SYNTHESIS OF C(3)-ALKYL CEPHEMS

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Abstract - C(3)-n-Butyl and n-hexyl cephems have been prepared by the conjugate addition of the appropriate organocuprate to the C(3)-chloro and C(3)-vinyl cephem.

We recently attempted to synthesize C(3)-alkyl cephem derivatives via the reaction of Grignard reagents on C(3)-halo and other C(3)-electron rich cephems. This reaction resulted in S(1)-C(2)-secocephems via a SET (single electron transfer) mechanism. We now report the use of organocuprate reagents to prepare various C(3)-alkyl cephem derivatives. Lithium organocuprates are known to undergo conjugate addition via a SET mechanism to give copper complexes which then undergo an intramolecular rearrangement to give the product. It was anticipated that the difference in the mode of transfer for the R group would result in the desired C(3)-alkyl cephem products. Indeed, the C(3)-chloro cephem A reacted with lithium dimethylcuprate to give a 50% yield of the C(3)-methyl compound 2. C(3)-S-Phenyl B also reacted with lithium dimethylcuprate to give 28% 2 plus 24% starting material, however, C(3)-OMe gave 39% Δ2 (isomerization of the double bond) plus 38% starting material, while the C(3)-morpholine-enamine gave 97% starting material. Under these conditions the C(3)-mesylate gave 58% enol, while the C(3)-diethylphosphonate3 gave 34% starting material.

\[
\begin{align*}
V \quad + & \quad \text{Me}_2\text{CuLi/THF} \quad - \quad 30^\circ\text{C} / 30 \text{ min} \quad \rightarrow \quad V \quad + \quad \text{OFCH}_2\text{CONH} \\
\text{A} \quad \text{Y} & \quad 50\% \\
\text{A} \quad \text{Cl} & \quad 28\% \\
\text{B} \quad \text{SPh} & \quad 28\%
\end{align*}
\]

Other esters of V-C(3)-chloro cephem, i.e. benzhydryl and trichloroethyl, work equally as well (39%, 37%), however, p-nitrobenzyl was unacceptable, resulting in decomposition.
Under the conditions described for the conversion of 1 to 2, lithium diphenylcuprate failed to react with 1A, while lithium diallylcuprate gave 37% of the C(3)-hydro derivative, that is the reduced product plus 43% starting material. Lithium di-n-butylcuprate reacted with 3 to give a 47-57% mixture of A2-C(3)-Cl 4 and A2-C(3)-n-butyl 5 (ca. 1:1). This mixture proved very difficult to separate by any means, as were the sulfoxides of 4 and 5. However, the chloro derivative 4 can be converted to the enol 6 via the enamine, thus drastically changing its Rf and allowing easy separation of 5 by silica chromatography.

\[
\begin{align*}
\text{2} & \quad 3 (\text{n-Bu})_2\text{CuLi/THF} \quad -78^\circ C/4 \text{ min} \\
& \quad \to \text{4} \quad \text{1:1} \quad 45-57\%
\end{align*}
\]

\[\text{BH} = \text{C} \text{HPH}_2\]

Compound 5 was then converted to the A3-derivative by sulfur oxidation and reduction.\(^4\)\(^5\)\(^6\)\(^7\) The side chain was then cleaved\(^6\)\(^7\) and the B-\(\alpha\)-phenylglycine derivative 7 was prepared.

The Corey-Posner reaction\(^8\) on the \(\Delta^2\)-iodomethyl derivative 8 with lithium di-n-butylcuprate gave 17% C(3)-amyl 9 plus 30% C(3)-methyl 10, i.e. the reduced product. This sequence has been studied by workers at Glaxo.\(^9\)

\[
\begin{align*}
\text{8} & \quad 3 (\text{n-Bu})_2\text{CuLi/THF} \quad -50^\circ C/15 \text{ min} \\
& \quad \to \text{2} \quad 17\% \\
& \quad \text{10} \quad 30\%
\end{align*}
\]
Another route to C(3)-lipophilic cepham, however, is via 1,6-conjugate addition of lithium di-n-butylcuprate with the C(3)-vinyl cepham\textsuperscript{10} \textsuperscript{11} which occurred in 82\% yield to give the exocyclic olefin 12\textsuperscript{11}. Proof of structure was by physical data (nmr, ir, mass spec.) and by the conversion to the C(3)-methoxy derivative 13.

