A Clean, Facile, and Stereospecific Synthesis of α-Oxoketene O,S-Acetals in Water

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Abstract: A facile and practical method for the stereospecific synthesis of α-oxoketene O,S-acetals in water has been developed. Catalyzed by tetrabutylammonium bromide at room temperature, the one-pot reaction of various β-dicarbonyl compounds, 2-bromoethanol, and carbon disulfide, in the presence of potassium carbonate, leads to the corresponding α-oxoketene O,S-acetals stereospecifically in good to excellent yields. The catalyst in the aqueous phase can be recycled after the separation of the organic products.

Key words: α-oxoketene, O,S-acetals, one-pot synthesis, stereospecificity, tetrabutylammonium bromide, water

Over the past decades, the utility of α-oxoketene S,S-acetals as versatile intermediates and odorless thiol equivalents in organic synthesis has been recognized. In contrast, the chemistry of α-oxoketene O,S-acetals has remained largely unexplored. Generally, α-oxoketene O,S-acetals are prepared via alkylation of xanthates or displacement of the alkylsulfanyl group of an α-oxoketene dithioacetal by an alkoxy group. However, these methods require a two-step operation starting from an active methylene compound. Although it has been reported that α-oxoketene O,S-acetals can be prepared directly from β-dicarbonyl compounds, 2-bromoethanol, and carbon disulfide under basic conditions, the product yields were relatively low (24–58%) because the corresponding α-oxoketene S,S-acetals were formed as the byproducts (18–26%). In a recent report by Vila and co-workers, some α-EWG ketene O,S-acetals (EWG = electron-withdrawing group) and analogues were synthesized from the reaction of dithiocarbonates (xanthates) with base and an alkylating agent through extrusion of sulfur. However, inseparable mixtures of geometrical isomers were observed when two different EWGs were present in the starting xanthates. In this paper, we would like to report a facile and practical method for the synthesis of α-oxoketene O,S-acetals. As a result, α-oxoketene O,S-acetals were synthesized stereospecifically from the reaction of β-dicarbonyl compounds, carbon disulfide, and 2-bromoethanol under basic conditions in a one-pot procedure with water as the solvent (Scheme 1).

The use of water as a solvent in organic chemistry was rediscovered in the 1980s in Breslow’s work, which showed that a hydrophobic effect can strongly enhance the rates of some organic reactions. Organic reactions in water, without the use of an organic solvent, also benefit from the fact that water is an easily available, inexpensive, safe, and environmentally benign solvent. Later, extensive work revealed that a variety of organic reactions including the aldol, allylation, Diels–Alder, Michael, Mannich-type, and even dehydration reactions can be realized in the presence of various catalysts, such as inverse phase-transfer catalysts and surfactant-type Lewis or Brønsted acids, in water. As part of our research on the chemistry of α-EWG ketene S,S-acetals and encouraged by our recent report on their clean syntheses, herein, the successful synthesis of α-oxoketene O,S-acetals in water is realized.

In the initial experiment, we first tested the reaction by mixing N-(2-methoxyphenyl)-3-oxobutanamide (1a, 1.0 equiv) with carbon disulfide (1.1 equiv), 2-bromoethanol (1.2 equiv), potassium carbonate (4.0 equiv), and tetrabutylammonium bromide (0.1 equiv) in water (10 mL); after 12 hours at room temperature, the desired N-(2-methoxyphenyl)-2-(1,3-oxathiolan-2-ylidene)-3-oxobutanamide (2a) was obtained in 61% yield together with the corresponding dithioacetal 3a (Table 1, entry 1) as a byproduct in 11% yield. To optimize the reaction conditions, several reactions were carried out and the results are listed in Table 1. It was found that the feed order of the reagents had a substantial effect on the dispersion of product (Table 1, entries 1–3). For example, following the procedure described in our previous work, the reaction was performed with 1a (1.0 equiv) and carbon disulfide (1.1 equiv) in the presence of potassium carbonate (4.0 equiv) and tetrabutylammonium bromide (0.1 equiv) in water (10 mL) at room temperature for one hour and subsequent alkylation with 2-bromoethanol (1.2 equiv) for another 12 hours to afford the desired 2a in 35% yield and the corresponding dithioacetal 3a in 60% yield (Table 1, entry 2). When the mixture of 1a (1.0 equiv), potassium carbonate (4.0 equiv), tetrabutylammonium bromide (0.1 equiv), and water (10 mL) was stirred at room temperature for one day...
hour and subsequent co-addition of carbon disulfide (1.1 equiv) and 2-bromoethanol (1.2 equiv) in one portion and then stirred for 13 hours, product 2a was obtained in 81% yield with a trace amount of 3a (entry 3). It was also found that 4.0 equiv of potassium carbonate and 10 mol% of tetra-butylammonium bromide was enough to provide 2a efficiently (entries 4–8). In addition, the catalyst (TBAB) can be recycled, at least several times, by reuse of the aqueous phase after the separation of organic products (entries 9–11). Surprisingly, 2a was found to be the only regioisomer (Z-configuration) with OCH2 cis to the acetyl group as observed in its X-ray diffraction analysis (Figure 1).14

