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Furanyl nucleosides: synthesis and kinetics of their formation

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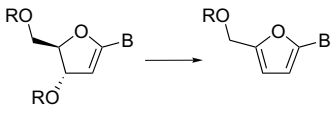
Abstract—The thermal reaction (at 140 °C) of various 1′,2′-didehydro-2′-deoxynucleosides afforded the corresponding furanyl nucleosides in good yields. The reaction kinetics were monitored by ^{1}H NMR and the mechanism in terms of 'four-center complex fission' is discussed.

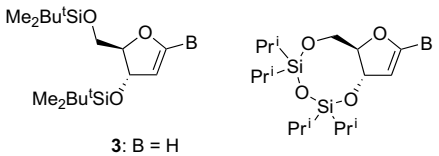
Furanyl nucleosides of type **2** are known as early as 1974 when Robins and co-workers found that the first prepared 1′,2′-didehydro-2′-deoxynucleosides **1** have the tendency to form these compounds under mild acidic conditions (Scheme 1).[1,2] Since then, improved methods of preparation of compounds **1** have been reported[3–5] and during their various functionalization, compounds **2** were often observed as by-products.[6] A variety of 2′-substituted 1′,2′-unsaturated uridines were also prepared and showed higher stability than the 2′-unsubstituted ones.[7] Exposure of 2′-deoxyguanosine in the solid state to O^{7+} heavy charged ions was reported to lead to furanylguanine among other sugar modified products.[8] Recently the formation of an oligonucleotide fragment containing a 3′-furanyladenine end was observed as a major direct strand break product upon photolysis of 5-bromouracil-containing oligonucleotides under anaerobic conditions.[9] Intermediate **1** is the most appropriate candidate as precursor of the observed product.

Herein, we report on the thermal reactions of various nucleosides **1** that afforded furanyl nucleosides **2** in good



1 **2**

Scheme 1.



3: B = H
4: B = U
5: B = A
6: B = A^{NPPh3}

7: B = U
8: B = A

Chart 1. Starting materials.

yields as well as on their reaction mechanism (Chart 1). The pyrimidine derivatives **4** and **7** were prepared from the corresponding 2,2′-anhydrouridine using LDA in THF at −78 °C,[3] whereas the purine derivatives **5**, **6**, and **8** were prepared following our reported procedure.[5] For comparison, the prototype glucal **3**, which is commercially available, was also investigated.

Heating a 0.1 M solution of any of the nucleosides **3**–**8** (1 mmol) in *o*-xylene, under reflux, led to the quantitative formation of the corresponding products **9**–**14**. The reaction time required for the disappearance of the starting material varied dramatically from less than 1 h for **6** to more than 3 d for the prototype glucal **3**. When the reaction was completed, the product was purified via flash column chromatography (20–50% ethyl acetate in hexanes). In all cases, the corresponding furanyl nucleosides **9**–**14** were isolated as the only nucleoside products in yields >90% (Table 1, Chart 2).[10]

In order to collect kinetic data for the above reaction, a perdeuterated benzene solution (0.6 mL) containing 60–90 mM of starting material and toluene as the internal

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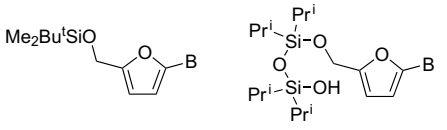
Table 1. Product studies and rate constants of thermolysis at 140 °C[a]

Substrate	Reaction time for >98% conversion	Product (yield, %)	k_d, s^{-1} at 140 °C
3	3 d[b]	**9** (95[c])	5.6×10^{-6}
4	1.5 d	**10** (95)	3.8×10^{-5}
5	6 h	**11** (90)	2.0×10^{-4}
6	0.6 h	**12** (93)	2.0×10^{-3}
7	2.5 d	**13** (92)	2.1×10^{-5}
8	1 d	**14** (93)	5.3×10^{-5}

[a] Product studies were performed in *o*-xylene and kinetics in perdeuterated benzene.
[b] 75% conversion.
[c] Based on the consumed starting material.



