One-Pot Synthesis of Substituted Isothiazol-3(2H)-ones: Intramolecular Annulation of α-Carbamoyl Ketene-S,S-acetals via PIFA-Mediated N–S Bond Formation

Jie Huang, a Yumei Lu, a Baofu Qiu, a Yongjiu Liang, a Nan Li, a Dewen Dong a,b

a Department of Chemistry, Northeast Normal University, Changchun, 130024, P. R. of China
b Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, P. R. of China
Fax +86(431)85098635; E-mail: dongdw663@nenu.edu.cn

Received 11 June 2007; revised 11 July 2007

Abstract: A facile and efficient synthetic route towards highly substituted isothiazol-3(2H)-ones 2 from readily available α-carbamoyl ketene-S,S-acetals 1 is presented. The key step features the formation of an N-acylnitrenium ion, generated from the oxidation of substituted amides with the hypervalent iodine reagent phenyliodin(III) bis(trifluoroacetate) (PIFA), and its succeeding intramolecular amidation to form a new N–S bond affording the title compounds.

Key words: α-carbamoyl ketene-S,S-acetals, isothiazol-3(2H)-ones, amidation, cyclization, hypervalent iodine reagent, trifluoroacetic acid

Isothiazol-3-ones and their benzo/hetero-fused analogues are of widespread interest due to their effective antifungal, antibacterial, and antipsychotic properties.1,2 The pharmacological importance of isothiazol-3-ones and their utility as intermediates in organic synthesis have directed considerable research activity towards the construction of the skeleton of such kind of heterocycles. Intensive research has generated numerous synthetic approaches, but although they have been demonstrated as useful protocols, some of them are of limited use because they lack generality and require not very accessible substrates and, in particular, employ highly toxic and corrosive agents such as chlorine gas, SO2Cl2, and SOCl2.3,4 To circumvent these problems, recently, the chlorine-free synthetic protocols have been developed including hypervalent iodine reagent mediated Pummerer-type reaction of sulfides,5 transamination of sulfenamides,6 and S-amidation/cyclization of 2,2′-dithio- or 2,2′-dithiodi-esters.7 Of these synthetic methods, the use of hypervalent iodine reagents proved to be an efficient route. As a hypervalent iodine reagent, phenyliodin(III) bis(trifluoroacetate) (PIFA) has attracted considerable attention of research on account of its ready availability, low toxicity, easy handling, and reactivity similar to that of heavy metal reagents.8 Its efficient utilization in metal-free transformations relies on both the extremely mild reaction conditions required and their ability to oxidize chemoselectively a wide range of functionalities such as amines, sulfides, and carbonyl compounds, among others.9

During the course of our studies on the synthesis and application of β-oxo amide derivatives in the synthesis of carbo- and heterocycles,10 we found that the readily synthesized α-carbamoyl ketene-S,S-acetals showed fascinating structural characteristics, especially their amoyl and alkylsulfanyl group patterns, and hence could be exploited in further organic transformations. Thus, we designed a strategy toward the synthesis of substituted isothiazol-3(2H)-ones 2 from readily available α-carbamoyl ketene-S,S-acetals 1, in which the PIFA-mediated oxidation of amides 1 and the subsequent trapping of the generated nitrogen electrophilic species by alkylsulfanyl moiety could form a new N–S bond (Scheme 1). As a result, we successfully achieved an efficient one-pot synthesis of substituted isothiazol-3(2H)-ones 2. Herein, we wish to report our preliminary results in this area.

Substrates, α-acetyl, α-carbamoyl ketene-S,S-acetals 1, were prepared from commercially available β-oxo amides in water in excellent yields following the procedure described in our previous work.11 With compounds 1a–r in hands, we selected 2-[bis(methylthio)methylene]-3-oxo-N-phenylbutanamide (1a) as the model compound to examine its behavior under different conditions. Upon treatment of 1a with PIFA (1.0 equiv) and trifluoroacetic acid (TFA, 3.0 equiv) in CH2Cl2 at room temperature for 10 hours, the reaction furnished a product after workup and purification (column chromatography) of the resulting mixture, which was characterized as 4-acetyl-5-(methylthio)-2-phenylisothiazol-3(2H)-one (2a) (50% yield) on the basis of its spectral and analytical data (Table 1, entry 1).

