SYNTHESIS OF HETEROCYCLES USING THIOAMIDE GROUPS

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Abstract—The utilities of thioamide groups as synthetic intermediates to heterocycles are presented.

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1. Introduction
2. Synthesis of Heterocycles using Ketene S,N-Acetals
3. Synthesis of Heterocycles using Metalloenamines
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1. INTRODUCTION
The thioamide group has increasingly been recognized as a useful synthon in organic syntheses and has been shown to be easily convertible to a variety types of functional groups (amines, enamines, ketene S,N-acetals, ketene S,S-acetals, α-cyanoenamines, thioimidates, amides, ketones, esters, etc.) and fully proved to be synthetically potential already in the total syntheses of vitamin B12 (sulfide contraction), indole alkaloids (thio-Claisen rearrangement) and other bioactive natural products. In addition, characteristic reactions of thioamides (aldol condensation, Michael addition, and carbophilic addition) with organometallics have been explored. We focus on the use of thioamides as versatile functional groups in the field of heterocyclic synthesis. In this review, our studies using thioamides as synthetic intermediates to heterocycles are presented.

2. SYNTHESIS OF HETEROCYCLES USING KETENE S,N-ACETALS
Ketene S,N-acetals (KSNA) derived from tertiary thioamides are regarded as
interesting α-alkylthio enamines. KSNA 1-8 are prepared from the corresponding tertiary thioamides according to the method of Gompper.4

KSNA are allowed to react with a variety of electrophiles to form carbon-carbon bond at the β-position. The intermediate so formed is susceptible to an attack by nucleophiles at the α position. Subsequent selective elimination of alkane-thiol group regenerates amine available for further manipulation (Scheme 1).

Scheme 1
Cycloaddition of KSNA 1-3 to aryl isocyanates is investigated.\(^\text{16}\) Annellation of 1-3 with 2 equiv. aryl isocyanates 9 under reflux in toluene proceeds to give pyrimidine-2,4-diones 10-12, respectively, in good yields.\(^\text{17}\) Hydrolysis of the enamine moiety of 10-12 with 10% hydrochloric acid easily provides barbituric acids 13-15. In this reaction, 1-3 are synthetically equivalent to 16 (Scheme 2). In a similar manner, the addition of cyclic KSNA 6-8 to 2 equiv. of 9 gave azacycloalka[2,3-d]pyrimidines 17-19.\(^\text{18}\) KSNA 6 and 7 are also reactive toward aryl isothiocyanates 20 and afford azacycloalka[2,3-d]pyrimidinedithiones 21 and 22.\(^\text{19}\) No pyrimidinedithiones are produced from the reaction of 1-3 and 8 with isothiocyanate (Scheme 3).

\[
\begin{align*}
1, 2, 3 & \quad + \quad 2 \text{ ArNCO}_9 \quad \xrightarrow{\text{H}^+} \quad 10, 11, 12 \\
10 & \quad R=H \\
11 & \quad R=\text{Me} \\
12 & \quad R=\text{Et}
\end{align*}
\]

\[
\begin{align*}
6, 7, 8 & \quad + \quad 9 \quad \xrightarrow{} \quad 17-19 \\
17 & \quad n=1 \\
18 & \quad n=2 \\
19 & \quad n=3
\end{align*}
\]

Scheme 2

\[
\begin{align*}
6, 7 & \quad + \quad 2 \text{ ArNCS}_20 \quad \xrightarrow{} \quad 21, 22 \\
21 & \quad n=1 \\
22 & \quad n=2
\end{align*}
\]

Scheme 3
Next, cycloaddition of KSNA 4 and 5 with 1,4-quinones is carried out.\textsuperscript{20} Annelation of 4 with benzoquinones 23-25 and naphthoquinones 26 and 27 under reflux in tetrahydrofuran (THF) or toluene as a solvent gives 2-aminobenzofurans 28-30 and naphtho[1,2-b]furans 31 and 32, respectively, which are formed by selective cycloaddition and demethanethiolation. Treatment of 5 with 23, 24, and 26 in boiling toluene provides 3-methylbenzofuranes 33 and 34 and 3-methylnaphtho[1,2-b]furan 35. We next turn our attention to further role of the enamine component of the furans products. Ring-expansion of 3-unsubstituted furans 28, 29, and 31 with dimethyl acetylenedicarboxylate in boiling dioxane gives rise to the ring enlarged oxepines 36-38, respectively. Next the utility of 28 as Michael donor is tried. Addition of 28 to Michael acceptors 39 provides 3-substituted benzofurans 40 as expected, which are transformed into the biologically interesting benzofuran-2-ones 41 by hydrolysis with 10% hydrochloric acid. In these reactions, 4 may be regarded as a synthetic equivalent of 42 (Scheme 4).

