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Self-sacrificing acetylation observed during attempted desilylation of 1-[4-benzenesulfonyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-5-*O*-methanesulfonyl-α-L-*threo*-pentofuranosyl]thymine

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ABSTRACT

Desilylation of 1-[4-benzenesulfonyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-5-*O*-methanesulfonyl-α-L-*threo*-pentofuranosyl]thymine (**4**) with Bu_4NF/THF, when carried out *at room temperature*, gave four products. Among these, there were 1-[3-*O*-acetyl-4-benzenesulfonyl-2-deoxy-5-*O*-methanesulfonyl-α-L-*threo*-pentofuranosyl]thymine (**7**) and thymine. A possible reaction mechanism is proposed, which suggests the origin of 3′-*O*-acetyl group of **7** and thymine as well as structures of the other two products (**9a** and **9b**).

1. Introduction

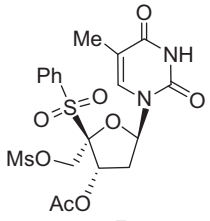
We have recently reported a method for the preparation of **2**,[1] having a benzenesulfonyl leaving group at the 4′-position, from thymidine-5′-aldehyde (**1**).[1,2] Compound **2**, after 5′-*O*-silylation, undergoes stereoselective nucleophilic substitution with organosilicon reagents in the presence of $SnCl_4$, as exemplified in Scheme 1 for the preparation of 4′-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)thymidine (**3**).[1]

To apply this chemistry to the synthesis of 4′-carbon-substituted analogues of 2′,3′-didehydro-3′-deoxythymidine (d4T), we were in need of **6**, and thought that desilylation of the 5′-*O*-methanesulfonyl derivative **4** with Bu_4NF would lead to the formation of the oxetane derivative **5** that is anticipated to undergo base-catalyzed elimination to yield **6**, as reported in the preparation of d4T.[3] However, upon reacting **4** with Bu_4NF in THF *at room temperature*, an unexpected reaction took place, which is the subject of the present communication.

2. Results and discussion

Compound **2**, 1-[4-benzenesulfonyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*threo*-pentofuranosyl]thymine, was mesylated in a conventional manner to give the 5′-*O*-mesylate (**4**) in 82% yield. When **4** was reacted with Bu_4NF (1.2 equiv) in THF *at room temperature* for 1 h, complete disappearance of **4** was confirmed by TLC (hexane/EtOAc = 1:3). After reaction overnight, careful TLC analysis of the reaction mixture in an alternative solvent system (CH_2Cl_2/MeOH = 10:1) revealed that, in addition to three products, thymine was also formed as a polar product. This was ascertained by ^1H NMR spectroscopy after short column chromatography (CH_2Cl_2/MeOH = 10:1) of the reaction mixture, but the actual yield of thymine could not be determined due to contamination by tetrabutylammonium salts. A mixture of the three other products was subjected to HPLC separation ($CHCl_3$/MeOH = 25:1).

The ^1H NMR spectrum of the fastest running product (t_R 7.4 min) in $CDCl_3$ showed that it has one acetyl group (δ 2.18, 3H, singlet) with the 5′-*O*-mesyl group remaining intact. Also, its H-3′ resonance appeared at a lower field (δ 6.23) when compared with that of **4** (δ 5.29). These data suggest the structure of this product to be the 3′-*O*-acetyl derivative **7**,[4] which was also supported by FAB-MS (*m*/*z* 503, M^++H). The isolated yield of **7** was 29%. Where has the 3′-*O*-acetyl group of **7** come from? We would like to propose a possible reaction mechanism as shown in Scheme 2, which also suggests the structures of the other two products.



