Rongxing Zhang*  
Zhaohua Yan*  
Dingyi Wang*  
Yuanxing Wang*b  
Sen Lin*a  
*a College of Chemistry, Nanchang University, Nanchang, Jiangxi 330031, P. R. of China  
serlin@ncu.edu.cn  
b State Key Laboratory of Food Science and Technology, Nanchang University, Nanchang, Jiangxi 330031, P. R. of China  
yuanxingwang@ncu.edu.cn

Abstract  
A direct and efficient method for the acetamidosulfenylation reaction of alkenes was developed, in which NaI was used as a catalyst, DMSO as the oxidant, nitriles as both the solvent and nucleophiles and stable, readily available Bunte salts as thiolating reagents. The reactions were carried out under mild conditions generating \( \beta \)-acetamido sulfides in good yields. Moreover, the reaction can be performed when alcohols are used as nucleophiles providing the corresponding \( \beta \)-alkoxy sulfides in moderate yields, respectively.

Key words  
alkenes, Bunte salts, \( \beta \)-acetamido sulfides, nitriles, nucleophiles

Organosulfur compounds, over the past decades, not only receive wide application in material science,1 but also play an important role in medicinal chemistry,2 natural products,3 and food chemistry.4 It is an effective strategy to obtain organosulfur products through the difunctionalization of alkenes in synthetic organic chemistry.5 Among them, sulfonylation of alkene employing various sulfur reagents has gained great attention and progress in recent years.6 Different sulfur sources, such as thiols,6a disulfides,6b arylsulfonyl chlorides,6c and arylsulfonyl cyanides,6d,6e have been well developed for these transformations. However, in order to meet the requirements for multifunctionalized organosulfur compounds, simpler, more effective, and green methods for difunctionalization of alkenes are still highly desirable.

\( \beta \)-Acetamido sulfides, as an important member in sulfur-containing compounds, exist widely as moieties in natural products and biologically active molecules,7 such as lactacystin,7a which is a proteasome inhibitor, frenolicin C7b with anticoxidial activity, and luensimycin D7c with antibacterial activities (Figure 1).

In the last years, the acetamidosulfenylation of alkene has emerged as a direct and efficient protocol for the synthesis of \( \beta \)-acetamido sulfides. Cui8a and Zheng,8b respectively, described a three-component oxidative acetamidosulfenylation of alkenes in which disulfides and thiols with unpleasant odor served as thiolating reagents (Scheme 1, a and b).

Bunte salts, which can be prepared by the reaction of sodium thiosulfate with various halides, are stable, readily available, and odorless solid compounds.9 They have been widely applied in the synthesis of organosulfur compounds.10 In 2014, Reeves reported the synthesis of sulfides via the reaction of Grignard reagent and Bunte salts.10a In 2015, Yi’s group described thia-Michael addition using

Figure 1  
Examples of \( \beta \)-acetamido sulfides

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Bunte salts. Very recently, Luo and Ji, respectively, explored the application of Bunte salts as thiolating reagents in the synthesis of 3-thioindoles. To the best of our knowledge, Bunte salts have not yet been applied in the sulfenylation reaction of alkenes. In consideration of the fact that the odorless and stable Bunte salts can be easily converted into disulfides in solvents, we envisioned that they should be better candidates as thiolating sources for the acetamidosulfenylation of alkenes. As a continuation of our project directed toward the C–S bond formation, herein we present a direct and efficient method for the acetamidosulfenylation reaction of alkenes in which NaI was used as a catalyst, DMSO as the oxidant, nitriles as both the solvent and nucleophiles, and Bunte salts as thiolating reagents (Scheme 1, c).

Initially, we conducted the reaction of styrene (1a, 0.30 mmol) with sodium s-benzyl thiosulfate (2a, 0.45 mmol) in the presence of (NH₄)₂S₂O₈ and iodine in acetonitrile at 80 °C for nine hours (Table 1, entry 1), but no desired product 4a was observed. It is worth noting that 4a was detected, respectively, in 56% and 58% yields when iodide salts such as NH₄I and NaI were used instead of iodine in acetonitrile at 80 °C for nine hours (Table 1, entry 1), but no desired product 4a was observed. Under the optimized reaction conditions, we investigated the scope and limitation of the reaction of sodium s-benzylthiosulfate (2a) with various alkene substrates, and the results are listed in Scheme 2. Styrenes having electron-rich and electron-poor groups on the benzene ring resulted in the formation of the corresponding β-acetamido sulfides in moderate yields (4d–h; Scheme 2). Notably, the reaction of cyclohexene as aliphatic alkene with sodium s-benzylthiosulfate (2a) also proceeds well generating 4i in good yield (4i; Scheme 2).

