AN UNPRECEDENTED REACTION OF DIETHYLAMINOSULFUR TRIFLUORIDE WITH FURANONES

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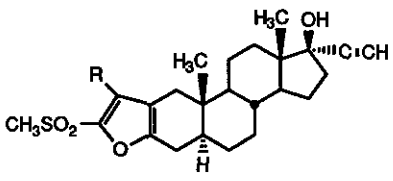
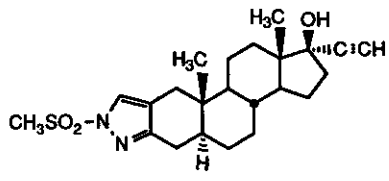
Abstract - Reaction of diethylaminosulfur trifluoride (DAST) with furanones did not provide the expected gem-difluoro compounds instead the methylene hydrogens of furanones were replaced by a fluorine and sulfinyl group.

We have recently reported the synthesis of the steroidal 5'-methylsulfonyl[2,3-*b*]furan (**1**), an antagonist that binds to the rat ventral prostate androgen receptor[1,2] similar to the known antiandrogenic steroidal 1'-methylsulfony[3,2-*c*]pyrazole (**3**).[3] Several reports[4] in the literature suggest that furans undergo oxidative metabolism to produce active metabolites which may be covalently linked to various macromolecules resulting in liver, lung, and/or kidney necrosis. During the course of analog preparation of **1** for strucure-activity relationships, we perceived the liabilities associated with the furan ring. Therefore, we were interested in



1 R=H
2 R=F



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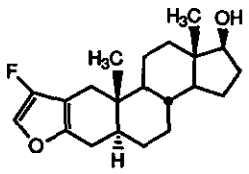
preparing the corresponding fluorinated steroidal furan derivative (**2**) which may be less susceptible to metabolic degradations while not significantly altering the pharmacological profile of **1**. The aim was to prepare the steroidal 4'-fluoro[3,2-*b*]furan (**4**) which upon further manipulations[1] would provide the desired compound (**2**).



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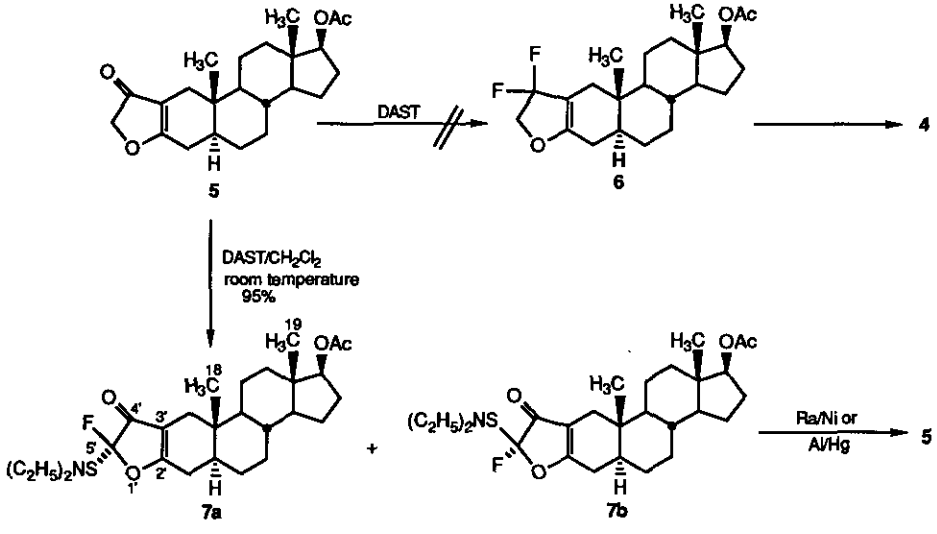
Syntheses of the fluorofurans have been successful only on a limited basis.[5] Only highly substituted fluoro-furans were isolable, otherwise a random mixture of unstable polyfluorinated furans were isolated in low yields. The majority of these reactions were performed utilizing fluorine gas, CF_3OF, SF_4, HF.Py and other fluorinating agents.[6,7]

Middelton[8] and others[9] have shown DAST to be an excellent agent for the replacement of various oxygen functionalities with fluorine in a variety of substrates such as alcohols and carbonyl compounds. Ketones are known to undergo gem-difluorination when treated with DAST.[8] This prompted us to utilize the previously described[1] intermediate furanone (**5**) (17-OAc was prepared from 17-OH, Ac_2O/Py, 90% yield) which should give the gem-difluoro derivative (**6**) when reacted with DAST following literature procedures.[9] Dehydrofluorination, either in the presence of base, or basic alumina should result in the formation of **4** (Scheme I).