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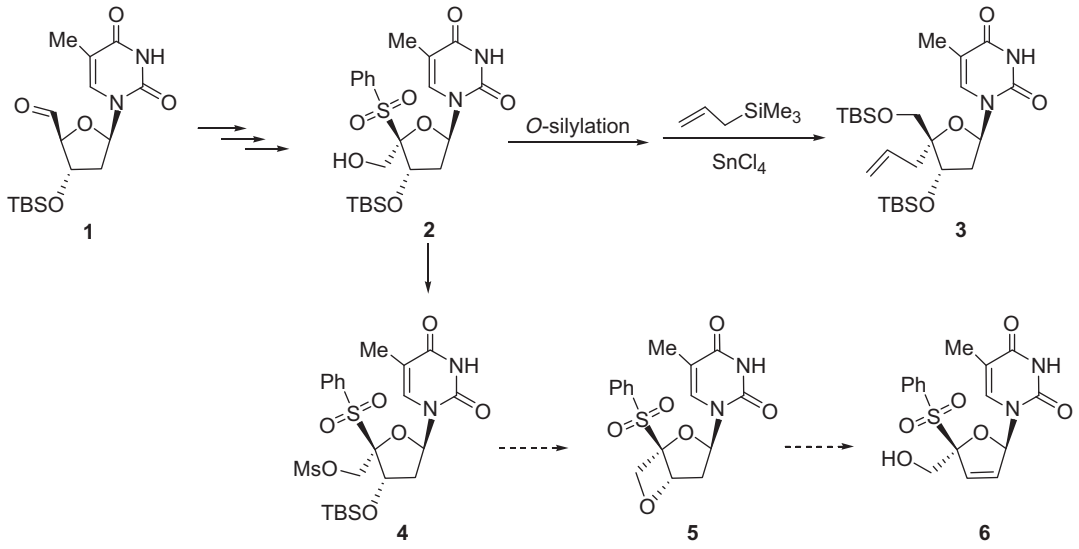
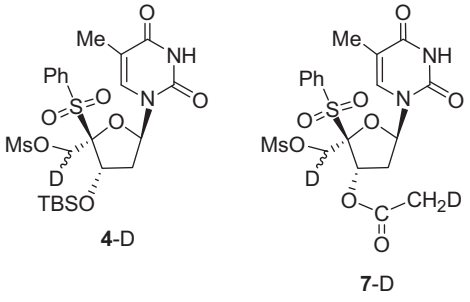
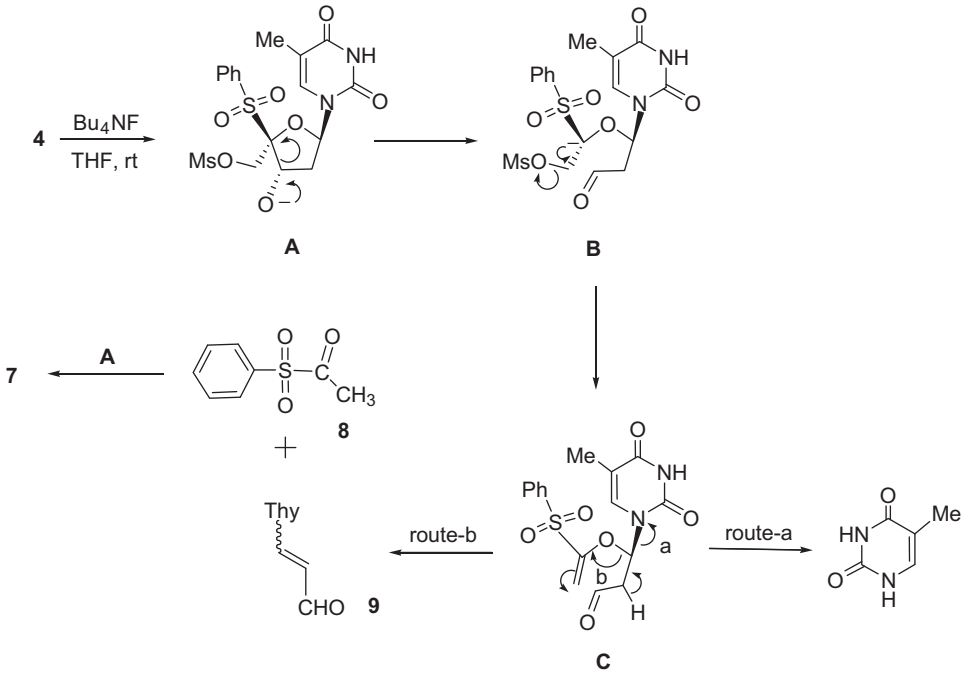


Scheme 1.