It is possible that the addition of electrophiles at the β-position of KSNA under mild condition gives β-substituted KSNA, which have high potentiality to be transformed with elaboration into heterocycles as formulated in Scheme 5 (eq. 1 and 2).

![Scheme 5](image)

First the examples of eq.1 are described. Reaction of KSNA 1, 6, and 7 with aryl isothiocyanates 20 at room temperature in ether gave 3-aminothiocarbonyl-α-methylthioenamines 43, 44, and 45, respectively, which appear to be an attractive new synthetic equivalent of 1,3-dicarbonyl compounds.\textsuperscript{21} However, the corresponding 1:1 adducts from 2, 3, and 8 are not obtained. The interesting
enamines 43, 44, and 45 undergo condensation with guanidine, acetamidine, and benzamidine as bisnucleophiles in the presence of sodium ethoxide in boiling ethanol to provide pyrimidines 46, 47, and 48, respectively. Similarly, the
use of hydrazine affords the corresponding pyrazoles 49, 50, and 51 (Scheme 6).

Addition of ethoxycarbonyl isothiocyanate to ether solutions of KSNA 6 and 7 gives 3-ethoxycarbonylaminothiocarbonyl-2-methylthioenamines 52 and 53, which appear to be attractive new synthetic equivalents of 1,5-dicarbonyl compounds. Compounds 52 and 53 are cyclized by reaction with primary amines as bionucleophiles in boiling ethanol affording monothiouracil derivatives 54 and 55, re-
spectively (Scheme 7).

![Scheme 7](image)

Next, the examples of eq. 2 are described. The 1:1 adduct 43 shown above undergoes the addition-elimination reaction with malononitrile as carbon nucleophile to afford the enamnonitrile 56. As described later, bis-lithio-ketene S,N-acetals derived from secondary thioamides are regarded as interesting metalloenamines and have been used as synthetic intermediates for heterocycles. Carbon-carbon bond-forming reaction of the bis-lithio-KSNA 57 [generated from 56 with 2 eq. of n-buthyllithium (n-BuLi)] with alkyl halides as electrophiles followed by cyclization yields 3-alkylpyridine-2-thiones 58 (Scheme 8).²³

![Scheme 8](image)
Addition of aryl isocyanates $9$ to KSNA $7$ and $8$ at ambient temperature in ether gave $1:1$ adducts $59$ and $60$, which are allowed to react with alternative aryl isocyanate to yield uracil derivatives $61$ and $62$, respectively (Scheme $9$).$^{24}$

$$
\begin{align*}
7, 8 + 9 & \rightarrow (CH_2)_n CONHAr \\
59 \text{ } n=2 \\
60 \text{ } n=3
\end{align*}
$$

Scheme $9$

3. SYNTHESIS OF HETEROCYCLES USING METALLOENAMINES

Three kinds of metallo-KSNA (I, II, and III) derived from thioamide groups belong to the interesting class of metalloenamines that react with many kinds of carbon electrophiles to form carbon-carbon bonds.

$$
\begin{align*}
\text{LDA} & \rightarrow \text{Li} \\
\text{nBuLi} & \rightarrow \text{SLi} \\
2 \text{ nBuLi} & \rightarrow \text{SLi}
\end{align*}
$$
We embark on studies to apply the reaction employing metalloenamines to heterocyclic synthesis. Although metallo-KSNA derived from thioimidates may be regarded as interesting metalloenamines, their chemistry has scarcely been studied. Metalloenamines 63-65, generated from cyclic thioimidates by treatment with lithium diisopropylamide (LDA), react with N-alkylisatoic anhydrides to afford azacycloalka[2,3-b]quinolin-4-ones 66-68, respectively (Scheme 10).

\[
\begin{align*}
\text{(CH}_2\text{n)}_n & \quad + \quad \text{X} \quad \text{N} \quad \text{O} \\
\text{Li} & \quad \text{SMe} & \quad \text{X} \quad \text{N} \quad \text{O} \\
\text{63 n=1} & \quad \text{66 n=1} \\
\text{64 n=2} & \quad \text{67 n=2} \\
\text{65 n=3} & \quad \text{68 n=3}
\end{align*}
\]