The optimization of the reaction conditions, including the feed ratio of PIFA, TFA and 1a, reaction temperature, solvents, and concentration of PIFA, were then investigated

SYNTHESIS 2007, No. 18, pp 2791–2796
Advanced online publication: 29.08.2007
© Georg Thieme Verlag Stuttgart · New York
as shown in Table 1. It seemed that variation of temperature had no significant influence on the reaction (Table 1, entries 2–3). But the decrease of concentration of PIFA would result in prolonged reaction time and low yield (Table 1, entry 4). Without PIFA, the reaction could not even take place at room temperature or under reflux (Table 1, entry 5). It was observed that the reaction proceeded with much difficulty without additive TFA (Table 1, entry 6). Similarly, the reaction proceeded sluggishly accompanied with much intact starting material when 1a was subjected to other solvents, such as DMF, THF, and acetonitrile (Table 1, entries 7–9). The optimal results were obtained when the reaction of 1a was performed with PIFA (1.2 equiv, 0.12 M) in CH₂Cl₂ at room temperature in the presence of TFA (3.0 equiv), in which the yield of 2a reached 65% (Table 1, entry 12).

Under the optimized conditions, a range of reactions of α-carbamoyle ketene-S,S-acetal 1b–r were next carried out with the aim to determine the scope of the key cyclization protocol with the respect to the amide and alkylsulfanyl motifs. Thus, when N-aryl amides 1b–g were treated with PIFA/TFA in CH₂Cl₂ at room temperature, the effectiveness of the synthetic protocol proved to be suitable affording the corresponding substituted isothiazol-3(2H)-ones 2 in moderate to good yields (Table 2, entries 2–7). The validity of this isothiazol-3(2H)-one synthesis was further evaluated by performing N-aryl amides 1h–r bearing different alkylsulfanyl groups under the identical conditions. The yields were slightly lower, and prolonged reaction time and high reaction temperature were required in some cases (Table 2, entries 12–16). This may be due to the presence of the bulkier alkylsulfanyl or N-arylamide group in substrates 1, which sterically inhibits its electrophilic reaction. Finally, we find no apparent explanation for the fact that, although a wide range of experimental conditions was tested on the N-alkyl amide substrates 1, they all failed to afford the desired heterocycles 2. In Correa’s recent work on the oxidization process for the construction of N–N linkages by employing amine moieties as the nucleophilic species, they found that the reaction was restricted to aromatic amides.⁸g These results suggested that the N-acylnitrenium ions, generated from the oxidization of substituted amides with PIFA, need sufficient stabilization of the electron-donating effect from a proper neighboring group, such as aryl group, to undergo further organic reactions.¹²,¹³ Nevertheless, we have presented here an alternative route for the N–S bond formation with access to the substituted isothiazol-3(2H)-ones 2. The richness of the functionality, e.g., acetyl and alkylsulfanyl groups on the ring of isothiazol-3(2H)-ones 2, may render them as extremely versatile intermediates for further synthetic transformations, such as Wittig reaction,¹⁴ Michael addition,¹⁵ and nucleophilic vinylic substitution (S₂V) reaction.¹⁶

In summary, a facile and efficient synthetic route towards highly substituted isothiazol-3(2H)-ones 2 from readily

---

**Table 1** The Reaction of α-Carbamoyl Ketene-S,S-acetal 1a with PIFA Under Different Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>PIFA (equiv/M)</th>
<th>TFA (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0/0.10</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>1.0/0.10</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>1.0/0.10</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>10</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>1.0/0.01</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>0/0</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>r.t./reflux</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>0</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>1.0/0.10</td>
<td>3.0</td>
<td>DMF</td>
<td>60</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>1.0/0.10</td>
<td>3.0</td>
<td>THF</td>
<td>60</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>1.0/0.10</td>
<td>3.0</td>
<td>MeCN</td>
<td>60</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>1.0/0.20</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>1.2/0.10</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>4</td>
<td>62</td>
</tr>
<tr>
<td>12</td>
<td>1.2/0.12</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>3</td>
<td>65</td>
</tr>
</tbody>
</table>

