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

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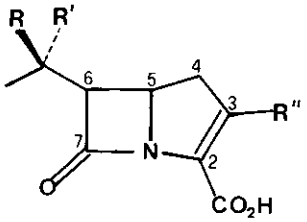
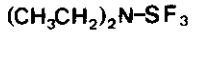
Abstract: Reactions of benzyl 3-(1-hydroxyethyl)-2-oxoazetidine-4-acetate with dialkylaminosulfur trifluorides under various conditions have been investigated. Formation of products was found to be highly dependent on temperature, presence or absence of base, and stereochemistry of the hydroxyethyl group.

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

Many methods are available for the introduction of fluorine[5], mostly via the hydroxyl group. Fluorinating agents such as diethylaminofluorochloroethane[6], metal fluorides/tetrabutylammonium fluoride[7], phenyltetrafluorophosphorane [8] and dialkylaminosulfur trifluorides[9] (DAST) have been developed, mainly for their uses in preparing fluorosteroids. Only a few applications have been reported in the β-lactam literature[10].





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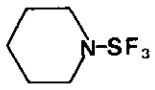

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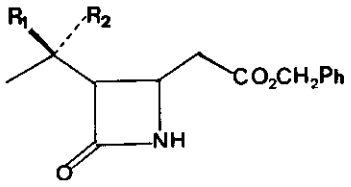
1 R = OH, R' = H, R'' = $SCH_2CH_2NH_2$

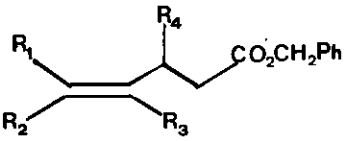
2 R = R' = H, R'' = $SCH_2CH_2NHCOCH_3$

3 R = OH, R' = CH_3, R'' = $SOCHCHNHCOCH_3$, etc.

4 R = OSO_3^-, R' = H, R'' = $SOCHCHNHCOCH_3$, etc.

For our study we chose the hydroxyethylazetidinones[11] 5a/b due to their facile preparation as well as their use as central intermediates in the synthesis of the carbapenem nucleus[11]. Treatment of the (R*)-alcohol 5a with diethylaminosulfur trifluoride 6[12] at low temperature (-78°C, CH_2Cl_2) led to instantaneous disappearance of the starting material and formation of a very unpolar, unstable compound in 43 % yield; the ir spectrum no longer shows the characteristic β-lactam absorption, but a new, intense band at 2255 cm^{-1}. Spectral data are in agreement with an allylic (E)-isocyanate 8a[13,14]. On treatment with n-butylamine (dioxane, 25°C, 5 min) urea 9a was obtained quantitatively. No trace of any fluorinated β-lactam products could be isolated.





5a R_1 = OH, R_2 = H

5b R_1 = H, R_2 = OH

10a R_1 = F, R_2 = H

10b R_1 = H, R_2 = F

11a R_1 = H, R_2 = $OSON(CH_2CH_3)_2$

11b R_2 = H, R_2 = OSON⟨⟩

8a R_1 = R_3 = H, R_2 = CH_3, R_4 = NCO

8b R_1 = CH_3, R_2 = R_3 = H, R_4 = NCO

9a R_1 = R_3 = H, R_2 = CH_3, R_4 = $NHCONH(CH_2)_3CH_3$

9b R_1 = CH_3, R_2 = R_3 = H, R_4 = $NHCONH(CH_2)_3CH_3$

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

TABLE I

entry	alcohol	conditions (°C)	fluorinating agent	isolated yield [%] of products 8a	8b	10a	11a	11b
1	5a	- 78	6	43	-	-	-	-
2	5a	- 78 to r.t.[d]	7	43	-	-	-	-
3	5b	- 78	6	21		20	8	-
4	5b	- 78	7	8		45[b]	-	10
5	5b	- 78 to r.t.	6	-[c]		25	-	-
6	5b	- 78 to r.t.	7	-[c]		40[b]	-	-
7	5b	- 78[d]	6	-		-	28	-
8	5b	- 78[d]	7	-		-	-	34
9	5b	- 78 to r.t.[d]	6	-		28	-	-
10	5b	- 78 to r.t.[d]	7	-		10	-	5
11	5b	- 78[e]	6	26		40	-	-
12	5b	- 78[e]	7	19		22	-	-
13	5b	-110	6	7		36[b]	7	-
14	5b	-110	7	5		30[b]	-	16

(a) Experiments were conducted in dry CH_2Cl_2 on a 3-10 mM scale. Work-up involved quenching with sodium bicarbonate solution, extraction and chromatographic purification.