Scheme 10

S-Lithio-KSNA 69, generated from N,N-dimethylacetothioamide as tertiary thioamide with n-BuLi, reacts with aryl isocyanates 9 at -78°C to 0°C to afford the monothiodiamides 70. Formation of thioiminium salts 71 with methyl iodide, followed by nucleophilic attack with malononitrile in the presence of 18-crown-6 as a catalyst and potassium fluoride as a base gives enaminonitriles 72. The carbon-carbon bond-forming reaction of bislithioketene O,N-acetals 73, generated from 72 with two equiv. n-BuLi, with a variety of electrophiles 74a-g followed by cyclization with work-up yield multifunctionalized 2-pyridones 75a-g (Scheme 11). Reaction using 74g is accelerated by the addition of boron trifluoride-ether. Similarly, azacycloalka[3,2-c]pyridin-2-ones 76 and 77 are synthesized from N-methylthiolactames as shown in Scheme 12.

Bis-Lithio-KSNA 78 and 79, generated from secondary thiolactams by treatment of two equiv. n-BuLi (0°C), react with aryl isothiocyanates to afford the dithioamides 80 and 81, respectively. Bismethylation of 80 and 81 with methyl iodide in the presence of potassium carbonate gives the dithioimidates 82 and 83 as 1,3-bis-electrophilic reagents, which are allowed to react with benzamidine as bis-nucleophile in the presence of sodium hydride to provide azacycloalka[2,3-
dipyrimidines 84 and 85, respectively (Scheme 13).^{30}

Scheme 11

Scheme 12
4. ELECTROPHILIC OLEFIN HETEROCYCLIZATION

Electrophilic alkene cyclization processes that form carbon-heteroatom bonds are of growing importance, particularly in the regio- and stereoselective synthesis of heterocycles leading to bioactive natural products (Scheme 14).\(^\text{31}\)

Although halogenolactonization is a well-established important synthetic tool,\(^\text{32}\) the analogous thiolactonization\(^\text{33}\) and lactamization\(^\text{34}\) have been less investigated. First we describe novel syntheses of 2-aminothiophenes via iodoiminothiolactonization of \(\gamma,\delta\)-unsaturated secondary thioamides.\(^\text{35}\) \(\gamma,\delta\)-Unsaturated secondary thioamides are readily accessible by three procedures (1. allylation of dianions generated from secondary thioamides; 2. thio-Claisen rearrangement;\(^\text{36}\) 3. allylation of active methyl groups followed by thioamidation with isothiocyanate) shown in Scheme 15. The \(\gamma,\delta\)-unsaturated secondary thioamides \(86a-y\) with iodine in THF undergo iodoiminothiolactonization to give the iminothiolactones \(87a-y\), which without isolation are converted by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the same flask into exo-olefins \(88a-y\). N-Acetylation of \(88a-y\) with acetyl chloride in the presence of DBU as a base and 4-dimethylaminopyridine (DMAP) as a catalyst followed by spontaneous aromatization gave 2-aminothiophenes \(89a-y\) (Scheme 16). This iodine-induced cyclization proceeded regio- (5-\text{exo-trigonal})\(^\text{37}\) and chemo-selectively (sulfur-carbon bond
Scheme 15

Scheme 16
Table. Preparation of 2-Aminothiophenes 89a-y from γ,δ-Unsaturated Secondary Thioamides 86a-y