As isolated yields of 2a.
available α-carbamoyl ketene-S,S-acetals 1 is described. The key step features the formation of a \( \text{N-acylanitrenium} \) ion, generated from the oxidization of substituted amides with PIFA, and its succeeding intramolecular amidation to form a new \( \text{N–S} \) bond affording the title compounds. The use of innocuous oxidizer PIFA, simplicity of execution, ready availability of substrates, and potential products make this synthetic strategy much attractive.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. \(^1\)H NMR and \(^13\)C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard at 25 °C on a Varian Inova-500 spectrometer. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm\(^{-1}\). Mass spectra were recorded on an Agilent 1100 LCMSD mass spectrometer using EI at 70 eV. Elemental analyses were conducted on a PE-2400 analyzer (PerkinElmer). Petroleum ether (PE) used was the fraction boiling in the range 30–60 °C.

### Table 2 The Reactions of α-Carbamoyl Ketene-S,S-acetals 1 with PIFA/TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp</th>
<th>Time</th>
<th>Product</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>Ph</td>
<td>2a</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Me</td>
<td>4-MeC(_6)H(_4)</td>
<td>r.t.</td>
<td>2b</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Me</td>
<td>4-MeOC(_6)H(_4)</td>
<td>r.t.</td>
<td>2c</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>Me</td>
<td>4-CIC(_6)H(_4)</td>
<td>r.t.</td>
<td>2d</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>Me</td>
<td>2-CIC(_6)H(_4)</td>
<td>r.t.</td>
<td>2e</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>Me</td>
<td>2-MeC(_6)H(_4)</td>
<td>r.t.</td>
<td>2f</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>Me</td>
<td>2-MeOC(_6)H(_4)</td>
<td>r.t.</td>
<td>2g</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>Et</td>
<td>Ph</td>
<td>2h</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>Et</td>
<td>4-MeC(_6)H(_4)</td>
<td>r.t.</td>
<td>2i</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>Et</td>
<td>4-MeOC(_6)H(_4)</td>
<td>r.t.</td>
<td>2j</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>Et</td>
<td>4-CIC(_6)H(_4)</td>
<td>r.t.</td>
<td>2k</td>
</tr>
<tr>
<td>12</td>
<td>1l</td>
<td>Et</td>
<td>2-CIC(_6)H(_4)</td>
<td>reflux</td>
<td>2l</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>Et</td>
<td>2-MeC(_6)H(_4)</td>
<td>reflux</td>
<td>2m</td>
</tr>
<tr>
<td>14</td>
<td>1n</td>
<td>Et</td>
<td>2-MeOC(_6)H(_4)</td>
<td>reflux</td>
<td>2n</td>
</tr>
<tr>
<td>15</td>
<td>1o</td>
<td>Bn</td>
<td>Ph</td>
<td>reflex</td>
<td>2o</td>
</tr>
<tr>
<td>16</td>
<td>1p</td>
<td>Bn</td>
<td>2-CIC(_6)H(_4)</td>
<td>reflux</td>
<td>2p</td>
</tr>
<tr>
<td>17</td>
<td>1q</td>
<td>Bn</td>
<td>2-MeC(_6)H(_4)</td>
<td>reflux</td>
<td>2q</td>
</tr>
<tr>
<td>18</td>
<td>1r</td>
<td>Bn</td>
<td>2-MeOC(_6)H(_4)</td>
<td>reflux</td>
<td>2r</td>
</tr>
</tbody>
</table>

*Isolated yields after silica gel chromatography.*

**Substituted Isothiazol-3(2H)-ones 2; 4-Acetyl-5-((methylthio)-2-phenylisothiazol-3(2H)-one (2a); Typical Procedure**

To a solution of 1a (0.28 g, 1.0 mmol) in CH\(_2\)Cl\(_2\) (5.0 mL) was added dropwise a solution of PIFA (0.52 g, 1.2 mmol) and TFA (0.23 mL, 3.0 mmol) in CH\(_2\)Cl\(_2\) (5.0 mL) at r.t. under stirring. After completion of the reaction as indicated by TLC, the mixture was quenched with sat. aq NaHCO\(_3\) (30 mL) and extracted with CH\(_2\)Cl\(_2\) (3 × 20 mL). The organic extracts were washed with brine (3 × 20 mL), dried (MgSO\(_4\)), filtered, and concentrated in vacuo. Purification was carried out by flash silica gel chromatography using PE–EtOAc (12:1) as eluent to give product 2a; yield: 0.17 g (65%); white solid; mp 97–98 °C.
**4-Acetyl-5-(methylthio)-2-p-tolylisothiazol-3(2H)-one (2b)**

White solid; mp 167–168 °C.