Use of less reactive organocuprates, for example lithium dimethylcuprate, resulted in lower yields (29\%) of the exomethylene derivative 16\textsuperscript{12}. The major product was 17 (57\%), presumably resulting from the Michael addition of the intermediate cuprate onto the starting material. The reaction of cuprate intermediates with electrophiles is well known.\textsuperscript{13}
The exocyclic double bond in 12 proved somewhat resistant to isomerization, requiring 5 equivalents of triethylamine in N,N-dimethylformamide at room temperature for 19 h. to give a 96% yield of a mixture of the olefins 14 after chromatography. Sulfur oxidation (162-163°C), reduction14 and side chain cleavage followed by acylation and deblocking gave the D-α-phenylglycine derivative 1815.

Table I shows the in-vitro microbiological activity of the various C(3)-alkyl-substituted cephems with the D-α-phenylglycine side chain. Increasing the lipophilic character at C(3) appears to enhance the gram positive activity with concomitant loss in the gram negative antibacterial activity.

**TABLE I**

<table>
<thead>
<tr>
<th>R</th>
<th>MIC (µg/ml)</th>
<th>E. coli</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Staph. aureus</td>
<td>Staph. epidermidis</td>
</tr>
<tr>
<td>CH₃</td>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>Et</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>n-C₄H₉</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>n-C₆H₁₃</td>
<td>0.5</td>
<td>2</td>
</tr>
</tbody>
</table>

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

5. A3-isomer of 5: m/e 556; ir (CHCl₃) 1775 cm⁻¹; nmr (CDCl₃) δ 0.80 (m, 3, Me), 1.24 (m, 4, CH₂), 2.32 (m, 2, 3'-CH₂), 3.20, 3.40 (AB, J=16 Hz, 2, C(2) protons), 4.52 (s, 2, PhOCH₂), 4.96 (d, J=4 Hz, 1, H₆), 5.76 (d, d, J=4 Hz, 1, H₇).
7. m/e 556; ir (CHCl₃) 1775 cm⁻¹; nmr (CDCl₃) δ 0.80 (m, 3, Me), 1.24 (m, 4, CH₂), 1.72 (s, 2, NH₂), 2.32 (m, 2, 3'-CH₂), 3.20, 3.40 (AB, J=16 Hz, 2, C(2) protons), 4.60 (d, J=5 Hz, 1, H₆), 4.85 (d, J=5 Hz, 1, H₇).
11. m/e 542; ir (CHCl₃) 1768 cm⁻¹; nmr (CDCl₃) δ 1.00 (t, J=7.8 Hz, 3, Me), 2.08 (m, 2, CH₂), 3.24, 3.36 (AB, J=12 Hz, 2, C(2) protons), 4.48 (s, 1, PhOCH₂), 5.54 (d, J=4 Hz, 1, H₆), 5.68 (d, d, J=4, 10 Hz, 1, H₇), 5.72 (m, 1, olefinic H).
12. m/e 560; ir (CHCl₃) 1768 cm⁻¹; nmr (CDCl₃) δ 0.90 (m, 3, CH₃), 1.33 (bs, 8, CH₂₈), 2.53 (bs, 2, C(3)-CH₂), 3.26 (s, 2, C(2) protons), 5.02-5.12 (DOH), 5.40 (s, 1, C(7) side chain methine), 5.72 d, J=4 Hz, 1, H₇, 7.52 (m, 5, Ph).

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