THE REACTION OF ENAMINOKETONES WITH BENZOYL ISOThIOCYANATE

Otoshiko Tsuge* and Akitaka Inaba

Research Institute of Industrial Science, Kyushu University,
Hakozaki, Higashi-ku, Fukuoka 812, Japan

The reaction of enaminoketone (1) with benzoyl isothiocyanate (I) in benzene afforded 2-thiopyridone derivatives, (2) [1:1 adduct - H₂O] and (3) [1:2 adduct - H₂S], and 3-benzamido-thiocarbamoyl compound (4) [1:1 adduct]: the relative yields depended upon the reaction conditions. On the other hand, enaminoketone (5) reacted with (1) in benzene to yield the 1-benzoyl-2-thiopyridone (6) [1:2 adduct - (HNCS + H₂O)], while the same reaction in dichloroethane gave the 2-thiopyridone (7) [1:2 adduct - H₂S].

We earlier reported that an enaminoketone, 4-(1-pyrrolidinyl)-3-penten-2-one (1), reacted with aryl isothiocyanates to yield 3-arylthiocarbamoyl derivatives (2) and/or 2-thiopyridones (3), depending upon the nature of aryl isothiocyanates and the reaction conditions. On the other hand, the reactions of enaminoketones of type (4) with acyl isothiocyanates afford 1:1 adducts (5), which are readily converted into thiopyrimidines (6) by dehydration. However, little attention has been paid to the reaction of enaminoketone of type (1) with acyl
isoithiocyanate.

For comparison with the reaction of enaminoketone \(1a\) with aryl isothiocyanates, and that of enaminoketones \(4\) with acyl isothiocyanates, it seemed of interest to investigate the reaction of enaminoketone of type \(1a\) with acyl isothiocyanate. This paper deals with the reaction of enaminoketones, \(1a\) and 1-phenyl-3-(1-pyrrolidinyl)-2-buten-1-one (1b), with benzoyl isothiocyanate (\(I\)).

When enaminoketone \(1a\) was allowed to react with 1 equiv of isothiocyanate \(I\) in benzene at room temperature, two products, \(2\) [colorless prisms, mp 243-245\(^\circ\) dec] and \(3a\) [yellow needles, mp 225-226\(^\circ\) dec], were formed, together with tarry material. The molecular formula of \(2\) \([C_{17}H_{18}N_{2}O_{2}S, m/e 298 (M^{+})]\) agreed with that of the compound derived from an 1:1 adduct with dehydration, and \(2\) was deduced to be 3-acetyl-6-phenyl-4-(1-pyrrolidinyl)-2-thiopyridone on the basis of its spectral data [ir \(\nu_{\text{max}}\) cm\(^{-1}\) 3160 (NH), 1700 (CO); nmr \(\delta\) (CDCl\(_3\)) 1.99, 3.36 (each 4H, m, pyrrolidinyl protons), 2.88 (3H, s, COCH\(_3\)), 6.28 (1H, s, =CH), 7.53 (5H, m, aromatic protons), 9.65 (1H, br, NH)].

The elemental analysis and molecular ion peak of \(3a\) indicated that 2 equiv
of J and 1 equiv of 1a had combined with the loss of hydrogen sulfide. On the basis of the spectral data and chemical conversion, 9a was assigned as 5-acetyl-3-benzoyl-6-benzamido-4-(1-pyrrolidinyl)-2-thiopyridone [ir νmax cm⁻¹ 3200 (NH), 1670, 1640 (CO); nmr δ (CDCl₃) 1.81, 3.31 (each 4H, m, pyrrolidinyl protons), 2.46 (3H, s, COCH₃), 7.4-8.2 (10H, m, aromatic protons), 12.3, 13.1 (each 1H, br, NH); mass m/e 445 (M⁺)].

Hydrolysis of 9a with 1N potassium hydroxide aqueous solution under reflux for 1 hr afforded 6-amino-5-acetyl-3-benzoyl-4-(1-pyrrolidinyl)-2-thiopyridone (10) quantitatively. 10: mp 198-200° dec; ir νmax cm⁻¹ 3360, 3260, 3160 (NH), 1640 (CO); nmr δ (CDCl₃) 1.76, 3.30 (each 4H, m, pyrrolidinyl protons), 2.31 (3H, s, COCH₃), 6.90 (2H, br, NH₂), 7.3-8.1 (5H, m, aromatic protons), 12.2 (1H, br, NH), mass m/e 341 (M⁺)].

