AN EFFICIENT CATALYST-FREE SYNTHESIS OF VINYL SULFIDES IN AQUEOUS-PHASE

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Abstract – An efficient catalyst-free synthesis of vinyl sulfides via the Michael addition of thiol compounds and tetrolic acid ester (or methyl propiolate) in water was carried out in good yields. The products were identified by IR, 1H NMR and HRMS techniques. The structures of 5b, 6b and 8a were confirmed by X-ray diffraction analysis further. This protocol has the advantages of shorter reaction time, mild conditions, easy work-up and environmental friendliness.

INTRODUCTION

Vinyl sulfides are the important synthetic intermediates in organic chemistry.1 They can be used as equivalents of enolate ions and Michael acceptors2 for synthesis of many polymeric materials, natural products, and synthetic reagents.3,4 Because of the importance of these compounds, there have been a number of reported methods for synthesizing vinyl sulfides.5 The conventional approaches to the synthesis of vinyl sulfides include the addition of thiols to alkynes under free-radical reactions,6,7 transition metal-catalyzed conditions,8-10 and the cross-coupling of vinyl halides and thiols.9,11 The Wittig reaction has also been utilized in the synthesis of vinyl sulfides.12 For instance, Montevecchi et al. successfully developed the addition reactions of benzenethiol with various mono- and disubstituted alkyl-acetylenes under radical conditions, affording the anti-Markovnikov product.13-16 Ogawa et al. reported the interesting finding that using Pd(OAc)2 catalyzed the addition of aromatic thiols to acetylenes to provide the Markovnikov adducts successfully.12 Yavari et al. reported the addition of benzo[d]thiazole-2-thiol to dialkyl acetylenedicarboxylates using isoquinoline as catalyst in CHCl3.18 These approaches involve various shortcomings such as use of organic solvents (halogenated solvents), requirement of special efforts for preparation of catalysts or use of costly catalysts.
In the past decade, the methodologies often address the growing concern about environmental safety and hazard, and the development of such economic and eco-friendly methodologies is the central focus in the area of green and sustainable chemistry. Water has been promoted as replacements to organic solvents in synthetic organic reactions, water represents one of the most economically and environmentally viable options. Although the use of water as a reaction solvent has received considerable attention in synthetic organic chemistry,\textsuperscript{19,20} Michael additions in water are relatively scarce.\textsuperscript{21} Especially, there are only a handful of reports on the thio-Michael addition in water. To the best of our knowledge, only Naidu et al. investigated the thia-Michael addition of thiols to dehydroalanine derivatives in water and Chakraborti et al. reported the conjugate addition of thiols to \(\alpha,\beta\)-unsaturated carbonyl compounds in water.\textsuperscript{21,22}

In continuation of green chemistry interest of methodologies, herein, we described a simple, efficient, catalyst-free green synthesis of vinyl sulfides in water. The synthetic strategy employed for the synthesis of dialkyl 2-(benzo\([d]\)thiazol-2-ylthio)fumarate (3), dialkyl 2-(5-amino-1,3,4-thiadiazol-2-ylthio)fumarate (5), methyl 3-(benzo\([d]\)thiazol-2-ylthio)acrylate (8) and methyl 3-(5-amino-1,3,4-thiadiazol-2-ylthio)acrylate (9) is depicted in Scheme 1.

\[\begin{align*}
1\text{a: } & \quad X = S \\
1\text{b: } & \quad X = O \\
2\text{a: } & \quad R = \text{Me} \\
2\text{b: } & \quad R = \text{Et} \\
3\text{a: } & \quad X = S, \quad R = \text{Me} \\
3\text{b: } & \quad X = S, \quad R = \text{Et} \\
3\text{c: } & \quad X = O, \quad R = \text{Me} \\
3\text{d: } & \quad X = O, \quad R = \text{Et} \\
4\text{a: } & \quad X = S \\
4\text{b: } & \quad X = O \\
4\text{c: } & \quad X = \text{NH}
\end{align*}\]