<table>
<thead>
<tr>
<th>run product</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( R^4 )</th>
<th>( R^5 )</th>
<th>yield, %(^a)</th>
<th>method(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 89a</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>57</td>
<td>A</td>
</tr>
<tr>
<td>2 89b</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>53</td>
<td>A</td>
</tr>
<tr>
<td>3 89c</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>25</td>
<td>A</td>
</tr>
<tr>
<td>4 89d</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>50</td>
<td>A</td>
</tr>
<tr>
<td>5 89e</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>47</td>
<td>A</td>
</tr>
<tr>
<td>6 89f</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>23</td>
<td>A</td>
</tr>
<tr>
<td>7 89g</td>
<td>-(CH₂)₃⁻</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td></td>
<td>36</td>
<td>A</td>
</tr>
<tr>
<td>8 89h</td>
<td>-(CH₂)₃⁻</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td></td>
<td>13</td>
<td>A</td>
</tr>
<tr>
<td>9 89i</td>
<td>-(CH₂)₄⁻</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td></td>
<td>20</td>
<td>A</td>
</tr>
<tr>
<td>10 89j</td>
<td>-(CH₂)₄⁻</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td></td>
<td>64</td>
<td>A</td>
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<tr>
<td>11 89k</td>
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<td>H</td>
<td>H</td>
<td>Me</td>
<td></td>
<td>54</td>
<td>A</td>
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<tr>
<td>12 89l</td>
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<td>H</td>
<td>H</td>
<td>H</td>
<td></td>
<td>85</td>
<td>A</td>
</tr>
<tr>
<td>13 89m</td>
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<td>H</td>
<td>H</td>
<td>Me</td>
<td></td>
<td>82</td>
<td>A</td>
</tr>
<tr>
<td>14 89n</td>
<td>-(CH₂)₅⁻</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td></td>
<td>86</td>
<td>A</td>
</tr>
<tr>
<td>15 89o</td>
<td>-(CH₂)₅⁻</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 89p</td>
<td>Bn</td>
<td>cyclohexyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>25</td>
<td>B</td>
</tr>
<tr>
<td>17 89q</td>
<td>Bn</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>23</td>
<td>B</td>
</tr>
<tr>
<td>18 89r</td>
<td>Bn</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>49</td>
<td>B</td>
</tr>
<tr>
<td>19 89s</td>
<td>Bn</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>37</td>
<td>B</td>
</tr>
<tr>
<td>20 89t</td>
<td>Bn</td>
<td>PhSO₂</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>19</td>
<td>B</td>
</tr>
<tr>
<td>21 89u</td>
<td>Bn</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>35</td>
<td>B</td>
</tr>
<tr>
<td>22 89v</td>
<td>Ph</td>
<td>PhSO₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>38</td>
<td>C</td>
</tr>
<tr>
<td>23 89w</td>
<td>Ph</td>
<td>PhSO₂</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>35</td>
<td>C</td>
</tr>
<tr>
<td>24 89x</td>
<td>Ph</td>
<td>PhSO₂</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>18</td>
<td>C</td>
</tr>
<tr>
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<td>PhNHCO</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>12</td>
<td>C</td>
</tr>
</tbody>
</table>

\(^a\) Overall yields of three-step sequences are shown.

\(^b\) Procedures of preparation for 86a-y (A=eq. 1), (B=eq. 2), and (C=eq. 3).
Iodine-induced cyclization of \( \gamma, \delta \)-unsaturated thioimidates is performed.\(^3\)\(^8\) \( \gamma, \delta \)-Unsaturated thioimidates 90a-d undergo regio- and diastereoselective iodine-induced cyclization to afford \( \gamma \)-lactams 91a-d (Scheme 17).

\[
\begin{align*}
\text{R}^2 \quad \text{SMe} \quad \text{R}^3 \quad \text{Bn} \\
\text{R}^1 \quad \text{N} \quad \text{R}^2 \\
\end{align*}
\]

\( 90a-d \) \hspace{1cm} \( 91a-d \)

Scheme 17

Iodolactamization of \( \gamma, \delta \)-unsaturated \( \beta \)-hydroxythioimidates 92-94 is carried out to afford 4-hydroxy-\( \gamma \)-lactams 95a,b-97a,b, respectively. It is predicted that the configuration of the major diasteromer 95a would be 4,5-\( \text{cis} \) owing to the 1,2-\( \text{cis} \) directing ability of the iodonium ion and the hydroxy group in the transition state of this cyclization.\(^3\)\(^9\) Its stereochemistry is determined by a stereocontrolled transformation of 95a into the key intermediate to (-)-detoxinine (Scheme 18).\(^4\)\(^0\)

\[
\begin{align*}
\text{R}^2 \quad \text{OR}^1 \text{SMe} \\
\text{R}^3 \quad \text{Bn} \\
\end{align*}
\]

92 \( \text{R}^1 \text{R}^2 = \text{H} \)
93 \( \text{R}^1 = \text{TBDMS}, \text{R}^2 = \text{H} \)
94 \( \text{R}^1 = \text{H}, \text{R}^2 = \text{Me} \)

\[
\begin{align*}
\text{R}^4 \quad \text{I} \\
\text{R}^1 \quad \text{R}^2 \\
\end{align*}
\]

\( 95a, b (12:1) \)
96a,b (7:1)
97a,b (10:1)

