted with 3-aryl-2-propenoyl chlorides 131 to give fused pyrimidine HCl salts 386 by conjugate addition, using refluxing pyridine/benzene (Scheme 117).\(^\text{(212)}\)

\[
\begin{align*}
\text{Ar} & \quad \text{Cl} \\
131 & \quad \text{pyridine} \\
\text{benzene} & \quad \text{reflux} \\
\text{S} \quad \text{N} \\
385 & \quad \text{N} \quad \text{N} \quad \text{Cl} \\
386 & \quad \text{Ar} = \text{Ph}, 4-\text{OMe-} \\
& \quad \text{C}_6\text{H}_4, 3-\text{NO}_2-\text{C}_6\text{H}_4 \\
& \quad 58-72\%
\end{align*}
\]

**Scheme 117**

A similar method delivered fused 1,2,4-triazoles 387 as the free bases (Scheme 118).\(^\text{(213,214)}\) Reactions in acetone (Ar = H, R = Ph, 4-OMe-C\(_6\)H\(_4\), 4-F-C\(_6\)H\(_4\)) produced the HCl salts (60-71%).\(^\text{(215)}\)

\[
\begin{align*}
\text{Ar} & \quad \text{Cl} \\
131 & \quad \text{pyridine} \\
\text{benzene} & \quad \text{reflux} \\
\text{S} \quad \text{N} \\
281 & \quad \text{N} \quad \text{N} \quad \text{R} \\
387 & \quad \text{Ar} = \text{Ph, 3,4-(OMe)}_2\text{-C}_6\text{H}_3, 4-\text{NO}_2- \\
& \quad \text{C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4, 1\text{-napthyl,} \\
& \quad 2\text{-thienyl, 3,4-methylenedioxyphenyl} \\
& \quad \text{R} = \text{H, Ph, 4-NO}_2\text{-C}_6\text{H}_4, 4\text{-OMe-C}_6\text{H}_4 \\
& \quad 50-81\%
\end{align*}
\]

**Scheme 118**

Benimidazole-2-thiones 307 and 3-aryl-2-propenoyl chlorides 131 were reacted with pyridine to give the \(b\)-fused benimidazole compounds 388. One benimidazole was prepared using K\(_2\)CO\(_3\)/TBAB/acetonitrile.
However, imidazoline-2-thiones 52 in pyridine only gave N-acylated products. Fortunately, reaction in acetone gave the desired compounds 389 as the HCl salts (Scheme 119).

Scheme 119

Conjugate addition of sulfanyl triazoles 281 to 4-arylidene-5-oxazolones 390 gave b-fused triazolo-5,6-dihydro-5,6-substituted-1,3-thiazin-4-ones 391 (Scheme 120). Presumably, Michael addition gave intermediates 392, and then nucleophilic attack by a nitrogen from the original thiourea led to products 391.

Scheme 120
Intramolecular conjugate addition of sulfanyltetrazole 393 gave \( b \)-fused tetrazole 394 (Scheme 121). \(^{218}\)

\[
\begin{align*}
&\text{Ph} - \text{HN} - \text{N} - \text{N} - \text{N} - \text{HS} - \text{Ph} \xrightarrow{\text{NaOEt, EtOH, reflux}} \text{Ph} - \text{HN} - \text{N} - \text{N} - \text{N} - \text{S} - \text{Ph} \\
&\text{393} \quad \text{394} \quad 60\%
\end{align*}
\]

**Scheme 121**

In a stepwise approach, cyclic thiourea 395 was treated with KOH to give salt 396. Reaction with 3-chloropropanoyl chloride 95 in refluxing ethanol then gave intermediate 397. Cyclization to 398 was accomplished with catalytic KI in refluxing ethanol (Scheme 122). \(^{219}\)

\[
\begin{align*}
&\text{HN} - \text{N} - \text{N} - \text{S} \xrightarrow{\text{KOH, EtOH, 0 °C}} \text{KN} - \text{N} - \text{N} - \text{S} \xrightarrow{\text{95, EtOH, reflux}} \text{KN} - \text{N} - \text{N} - \text{S} - \text{N} - \text{S} - \text{N} - \text{S} \xrightarrow{\text{KI, EtOH, reflux}} \\
&\text{395} \quad \text{396} \quad 99\% \quad \text{397} \quad 75\% \quad \text{398} \quad 98\%
\end{align*}
\]