Scheme I

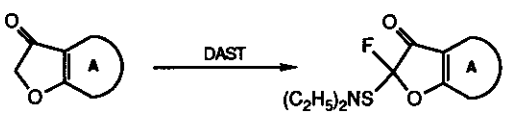


Reaction of the furanone (**5**) (1 mmol) with DAST (3 mmol) in CH_2Cl_2 at room temperature (16 h) resulted in the formation of a non-separable diastereoisomeric mixture of **7** (**a** and **b**) in 95% yield after basic (5% $NaHCO_3$) workup instead of the expected gem-difluoro compound (**6**). The structural assignment of **7a** and

7b was made on the basis of ms, ir, ^{1}H-nmr, ^{13}C-nmr, ^{19}F-nmr spectra and elemental analysis.[10] The ^{1}H-nmr showed two sets of C-18 and C-19 methyl protons as well as two sets of the triplets (δ 1.11 and 1.12) and quartets (δ 3.06 and 3.08) for **7a** and **7b** with nearly identical integrations indicating a 1:1 mixture of the compounds. The loss of methylene protons on the furanone at δ 4.35 indicated disubstitution at C-5' position. In the ^{13}C-nmr, the quaternary carbon C-5' bearing the F-5' appeared as two sets of doublets at 115.95;120.14 ppm (J_{CF}=282.7 Hz) and the carbonyl carbon (C-4') also exhibited two sets of doublets at 192.82;195.11 ppm (J_{CF}=18.58 Hz) confirming the mixture. The long range coupling of F-5' with the ring junction quaternary carbons, C-2' [184.04; 184.18 ppm, (J_{CF}=9.8 Hz)] and C-3'[111.25; 113.30 ppm, J_{CF}=2.9 Hz)] revealed the attachment of the fluorine at the carbon bearing the sulfur and oxygen. The structure of the diasteroisomeric mixture (**7a** and **7b**) was further confirmed by ^{19}F-nmr ($CDCl_3$/$CFCl_3$ as internal standard) which displayed two peaks of equal intensity at 68.52 and 68.54 ppm after the expansion of the spectrum.

Attempted desulfurization of **7a** and **7b** with either Al/Hg or RaNi/EtOH resulted not only in cleavage of the C-S bond but cleavage of the relatively stable C-F bond also took place to give the starting material (**5**) in nearly quantitative yield. This further suggested that the fluorine and the sulfur groups have been attached to the C-5' position of the heterocyclic steroid.

This unusual reaction of DAST was not limited to steroidal furanones. Other furanones such as 2,3-dihydrobenzofuran-3-one (**8**)[11] and 4,5,6,7-tetrahydro-3(2*H*)-bezofuranone (**9**)[12] also reacted with DAST to give the products **10**[13] and **11**[14] as yellow oils in 50% and 87% respectively after chromatography. However, these compounds were unstable compared to **7** (**a** and **b**) and slowly decomposed to unidentifiable materials at room temperature. Decomposition may account for the lower yield of **10**. The structural assignment of these compounds was made as described above for the steroidal furanone.



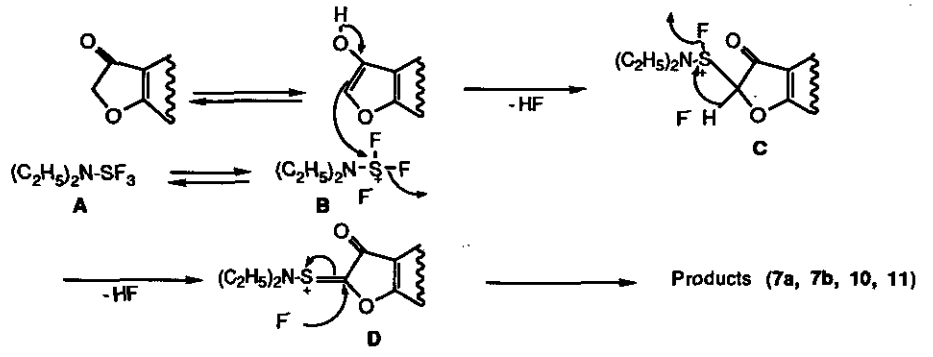
8 A = CH=CH-CH=CH
9 A = CH_2-CH_2-CH_2-CH_2

10 A = CH=CH-CH=CH
11 A = CH_2-CH_2-CH_2-CH_2

The mechanism of the reaction has not been established in detail. However, the formation of the products has led us to postulate the mechanism as depicted in Scheme II. DAST may exist in an equilibrium between **A** and **B**[9] and the enol form of the furanone attacks the sulfur cation to give intermediate **C** after loss of HF. After removal of

another equivalent of HF, F^- attacks the carbon of the sulfinium cation intermediate **D** non-selectively forming the diastereoisomeric mixture observed in the case of steroidal furanone **5**. Reaction of enolizable ketone, such as ethylacetoacetate, with DAST has been reported[15] to give unique fluorinated compound, but not similar to that described in here.