9: B = H
10: B = U
11: B = A
12: B = A^{NPPh3}
13: B = U
14: B = A

Chart 2. Reaction products.

standard was sealed under an inert atmosphere in an NMR tube and then completely immersed in an oil bath set at 140 °C. The reaction was followed by ^{1}H NMR spectroscopy by monitoring either the disappearance of starting material or the formation of the product. Figure 1 shows the first-order semi-logarithmic plot for the disappearance of prototype **3** and the derivatives **4**, **5**, and **7**. The unimolecular rate constants were obtained from the slope of these linear plots. The data for all substrates are reported in Table 1.

The rate constants for silanol elimination depend both on the nature of the protecting group and of the base present. In the series of *t*-BuMe$_2$Si protected nucleosides

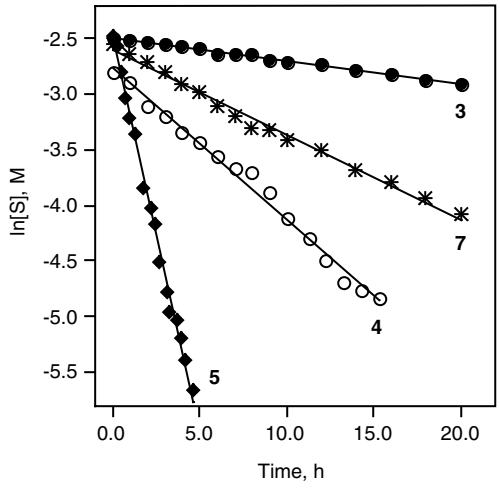
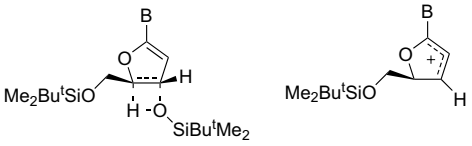


Figure 1. Semi-logarithmic plots for the disappearance of compounds **3** (●), **7** (∗), **4** (○), and **5** (◆) versus time.



15 **16**

Scheme 2.

the rate constants varied as much as 350 times in the order **3** < **4** < **5** < **6**. Thus, by replacing the H1′ in prototype **3** with uracil or adenine moieties the rate constant increased 6.8 and 36 times, respectively (Fig. 1, compounds **3**, **4**, and **5**). By replacing the NH_2 group of adenine by N=PPh$_3$ the rate constant is further increased 10 times. On the other hand, the thermolysis of cyclic silylated derivatives **7** and **8** occurs a few times more slowly than the corresponding derivatives **4** and **5** (Table 1), which can be attributed to the increased stability of these cyclic derivatives. These reactions seem to be analogous of the four-center elimination reaction of HX from RX, where X = Cl, Br, I, OH, and OCH_3.[12] We believe that a four-membered cyclic transition state like **15** is the most reasonable path (Scheme 2).

Nevertheless, we also considered the possibility of an E_1-type elimination that would initially generate a stabilized allylic cation such as **16**. The intermediacy of such a charged species would be expected to be favored in a polar medium and this predicts a rate enhancement for the elimination reaction in polar solvents. Therefore, we run the kinetics for the thermal reaction of compound **5** in methanol-d_4. Methanol can also function as a trap for a putative allylic carbocation as we have observed in a similar system.[13] The reaction proceeded with the formation of the furanyl nucleoside **11** as observed in benzene. The rate constant for the furanyl nucleoside formation was found to be 2.3×10^{-4} at 140 °C, virtually identical to the one observed in benzene-d_6 (See Table 1). This finding corroborates with the four-center elimination mechanism proposed above as it is expected to exhibit similar rates in polar and nonpolar media.

Assuming a preexponential factor similar to those reported, that is, $\log(A/s^{-1}) = 13.5$,[12] we calculated an E_a of 35.4 kcal/mol for the prototype glucal, and values of 33.9, 32.5, and 30.6 kcal/mol for the 1′,2′-didehydro derivatives **4**, **5**, and **6**, respectively. Thus, by replacing the hydrogen with uracil or adenine substituents, the E_a decreases by 1.5 and 2.9 kcal/mol, respectively, which is in agreement with the expected ability of the two bases to conjugate the furan ring.[14] The decrease of 1.9 kcal/mol in the E_a for the thermolysis of **6** with respect to **5** is assigned to a higher conjugation ability of the base substituent due to the presence of N=PPh$_3$ group.