**Scheme 122**

When the thiolactams 399 used as in Scheme 126 had two methyl groups on the carbon \( \alpha \) to the thione, elimination could not occur and the products were isolated as betaines 403 (Scheme 123). \(^{220}\)

\[
\begin{align*}
&\text{HN} - \text{N} - \text{N} - \text{S} \xrightarrow{\text{Cl\textsubscript{2}O, THF, reflux}} \text{RN} - \text{N} - \text{N} - \text{S} - \text{N} - \text{S} - \text{N} - \text{S} \xrightarrow{\text{ether, -78 °C to rt}} \\
&\text{399} \quad \text{400} \quad \text{401} \quad \text{402} \quad \text{403} \quad R = \text{Ph, Me, H} \quad n = 1, 2 \quad 91-100\%
\end{align*}
\]

**Scheme 123**

2.4.10. \( b \)-Fused 2,3,5,6-tetrahydro-1,3-thiazin-4-ones with an exocyclic C=C. Sulfanyl imidazoles 404/407 were intramolecularly cyclized to 406/408 with solid-supported carbodiimide 405 in two different ways. One
method involved CH₂Cl₂/DMF at room temperature. Alternatively, the reaction was performed with in the same solvents under microwave irradiation (Scheme 124).

Scheme 124

Intramolecular cyclization of indole bis-(methyl thioalkanoate) 409 provided compound 410 (Scheme 125). This was done either neat at 185-190 °C, or in refluxing tetralin (206 °C) and is similar to the reaction in Scheme 100.

Scheme 125
Reaction of thiolactams 411 with either malonyl dichloride 16 or (chlorocarbonyl)phenyl ketene 401 gave \( b \)-fused compounds 412 with an exo C=C at C2 and a carbonyl at C6. This same transformation also occurred with carbon suboxide (C\(_3\)O\(_2\)) (Scheme 126).\(^{224}\)

\[
\text{Scheme 126}
\]

Thiolactams 414 were reacted with 3-aryl-2-propenoyl chlorides 131 in the presence of pyridine to yield compounds 415 via conjugate addition (Scheme 127).\(^{225}\)

\[
\text{Scheme 127}
\]

2.4.11. \( b \)-Fused 2,3,5,6-tetrahydro-1,3-thiazin-4-ones. An intramolecular cyclization of an aldehyde\(^{226}\) or its dimethyl acetal 416\(^{227}\) was achieved by treatment with trifluoroacetic acid (TFA), which both deprotected the sulfur and catalyzed the cyclization. The reaction was diastereoselective. The authors posited that the amido nitrogen attacked the aldehyde to give a cyclic iminium ion 417, and then a second cyclization occurred by attack of the sulfur, which occurred in a diastereoselective fashion to give 418 (Scheme 128).\(^{227}\)
In chemistry similar to Scheme 128, treatment of compounds 419 with TFA, thioanisole, and water (90:5:5) gave cyclized compounds 420 (Scheme 129).\textsuperscript{7,228,229} The same reaction had earlier been used to make peptide-heterocycle hybrids.\textsuperscript{230,231} T3P 159 in DIPEA has been used to prepare \( \text{b-fused} \) compounds 422 starting from either 3-sulfanylpropanoic acid (190) or from \( N \)-acetylcysteine (187, \( R = \text{NHAc} \)) (Scheme 130). Another example used a ketimine instead of 421.\textsuperscript{133}

3-Sulfanylpropanoic acid 190 has also been reacted with imines generated \textit{in situ} by a tandem Staudinger / \textit{aza-Wittig} reaction of azido sugars 423.\textsuperscript{175,176} The three reactions were done in one pot with microwave irradiation of the toluene solution (Scheme 131). The pathway is presumably the same as in Scheme 107 and similar to the reactions shown in Schemes 108 and 140.
2.4.12. Simultaneously b- and e-fused systems. 2-Chloropyridine-3-carbonyl chloride 244 was converted in a cascade reaction to the triheterocyclic imidazole product 425 in high yield (Scheme 132).\textsuperscript{161} 1,10-Phenanthroline 300 was used as a ligand. The benzimidazole was also prepared.