To test the general applicability of this protocol, a series of active methylene compounds 1b–p were selected for investigation. Subjected to the optimized reaction conditions as described in Table 1, entry 3, acetylacetamide compounds 1a–j (Table 2, entries 1–10) were converted into the corresponding O,S-acetals 2a–j in high yields. In addition, the O,S-acetals 2k–p (Table 2, entries 11–16) were obtained in moderate to good yields starting from active methylene compounds 1k–p. It is worth noting that products 2k–m were also formed stereospecifically (Z or E configuration).

Based on the experimental results mentioned above, a possible mechanism for the reaction of 1 with carbon disulfide and 2-bromoethanol is proposed as shown in Scheme 2. The intermediate 1,3-oxathiolane-2-thione A is initially generated in the presence of potassium carbonate. Next nucleophilic attack of the deprotonated active methylene compounds 4 on A occurs to form intermediate 6, which could be stabilized by the intramolecular

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**Table 1** Reaction of 1a with Carbon Disulfide and 2-Bromoethanol in Water under Different Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>TBAB (mmol)</th>
<th>K2CO3 (mmol)</th>
<th>H2O (mL)</th>
<th>Time (h)</th>
<th>Yield (%) 2a</th>
<th>3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>20</td>
<td>10</td>
<td>12</td>
<td>61</td>
<td>11</td>
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<td>2</td>
<td>0.5</td>
<td>20</td>
<td>10</td>
<td>13</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>20</td>
<td>10</td>
<td>14</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>15</td>
<td>10</td>
<td>18</td>
<td>61</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>25</td>
<td>10</td>
<td>14</td>
<td>82</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>1.25</td>
<td>20</td>
<td>10</td>
<td>12</td>
<td>80</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>0.25</td>
<td>20</td>
<td>10</td>
<td>16</td>
<td>54</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>0.0</td>
<td>20</td>
<td>10</td>
<td>24</td>
<td>0</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>2nd use</td>
<td>20</td>
<td>0</td>
<td>14</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>3nd use</td>
<td>20</td>
<td>0</td>
<td>14</td>
<td>77</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>4nd use</td>
<td>20</td>
<td>0</td>
<td>15</td>
<td>70</td>
<td>trace</td>
</tr>
</tbody>
</table>

*a 1a (5 mmol), CS2 (6 mmol), 2-bromoethanol (5.5 mmol) were added in all the reactions.

*b Isolated yields.

*c The substrate was recovered in 36% yield.

*d The substrate was recovered in 29% yield.

*e Aqueous filtrate from entry 3.

*f Aqueous filtrate from entry 9.

*g Aqueous filtrate from entry 10.