In conclusion, the thermal reaction of 1′,2′-didehydro nucleosides corresponds to a convenient preparation of furanyl nucleosides that appears to proceed via a 'four-center complex fission' where the nature of the base plays an important role for the reactivity trends.

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10. Compounds **9**[11] and **10**[3] were characterized through comparison with literature data. (**11**). ^{1}H NMR (200 MHz, C_6D_6) δ 0.04 (6H, s, SiMe), 0.94 (9H, s, Si^{t}Bu), 4.40 (2H, s), 5.58 (2H, br s, NH_2), 6.04 (1H, d, $J = 3.4$ Hz), 6.68 (1H, d, $J = 3.4$ Hz), 7.66 (1H, s, 2-H), 8.63 ppm (1H, s, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.9 (2×CH_3), 18.6 (C), 26.1 (3×CH_3), 58.2 (CH_2), 100.3 (CH), 109.7 (CH), 119.6 (C), 138.0 (CH), 140.8 (C), 149.3 (C), 151.4 (C), 154.3 (CH), 156.0 ppm (C). MS (ESI, 70 eV) m/z (relative intensity) 346.5 (M+H$^+$, 100), 136.2 (B+H$^+$, 54). Anal. Calcd for $C_{16}H_{23}N_5O_2Si$: C, 55.63; H, 6.71; N, 20.27. Found: C, 55.72; H, 6.69; N, 20.19. (**12**). Mp = 141–144 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (6H, s, SiMe), 0.90 (9H, s, SiBu^t), 4.66 (2H, s, 5′-H), 6.37 (1H, d, $J = 3.2$ Hz), 6.59 (1H, d, $J = 3.2$ Hz), 7.4–7.6 (9H, m, PPh_3), 7.85–7.95 (6H, m, *o*-Ph) 8.07 (1H, s, H-8), 8.20 ppm (1H, br s, H-2). ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.1 (2×CH_3), 25.9 (3×CH_3), 29.7 (C), 58.0 (CH_2), 99.9 (CH), 109.4 (CH), 128.4, 128.6, 132.1, 133.3, 133.5 (3×CH), 137.0 (CH), 151.3 (C), 152.4 (CH). IR (KBr): 2926, 2854, 1626, 1580, 1549, 1452, 1289, 1122, 840 cm^{-1}. Anal. Calcd for $C_{34}H_{36}N_5O_2PSi$: C, 67.42; H, 5.99; N, 11.56. Found: C, 67.25; H, 6.00; N, 11.60. (**13**). ^{1}H NMR (200 MHz, C_6D_6) δ 1.00–1.03 (28H, Si^{i}Pr), 4.73 (2H, s), 5.70 (1H, d, $J = 8.0$ Hz), 6.38 (2H, AB_q, $\Delta\delta = 7.8$ Hz, $J_{AB} = 3.9$ Hz), 7.44 (1H, d, $J = 8.0$ Hz), 9.20 ppm (1H, br s, NH). MS (ESI, 70 eV) m/z (relative intensity) 469.6 (M+H$^+$, 100), 113.4 (B+H$^+$, 36). Anal. Calcd for $C_{21}H_{36}N_2O_6Si_2$: C, 53.81; H, 7.74; N, 5.98. Found: C, 53.70; H, 7.70; N, 6.00. (**14**). ^{1}H NMR (200 MHz, C_6D_6) δ 1.19–1.23 (28H, Si^{i}Pr), 4.78 (2H, s), 6.15 (1H, d, $J = 3.3$ Hz), 6.22 (2H, br s, NH_2), 6.49 (1H, d, $J = 3.3$ Hz), 7.71 (1H, s, 2-H), 8.60 ppm (1H, s, 8-H). MS (ESI, 70 eV) m/z (relative intensity) 492.5 (M+H$^+$, 100), 136.3 (B+H$^+$, 25). Anal. Calcd for $C_{22}H_{37}N_5O_4Si_2$: C, 53.74; H, 7.58; N, 14.24. Found: C, 53.90; H, 7.62; N, 14.20.
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