In a less useful version, triheterocyclic compound 425 was synthesized in a two-step process (Scheme 133). First, thiourea 294 was reacted with 2-iodopyridine-3-carbonyl chloride 427 in the presence of Cul/tetrabutylammonium bromide (TBAB)/Cs\textsubscript{2}CO\textsubscript{3}/DMF at 130 °C. This gave the sulfide 428, which was cyclized by treatment with EDC to give the imidazole 425 in low yield. A benzimidazole was also prepared in this manner.\textsuperscript{160}

As in Scheme 95, copper acetate has been used to prepare tricyclic benzimidazoles 430 and 432 (Scheme 134).\textsuperscript{165}
Scheme 134

Reaction of 2-chloroquinoline-3-carboxylic acids 433 with sulfanyltriazoles 434 led to tetracyclic compounds 435 (Scheme 135).²³²

Scheme 135

Microwave-accelerated Pfitzinger reaction of isatin 257 with benzimidazole derivatives 436 under basic conditions gave tetracyclic compounds 437. Both yields and rates were improved compared to conventional heating. Upon either heating the neat solid, microwave irradiation of the neat solid, or refluxing in DMSO, cyclization to pentacyclic 438 occurred (Scheme 136). Yields of 438 were similar in each case.²³³

Scheme 136
Indole-fused 1,3-pyridothiazin-4-ones with an exocyclic C=C at the 2-position have been synthesized in two ways by the same group. In one route, excess methyl 2-(chlorosulfanyl)benzoate was reacted with indole in DMF and 1,2-dichloroethane to give the bis-sulfide. Compound was cyclized to by heating to 145 °C (Scheme 137). In the second route, 2-chloropyridine-3-carboxylic acid was reacted with thioindole in the presence of copper to give the sulfide. Treatment of with polyphosphate ester catalyst in CHCl₃ gave product (Scheme 138).

Microwaves have been used to accelerate the reaction of 2-sulfanylpyridine-3-carboxylic acid with cyclic imine (Scheme 139).

Analogous to chemistry discussed earlier (Schemes 107, 108, and 131), 2-sulfanylpyridine-3-carboxylic acid has been reacted with imines generated in situ by a tandem Staudinger/aza-Wittig reaction of sugars with an azide group. The three reactions were done in one pot with microwave irradiation of the toluene solution (Scheme 140). Triphenylphosphine was added to 2-sulfanylpyridine-3-carboxylic acid and the azide and microwaved in toluene at 100 °C to generate the imine. Unlike the earlier examples, DCC was added before the mixture was microwaved again in toluene at 100 °C to effect the cyclization to. The pathway was similar to that of Scheme 107.
2.5. **Bridged systems.** Formation of 450, a 2,3,5,6-tetrahydro-1,3-thiazin-4-one with a bridged seven-membered nitrogen heterocycle, was achieved by acid-catalyzed intramolecular double cyclization of 449 (Scheme 141, stereochemistry not shown for simplicity). The acid catalyst released the starting material from the resin, removed the diethyl acetal and trityl protecting groups, and facilitated the nucleophilic attack of the amide nitrogen on the deprotected aldehyde to give the seven-membered cyclic iminium ion 451, which was then attacked by the sulfur to form 450.\(^{235}\)

Another method for constructing a bridged system started with 452, which was converted into 454 by trimethylsilylation of the ethoxy group in 452 with TMSBr, followed by intramolecular attack of the benzyl sulfide to give bicyclic sulfinium ion 453. Debenzylation then gave 454 (Scheme 142).\(^{236}\)
Betaine 402 (see Scheme 123 for preparation) was reacted with 4-phenyl-1,2,4-triazoline-3,5-dione 455 to give the bridged 2,3,5,6-tetrahydro-1,3-thiazin-4,6-dione compound 456 (Scheme 143).²²⁰

![Scheme 143]

Betaines such as compound 402 could also be reacted with carbon-carbon double bonds in various types of compounds and converted into bridged 2,3,5,6-tetrahydro-1,3-thiazin-4,6-dione compounds 458, 460, 462, and 464 by dipolar cycloaddition (Scheme 144).²²⁰

![Scheme 144]
Intramolecular dipolar cycloaddition of a betaine with a tethered alkene was also shown to give bridged systems, such as in Scheme 145. Other variants were also reported.

Scheme 145

Thiolactams, such as 467, with a tethered alkene were reacted with carbon suboxide 402 to generate the betaine 468 in situ, which then cyclized as above to provide the bridged product 469 (Scheme 146). Some other examples were provided as well.

