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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3851–3854

Probing of PSE acetal protection for nucleoside chemistry

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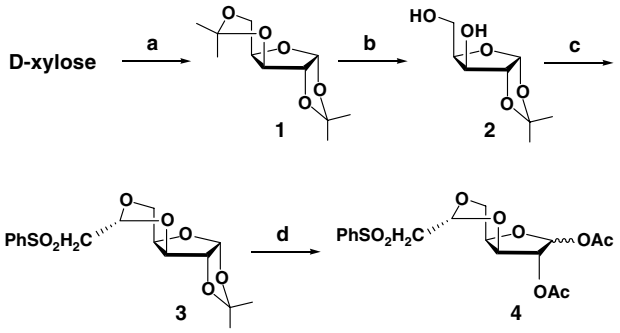
Received 9 March 2007; revised 23 March 2007; accepted 27 March 2007
Available online 2 April 2007

Abstract—The use of phenylsulfonylethylidene (PSE) acetal as a new 3′,5′-bridged protecting group in nucleoside chemistry is reported. The PSE acetal demonstrates to be compatible with Lewis acids used in standard glycosylation reactions. In addition, a selective 2′-O-deacylation from a 3′,5′-*O*-(phenylsulfonyl)-2′-*O*-acetyl nucleoside can be achieved, giving access to subsequent chemical modifications in 2′ position. However, the PSE acetal cleavage surprisingly appeared to be purine/pyrimidine base dependent.

Nucleoside analogues are an important class of clinically useful drugs possessing antiviral[1] and anticancer activities.[2] In most cases, the synthesis of such biologically active compounds involves reaction of persilylated heterocyclic bases with peracylated sugars in the presence of a Lewis acid catalyst, such as $SnCl_4$ or TMSOTf, followed by chemical modifications on the sugar residue. This synthetic strategy requires multiple steps related to the selective introduction-cleavage of hydroxyl protecting groups.[3] Recently, phenylsulfonylethylidene (PSE) acetal, was introduced as a new protection for 1,2 and 1,3-diols[4] owing to its atypical properties.[5] Indeed, PSE acetals are resistant to acid-catalyzed hydrolysis, whereas they can be removed under reductive or basic conditions. In this respect, we have evaluated the potential of the PSE acetal as a new protective group in nucleoside chemistry.



Scheme 1. Reagents and conditions: (a) Me_2CO, H_2SO_4, $CuSO_4$, rt, 15 h; (b) HCl 0.2%, 6 h, rt, 92% (two steps); (c) NaH, BPSE, Bu_4NBr, THF, rt, 12 h, 88%; (d) (i) 80% AcOH, reflux, 3 h, (ii) Ac_2O, DMAP, C_5H_5N, 12 h, 87% (2 steps).

The study began with the preparation of 1,2-di-*O*-acetyl-3,5-*O*-(2-phenylsulfonyl)ethylidene-D-xylofuranose **4** (Scheme 1) as a new osidic condensable precursor. Compound **4** was synthesized in five steps from commercially available D-xylose in 70% overall yield. Briefly, D-xylose was converted into 1,2-*O*-isopropylidene-D-xylofuranose **2** following a synthetic pathway previously reported by Gosselin et al.[6] Conversion of **2** into previously described PSE acetal derivatives **3** was performed in 88% yield in accordance with the literature.[4] In a preliminary assay, hydrolytic cleavage of the isopropylidene group from compound **3** and acetylation of the hemiacetal intermediate was attempted in one step using H_2SO_4/AcOH/Ac_2O. Unfortunately, the desired product was isolated in poor yield. However, applying a two-step procedure (80% AcOH under reflux, then Ac_2O/pyridine/DMAP cat.) provided in good yield compound **4** as an inseparable mixture of two anomers[7] (α/β 1/3, anomeric ratio based on ^1H NMR spectra).