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**Figure 1** The ORTEP drawing of 2a
In summary, a clean, facile, practical and stereospecific synthesis of α-oxoketene O,S-acetals has been developed based on the reaction of active methylene compounds with carbon disulfide and 2-bromoethanol catalyzed by tetrabutylammonium bromide in the presence of potassium carbonate in water. The simple procedure, mild conditions, good yields, and, especially, the relation to the current environmental concerns, make this protocol most attractive for academic research and practical applications.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel; PE = petroleum ether. 1H NMR and 13C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400–4000 cm–1. Compounds 2k,1n,o are known compounds. 3

(Z)-N-(2-Methoxyphenyl)-2-(1,3-oxathiolan-2-ylidene)-3-oxobutanamide (2a); Typical Procedure

3-Oxo-N-phenylbutanamide 1a (0.885 g, 5 mmol), K$_2$CO$_3$ (2.758 g, 20 mmol), and TBAB (0.161 g, 0.5 mmol) were dissolved in H$_2$O (10 mL) at r.t. and stirred for 1.0 h. Then the mixture of CS$_2$ (0.456 g, 6 mmol) and 2-bromoethanol (0.682 g, 5.5 mmol) was added dropwise. The resulting mixture was stirred for another 13.0 h at r.t. The precipitated solid was collected by filtration, washed with H$_2$O (3 × 10 mL). The crude product was purified by flash column chromatography (PE–Et$_2$O, 1:2) to afford 2a (1.186 g, 81%) as a white solid; mp 124–126 °C.

IR (KBr): 2360, 1646, 1362, 1119, 746 cm–1.

$^*$ Isolated yields.

$^\text{a}$ A trace amount of 3 was detected.

Table 2: Preparation of α-Oxoketene O,S-Acetals 2 from Active Methylene Compounds 1 in Water

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Time (h)</th>
<th>Yield (% of 2/5$^a$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Me</td>
<td>2-MeOC$_2$H$_5$NH</td>
<td>14</td>
<td>81/–$^b$</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Me</td>
<td>2-CIC$_2$H$_5$NH</td>
<td>12</td>
<td>82/–$^b$</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>Me</td>
<td>2-MeC$_6$H$_4$NH</td>
<td>12</td>
<td>86/–$^b$</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>Me</td>
<td>NHPh</td>
<td>13</td>
<td>80/–$^b$</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>Me</td>
<td>4-ClC$_6$H$_4$NH</td>
<td>15</td>
<td>82/–$^b$</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>Me</td>
<td>4-MeC$_6$H$_4$NH</td>
<td>13</td>
<td>76/–$^b$</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>Me</td>
<td>4-MeOC$_6$H$_4$NH</td>
<td>16</td>
<td>81/–$^b$</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>Me</td>
<td>2,4-Me$_2$C$_6$H$_4$NH</td>
<td>14</td>
<td>80/–$^b$</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>Me</td>
<td>NHMe</td>
<td>12</td>
<td>67/10</td>
</tr>
<tr>
<td>10</td>
<td>2j</td>
<td>Me</td>
<td>NH$_2$</td>
<td>13</td>
<td>70/8</td>
</tr>
<tr>
<td>11</td>
<td>2k</td>
<td>Me</td>
<td>OEt</td>
<td>22</td>
<td>65/12</td>
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<tr>
<td>12</td>
<td>2l</td>
<td>Me</td>
<td>Ph</td>
<td>20</td>
<td>70/10</td>
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<tr>
<td>13</td>
<td>2m</td>
<td>Ph</td>
<td>OEt</td>
<td>14</td>
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<tr>
<td>14</td>
<td>2n</td>
<td>Me</td>
<td>Me</td>
<td>20</td>
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<tr>
<td>15</td>
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<tr>
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<td>2p</td>
<td>Ph</td>
<td>Ph</td>
<td>19</td>
<td>54/16</td>
</tr>
</tbody>
</table>

Scheme 2 A proposed mechanism for the reaction of 1 with carbon disulfide and 2-bromoethanol in the presence of tetrabutylammonium bromide and potassium carbonate in water.

Synthesis 2009, No. 5, 824–828 © Thieme Stuttgart · New York
13C NMR (125 MHz, CDCl3): δ = 28.9, 33.0, 55.8, 74.3, 107.9, 122.2 (2 C), 133.2, 135.9, 164.0, 168.3, 197.4.

MS (EI): m/z = 298.2 [M + 1]⁻.

Anal. Calcd for C12H12ClNO3S: C, 52.44; H, 4.06; N, 4.70. Found: C, 52.09; H, 4.27; N, 4.95.

13C NMR (125 MHz, CDCl3): δ = 29.9, 33.1, 74.6, 107.4, 122.2, 123.7, 123.9, 127.1, 129.1, 135.8, 164.5, 187.0, 197.2.