\textbf{Scheme 1.} The synthesis of vinyl sulfides
RESULTS AND DISCUSSION

Optimization of the reaction conditions was carried out by taking benzo[d]thiazole-2-thiol (1a), dimethyl acetylenedicarboxylate (2a) as the model substrates. The results are summarized in Table 1. Initially, a solution of equimolar amounts of benzo[d]thiazole-2-thiol (1a), and dimethyl acetylenedicarboxylate (2a) in water was stirred at rt for 10 h. To our delight, the desired product was obtained in 65% yield (Table 1, entry 1). Subsequently, the influences of material ratio were screened and a range of different reaction temperature and time were examined to improve the yields. Thus, the optimized yield of the desired product was obtained by carrying out the reaction in the material ratio of 1a/2a (1:1.2) at 80 °C for 2 h (Table 1, entry 10).

Table 1. The optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Molar ratio of (1a/2a)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 : 1.0</td>
<td>rt</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1.0 : 1.1</td>
<td>rt</td>
<td>10</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>1.0 : 1.2</td>
<td>rt</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1.0 : 1.5</td>
<td>rt</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>1.0 : 1.2</td>
<td>rt</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>1.0 : 1.2</td>
<td>rt</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>1.0 : 1.2</td>
<td>rt</td>
<td>24</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>1.0 : 1.2</td>
<td>50</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>1.0 : 1.2</td>
<td>60</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>1.0 : 1.2</td>
<td>80</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>1.0 : 1.2</td>
<td>90</td>
<td>2</td>
<td>88</td>
</tr>
</tbody>
</table>

With the optimal reaction conditions in hand, we investigated the scope of the reaction (Table 2 and Table 3). The benzo[d]oxazole-2-thiol (1b), 1H-benzo[d]imidazole-2-thiol (1c), 5-amino-1,3,4-thiadiazole-2-thiol (4) and diethyl acetylenedicarboxylate (2b) were employed under the optimized reaction conditions. Satisfactorily, the benzo[d]oxazole-2-thiol (1b), 5-amino-1,3,4-thiadiazole-2-thiol (4) and diethyl acetylenedicarboxylate (2b) afforded the corresponding
vinyl sulfides with good yields (3 and 5). Interestingly, the reaction of 1H-benzo[d]imidazole-2-thiol (1b) and dimethyl acetylenedicarboxylate (2a) underwent another direction to give access to thiazolidinone 6 (Table 2). Moreover, the same anti-Markovnikov type vinyl sulfides 8 and 9 were obtained via the addition of the corresponding thiols to terminal alkynes methyl propiolate (7) (Table 3).

### Table 2. Synthesis of vinyl sulfides 3, 5 and 6

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 + 2 → 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 + 2 → 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b + 2 → 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a, 88%</td>
<td>3b, 83%</td>
<td>3c, 84%</td>
</tr>
<tr>
<td>3d, 82%</td>
<td>5a, 87%</td>
<td>5b, 86%</td>
</tr>
<tr>
<td>6a, 85%</td>
<td>6b, 85%</td>
<td></td>
</tr>
</tbody>
</table>

*a isolated yield

The structures of compounds 3, 5, 6, 8, and 9 were deduced from their IR, ¹H NMR and high-resolution mass spectrometry (HRMS). For example, the ¹H NMR spectrum of 5b exhibited two singlets arising from the vinyl (6.70 ppm) and amino groups (5.79 ppm) and two multiplets representing the two methine (4.27 and 4.14 ppm) and two triplet peak representing the methyl groups for 13 protons. The HRMS spectrum of 5b displayed the molecular ion peak at m/z = 304, which is consistent with the proposed 1:1 adduct of 5-amino-1,3,4-thiadiazole-2-thiol and dimethyl acetylenedicarboxylate. The IR spectrum of 5b showed strong absorptions at 1735 and 1261 cm⁻¹, which are attributed to two ester carbonyls and C-S-C stretching. For compounds 8 and 9, the compounds of (E)-8 and (E)-9 were obtained under the same
reaction conditions, the structure of 8a was confirmed by single-crystal X-ray analysis and NOESY analysis. The coupling constants of vinyl protons of (Z)-products 8 and 9 are smaller than those of (E)-products, which is consistent with literature reports.\textsuperscript{18,23}