Next, the participation of various Bunte salts and aryl nitriles in this protocol were studied, and the results are shown in Scheme 3. The use of sodium s-(4-methyl)benzylthiosulfate and sodium s-benzylthiosulfates possessing electron-poor groups on benzene ring resulted in the formation of the corresponding β-acetamido sulfides in moderate yields (5b–d; Scheme 3).

### Table 1 Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodide (mol%)</th>
<th>Oxidant (equiv)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂ (20)</td>
<td>(NH₄)₂S₂O₈ (2.0)</td>
<td>80</td>
<td>n.r.</td>
</tr>
<tr>
<td>2</td>
<td>TBAI (20)</td>
<td>(NH₄)₂S₂O₈ (2.0)</td>
<td>80</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>NaI (20)</td>
<td>(NH₄)₂S₂O₈ (2.0)</td>
<td>80</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>NH₄I (20)</td>
<td>(NH₄)₂S₂O₈ (2.0)</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>NaI (20)</td>
<td>K₂S₂O₈ (2.0)</td>
<td>80</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>NaI (20)</td>
<td>TBHP (2.0)</td>
<td>80</td>
<td>n.r.</td>
</tr>
<tr>
<td>7</td>
<td>NaI (20)</td>
<td>DTTBP (2.0)</td>
<td>80</td>
<td>n.r.</td>
</tr>
<tr>
<td>8</td>
<td>NaI (20)</td>
<td>DDQ (2.0)</td>
<td>80</td>
<td>n.r.</td>
</tr>
<tr>
<td>9</td>
<td>NaI (20)</td>
<td>DMSO (2.0)</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>I₂ (10)</td>
<td>DMSO (2.0)</td>
<td>80</td>
<td>47</td>
</tr>
<tr>
<td>11</td>
<td>NaI (20)</td>
<td>DMSO (2.0)</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>12</td>
<td>NaI (20)</td>
<td>DMSO (2.0)</td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td>13</td>
<td>NaI (20)</td>
<td>DMSO (1.0)</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>14</td>
<td>NaI (20)</td>
<td>–</td>
<td>100</td>
<td>n.r.</td>
</tr>
<tr>
<td>15</td>
<td>NaI (10)</td>
<td>DMSO (2.0)</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>16</td>
<td>–</td>
<td>DMSO (2.0)</td>
<td>100</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.30 mmol), 2a (0.45 mmol), 3a (1.5 mL), H₂O (0.60 mmol), 9 h in a sealed tube.

* Yield of isolated product.
decreased when aryl nitriles as nucleophiles were employed, which probably resulted from steric hindrance especially in the case of 5f (5e–g, Scheme 3). On the other hand, sodium s-arylthiosulfate possessing 4-methyl on the benzene ring was used in reaction with good yield (5h; Scheme 3), similarly, sodium s-(4-chloro)phenylthiosulfate underwent the same acetamidosulfenylation reaction with the formation of 5i in 62% yield (5i; Scheme 3) which may be influenced by electron-poor effect. Moreover, aliphatic Bunte salt can participate in the reaction with good yield (5j; Scheme 3).

Furthermore, the potential industrial application of this reaction was demonstrated on a gram scale. As shown in Scheme 4, the reaction could afford 1.62 grams of 4a in 71% yield, demonstrating the potential applications of the reaction for a large-scale synthesis of β-acetamido sulfides.
To extend the scope of sulfenylation of alkenes with Bunte salts as thiolating reagent, we tested other nucleophiles. The reactions of sodium s-benzyl thiosulfate (2a) with styrene (1a) and alcohols 6 were carried out, and the results are shown in Scheme 5. The results show that the alkoxy sulfenylation of styrene can proceed well although β-alkoxy sulfides were only obtained in moderate yields.