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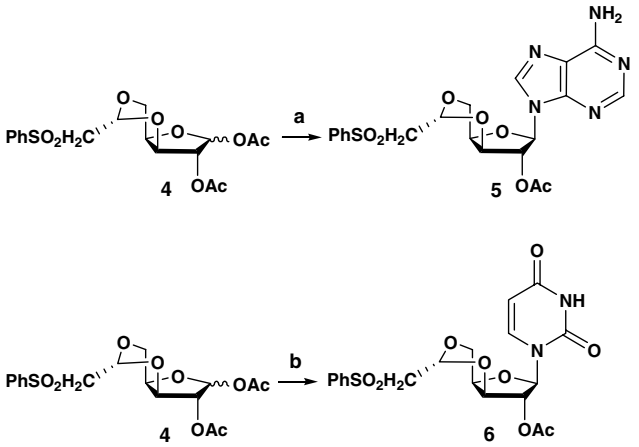
doi:10.1016/j.tetlet.2007.03.153



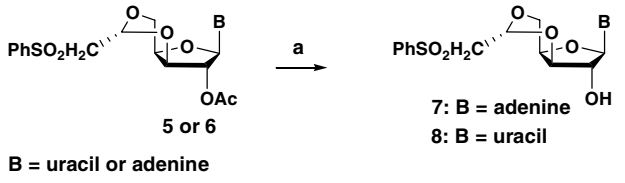
Scheme 2. Reagents and conditions: (a) adenine, $SnCl_4$, CH_3CN, rt, 12 h, 70%; (b) uracil, BSA, CH_3CN, reflux, 2 h then compound **4**, TMSOTf, 0 °C to rt, 12 h, then reflux 4 h, 89%.

In order to evaluate the potential interest of the PSE acetal as protecting group in nucleoside synthesis, two routine coupling methods (Saneyoshi[8] or Vorbrüggen[9] conditions) were applied starting from compound **4**, to give respectively (owing to 2-*O*-acyl participation)[10] the corresponding protected adenine and uracil β-D-*xylo*-nucleoside derivatives **5**[11] and **6**[12] (Scheme 2). The exclusive presence of the regio-isomers *N*-9 and *N*-1 was fully established from their ^1H, ^{13}C NMR and UV spectra.

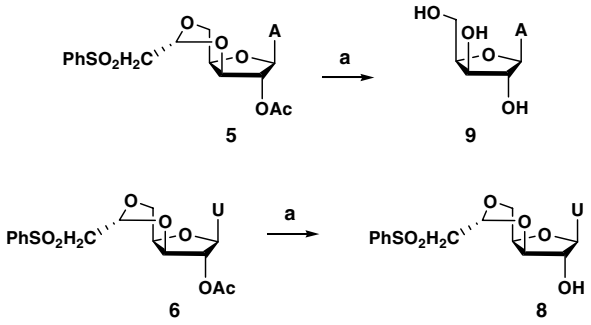
In the case of uracil *xylo*-nucleoside derivative **6**, the yield of the glycosylation step (89%) was improved in comparison with those usually obtained. For example, the same reaction conditions applied to 1,2,3,5-tetra-acetoxy-D-xylofuranose only gave a 70% yield of the corresponding uracil *xylo*-nucleoside.[13] Further studies are in progress to rationalize this result, which probably originates from steric and/or electronic effects attributable to the PSE acetal.

Modification of the sugar moiety of nucleosides may produce marked changes in the spectrum of their biological activity and degree of selective toxicity, as well as in their chemical and physical properties. In particular, modification of the 2′- and/or 3′-positions[14] has resulted in compounds with a broad range of biological activity.

In order to study the orthogonality of the PSE acetal with the 2′-*O*-acetyl protection, compounds **5** and **6** have been selectively 2′-O-deacylated (K_2CO_3, MeOH, room temperature, Scheme 3) in good yield to respectively afford *xylo*-nucleosides **7** (mp 212 °C) and **8** (mp 136 °C). This selective 2′-O-deacylation could thus lead to subsequent chemical modifications on that position.



Scheme 3. Reagents and conditions: (a) K_2CO_3, MeOH, rt, 5 h, 90% for adenine and 87% for uracil.



