Short Note

(1R,5S)-6-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one

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Abstract: Efficient large-scale and feasible industrial synthesis of the 1-oxacephem core structure from 6-aminopenicillanic acid (6-APA) has been reported for several decades. Via the industrial synthesis route, a byproduct (compound 9) containing a butenolide unit was purified and characterized by NMR and HRMS in this work. It is worth noting that compound 9 is an entirely new compound. Additionally, a plausible mechanism and effects on the formation of 9 by different Lewis acids were proposed. The discovery of compound 9 could improve the purity of this feasible industrial synthesis and provide considerable cost savings.

Keywords: industrial feasible synthesis; 6-APA; butenolide; 1-oxacephem

1. Introduction

Antibacterial substances are of great importance and necessity in treating infectious diseases caused by pathogenic bacteria [1–3]. Due to its unique antimicrobial activity and novel structure among the synthetic antibiotics, the 1-oxacephem core structure as an important pharmaceutical scaffold has attracted immense interest from medicinal chemists [4–6]. A variety of synthetic compounds prepared from the 1-oxacephem intermediate, including prominent antibiotics such as Flomoxef, Moxalactam, and OCP-9-176 (Figure 1), have a broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria [7–9].

A feasible industrial route by which to synthesize 1-oxacephem 8 in good yield starting from commercially available 6-aminopenicillanic acid (6-APA) (Figure 2) was reported by Nagata of the Shionogi company [10,11]. In this sophisticated method designed to retain all the carbon atoms, preparing epoxazolinoazetidinones having an unconjugated ester moiety at the β-lactam nitrogen was a breakthrough. However, byproducts of and probable mechanisms in this industrial synthesis of 1-oxacephem 8 have not been systematically explored. In this work, we focused on the byproduct 9 ((1R,5S)-6-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one).
2. Results and Discussion

Intramolecular etherification proceeded from the less-hindered β side with stereoselectivity to furnish a versatile exomethylene intermediate 7 in 79% yield and accompanied by a byproduct 9 in 15% yield. The probable mechanism which afforded the butenolide 9 catalyzed by boron fluoride ethyl ether involved two reactions: (a) an intramolecular transesterification and (b) isomerization of the double bond promoted by a Lewis acid (Scheme 1).

Systematic studies of the reaction conditions to obtain byproduct 9 in highest yield revealed that Lewis acids played key roles (Table 1). When the reaction was catalyzed by BF$_3$·Et$_2$O and Yb(OTf)$_3$, the major product was compound 7 (Table 1, entries 1 and 6) with yields of 90% and 56%, respectively. Our best result was achieved with BF$_3$·Et$_2$O at 25 °C, conditions in which 7 was formed in 90% yield, along with only a small amount of readily separable 9 (Table 1, entry 1). When the Lewis acid was changed to LiCl or ZnCl$_2$, byproduct 9 was obtained as a dominant product (Table 1, entries 2, 3, 4).

To our surprise, when EtOH was used as the solvent instead of EtOAc (Table 1, entry 3), the yield of byproduct 9 increased to 92%. These results suggested that ethyl alcohol and Lewis acid LiCl were suitable for this transformation to generate the byproduct 9 in an excellent yield.
Scheme 1. The probable mechanism of formation of 9 catalyzed by a Lewis acid (BF$_3$·Et$_2$O).

Table 1. Screening of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid $^a$</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Yields of 7 $^b$</th>
<th>Yields of 9 $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$·Et$_2$O</td>
<td>25 °C</td>
<td>EtOAc</td>
<td>90%</td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>LiCl</td>
<td>25 °C</td>
<td>EtOAc</td>
<td>33%</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>LiCl</td>
<td>25 °C</td>
<td>EtOH</td>
<td>1%</td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl$_2$</td>
<td>25 °C</td>
<td>EtOAc</td>
<td>29%</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>FeCl$_3$</td>
<td>25 °C</td>
<td>EtOAc</td>
<td>46%</td>
<td>42%</td>
</tr>
<tr>
<td>6</td>
<td>Yb(OTf)$_3$</td>
<td>25 °C</td>
<td>EtOAc</td>
<td>56%</td>
<td>36%</td>
</tr>
</tbody>
</table>

$^a$ 1 mol % Lewis acid was used. $^b$ Isolated yields.

3. Materials and Methods

3.1. General Information

All the reactions were monitored by thin-layer chromatography. The byproducts were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200–300 mesh, Qingdao, China). Melting points were determined on a Beijing Keyi XT4A apparatus (Beijing synthware glass, Beijing, China). All NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer (Agilent, Santa Clara, CA, USA) with TMS as the internal standard. Chemical shifts are given as δ ppm values relative to TMS. Mass spectra (MS) were recorded on an Esquire 3000 mass spectrometer (Varian, Palo Alto, CA, USA) by electrospray ionization (ESI).

3.2. Synthesis of (1R,5S)-6-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (9)

A solution of LiCl (1 mol %) was added to intermediate 6 (1 eq, 1 g) in EtOH (10 mL) in a round-bottom flask and reacted at room temperature for 7 h. The reaction system was evaporated to give a residue, which was purified by silica gel flash column chromatography (EtOAc/n-hexane = 1:7) to afford the product 9, yield 92%. White solid; m. p. 199.2–200.3 °C; [α]$^D_{25}$ + 18.9° (C 1.05, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J$ = 7.4 Hz, 2H), 7.54 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 6.81 (d, $J$ = 3.3 Hz, 1H), 5.45 (d, $J$ = 3.3 Hz, 1H), 4.73 (s, 2H), 2.18 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ
168.64, 167.16, 163.73, 148.48, 132.40, 128.59, 128.50, 126.73, 119.77, 84.70, 82.26, 71.77, 13.17; HRMS (ESI): m/z calcd for C_{15}H_{12}N_{2}O_{4} (M + H)^{+}, 285.0875; found, 285.0880.

4. Conclusions

In summary, byproduct 9 was obtained in the industrial synthesis of the 1-oxacephem core structure from 6-aminopenicillanic acid. To the best of our knowledge, this is the first report about the byproduct 9. We explored the effects on the formation of azetidinone-fused butenolide 9 caused by different Lewis acids and explored its probable mechanism of formation. The study of byproduct 9 is valuable for efficient large-scale and feasible industrial synthesis of the 1-oxacephem core structure.

Supplementary Materials: Supplementary materials are available online.

Author Contributions: D.-J.F. and E.Z. designed and synthesized the compounds. V.P., M.-A.T., L.S. and X.Z. revised the manuscript. D.-J.F. wrote the manuscript and H.-M.L. was responsible for the correspondence of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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