<table>
<thead>
<tr>
<th>( \text{Table 3. Synthesis of compounds 8 and 9} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{1} ) ( \text{7} ) ( \text{8} )</td>
</tr>
<tr>
<td>( \text{2} ) ( \text{7} ) ( \text{9} )</td>
</tr>
</tbody>
</table>

Unambiguous evidence for the structures of 5b, 6b and 8a were obtained from single-crystal X-ray analysis. The diagram of the three compounds 5b, 6b and 8a were shown in Figure 1.

\( \text{8a, 85\%} \) \( \text{8b, 86\%} \) \( \text{8c, 85\%} \) \( \text{9, 85\%} \)  

\textsuperscript{a}isolated yield

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Crystal structures of compounds 5b, 6b and 8a}
\end{figure}
In summary, we have developed an efficient methodology for the Michael addition of thiol compounds to tetrolic acid ester (or methyl propiolate) providing an easy synthesis of vinyl sulfides. Features of this strategy include catalyst-free, water as green solvent, short reaction time, simple operation, and good yields. The method is highly valuable in view of the synthetic and product importance of vinyl sulfides of this type.

**EXPERIMENTAL**

All reagents and solvents were acquired from commercially available suppliers and used without further purification, unless specified. $^1$H NMR spectra were recorded on a Bruker 400 MHz spectrometer in CDCl$_3$ using TMS as the internal standard. IR spectra were recorded on a Nicollet 740 FT-IR spectrometer. HRMS were measured on an Agilent Technologies 6510, Q-TOFLC/MS ESI Technique. Melting points were determined in capillaries and are uncorrected. All reactions were monitored using thin layer chromatography (TLC) on pre-coated silica gel 60 F$_{254}$ (mesh); spots were observed under UV light.

**General procedure for the synthesis of vinyl sulfides**

A solution of benzo[d]thiazole-2-thiol 1a (or the corresponding compounds 1c and 4) (5 mmol), dimethyl acetylenedicarboxylate 2a (or diethyl acetylenedicarboxylate 2b) (6 mmol) in water (10 mL) was completed by stirring at 80 °C for 2 h (TLC tracking). After the reaction was completed, the solid was filtered and recrystallized with 95% EtOH and dried. The pure products 3a and 5 were obtained (the oily substance was extracted with EtOAc, dried, and the solvent was evaporated to obtain other product 3b, 3c and 3d). The synthetic methods of compounds 6, 8 and 9 are similar to those of compounds 3 and 5, except that the corresponding starting materials are used.

**Dimethyl 2-(benzo[d]thiazol-2-ylthio)fumarate (3a):** Yellow powder, yield: 88%. mp 157-158 °C; IR (KBr) ν: 3060, 2950, 1732, 1600, 1427, 759 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, $J = 8.0$ Hz, 1H, ArH), 7.78 (d, $J = 7.5$ Hz, 1H, ArH), 7.46-7.39 (m, 1H, ArH), 7.34 (m, 1H, ArH), 6.92 (s, 1H, CH), 3.81 (s, 3H, OCH$_3$), 3.61 (s, 3H, OCH$_3$); HRMS (ESI) calcd for C$_{13}$H$_{11}$NO$_4$S$_2$ [M+H]$^+$ 310.0207, found 310.0208.