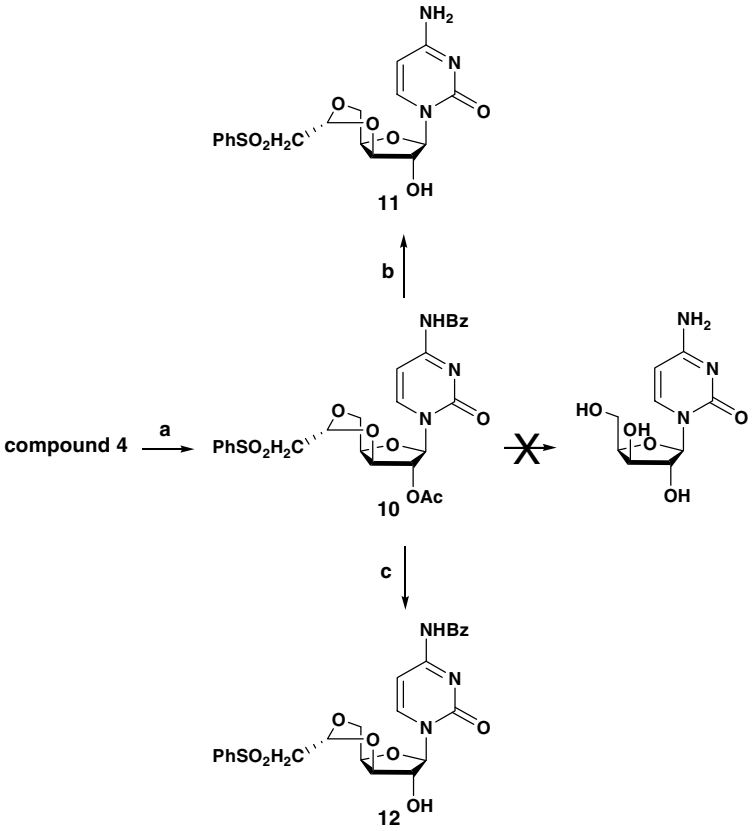
Scheme 4. Reagents and conditions: (a) KOH/EtOH 0.6 M, reflux, 8 h, 75% for adenine, 79% for uracil.

We then studied the PSE acetal cleavage, which can be effected under either basic or reductive conditions.[4,5] Thus, treatment of **5** with KOH in refluxing methanol for 8 h gave 9-β-D-xylofuranosyladenine **9**[15] in 75% yield. Surprisingly however, under the same conditions compound **6** only afforded the 2′-O-deacylated nucleoside **8** (79%, Scheme 4).

Several other methods were attempted (Cs_2CO_3/EtOH, $LiNH_2/NH_3$/THF, NaOH/H_2O, LDA/THF, $LiAlH_4$/THF),[4] but all of them either led to the 2′-O-deacylated compound **8** or to degradation of the starting material. The difference observed in the reactivity of nucleoside analogues **5** and **6** might be explained by the formation in the uracil series of the *N*-3-anion, resulting from the basic conditions required for the PSE cleavage. Thus, the reaction which occurs between the methylene group adjacent to the sulfone and bases to achieve PSE acetal cleavage via a β-elimination, would be prevented by the negative charge present on the pyrimidine heterocycle. In order to confirm this hypothesis, a coupling reaction between compound **4** and N^4-benzoyl cytosine, following Vorbrüggen conditions, was performed to produce compound **10** in 78% yield (Scheme 5). Nevertheless, as for compound **6**, the PSE acetal cleavage remained unsuccessful. KOH in methanol gave the 2′-O-deacylated and 4-N-debenzoylated nucleoside **11** in 76% yield, whereas $LiNH_2$ in THF/NH_3 selectively afforded the 2′-O-deacylated nucleoside **12** in 89% yield.

These preliminary results seem to indicate that differences observed for hydrolysis of the PSE acetal in the purine or pyrimidine nucleoside series is not directly related to the deprotonation of the aglycon under the used basic conditions, but seems to be affected by the nature of the constituting heterocyclic base.

In summary, we have established that the stability of the PSE acetal is compatible with usual glycosylation conditions. Furthermore, starting from a 3′,5′-*O*-(2-phenylsulfonyl)ethylidene-2′-*O*-acetyl nucleoside, an efficient selective 2′-O-deacylation can be achieved, opening access to subsequent chemical modifications at the 2′ posi-



Scheme 5. Reagents and conditions: (a) N^4-Bz cytosine, BSA, CH_3CN, reflux, 2 h then compound **4**, TMSOTf, 0 °C to rt, 12 h, then reflux 4 h, 75%; (b) KOH, EtOH, reflux, 8 h, 76%; (c) $LiNH_2$, NH_3/THF, −50 °C to rt, 89%.

tion. Nevertheless, the reactivity of the PSE acetal moiety appeared unusual; when introduced on a nucleoside skeleton, the removal of the protective group under basic conditions does not follow a general rule, as being successful in the case of adenine *xylo*-nucleoside, but unsuccessful with *xylo*-nucleoside derivatives of uracil and cytosine. The nature of the base (purine or pyrimidine) seems to be at the origin of this different reactivity. In order to confirm this hypothesis, further investigations are in progress in our laboratory.