Desilylation of **4** gives rise to the 3′-alkoxide **A**, which undergoes furanose ring opening leading to **B** or, through subsequent elimination of the mesyloxy group, to **C**. Upon deprotonation of the α-hydrogen of the formyl group in **C**, there could be two possible elimination pathways. In route-a, the thymine moiety serves as a leaving group (the formation of thymine was actually observed as mentioned the above). On the other hand, when elimination takes place through route-b, acetyl phenyl sulfone (**8**) as well as **9** should result. Since **8** is expected to serve as an acetylating reagent,[5] its reaction with **A** would lead to the formation of **7**.

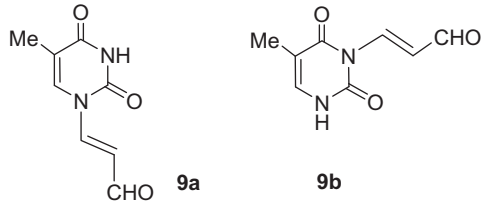
To obtain convincing evidence for the proposed mechanism regarding the formation of **7**, the 5′-monodeuterated **4** (**4**-D, a mixture of two diastereomers with a ratio of 2:3, isotopic purity >99%) was prepared from **1**.[6] When **4**-D was reacted with Bu_4NF in THF at room temperature overnight, **7**-D was isolated in 33% yield by HPLC. That **7**-D contains the 3′-*O*-monodeuterated acetyl group became clear from its ^1H NMR spectrum measured in $CDCl_3$, in which the characteristic splitting due to the presence of deuterium ($J_{H,D}$) was present: δ 2.17 (2H, triplet, $J_{H,D}$ = 2.0 Hz, $COCH_2D$).





Scheme 2.

As regard to **9**, which was found to be a mixture of two compounds, we initially thought that these were geometrical isomers, since these compounds after HPLC separation gave identical M^++H (m/z 181) by FAB-MS and their ^{1}H NMR spectra measured in DMSO-d_6 showed for each the presence of the thymine moiety, an aldehyde proton and two vinylic protons. The ^{1}H NMR data of the faster running product (**9a**)[7] (t_R 8.8 min, obtained in 15% yield) were found to be in full agreement with those reported for (*E*)-3-(thymin-1-yl)propenal.[8,9] However, the slower running product (t_R 10.3 min, obtained in 7% yield) gave a slightly larger vinylic coupling constant (J = 14.8 Hz) than that of **9a** (J = 14.6 Hz), which is certainly inconsistent with the (*Z*)-configuration. Unambiguous structure determination that the slower running product is (*E*)-3-(thymin-3-yl)propenal (**9b**) came from a HMBC experiment: multiple bond connectivity was observed between H-3 (δ 8.18) of the propenal portion and both C-2 (δ 149.88) and C-4 (δ 162.73) carbonyl carbons of the thymine moiety.[10] At the present time, we have no evidence to explain the mechanism for the formation of **9b**.[11,12]



Finally, it should be mentioned that the formation of **7**, **9a**, **9b** and thymine from **4** can be avoided by conducting the reaction at −78 °C. Thus, after reaction at this temperature for 6 h, **4** gave the desilylated product in 72% yield. Anticipated formation of the oxetane **5** (Scheme 1) was not observed.

3. Conclusion

An attempted desilylation of **4** with Bu_4NF in THF at room temperature gave unexpected products **7**, **9a**, **9b** and thymine. Their structures were speculated based on a possible reaction mechanism shown in Scheme 2. Convincing mechanistic evidence for the formation of **7** was obtained by employing the 5′-monodeuterated **4** (**4**-D).

