Divergent and chemoselective transformations of thioamides with designed carbene equivalents

Masato Saito,[a] Yusuke Kobayashi,[a] Yoshiji Takemoto*[a]

Abstract: The reactions of thioamides with ortho-nitro-substituted iodonium ylides proceeded under mild conditions to give enaminones or thiazoles, depending on the iodonium ylide used. This protocol allowed the use of protic solvents, including aqueous solutions, and therefore coupling reactions with complex molecules such as peptides or steroids were possible. A mild and efficient method for the synthesis of various iodonium ylides was established. A DFT calculation suggested that halogen bonding between thioamide and iodonium ylide was important in this chemoselective coupling reaction. The potential use of enaminones conjugated with pharmaceuticals as prodrugs was also demonstrated.

Thioamides have attracted much attention because they are isosteres of amides, but with higher lipophilicities and stabilities. Many studies of peptides and proteins with thioamide moieties have been conducted.[1] An increasing number of methods for the introduction of thioamides at desired positions of peptides are being developed.[2] In addition, thioamides have high nucleophilicities and their selectiv transformations have recently been studied.[3] In particular, the reactions of thioamide groups, which are rarely found in biomolecules, have potential applications in chemoselective biocoupling, which is one of the most important tools for drug discovery and in chemical biology.[4,5] However, only a few examples of such reactions have been reported. These reports include transition-metal-catalyzed coupling reactions with carbene equivalents.[6] Use of diazomalonates as precursors gave enaminones (Scheme 1A, eq. 1),[6a–c] whereas thiazoles were obtained when α-diao ketoesters were used as the carbene precursors (Scheme 1A, eq. 2).[6b,c] Both products were supposedly obtained through C–S bond formation. Although enaminones[6] and thiazoles[7] are both attractive pharmacophores with specific properties, these reactions generally require high temperatures because of the formation of inert complexes through thioamide coordination to the metal catalyst. It is therefore difficult to apply these reactions to heat-labile molecules such as proteins. Undesired O–H insertion[8] of metal carbeneoids into polar solvents such as alcohols also prevents thioamide use with complex molecules, which are difficult to dissolve in non-polar solvents.

Herein, we report a highly chemoselective coupling reaction of various thioamides with a variety of carbene equivalents in protic solvent under mild conditions. We therefore focused on iodonium ylides (Scheme 1A, eqs. 3, 4) as carbene equivalents because hypervalent iodine compounds, including iodonium ylides, have recently been reported to have α-holes,[9] and they are expected to form halogen bonds (XB) selectively with soft Lewis bases[10] such as thioamides, even in the presence of a polar functional group such as an alcohol. However, the use of iodonium ylides as electrophiles (Scheme 1A, eq. 4) has been less studied[11,12] than metal carbeneoid precursors (Scheme 1A, eq. 3). This limitation is because of the poor solubility and instability of iodonium ylides, and side reactions such as nucleophile dimerization (Scheme 1A, eq. 5). The strongly basic conditions needed for their preparation[13–15] also hinder the synthesis of a range of iodonium ylides.

Scheme 1. Summary of this work

To solve these problems, we focused on the effects of ortho substituents on the solubility and stability of iodonium ylides[16b,17] and hypervalent iodine compounds.[18] We envisaged that introduction of an ortho substituent would decrease side reactions by blocking one of the α-holes, and chemoselective coordination of thioamide to iodonium ylide would
promote C–S bond formation (Scheme 1B, eqs. 7, 8). In particular, the introduction of an ortho nitro group would enhance the reactivity of the corresponding precursor, Ar(III)(OAc), which would enable condensations with various active methylene compounds under mild conditions to produce iodonium ylides with broad functional group tolerance (Scheme 1B, eq. 6). We also envisioned the application of the method to enaminone-based prodrug (Scheme 1B, eq. 9) and thiazole-tethered conjugation of two complex molecules.

Table 1. Optimization of reaction conditions for chemoselective transformation of thioamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbene equivalent</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Rh₂(OAc)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CH₂OH</td>
<td>79&lt;sup&gt;[b]&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>CuBr</td>
<td>CH₂OH</td>
<td>81&lt;sup&gt;[b]&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1st</td>
<td>CH₂OH</td>
<td>81&lt;sup&gt;[b]&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>none</td>
<td>CH₂OH</td>
<td>82&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>none</td>
<td>CH₂OH</td>
<td>71&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>none</td>
<td>CH₂OH</td>
<td>79&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>7a</td>
<td>none</td>
<td>CH₂OH</td>
<td>71&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>5a</td>
<td>toluene</td>
<td></td>
<td>71&lt;sup&gt;[a]&lt;/sup&gt;</td>
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<td>9</td>
<td>5a</td>
<td>THF</td>
<td></td>
<td>71&lt;sup&gt;[a]&lt;/sup&gt;</td>
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<tr>
<td>10</td>
<td>5a</td>
<td>DMF</td>
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<td>79&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>5a</td>
<td>DMF/H₂O</td>
<td></td>
<td>71&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
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[a] Isolated yields  [b] Not detected.  [c] 1.0 equiv of TEMPO was added.

