REATIONS OF 3-(1-HYDROXYETHYL)-AZETIDINONES
WITH DIALKYLAMINOSULFUR TRIFLUORIDES

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Abstract: Reactions of benzy1 3-(1-hydroxyethyl)-2-oxoazetidine-4-acetate with
dialkylaminosulfur trifluorides under various conditions have been investigated.
Formation of products was found to be highly dependent on temperature,
presence or absence of base, and stereochemistry of the hydroxyethyl group.

In connection with the total synthesis of carbapenem antibiotics related to thienamycin (1), PS-5 (2),
carpetimycin (3), and olivamic acids (4) we were interested in the effect of a fluorine atom on the C-6
substituent (e.g. 1, R=F) and in the biological properties of this class of compounds.

Many methods are available for the introduction of fluorine5, mostly via the hydroxyl group. Fluorinating
agents such as diethylaminofluorochloroethane6, metal fluorides/tetrabutylammonium fluoride7,
phenyltetrafluorophosphorane8 and dialkylaminosulfur trifluorides9 (DAST) have been developed, mainly for
their uses in preparing fluorosteroids. Only a few applications have been reported in the β-lactam
literature10.

\[
\begin{align*}
&\text{(CH}_2\text{CH}_2)_2N-\text{SF}_3 \\
&\sim \\
1 \quad R = \text{OH}, R' = \text{H}, R'' = \text{SCH}_2\text{CH}_2\text{NH}_2 \\
2 \quad R = R' = \text{H}, R'' = \text{SCH}_2\text{CH}_2\text{NHCOCH}_3 \\
3 \quad R = \text{OH}, R' = \text{CH}_3, R'' = \text{SOCH}_2\text{NHCOCH}_3, \text{etc.} \\
4 \quad R = \text{OSO}_3\text{H}, R' = \text{H}, R'' = \text{SOCH}_2\text{NHCOCH}_3, \text{etc.}
\end{align*}
\]
For our study we chose the hydroxyethylazetidinones\textsuperscript{11} \textsuperscript{5a/b} due to their facile preparation as well as their use as central intermediates in the synthesis of the carbapenem nucleus\textsuperscript{11}. Treatment of the (R\textsuperscript{#})-alcohol \textsuperscript{5a} with diethylaminosulfur trifluoride \textsuperscript{6}\textsuperscript{12} at low temperature (-78°C, CH\textsubscript{2}Cl\textsubscript{2}) led to instantaneous disappearance of the starting material and formation of a very un polar, unstable compound in 43 % yield; the ir spectrum no longer shows the characteristic \(\beta\)-lactam absorption, but a new, intense band at 2255 cm\textsuperscript{-1}. Spectral data are in agreement with an allylic (E)-isocyanate \textsuperscript{8a}\textsuperscript{13,14}. On treatment with n-butylamine (dioxane, 25°C, 5 min) urea \textsuperscript{9a} was obtained quantitatively. No trace of any fluorinated \(\beta\)-lactam products could be isolated.

Subjecting the (S\textsuperscript{#})-alcohol \textsuperscript{5b} to identical reaction conditions afforded a mixture of products. The crystalline fluoride \textsuperscript{10a} was obtained in 20 % yield; the presence of fluorine was evident from the characteristic large \(\textsuperscript{1}H\textsuperscript{-19}F\) coupling constants in the \(\textsuperscript{1}H\text{-nmr}\textsuperscript{15}. Besides \textsuperscript{10a}, an inseparable 3:2 mixture (by nmr-integration) of allylic isocyanates \textsuperscript{8a} and \textsuperscript{8b} could be isolated (21 %). They again were further characterized by conversion to n-butyl ureas \textsuperscript{9a} and \textsuperscript{9b}. An additional component of the product mixture was shown to be the diastereomeric sulfimates \textsuperscript{11a}\textsuperscript{16}. In order to increase the yield of the desired product \textsuperscript{10a}, different reaction conditions and an alternative fluorinating agent have been investigated. The results are summarized in table I.
TABLE I