In order to attain further insight into the reaction mechanism, we tried three reactions as contents of control experiments, and the results are outlined in Scheme 4. First, the reaction of 1a with 2a in the presence of 2,6-di-tert-butylphenol as free-radical inhibitor was not terminated and it still proceeds smoothly (Scheme 6, eq. 1). Sodium s-benzyl sulfoxioate (2a) can be successfully transformed into dibenzyl disulfide (8a) in 95% yield under the standard conditions in the absence of NaI and DMSO (Scheme 6, eq. 2). No corresponding products were observed when sodium s-benzyl sulfoxioate (2a) was replaced by dibenzyl disulfide (8a, Scheme 6, eq. 3). The above results show that the reaction mechanism of 1a with 2a might not be a radical pathway, and the disulfide might be an intermediate.
On the basis of the reported literature\textsuperscript{8,11–14} and the above results of control experiments, a plausible mechanism is depicted in Scheme 7. Under the heating conditions, the hydrolysis of Bunte salts A in the presence of water leads to the formation of species bisulfite anion and thiol or thiol anion B in the reaction mixture.\textsuperscript{11} The disulfide C are thus generated through the attack by thiol or thiol anion B on another Bunte salt A.\textsuperscript{12} Next, the reaction of disulfide C with I\textsubscript{2} to gives RSI D which is an electrophilic species,\textsuperscript{13a} and an intermediate F appeared via the attack of alkene E by RSI D.\textsuperscript{8,13b} The subsequent reaction of the intermediate F with nitriles followed by Ritter reaction, alcohol affords \(\beta\)-acetamido sulfides G, and \(\beta\)-alkoxy sulfides I with the release of HI.\textsuperscript{14} Finally, two molecules of HI were oxidized by DMSO and transformed into molecular I\textsubscript{2} accompanied by the formation of water and dimethyl sulfide.\textsuperscript{13a,15}

**Scheme 7** Plausible reaction mechanism

In summary, a direct and facile method has been developed for the synthesis of \(\beta\)-acetamido sulfides through the acetamidosulfenylation of alkenes in moderate to good yields in which odorless solid Bunte salts were used as thiolating reagents, NaI as a catalyst, DMSO as the mild oxidant, and nitriles as both the solvent and nucleophiles.\textsuperscript{16} Furthermore, the reaction can be extended for alcohols substrate leading to the synthesis of \(\beta\)-alkoxy sulfides, respectively.

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**Supporting Information**

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**References and Notes**


(16) General Procedure for the Synthesis of Compound 4 or 5
NaI (0.06 mmol) and Bunte salt $2^2$ (0.45 mmol) were added to a solution of nitrile $3$ containing alkene $1$ (0.30 mmol), followed by the addition of DMSO (0.60 mmol). The reaction mixture was stirred in a sealed tube at 100 °C for 9 h. After completion of the reaction, the reaction mixture was diluted with EtOAc, and quenched with sat. Na$_2$S$_2$O$_3$ solution and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated in vacuo, and the residue was subjected to column chromatography using EtOAc in PE as the eluent to afford the pure target product $4$ or $5$. Compound $4b$ was obtained in 82% yield (73.7 mg) according to the general procedure for the synthesis of $4$ as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.32–7.23 (m, 5 H), 7.12 (s, 4 H), 6.03 (d, $J$ = 8.0 Hz, 1 H), 5.12 (q, $J$ = 8.0 Hz, 1 H), 3.59 (q, $J$ = 12 Hz, 2 H), 2.86–2.74 (m, 2 H), 2.32 (s, 3 H), 1.95 (s, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 169.5, 138.0, 137.7, 137.4, 129.4, 129.0, 128.5, 127.1, 125.4, 51.8, 37.1, 36.4, 23.4, 21.1. ESI-HRMS: m/z calcld for C$_{10}$H$_{15}$NOS [M + Cl$^+$]: 334.1027; found: 334.1036.

General Procedure for the Synthesis of Compound 7
NaI (0.06 mmol) and $2a$ (0.45 mmol) was added to a solution of acetonitrile $3a$ containing styrene $1a$ (0.30 mmol) and alcohol (100 $\mu$L) or 2-allylphenol $6d$ (0.3 mmol), followed by DMSO (0.60 mmol). The reaction mixture was stirred at 90 °C for 6–9 h. After completion of the reaction, the reaction mixture was diluted with EtOAc, quenched with sat. Na$_2$S$_2$O$_3$ solution and extracted twice with EtOAc (2 × 15 mL). The organic layer was washed with water and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated in vacuo, and the residue was subjected to column chromatography using EtOAc in PE as the eluent to afford the pure target product $7$. Compound $7a$ was obtained in 42% yield (32.7 mg) according to the general procedure for the synthesis of $7$ as a colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.37–7.21 (m, 10 H), 4.31 (q, $J$ = 8.0 Hz, 1 H), 3.69 (q, $J$ = 12.0 Hz, 1 H), 3.42–3.33 (m, 1 H), 2.84 (q, $J$ = 8.0 Hz, 1 H), 2.60 (q, $J$ = 8.0 Hz, 1 H), 1.20 (t, $J$ = 8.0 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 141.6, 138.6, 129.0, 129.4, 128.4, 128.4, 127.8, 126.9, 126.7, 82.3, 64.5, 38.7, 37.2, 15.3. ESI-HRMS: m/z calcld for C$_{17}$H$_{20}$OS [M + Na$^+$]: 295.1127; found: 295.1120.