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

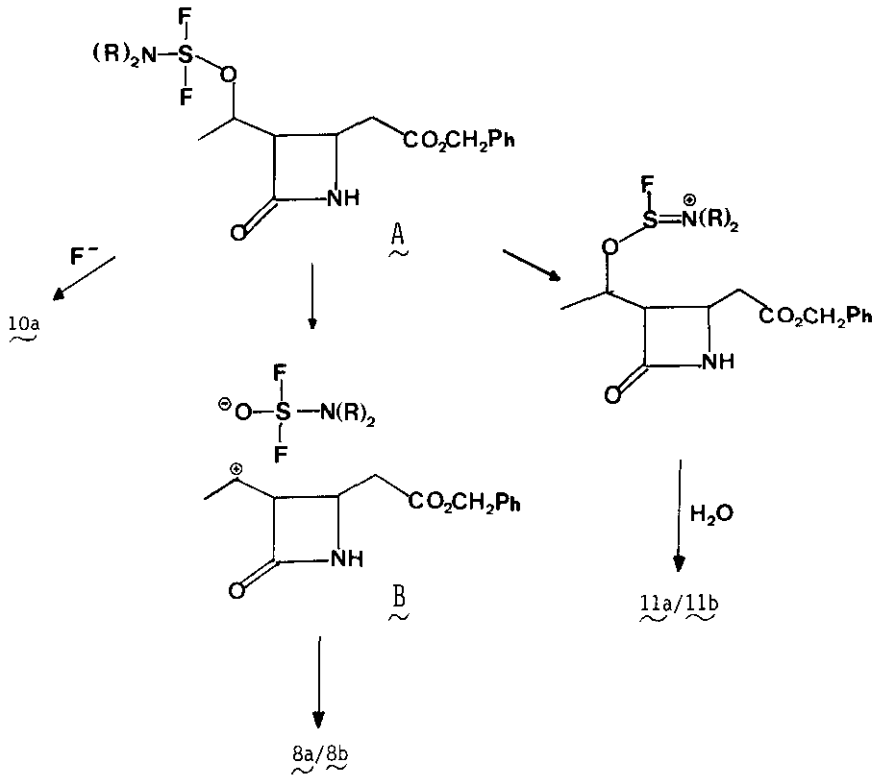
(c) Product may have decomposed on warming.

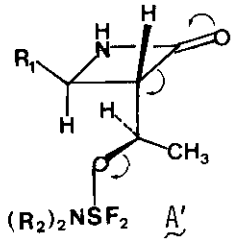
(d) 2 equivalents of pyridine were added.

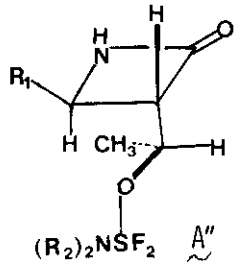
(e) 2 equivalents of potassium fluoride were added.

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[12]. 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 sulfinates 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

B. Only at higher temperature did the subsequent displacement occur (entry 5,6,9,10). Direct displacement of the leaving group by fluoride (S_N2) 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)[17].







The preferred course of reaction of the (R*)-alcohol 5a is stereospecific fragmentation into (E)-olefin 8a, presumably via intermediate A', which has the ideal conformation for such a pathway. The analogous intermediate A" derived from 5b is sterically more hindered and preference for a different conformation is likely, thus leading to the observed products. Piperidinosulfur trifluoride 7[18] 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 elsewhere[19].

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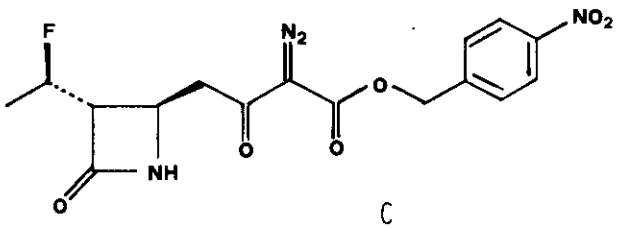
13) Satisfactory microanalytical and/or high resolution mass spectral data were obtained for all new compounds reported.

14) Selected physical data: 8a: oil; ir($CHCl_3$) 2255, 1730 cm^{-1}; nmr($CDCl_3$) 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 (ddq, 1, J = 15.5, 7, 1.8 Hz); 5.75 (dqd, 1, J = 15.5, 7, 1 Hz); 7.37 (s, 5). 9a: oil; ir($CHCl_3$) 1730, 1660, 1520 cm^{-1}; nmr ($CDCl_3$) 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, 6, 1.5 Hz); 5.63 (dqd, 1, J = 15, 6.5, 1 Hz); 7.36 (s, 5). 8a/8b: oil; nmr ($CDCl_3$) additional signals at δ 2.50, 4.80, 5.45 and 5.73, corresponding to the (Z)-olefin. 9a/9b: oil; nmr($CDCl_3$) additional signals at δ 5.00 and 5.44, corresponding to the (Z)-olefin. 10a: mp 40-3°C; ir($CHCl_3$) 1765, 1730 cm^{-1}; nmr($CDCl_3$) 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($CHCl_3$) 1760, 1730, 1170 cm^{-1}; nmr($CDCl_3$) 1:1 mixture of diastereoisomers; δ 1.14 (t, 6, J = 7.2 Hz); 1.38, 1.42 (d, 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(CH_2Cl_2) 1770, 1730, 1155 cm^{-1}; nmr($CDCl_3$) 3:1 mixture of diastereoisomers; δ 1.41, 1.42 (d, 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.



C

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.

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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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