**Diethyl 2-(benzo[d]thiazol-2-ylthio)fumarate (3b):** Pale yellow oil, yield: 83%; IR (KBr) ν: 3061, 2981, 1732, 1598, 1463, 856, 759 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (d, $J = 8.1$ Hz, 1H, ArH), 7.77 (d, $J = 7.9$ Hz, 1H, ArH), 7.41 (t, $J = 9.0$ Hz, 1H, ArH), 7.33 (t, $J = 7.6$ Hz, 1H, ArH), 6.91 (s, 1H, CH), 4.25 (m, 2H, OCH$_2$), 4.04 (m, 2H, OCH$_2$), 1.30 (t, $J = 7.1$ Hz, 3H, CH$_3$), 0.96 (t, $J = 7.1$ Hz, 3H, CH$_3$); HRMS (ESI) calcd for C$_{15}$H$_{15}$NO$_4$S$_2$ [M+H]$^+$ 338.0534, found 338.0521.
Dimethyl 2-(benzo[d]oxazol-2-ylthio)fumarate (3c): Pale yellow oil, yield: 84%; IR (KBr) ν: 3064, 2952, 1751, 1603, 1501, 891, 773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.66-7.59 (m, 1H, ArH), 7.49-7.41 (m, 1H, ArH), 7.34-7.25 (m, 2H, ArH), 7.01 (s, 1H, CH), 3.82 (s, 3H, OCH₃), 3.64 (s, 3H, OCH₃); HRMS (ESI) calcd for C₁₃H₁₁NO₅S [M+H]⁺ 294.0437, found 294.0436.

Diethyl 2-(benzo[d]oxazol-2-ylthio)fumarate (3d): Orange oil, yield: 82%; IR (KBr) ν: 3064, 2983, 1732, 1600, 1473, 804, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.66-7.55 (m, 1H, ArH), 7.49-7.37 (m, 1H, ArH), 7.34 – 7.21 (m, 2H, ArH), 7.00 (s, 1H, CH), 4.26 (m, 2H, OCH₂), 4.07 (m, 2H, OCH₂), 1.30 (t, J = 7.1 Hz, 3H, CH₃), 0.96 (t, J = 7.1 Hz, 3H, CH₃); HRMS (ESI) calcd for C₁₅H₁₅NO₅S [M+H]⁺ 322.0749, found 322.0749.

Dimethyl 2-(5-amino-1,3,4-thiadiazol-2-ylthio)fumarate (5a): Yellow powder, yield: 87%. mp 154-156 ⁰C; IR (KBr) ν: 3429, 3110, 1730, 1698, 1505, 1255, 861, 770 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.75 (s, 1H, CH), 5.80 (s, 2H, NH₂), 3.85 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃); ¹³C NMR (400 MHz, d₆-DMSO) δ 172.2, 165.3, 163.7, 145.3, 144.9, 122.1, 53.7, 52.7; HRMS (ESI) calcd for C₈H₆N₃O₄S₂ [M+H]⁺ 276.0120, found 276.0113.

Diethyl 2-(5-amino-1,3,4-thiadiazol-2-ylthio)fumarate (5b): Yellow powder, yield: 86%. mp 110-112 ⁰C; IR (KBr) ν: 3287, 3103, 1735, 1500, 1247, 865, 766 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.73 (s, 1H, CH), 5.81 (s, 2H, NH₂), 4.32 (m, 2H, OCH₂), 4.19 (m, 2H, OCH₂), 1.37 (t, J = 8.0 Hz, 3H, CH₃), 1.24 (t, J = 8.0 Hz, 3H, CH₃); HRMS (ESI) calcd for C₁₀H₁₃N₃O₄S₂ [M+H]⁺ 304.0433, found 304.0426.

(Z)-Methyl 2-(3-oxobenzo[d]thiazolo[3,2-α]imidazol-2(3H)-ylidene)acetate (6a): Yellow powder, yield: 85%. mp 190-191 ⁰C; IR (KBr) ν: 3061, 1725, 1698, 1514, 1451, 762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 7.4 Hz, 1H, ArH), 7.67 (d, J = 8.3 Hz, 1H, ArH), 7.37 (m, 2H, ArH), 7.23 (s, 1H, CH), 3.92 (s, 3H, CH₃); HRMS (ESI) calcd for C₁₂H₁₂N₂O₃S [M+H]⁺ : 261.0335, found 261.0334.