Scheme 146

3. Reactivity

3.1. Reactivity of the ring atoms with electrophiles

2-Imino-1,3-benzthiazin-4-ones 470 (see Scheme 171 for preparation) were N-alkylated by treatment with sodium methoxide followed by an alkyl halide 471 (Scheme 147).
Scheme 147

2-Methylidene-1,3-benzothiazin-4-ones 473 were N-alkylated by phenacyl chlorides 474 with K$_2$CO$_3$ in DMF (Scheme 148).$^{239}$

Scheme 148

Protection of the nitrogen of 2,3,5,6-tetrahydro-1,3-thiazin-4-one 476 with a Boc group (N-acylation) was done with the anhydride and DMAP (Scheme 149).$^{240}$

Scheme 149

*b*-Fused benzimidazo-2,3-dihydro-1,3-thiazin-4-one 478 when reacted with alkyl bromides 479 at 130 °C gave amide bond cleavage along with N-alkylation (Scheme 150).$^{241}$ However, when the analog 481 was reacted with benzyl bromide 482 in the same manner, cleavage of the S-C6 bond occurred to give 483 (Scheme 151).$^{241}$
Treatment of 481 with bromoacetophenone 61, on the other hand, gave \( N,N' \)-dialkylated product 484 (Scheme 152).\(^{241}\)

Vinylation of \( b \)-fused 2-imino-5,6-dihydro-1,3-thiazin-4-one 486 with benzaldehyde 195 gave an exocyclic C=C moiety at the C-5 position, \( \alpha \) to the C4 carbonyl (Scheme 153).\(^{204}\) \( b \)-Fused 6-oxo-2-imino-5,6-dihydro-1,3-thiazin-4-one 489 was similarly vinylated with 4-nitrobenzaldehyde 488 (Scheme 154).\(^{209}\)
Scheme 154

Oxidation of \( b \)-fused benzimidazole 491 with hydrogen peroxide/acetic acid caused cleavage of the S-C2 and N3-C4 bonds, giving loss of 2-sulfopropanoic acid 492 (Scheme 155), similar to reactivity previously reported for 2,3-dihydro-1,3-benzothiazin-4-ones.

Scheme 155

However, when there was an aryl substituent on C6, treatment of \( b \)-fused benzimidazole 5,6-dihydro-1,3-thiazin-4-ones 388 with 30% hydrogen peroxide in acetic acid led to cleavage of the S-C6 and N3-C4 bonds (Scheme 156).

Scheme 156

Cleavage of the S-C6 bond in 481 was also the result of an attempt to make the methyl \( p \)-toluenesulfonate salt 497, which evidently decomposed to give 498 (Scheme 157).
The sulfur in various 2,3-dihydro-1,3-thiazin-4-ones was oxidized selectively to the sulfoxides 500-503 using Oxone® (Scheme 158).  

Sulfoxidation of 2,3-dihydro-1,3-benzothiazin-4-one 504 with iodosobenzene in the presence of a chiral manganese catalyst 505 gave the desired sulfoxide 506, but in only 13% ee (Scheme 159).
Oxidation of sulfides 507 to the sulfones 508 was done with a tungsten catalyst, similar to a method noted in the prior review (Scheme 160).\textsuperscript{5}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {507};
\node at (2,0) {508};
\node at (4,0) {R = H, OMe};
\node at (4.5,0) {63-78\%};
\node at (0,2) {R \text{=} H, \text{OMe}};
\node at (2,2) {AcOH\newline55\degree C};
\node at (4,2) {Na\textsubscript{2}WO\textsubscript{4}\newlineH\textsubscript{2}O};
\end{tikzpicture}
\end{center}

Scheme 160

\textit{KMnO\textsubscript{4} with H\textsubscript{2}SO\textsubscript{4} in H\textsubscript{2}O/CH\textsubscript{2}Cl\textsubscript{2} was used to oxidize sulfide 509 to sulfone 510 (Scheme 161).\textsuperscript{211}}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {509};
\node at (2,0) {510};
\node at (4,0) {58\%};
\node at (0,2) {H\textsubscript{2}O\newlineCH\textsubscript{3}Cl};
\node at (2,2) {H\textsubscript{2}SO\textsubscript{4}};
\node at (4,2) {KMnO\textsubscript{4}};
\end{tikzpicture}
\end{center}

Scheme 161

The triphenyltin chloride complex 513 of 2,3-diphenyl-2,3,5,6-tetrahydro-1,3-thiazin-4-one 511 was readily prepared (Scheme 162).\textsuperscript{247} However, attempts to make the complex of 2,3-diphenyl-5,6-dihydro-1,3-benzothiazin-4-one 514 gave only the sulfoxide 502.\textsuperscript{244}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {511};
\node at (2,0) {512};
\node at (4,0) {513};
\node at (0,2) {Ph};
\node at (2,2) {Ph\text{SnCl}};
\node at (4,2) {acetone};
\end{tikzpicture}
\end{center}