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>conditions</th>
<th>fluorinating agent</th>
<th>isolated yield [%] of products</th>
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<tr>
<td></td>
<td></td>
<td>(°C)</td>
<td>8a</td>
<td>8b</td>
</tr>
<tr>
<td>1</td>
<td>5a</td>
<td>-78</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>-78 to r.t.</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td>-78</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>5b</td>
<td>-78</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>5b</td>
<td>-78 to r.t.</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>5b</td>
<td>-78 to r.t.</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>5b</td>
<td>-78</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>5b</td>
<td>-78</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>5b</td>
<td>-78 to r.t.</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>5b</td>
<td>-78 to r.t.</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>5b</td>
<td>-78</td>
<td>6</td>
<td>26</td>
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<td>-110</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

(a) Experiments were conducted in dry CH₂Cl₂ on a 3-10 mM scale. Work-up involved quenching with sodium bicarbonate solution, extraction and chromatographic purification.

(b) ¹H-nmr of the material obtained after chromatography indicated the presence of ca. 10% impurities, which were removed by crystallization.

(c) Product may have decomposed on warming.

(d) 2 equivalents of pyridine were added.

(e) 2 equivalents of potassium fluoride were added.

The formation of the products can be rationalized by assuming initial formation of the intermediate A, in which one fluorine atom of the DAST-reagent is replaced by the alkoxy group. In the reaction with the (S*)-alcohol 5b this is relatively stable at lower temperature (entry 3, 4, 13, 14) or in the presence of pyridine and afforded the diastereomeric sulfimates 11a/11b on hydrolytic work-up. In the latter case (entry 7, 8) these were the only products which could be isolated. This might be due to the neutralization of the acid formed, which protonates the amino function and enhances the leaving group character to form intermediate
Only at higher temperature did the subsequent displacement occur (entry 5,6,9,10). Direct displacement of the leaving group by fluoride (SN2) would give the observed fluoroazetidinone 10a with inverse stereochemistry. Fragmentation of B would lead to the isomeric isocyanates 8a/8b, which could not be suppressed by addition of solid potassium fluoride (entry 11,12).
The preferred course of reaction of the (R')-alcohol 5a is stereospecific fragmentation into (E)-olefin 8a, presumably via intermediate A1', which has the ideal conformation for such a pathway. The analogous intermediate A2' derived from 5b is sterically more hindered and preference for a different conformation is likely, thus leading to the observed products. Piperidinosulfur trifluoride 718 was almost as effective as diethylaminosulfur trifluoride 6 in the fluorination reaction. We are at present investigating other fluorinating agents to optimize the yield. Transformation of these fluoroazetidinones into carbapenem antibiotics and their biological properties will be reported elsewhere19.

ACKNOWLEDGEMENT: We thank Dr. H. Vyplel for providing the DAST reagents and many helpful discussions, Dr. G. Schulz for the spectral data and Dr. H. P. Weber for the X-ray analysis15.

NOTES AND REFERENCES:
5) W.A. Sheppard and C.M. Sharts, Org. React., 1974, 21, 125.
13) Satisfactory microanalytical and/or high resolution mass spectral data were obtained for all new compounds reported.
14) Selected physical data: 8a: oil; ir(CHCl3) 2255, 1730 cm⁻¹; nmr(CDC13) 1.68 (dm, 3, J = 5.5 Hz); 2.59
(dd, 1, J = 16.8, 6.3 Hz); 2.62 (dd, 1, J = 16.8, 8 Hz); 4.44 (m, 1); 5.16 (s, 2); 5.44 (dq, 1, J = 15.5, 7.18 Hz); 5.75 (dqd, 1, J = 15.5, 7. 1 Hz); 7.37 (s, 5). 9aa: oil; ir(CHCl₃) 1730, 1660, 1520 cm⁻¹; nmr (CDCl₃) δ 0.92 (t, 3, J = 7.5 Hz); 1.25-1.42 (m, 4); 1.64 (dm, 3, J = 6 Hz); 2.64 (d, 2, J = 6 Hz); 3.07-3.18 (m, 2); 4.38 (br, 1); 4.57 (m, 1); 5.00 (br, 1); 5.10 (d, 1, J = 12.5 Hz); 5.14 (d, 1, J = 12.5 Hz); 5.45 (ddq, 1, J = 15.5, 7. 1.8 Hz); 5.75 (dqd, 1, J = 15.5, 7.1 Hz); 7.36 (s, 5). 8a/8b: oil; nmr (CDCl₃) additional signals at δ 2.50, 4.80, 5.45 and 5.73, corresponding to the (Z)-olefin. 9a/9b: oil; nmr(CDCI₃) additional signals at δ 5.00 and 5.45, corresponding to the (Z)-olefin.