IR (KBr): 1669, 1648, 1510, 1454, 1326, 808 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 2.37 (s, 3 H), 2.47 (s, 3 H), 2.62 (s, 3 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 192.8, 169.3, 164.1, 137.1, 132.2, 129.0, 124.2, 116.6, 27.4, 20.1, 14.1.


**4-Acetyl-5-(methylthio)-2-thiophenylisothiazol-3(2H)-one (2c)**

White solid; mp 164–165 °C.

IR (KBr): 1665, 1512, 1452, 1302, 1251, 823 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 2.46 (s, 3 H), 2.62 (s, 3 H), 3.83 (s, 3 H), 6.96 (d, J = 9.0 Hz, 2 H), 7.38 (d, J = 9.0 Hz, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 192.9, 169.3, 164.3, 158.3, 127.2, 126.4, 116.5, 54.6, 27.3, 14.1.

MS: m/z: calcd: 295.0; found: 296.1 (M + 1)⁺.

Anal. Calcd for C₁₄H₁₅NO₂S₂: C, 52.86; H, 4.44; N, 4.74. Found: C, 52.73; H, 4.50; N, 4.67.

**4-Acetyl-5-(chlorophenyl)-2-(methylthio)isothiazol-3(2H)-one (2d)**

White solid; mp 176–178 °C.

IR (KBr): 1674, 1647, 1558, 1489, 1309, 1273, 818 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 2.51 (s, 3 H), 2.63 (s, 3 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.51 (d, J = 9.0 Hz, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 193.7, 170.7, 164.8, 134.5, 133.4, 129.6, 126.1, 117.5, 28.4, 15.2.


**4-Acetyl-5-(chlorophenyl)-2-thiophenylisothiazol-3(2H)-one (2e)**

White solid; mp 177–178 °C.

IR (KBr): 1666, 1640, 1470, 1435, 1301, 1184, 1075, 759, 682 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 2.52 (s, 3 H), 2.67 (s, 3 H), 7.43–7.50 (m, 3 H), 7.60 (d, J = 8.5 Hz, 1 H).

13C NMR (125 MHz, CDCl₃): δ = 193.8, 172.4, 165.7, 134.1, 132.6, 131.3, 131.0, 127.9, 116.6, 28.3, 15.2.

Anal. Calcd for C₁₃H₁₃ClNO₂S₂: C, 55.89; H, 4.69; N, 5.01. Found: C, 56.01; H, 4.61; N, 4.92.
4-Acetyl-2-(2-chlorophenyl)-5-(ethylthio)isothiazol-3(2H)-one (2n)
White solid; mp 78–80 °C.
IR (KBr): 1616, 1520, 1453, 1372, 1181, 1120, 620 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 1.48 (t, J = 7.5 Hz, 3 H), 2.63 (s, 3 H), 2.90 (q, J = 7.5 Hz, 2 H), 7.39–7.46 (m, 3 H), 7.56 (d, J = 8.0 Hz, 1 H).

13C NMR (125 MHz, CDCl3): δ = 139.3, 171.4, 165.9, 134.3, 132.9, 131.5, 131.0, 128.2, 116.5, 28.7, 26.7, 13.2.

Anal. Calc'd for C₁₅H₁₄ClNO₂S₂: C, 49.75; H, 3.85; N, 4.46; Found: C, 49.43; H, 3.78; N, 4.54.

4-Acetyl-2-(2-methoxyphenyl)isothiazol-3(2H)-one (2o)
White solid; mp 152–153 °C.
IR (KBr): 1670, 1640, 1438, 1315, 1240, 749, 703 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 2.23 (s, 3 H), 2.61 (s, 3 H), 4.09 (s, 2 H), 7.24–7.29 (m, 2 H), 7.32–7.36 (m, 5 H), 7.37–7.40 (m, 2 H).

13C NMR (125 MHz, CDCl3): δ = 192.7, 167.9, 163.7, 136.6, 132.4, 132.3, 130.1, 128.7, 127.8, 127.5, 127.2, 125.9, 115.7, 35.9, 27.0, 16.7.


References