Scheme 162

Oxidation of the 5,6 C-C by dehydrogenation was shown in Schemes 7, 18, and 87. Reaction of 5-cyano-6-amino-1,3-thiazin-4-ones 72 with \(\beta\)-ketoalkyl halides 515 and triethylamine gave thienopyrimidone products 516.\textsuperscript{39} This was explained by base-promoted Dimroth rearrangement to give an exo sulfur anion 518, which then attacked the alkyl halide 515. The subsequently formed enolate ion 520 then attacked the nitrile, leading to the fused ring 516 (Scheme 163).\textsuperscript{39} The formation of compounds 518 had been earlier demonstrated by hydrolysis of 72 with aqueous KOH, which gave the potassium salts of 518 (\(R^1 = \text{Et, Ph; } R^2 = \text{H; } R^3 = \text{Ph, 4-NO}_2\text{-C}_6\text{H}_4\); 75-82\%).\textsuperscript{37}
Scheme 163

When 6-anilino-5-cyano-1,3-thiazin-4-one 521 was treated with bromoacetonitrile 522 and aqueous KOH, a product 523 similar to 516 was obtained (Scheme 164). The mechanism was presumed to be similar to Scheme 163, with an intermediate akin to 516. Other examples were demonstrated.

Scheme 164

When the reaction in Scheme 163 had an adamantylidene group at C2 (524), a different outcome resulted due to steric hindrance (Scheme 165). It was proposed that the thiophene 527 therefore formed first.
Scheme 165

When 72 was treated with alkyl halides and base, the thienville ring did not form.\textsuperscript{17,37,38,41} Using benzyl chloride 528 with Et\textsubscript{3}N/EtOH\textsuperscript{37,38,41} or aqueous KOH,\textsuperscript{17} the reaction stopped after S-alkylation. Some examples are shown in Scheme 166.\textsuperscript{37}

Scheme 166

When compound 521 was reacted with ethyl iodide 530 and K\textsubscript{2}CO\textsubscript{3}, the product was ethylated at both S and N (Scheme 167).\textsuperscript{38} However, the phenylene-bridged \textit{bis-}(2,3-dihydro-1,3-thiazin-4-ones) 532 under the same conditions only alkylated the sulfurs (Scheme 168).\textsuperscript{17} Another compound similar to 521 also gave only S-ethylation.\textsuperscript{41}
Dimethyl sulfate in aqueous KOH similarly gave the S-methylated products (some examples shown in Scheme 169).\textsuperscript{17,37,38,41} When the C2 substituent on 72 was bulky adamantanyl, dimethyl sulfate/KOH(aq) gave ring opening and loss of adamantanone.\textsuperscript{37}

When ethyl bromoacetate/aqueous KOH was used, some cases produced thienyl compounds like 516 and some cases stopped at S-alkylation products like 519.\textsuperscript{17,38,41}

Bridged compound 454 (see Scheme 142 for preparation) was selectively deprotonated by LDA at the bridgehead C2 position of the 1,3-thiazin-4-one ring, which was α to another carbonyl. Treatment with benzaldehyde 195 gave the alkylated product 535. After two-step reduction of the alcohol, compound 536 was deprotonated again with lithium disopropylamide (LDA), and elimination gave the thiolate ion 537, which was trapped as the trityl disulfide 539 (Scheme 170).\textsuperscript{236}
3.2. Reactivity of the ring atoms with nucleophiles

Reaction of the 2-amino-1,3-benzothiazin-4-one 540 with anilines 201 and HCl at 150 °C gave compounds 470 (Scheme 171). \(^{238}\)

![Scheme 170](image)

Similarly, reaction of \(\text{b-fused benzimidazole 491 with ammonia, hydrazine or benzylamine in refluxing ethanol gave products 543 (Scheme 173).}^{241}\) The same reaction with a 6-aryl group (Ph, 4-OMe-C\(_6\)H\(_4\)) on the
1,3-thiazin-4-one ring gave products 455 when $R = H$ and $NH_2$ (70-86%) (Scheme 173), but benzylation caused cleavage of both the S-C6 and N3-C4 bonds.241

Scheme 173

$b$-Fused triazolo-compounds 546 also reacted differently with amines depending on the conditions and the structure of 546 (Scheme 174).248 In refluxing ethanol, N3-C4 cleavage occurred, giving 547. At higher temperatures, refluxing in the amine 82 alone, when $R^1 = H$, S1-C6 bond cleavage gave 548. When $R^1 \neq H$ however, both cleavages occurred, giving 549 and 548.