10a: mp 40-3°C; ir(CHCl₃) 1765, 1730 cm⁻¹; nmr(CDCl₃) δ 1.45 (dd, 3, J = 24, 6.5 Hz); 2.68 (dd, 1, J = 16, 9 Hz); 2.86 (dd, 1, J = 16, 5.5 Hz); 3.01 (ddd, 1, J = 18.5, 7, 2.5 Hz); 4.02 (ddd, 1, J = 9, 5.5, 2.5 Hz); 4.97 (dq, 1, J = 48, 6.5 Hz); 5.18 (s, 2); 6.25 (br, 1); 7.40 (s, 5). 11a: oil; ir(CHCl₃) 1760, 1730, 1170 cm⁻¹; nmr(CDCI₃) 1:1 mixture of diastereoisomers; δ 1.14 (t, 6, J = 7.2 Hz); 1.38, 1.42 (dd, 3, J = 6.8 Hz); 2.60 (dd, 1, J = 17, 8 Hz); 2.86 (dd, 1, J = 17, 5.4 Hz); 3.00-3.30 (m, 5); 3.86, 4.03 (ddd, 1, J = 8, 5.4, 2.5 Hz); 4.46 (dq, J = 6.8, 3.5 Hz); 4.52 (dq, J = 6.8, 4.5 Hz, together with signals at 4.46 integrated for one H); 5.14 (s, 2); 6.10 (br, 1); 7.38 (s, 5). 11b: mp 71-3°C; ir(CH₂Cl₂) 1770, 1730, 1155 cm⁻¹; nmr(CDCl₃) 3:1 mixture of diastereoisomers; δ 1.41, 1.42 (dd, 3, J = 6.5 Hz); 1.40-1.60 (m, 6); 2.65 (dd, 1, J = 16.7, 8.8 Hz); 2.81 (dd, 1, J = 16.7, 4.9 Hz); 2.95-3.22 (m, 5); 3.88, 4.03 (ddd, 1, J = 8.8, 4.9, 2.5 Hz); 4.52 (dq, J = 6.5, 4.2 Hz); 4.46 (dq, J = 6.5, 3.4 Hz, together with the signals at 4.52 integrated for one H); 5.14 (s, 2); 6.01 (br, 1); 7.37 (s, 5).

15) Proton magnetic resonance studies did not permit conclusive assignment of the stereochemistry of the fluorine atom as shown, although mechanistic considerations suggest the structure given to be the most probable one. Since the other isomer 10b has not been prepared, we have transformed 10a in a three-step sequence to the crystalline diazoketone C and an X-ray crystallographic study was performed on this compound.
The relative stereochemistry of the fluorine atom was found to be as inferred. A detailed report of the X-ray data, together with its synthesis and further transformation, will be reported shortly elsewhere.

16) Similar sulfinates have been reported in the reaction of DAST with steroids; M. Biollaz and J. Kalvoda, Helv. Chim. Acta, 1977, 60, 2703.


19) Abstract has been submitted to the North American Medicinal Chemistry Symposium, to be held on June 20-24, 1982, in Toronto, Canada.

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