Scheme 1
On the other hand, the reaction of \( \text{Ja} \) with 0.5 equiv of \( \mathcal{Z} \) at room temperature afforded 3-benzoylthiocarbamoyl-4-(1-pyrrolidinyl)-3-penten-2-one (11), mp 128-129° dec, as orange prisms. The ir spectrum of 11 exhibited no well-defined bands ascribable to \( \nu_{\text{NH}} \) absorptions, but the following spectral data supported the assigned structure [ir \( \nu_{\text{max}}^{\text{KBr}} \) 1700 cm\(^{-1}\) (CO); nmr 6 (CDCl\(_3\)) 1.83 (3H, s, CH\(_3\)), 2.17, 3.92 (each 4H, m, pyrrolidinyl protons), 2.75 (3H, s, CO-CH\(_3\)), 7.8-8.3 (5H, m, aromatic protons), 14.82 (1H, br, NH); mass m/e 298 (M\(^+\)-H\(_2\)O)]. The spectral data also indicate that 11 exists as the chelating form\(^6\) as shown in Scheme 1. The results under various reaction conditions are given in Table 1.

Table 1 Reaction of \( \text{Ja} \) with \( \mathcal{Z} \) in benzene

<table>
<thead>
<tr>
<th>( \frac{\text{Ja}/\mathcal{Z}}{\text{mol/mol}} )</th>
<th>Temp. °C</th>
<th>Time hr</th>
<th>( \mathcal{Z} )</th>
<th>( \text{9a} )</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>room temp.</td>
<td>10</td>
<td>13.2</td>
<td>4.7</td>
<td>--</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>3 days</td>
<td>1.0</td>
<td>12.4</td>
<td>--</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td>20</td>
<td>--</td>
<td>25.8</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>69.6</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>2</td>
<td>--</td>
<td>27.0</td>
<td>--</td>
</tr>
</tbody>
</table>

Upon heating at 150° for 30 min or treatment with 6.5N potassium hydroxide aqueous solution at room temperature for 5 hr, 11 was transformed into \( \mathcal{Z} \) in 38 or 42% yield respectively. In addition, 11 reacted with 1 equiv of \( \mathcal{Z} \) in boiling 1,2-dichloroethane to form 9a in 39% yield. Thus, the formation of \( \mathcal{Z} \) and 9a can be interpreted as arising from 11.

The reaction of enaminoketone \( \text{Jb} \) with 1 equiv of \( \mathcal{Z} \) in benzene at room
temperature for 5 hr did not form the expected products of types 8 and 9a, but 1,3-dibenzoyl-6-phenyl-4-(1-pyrrolidinyl)-2-thiopyridone (12) whose structure corresponded to the compound derived from an 1:2 adduct of 1b and 2 with the loss of water and of hydrogen isothiocyanate, was obtained in 42.2% yield. However, the same reaction in 1,2-dichloroethane at room temperature gave 3,5-dibenzoyl-6-benzamido-4-(1-pyrrolidinyl)-2-thiopyridone (9b) in 15.4% yield. The structures of 12 and 9b were deduced on the basis of their spectral data.  

12: yellow prisms; mp 254-255° dec; ir νKBr max 1685 cm⁻¹ (CO); nmr δ (CDCl₃) 1.89, 3.45 (each 4H, m, pyrrolidinyl protons), 7.2 (1H, s, =CH), 7.1-8.3 (15H, m, aromatic protons); mass m/e 464 (M⁺), 359 (M⁺ - PhCO, base peak).

9b: yellow needles; mp 242° dec; ir νmax 3180 (NH), 1652 (CO); nmr δ (DMSO-d₆) 1.40, 3.0 (each 4H, m, pyrrolidinyl protons), 7.3-8.2 (15H, m, aromatic protons), 11.0, 13.0 (each 1H, br, NH); mass m/e 507 (M⁺), 402 (M⁺ - PhCO, base peak).

Recently, Carney, et al.⁷ found that ethyl 2-benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate (14), whose structure is the same as that of 2, was formed in the reaction of ethyl β-dimethylaminocrotonate with 2 in chloroform. They also proposed a complicated reaction pathway via the pyrylium intermediate 13.

The pathway of formation of 9 from 1 and 2 may be similar to that proposed.
by Carney et al.; this is now under investigation.

REFERENCES


2 O. Tsuge and A. Inaba, ibid., 1973, 46, 2221.


5 J. Goerdeler and D. Wieland, ibid., 1967, 100, 47.

6 3-Arylthiocarbamoyl-4-(1-pyrrolidinyl)-3-penten-2-ones exist as the same chelating forms that 11 does.2


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