Scheme 18

A high 1,3-\textit{trans} selectivity in the iodolactamization of \( \gamma, \delta \)-unsaturated \( \alpha \)-
alkyl thioimidates 98-101 is observed. In view of the conformational flexibility of the five-membered ring transition state, the stereocontrol due to the homoallylic substituent is not expected to be high in contrast to the control shown by the allylic substituent. This interesting trans-stereoselectivity may be rationalized as follows. Among possible cyclic transition states, the most likely one, the 1,3-di-quasi-equatorial transition state 106b, may be discounted owing to A(1,2) strain between R and the methylthio group. The strain forces the substituent R to take a quasi-axial orientation and hence the iodoalkyl group a quasi-equatorial orientation as transition state 106a. The structure of 102a is confirmed by X-ray crystallographic analysis and 104a is converted into the racemic intermediate to trans-4-cyclohexyl-L-proline, which is a constituent of foseno-pril (Andiotensin converting enzyme inhibitor) (Scheme 19).43

Next iodolactamization in δ,ε-unsaturated thioimidates is tried. Allylation of dianions of 3-benzenesulfonylpropionamides as homoenolates44 give δ,ε-unsaturated secondary amides, which are transformed by successive desulfonation, thionation, and methylation into the corresponding δ,ε-unsaturated thioimidates 107. Iodolactamization of 107 proceeds regioselectively to provide δ-lactames 108 (Scheme 20).45

5. MISCELLANEOUS

Cyclic thioimidates are important building blocks for the synthesis of N-heterocycles such as alkaloids.7 We are interested in exploring the utilization of cyclic thioimidates in a heterocyclic synthesis.46 A common intermediate, the quinolizidine 109 obtained by annelation of a cyclic thioimide with Nazarov's reagent47 in the presence of mercuric chloride, is stereospecifically transformed into (S)-epilupinine and (R)-lupinine as shown in Scheme 21.48 Stereospecific reduction of 109 with diisobutylaluminum hydride in the presence of triethylamine gives the trans-saturated β-ketoester, which is transformed by successive thioacetalization, desulfurization, and reduction into (S)-epilupinine. Chemoselective thionation of 109 with Lawesson's reagent49 provides the enaminothio ketone, which is converted by desulfurization followed by stereospecific reduction with sodium borohydride into (S)-lupinine.

As azacycloalkanes such as pyrrolidines, piperidines, and perhydroazepines are
Scheme 19

MeS

\begin{align*}
98 \quad & R^1 = \text{Ph}, \quad R^2 = \text{Me} \\
99 \quad & R^1 = \text{Bn}, \quad R^2 = \text{Me} \\
100 \quad & R^1 = \text{Bn}, \quad R^2 = \text{c. hexyl} \\
101 \quad & R^1 = \text{Bn}, \quad R^2 = \text{Ph}
\end{align*}

102a, b (6:1)

103a, b (12:1)

104a, b (13:1)

105a, b (14:1)

Scheme 20

MeS

\begin{align*}
106a & \quad \xrightarrow{I_2} \quad 102a-105a \\
106b & \quad \xrightarrow{I_2} \quad 102b-105b
\end{align*}

\begin{align*}
104a & \xrightarrow{I_2} \quad \text{Bn} \xrightarrow{\text{OH}} \quad \text{Bn} \xrightarrow{\text{CO}_2\text{H}}
\end{align*}

107

\begin{align*}
108 & \quad \xrightarrow{I_2} \quad \text{Bn}
\end{align*}
integral features of naturally occurring alkaloids, the development of functionalization methods for these ring systems is an important synthetic problem. One of the synthetic attempts in this direction has involved the nucleophilic addition of organometals to the carbonyl moiety of the corresponding lactams. Alkynyl azacycloalkanes 112 are synthesized by the addition reaction of lithium acetylides to S-methylamidinium salts 111 of thiolactams followed by a lithium aluminum hydride reduction of the adducts. This alkynylation is applied to a synthesis of trans-2-butyl-5-heptylpyrrolidine, a constituent of ant venom.\textsuperscript{50} Thionation of 5-butylpyrrolidin-2-one prepared by our new method\textsuperscript{51} followed by methylation yields amidinium salt 113. Alkynylation of 113 with lithium hexylide followed by reduction gives a mixture of trans and cis compounds 114a,b. After separation, 114a (trans) undergoes both reduction and hydrogenolysis with palladium hydroxide to afford trans-2-butyl-5-heptylpyrrolidine (Scheme 22).\textsuperscript{52}
Scheme 22

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