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References and notes

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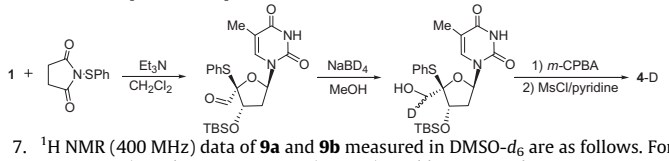
3. Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205.
4. Physical data for **7**: ^{1}H NMR ($CDCl_3$) δ 2.05 (3H, d, J = 1.2 Hz, 5-Me), 2.18 (3H, s, Ac), 2.47 (1H, ddd, J = 2.2, 6.3, and 14.4 Hz, H-2′), 2.87 (3H, s, SO_2Me), 2.84–2.92 (1H, m, H-2′), 4.40 and 4.47 (2H, each as d, J = 11.5 Hz, H-5′), 6.23 (1H, dd, J = 2.2 and 6.6 Hz, H-3′), 6.77 (1H, dd, J = 6.3 and 9.0 Hz, H-1′), 7.61–7.89 (6H, m, J = 1.2 Hz, H-6 and Ph), 9.17 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.72, 20.68, 37.16, 37.94, 64.59, 72.04, 86.04, 99.21, 113.06, 129.48, 130.31, 134.37, 134.74, 135.26, 150.56, 163.21, 169.01; FAB-MS (m/z) 503 (M^++H).
5. Reaction between *p*-anisoyl *p*-tolyl sulfone and MeOH has been reported to give methyl *p*-anisate: Schank, K.; Werner, F. *Liebigs Ann. Chem.* **1980**, 1477.
6. Reaction sequence for the preparation of **4**-D from **1** is shown below. For detailed experimental procedures, see Ref. 1.



7. ^{1}H NMR (400 MHz) data of **9a** and **9b** measured in DMSO-d_6 are as follows. For **9a**: δ 1.83 (3H, d, J = 1.2 Hz, 5-Me), 6.47 (1H, dd, J = 7.6 and 14.6 Hz, CH=C*H*–CHO), 8.04 (1H, d, J = 1.2 Hz, H-6), 8.16 (1H, d, J = 14.6 Hz, C*H*=CHCHO), 9.57 (1H, d, J = 7.6 Hz, CHO), 11.83 (1H, br, NH). For **9b**: δ 1.81 (3H, d, J = 1.2 Hz, 5-Me), 7.09 (1H, dd, J = 7.8 and 14.8 Hz, CH=C*H*CHO), 7.44 (1H, d, J = 1.2 Hz, H-6), 8.18 (1H, d, J = 14.8 Hz, C*H*=CHCHO), 9.57 (1H, d, J = 7.8 Hz, CHO), 11.34 (1H, br, NH).
8. Johnson, F.; Pillai, K. M. R.; Grollman, A. P.; Tseng, L.; Takeshita, M. *J. Med. Chem.* **1984**, *27*, 954.
9. Compound **9a** has been isolated as a product of bleomycin-induced strand-scission of DNA: Giloni, L.; Takeshita, M.; Johnson, F.; Iden, C.; Grollman, A. P. *J. Biol. Chem.* **1981**, *256*, 8608.
10. Additional evidence for the N^3-substituted regiochemistry of **9b** is that addition of D_2O to the ^{1}H NMR sample sharpened the H-6 signal.
11. One referee pointed out the possibility that **9b** may result from addition–elimination reaction between **9a** and N^3-anion of thymine. We agree that **9b** derives presumably from **9a**. However, as cited in Ref. 12, it is known that addition of thymine to Michael acceptors in the presence of DBU takes place exclusively at the N^1-position. Therefore, for the formation of **9b**, we assume that the nucleophile reacting with **9a** would be not thymine itself but certain N^1-substituted thymine derivative(s).
12. Scheiner, P.; Geer, A.; Bucknor, A.-M.; Imbach, J.-L.; Schinazi, R. F. *J. Med. Chem.* **1989**, *32*, 73.