MS (EI): m/z = 298.1 [M + 1]⁻.

Anal. Calcd for C12H10ClNO3S: C, 59.30; H, 4.98; N, 5.32. Found: C, 58.70; H, 4.79; N, 5.21.

13C NMR (125 MHz, CDCl3): δ = 29.9, 33.1, 55.4, 74.4, 107.4, 113.9 (2 C), 122.2 (2 C), 131.7, 155.9, 164.0, 186.3, 197.4.

MS (EI): m/z = 294.3 [M + 1]⁻.

Anal. Calcd for C11H12ClNO3S: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.16; H, 4.88; N, 4.81.

13C NMR (125 MHz, CDCl3): δ = 18.3, 29.9, 33.19, 74.5, 107.5, 121.9, 123.8, 126.3, 128.3, 130.1, 136.8, 164.2, 186.8, 197.5.

MS (EI): m/z = 278.1 [M + 1]⁻.

Anal. Calcd for C11H10NO3S: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.35; H, 5.28; N, 5.21.

13C NMR (125 MHz, CDCl3): δ = 30.1, 33.4, 74.7, 107.6, 120.7 (2 C), 123.9, 129.0 (2 C), 138.7, 164.5, 186.9, 197.7.

MS (EI): m/z = 264.0 [M + 1]⁻.


13C NMR (125 MHz, CDCl3): δ = 30.2, 33.4, 74.8, 107.5, 121.9 (2 C), 128.7, 128.9 (2 C), 137.4, 164.6, 187.1, 197.7.

MS (EI): m/z = 235.9 [M + 1]⁻.

Anal. Calcd for C9H17ClNO3S: C, 52.44; H, 4.06; N, 4.70. Found: C, 52.06; H, 4.24; N, 4.98.

13C NMR (125 MHz, CDCl3): δ = 18.1, 20.8, 29.9, 33.1, 74.4, 107.6, 122.2, 126.8, 128.5, 130.8, 133.5, 134.3, 154.9, 164.2, 197.5.

MS (EI): m/z = 292.1 [M + 1]⁻.


13C NMR (125 MHz, CDCl3): δ = 18.1, 20.8, 29.9, 33.1, 74.4, 107.6, 122.2, 126.8, 128.5, 130.8, 133.5, 134.3, 154.9, 164.2, 197.5.

MS (EI): m/z = 292.1 [M + 1]⁻.


13C NMR (125 MHz, CDCl3): δ = 25.9, 29.8, 33.0, 73.1, 107.2, 166.7, 185.3, 197.1.


Anal. Calcd for C9H16NOS: C, 47.75; H, 5.51; N, 6.96. Found: C, 47.42; H, 5.63; N, 7.09.

13C NMR (125 MHz, CDCl3): δ = 29.9, 33.0, 74.4, 107.0, 168.1, 186.0, 196.5.

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**Ethyl 2-(1,3-Oxathiolan-2-ylidene)-3-oxo-3-phenylpropanoate (2m)**

White solid; mp 60–62 °C.

IR (KBr): 1647, 1616, 1595, 1256, 1004, 536 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.03 (t, J = 7.5 Hz, 3 H), 2.36 (t, J = 7.0 Hz, 2 H), 4.11 (q, J = 7.0 Hz, 2 H), 4.48 (t, J = 7.0 Hz, 2 H), 7.44 (t, J = 7.5 Hz, 2 H), 7.43 (d, J = 7.5 Hz, 1 H), 7.85 (d, J = 7.0 Hz, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 7.44, 17.44, 31.4, 39.7, 117.0, 123.8, 128.3, 131.4, 132.8, 140.3, 166.8, 191.5.

**MS (EI):** m/z = 279.0 [M + 1].


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**References**


(14) Crystal data for 3d: C₁₅H₁₉NO₅S, white needle crystals, M = 293.33, monoclinic, C2/c; a = 15.640(5) Å, b = 8.249(5) Å, c = 23.035(5) Å, α = 90.00(5)°, β = 106.460(5)°, γ = 90.00(5)°, V = 2850(2) Å³, Z = 8, T = 293 (K), F_max = 1232, R = 0.0490, oR² = 0.1237. The CCDC deposition number 661621.