With the optimum reaction condition in hand, we investigated the substrate scope of the reaction between thioamides and a nitro-substituted iodonium ylide (Figure 1). Various primary thioamides were tolerated in the reaction with iodonium ylides. Thioamides derived from glycinamide and oleamide gave enaminones in 71% and 81% yields, respectively (Figure 1, 2a, 2c). This reaction was also applicable to a substrate with an azide moiety (2d), which could potentially be used for further functionalization via nitrene insertion<sup>[10]</sup> or click reactions<sup>[20]</sup> in the presence of a metal catalyst. Although enaminone 2e was obtained from cyclohexanethioicarbonamide in 62% yield, desulfurization did not occur when thiopivaloylamide was used, because of steric hindrance, and thiazole 2f was obtained in 67% yield. This reaction can also be conducted with the thioasparagine residue of a dipeptide (2g), indicating the potential of this method for late-stage functionalization of more complex peptides with thioamide moieties. This reaction was then applied to secondary thioamides. The desired enaminone was obtained in 79% yield from the simple thioanilide 2h. The reactions with secondary thioamides were performed at room temperature. A substrate with thioamide moieties as the main
peptide chain gave the target product 2i in 98% yield. Finally, this reaction was applied to the functionalization of pharmaceuticals. The thioamide derived from the aromatase inhibitor aminoglutethimide, \[21\] which has been used as the second- or third-line choice in the treatment of hormone-sensitive metastatic breast cancer, reacted with 5a to give enaminone 2l in 92% yield. It is worth mentioning that the reaction proceeded even when alkyne functional groups were present, which could be further functionalized with azide-containing probes or biomolecules through the orthogonal click reaction. \[20\]

Scheme 2. Release of aminoglutethimide

To demonstrate the utility of this reaction, the selective cleavage of this enaminone moiety for the potential prodrug applications was investigated (Scheme 2). The reaction of enaminone 2i, which contained aminoglutethimide, in an acidic solvent released aminoglutethimide almost quantitatively. The poor pharmacokinetics of aminoglutethimide\[21\] might be improved by functionalization based on this methodology.

![Scheme 2](image)

Figure 2. Substrate scope for synthesis of iodonium ylides

We next investigated the transformation of a \(\beta\)-ketoester-derived iodonium ylide to a thiazole by coupling with a thioamide (Figure 2.3). We envisioned that this thiazole synthesis could be used to link complex molecules via thiazole pharmacophores. This strategy requires the introduction of complex molecules into iodonium ylides. However, the conditions generally used to access iodonium ylides (e.g., use of KOH or KOMe in methanol or acetonitrile) would lead to decomposition or epimerization of complex molecules. After various screenings of solvents, bases, and additives, we identified the appropriate reaction conditions for the preparation of various iodonium ylides (Figure 2). A mixture of 2-iodobenzene diacetate 7, an active methylene compound 8 (1.1 or 2.0 equiv), 2,6-lutidine (5.0 equiv), and hexafluoro-2-propanol (HFIP) (2.0 equiv) in acetonitrile at 0 \(^\circ\)C gave the corresponding iodonium ylides in moderate to excellent yields. \[22\] This method gave the dimethyl malonate-derived iodonium ylide in 78% yield (Figure 2, 5a). As well as diester-containing iodonium ylides, ketoester-containing iodonium ylides were synthesized. The product derived from tert-butyl acetoacetate was obtained in 62% yield (5b). Complex molecules such as dioxigen and dipeptides (5c and 5d) were synthesized without any decomposition or epimerization, in 80% and 56% yields, respectively. These iodonium ylides were stable even when subjected to silica-gel column chromatography, presumably because of the ortho effect. Iodonium ylides bearing a protected sugar moiety (5e) or an alkyne group (5f) were synthesized under these reaction conditions.

![Figure 3](image)

Figure 3. Substrate scope for synthesis of thiazoles

We then investigated the reactions of the above prepared functionalized iodonium ylides 5a-f with thioamides to give thiazoles (Figure 3). When the iodonium ylides were reacted with oleamide derivatives, the desired thiazole 9 was obtained in 62% yield, although the addition of acetic acid was required for dehydration. We then conducted the reaction with complex iodonium ylides 5c-e, bearing dioxigen, dipeptide, and sugar moieties. These ylides were effectively converted to the
corresponding thiazoles (10–12) in 59%, 42%, and 66% yield, respectively. An alkyne group was also tolerated under the reaction conditions. Finally, we tried to use the reaction to introduce a sugar into a peptide. Iodonium ylide 5e reacted rapidly with the thioasparagine residue of a dipeptide to furnish the desired thiazole 14 in 57% yield. The introduction of the sugar moiety could improve the physical properties of the bioactive molecules, and this example showed the potential of this method for achieving conjugation of two complex molecules.

These results suggest that the ortho nitro substituent would control the coordination mode (Figure S1–S3), leading to selective formation of the desired C=S bond rather than lowering the activation energy of C=S bond formation.

In conclusion, we have developed a chemoselective reaction of thioamides with iodonium ylides. Halogen bonding interactions between the species are responsible for the high chemoselectivity and wide functional group tolerance in polar solvents. In addition, the ortho substituent on the iodonium ylides can control the coordination mode of the nucleophile via σ-holes, suppressing undesired side reactions. These findings would enhance chemoselective coupling reactions using hypervalent iodine compounds. This improved method for iodonium ylide preparation will also enable the development and expansion of carbenoid chemistry. A detailed mechanistic study and investigation of applications of this reaction in bioconjugation are underway in our laboratory.

**Experimental Section**

To a solution of thioamide 1a (17.6 mg, 0.05 mmol) in MeOH (1.0 mL) was added iodonium ylide 5a (28.4 mg, 0.075 mmol) at the indicated temperature. After being stirred at the same temperature for 12 hours, the crude mixture was directly purified by preparative TLC (Eluent: n-hexane/EtOAc = 75/25) to give desired products 2a (18.2 mg, 81%).

**Acknowledgements**

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**Keywords:** halogen bonding • hypervalent compounds • thiazole • enammine • chemoselective reaction

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[22] See the Supporting Information for details.


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Page No. – Page No.

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