(Z)-Ethyl 2-(3-oxobenzo[d]thiazolo[3,2-α]imidazol-2(3H)-ylidene)acetate (6b): Yellow powder, yield: 85%. mp 156-157 ⁰C; IR (KBr) ν: 3065, 1732, 1685, 1476, 932, 75 7cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 7.4 Hz, 1H, ArH), 7.67 (d, J = 8.3 Hz, 1H, ArH), 7.37 (m, 2H, ArH), 7.23 (s, 1H, CH), 3.92 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 165.3, 157.6, 155.2, 148.9, 144.8, 130.1, 126.5, 124.9, 122.0, 120.1, 112.9, 62.4, 14.2; HRMS (ESI) calcd for C₁₃H₁₀N₂O₃S [M+H]⁺ 275.0484, found 275.0490.

(Z)-Methyl 3-(benzo[d]thiazol-2-ylthio)acrylate (8a): Yellow powder, yield: 85%. mp 190-191 ⁰C; IR (KBr): 3061, 1725, 1698, 1514, 1451, 762cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 12.0 Hz, 1H, CH), 7.69 (d, J = 8.0 Hz, 1H, ArH), 7.54 (d, J = 8.0 Hz, 1H, ArH), 7.38 – 7.34 (m, 2H), 6.29 (d, J = 12.0 Hz, 1H, CH), 3.86 (s, 3H, CH₃); HRMS (ESI) calcd for C₁₁H₈NO₂S₂ [M+H]⁺ 252.0156, found 252.0153.

(Z)-Methyl 3-(benzo[d]oxazol-2-ylthio)acrylate (8b): Yellow powder, yield: 86%. mp 156-157 ⁰C; IR (KBr): 3065, 1732, 1685, 1476, 932, 757 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, J = 8.0 Hz, 1H, CH), 7.99 (d, J = 8.0 Hz, 1H, ArH), 7.85 (d, J = 8.0 Hz, 1H, ArH), 7.52 (t, J = 8.0 Hz, 1H, ArH), 7.41 (t,
$J = 7.6$ Hz, 1H, ArH), 6.22 (d, $J = 8.0$ Hz, 1H, CH), 3.84 (s, 3H, CH$_3$); HRMS (ESI) calcd for C$_{11}$H$_9$NO$_3$S [M+H]$^+$ 236.0385, found 236.0381.

(Z)-Methyl 3-(1H-benzo[d]imidazol-2-ylthio)acrylate (8c): White powder, yield: 85%. mp 143-146 °C; IR (KBr) v: 3265, 1780, 1569, 1437, 813, 735 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.44 (d, $J = 12.0$ Hz, 1H, CH), 7.63 (s, 2H, ArH), 7.33-7.32 (m, 3H, ArH), 6.28 (d, $J = 12.0$ Hz, 1H, CH), 3.90 (s, 3H, CH$_3$); HRMS (ESI) calcd for C$_{11}$H$_{10}$N$_2$O$_2$S [M+H]$^+$ 235.0497, found 235.0501.

(Z)-Methyl 3-(5-amino-1,3,4-thiadiazol-2-ylthio)acrylate (9): White powder, yield: 85%. mp 93-95 °C; IR (KBr) v: 3262, 3123, 1693, 1510, 1222, 1165, 932, 798 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 12.0$ Hz, 1H, CH), 6.14 (d, $J = 12.0$ Hz, 1H, CH), 5.13 (s, 2H, NH$_2$), 3.82 (s, 3H, CH$_3$); $^{13}$C NMR (400 MHz, $d_6$-DMSO) $\delta$ 171.3, 166.6, 148.7, 145.5, 115.0, 52.1; HRMS (ESI) calcd for C$_6$H$_7$N$_3$O$_2$S$_2$ [M+H]$^+$ 218.0061, found 218.0058.

ACKNOWLEDGEMENTS

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