Scheme 174
Reaction of b-fused quinazole compound 551 with hydrazine 552 in refluxing ethanol gave 553, in which both the S-C2 and N3-C4 bonds had been broken (Scheme 175).  

![Scheme 175]

Acidic hydrolysis of the 2-ethoxy-2,3,5,6-tetrahydro-1,3-thiazin-4-one 213 (see Scheme 65 for synthesis) with aqueous HCl produced ring-opened compound 554 (Scheme 176). The proposed pathway was elimination of ethanol, then addition of ethanol to the carbonyl, followed by N3-C4 bond cleavage and hydrolysis. Boron trifluoride heated in toluene, followed by addition of water, also worked.  

![Scheme 176]

Amide hydrolysis of triazole compounds 387 took place in 95 °C water (Scheme 177).
Scheme 177

Basic methanolysis of 6-carboxymethyl-1,3-thiazin-4-one 559 generated dimethyl acetylenedicarboxylate 558 (Scheme 178). However, treatment of 560 with methanol and sulfuric acid hydrolyzed the ester to the acid, leaving the ring unaffected. \(^{156}\)

Scheme 178

Basic hydrolysis of \(b\)-fused benzimidazoles 388 broke the N3-C4 bond to give the carboxylic acids 562 (Scheme 169). \(^{156}\)

Scheme 179

Reaction of 2,3-dihydro-1,3-benzothiazin-4-one 165 (see Scheme 47 for preparation) with \(P_2S_5\) and pyridine gave the thiolactam 563 (Scheme 180). \(^{108}\) Two similar conversions were done with \(P_2S_5\) in hexamethyldisiloxane (HMDSO) at 120 °C with microwave irradiation (Scheme 181). \(^{108}\)
Reduction of the C2-N3 double bond with NaBH₄ was shown in Scheme 50.

### 3.3. Other reactions of the ring atoms

The 4,6-dione 566 was diazotized at C5 and then reacted with cyclohexene in a rhodium-catalyzed cyclopropanation reaction (Scheme 182).²²⁴

Bridged heterocycles such as 466 and others in Schemes 144 and 145 upon sufficient heating lost COS 570 (Scheme 183).²²⁰,²²⁴,²³⁷
4. Conclusions

Clearly, there have been many advances in the chemistry of these important heterocycles since 1994. Although the review of the syntheses was broken into different types of structures, there is a lot of commonality in the approaches. Thus, while the reader may be looking for methods to make one type of ring, the answer may be found in approaches used for another type of 1,3-thiazin-4-one. Commonality can also be seen in the review of the reactions, and these were in fact organized by reaction type. Thus, a broad view of the 1,3-thiazin-4-ones should be taken by researchers in this area.

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Author’s Biographies

Lee J. Silverberg was born in 1963. He attended college at George Washington University in Washington, D.C., earning a B.S. in Chemistry with a minor in Journalism. He then went to the University of Delaware for graduate work in Organic Chemistry. He worked with two advisors while there. From 1987-1989 he trained with Prof. Richard F. Heck, doing palladium-catalyzed reactions of alkynes with vinyl and aryl halides. Upon Prof. Heck’s retirement, he went to the lab of Prof. Douglass F. Taber, where he studied ruthenium-catalyzed enantioselective hydrogenation of β-keto esters and completed a synthesis of natural product (+)-brefeldin A. After graduation in 1991, he went to work for Bristol-Myers Squibb in process research and development. He later worked for Johnson Matthey Pharmaceutical Materials and Merck, successfully developing processes for many APIs along the way. In 2009, Dr. Silverberg reentered academia, teaching one semester at Camden County College in New Jersey before joining Pennsylvania State University, Schuylkill Campus, in Fall 2009. He is still there and currently an Associate Professor. He teaches General Chemistry and Organic Chemistry. His research is in the area of heterocyclic compounds and his lab group is exclusively undergraduates.
Quentin J. Moyer was born in 1995 and grew up in Schuylkill County, PA where he ultimately attended college at the Pennsylvania State University Schuylkill Campus. He entered college in 2014 as a nursing student but chose to study biology after finishing a semester of clinical education at the Reading Hospital School of Health Sciences. He became affiliated with Lee Silverberg’s laboratory soon after in 2016, contributing to projects involving the 1,3-thiazin-4-one scaffold. He is currently a first-year medical student at Harvard and contributing to clinical research at the Boston Children’s Hospital Department of Plastic Surgery. He enjoys performing with his bands, short film production, and his old Volvos.