Scheme II



In summary we have shown that the highly enolizable ketones such as furanones do not undergo the usual ketone-DAST reaction to form gem-difluoro compounds, instead the active methylene protons of furanones were replaced by a fluorine and sulfinyl group. A possible mechanism was proposed to accommodate the formation of the products.

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9. For a comprehensive review on fluorinations with DAST see M. Hudlicky,'Organic Reactions: Fluorination with DAST', Vol. 35, ed. by A. S. Kende, John Wiely and Sons, Inc., New York, 1988, pp. 513-637.

10. mp 125-127°C (CH_2Cl_2:Hexane); ir (KBr) 1738, 1718, 1640 cm^{-1}; ms (CI) MH^+ 494; ^{1}H-nmr (300 MHz, $CDCl_3$/TMS) δ 0.74, 0.75, 0.77(C_{18} and C_{19}, 6H), 1.11(3H, t, J=7.0 Hz), 1.12(3H, t, J=7.0 Hz), 1.00-2.32(20H, m), 2.02(3H, s), 3.06(2H, q, J=6.9 Hz), 3.08(2H, q, J=7.0 Hz), 4.57(1H, t, J= 8.4 Hz); ^{13}C-nmr (67.8 Hz, $CDCl_3$/TMS) ppm 11.66, 11.97, 13.82, 13.88, 20.60, 21.10, 23.46, 27.44, 28.34, 28.39, 29.68, 29.80, 30.94, 32.18, 32.32, 35.21, 35.26, 35.60, 36.65, 41.38, 41.42, 42.43, 50.42, 50.45, 52.69, 53.23, 53.30, 82.57, 111.25, 111.29, 115.94, 116.05, 120.13, 120.21, 171.12, 184.03, 184.18, 192.82, 192.91, 193.11, 193.18; Anal. Calcd: C, 65.69; H, 8.17; N, 2.84; F, 3.85; S, 6.49; O, 12.96. Found: C, 65.89; H, 8.18; N, 2.86; F, 3.73; S, 7.00; O, 12.50.

11. Commercially available from Lancaster Synthesis.

12. S. Glen and R. Dolmazon, J. Het. Chem., 1983, **20**, 543. Compound (**9**) could also be prepared from cyclohexanone following the method described for the preparation of **5** in reference 1.

13. Chromatographed oil; ir (neat) 1722, 1600 cm^{-1}; ms (CI) MH^+ 256; ^{1}H-nmr (300 MHz, $CDCl_3$/TMS) δ 1.05(3H, t, J=6.9 Hz), 3.75(2H, q, J=7.1 Hz), 7.18(2H, m), 7.65(2H, m); ^{13}C-nmr (67.8 MHz, $CDCl_3$/TMS) ppm 13.78, 52.54, 113.05,116.22;120.41(J_{CF}=284.0 Hz),123.76, 125.50, 138.93, 168.36;168.40,190.80;191.10(J_{CF}= 9.2 Hz); ^{19}F-nmr ($CDCl_3$/$CFCl_3$) ppm 68.50.

14. Chromatographed oil; ir (neat) 1729, 1639cm^{-1}; ms (CI) MH^+ 260; ^{1}H-nmr (300 MHz, $CDCl_3$/TMS) δ 1.13(3H, t, J=7.1 Hz), 1.67(2H, m), 1.84(2H, m), 2.21(2H, m), 2.43(2H, m), 3.11(2H, q, J=7.0 Hz); ^{13}C-nmr (67.8 Hz, $CDCl_3$/TMS) ppm 13.82, 17.94, 21.30, 21.44, 25.32, 52.67, 112.18, 115.64;119.83(J_{CF}=284.6 Hz), 185.43, 192.24;192.53(J_{CF}=19.3 Hz); ^{19}F-nmr ($CDCl_3$/$CFCl_3$) ppm 68.95.

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