References and notes

1. De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133.
2. Matsuda, A.; Sasaki, T. *Cancer Sci.* **2004**, *95*, 105–111.
3. Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385–423.
4. Chery, F.; Rollin, P.; De Lucchi, O.; Cossu, S. *Synthesis* **2001**, 286–292.
5. (a) Cabianca, E.; Chery, F.; Rollin, P.; Tatibouët, A.; De Lucchi, O. *Tetrahedron Lett.* **2002**, *43*, 585–587; (b) Chevalier-du Roizel, B.; Cabianca, E.; Tatibouët, A.; Rollin, P.; Sinaÿ, P. *Tetrahedron* **2002**, *58*, 9579–9583; (c) Cabianca, E.; Tatibouët, A.; Rollin, P. *Polish J. Chem.* **2005**, *79*, 317–322.
6. Gosselin, G.; Bergogne, M. C.; Imbach, J.-L. In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques, Part 4*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1991; pp 41–45.
7. *Selected physicochemical data for compound* **4**. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ 1.98 (s, $CH_3\alpha$), 2.00 (s, $CH_3\beta$), 2.07 (s, $CH_3\beta$), 3.44 (br d, $J = 5.0$ Hz, 2H, H-α and H-β), 3.90 and 4.12 (ABX, $J = 13.5$, 2.0 Hz, 2H, H-5α), 3.90 and 4.18 (AB, $J = 12.8$ Hz, 2H, H-5β), 3.97 (br s, 1H, H3-β), 4.04 (br s, 1H, H-3α), 4.26 (d, 1H, H-4α and H-4β), 4.81 (s, 1H, H-2β), 4.94 (d, 1H, $J = 4.5$ Hz, H-2α), 5.02 (t, $J = 5.0$ Hz, 1H, H-6α and H-6β), 5.97 (s, 1H, H-1β), 6.34 (d, $J = 4.5$ Hz, 1H, H-1α), 7.51–7.56 (m, 2H), 7.61–7.66 (m, 1H), 7.85–7.88 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 20.3 ($CH_3\alpha$), 20.6 ($CH_3\beta$), 20.7 ($CH_3\alpha$), 21.0 ($CH_3\beta$), 60.0 (C-7α), 60.2 (C-7β), 65.8 (C-5α), 66.0 (C-5β), 72.2 (C-3α), 74.4 (C-3β), 75.9 (C-4β), 76.3 (C-2α), 78.4 (C-4α), 80.1 (C-2β), 94.5 (C-6β), 94.8 (C-6α), 95.4 (C-1α), 99.9 (C-1β), 128.2 (CH_{arom}), 128.9 (CH_{arom}), 133.8 (CH_{arom}), 133.9 (CH_{arom}), 139.8 (C_{arom}), 139.9 (C_{arom}), 169.0 (CO), 169.5 (CO). MS (FAB, GT) 423 $(M+Na)^+$, 341 $(M-AcOH)^+$.
8. Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull.* **1979**, *27*, 2518.
9. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255.
10. Baker, B. R. In *The CIBA Foundation Symposium on the Chemistry and Biology of the Purines*; Wolstenholme, G. E. W., O'Connor, C. M., Eds.; Churchill: London, 1957; pp 120–133.
11. *Selected physicochemical data for compound* **5**. Mp 123 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ 2.17 (s, 3H, CH_3), 3.43 (ddd, $J = 14.7$, 6.4, 4.2 Hz, 2H, H-7′), 4.05 and 4.39 (ABX, $J = 13.4$, 1.8 Hz, 2H, H-5′), 4.15 (br s, 1H, H-3′), 4.30 (d, $J = 2.2$ Hz, 1H, H-4′), 4.94 (s, 1H, H-2′), 5.10 (dd, $J = 6.3$, 4.3 Hz, 1H, H-6′), 5.64 (br s, 2H, NH_2), 6.16 (s,

1H, H-1′), 7.35–7.43 (m, 3H, H_{arom}), 7.76–7.80 (m, 2H, H_{arom}), 7.97 (s, 1H, H-2), 8.32 (s, 1H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 20.7 (CH_3), 59.5 (C-7′), 66.0 (C-5′), 74.5 (C-3′), 76.8 (C-4′), 79.9 (C-2′), 88.4 (C-1′), 95.0 (C-6′), 119.5 (C-5), 128.0 (CH_{arom}), 128.7 (CH_{arom}), 133.5 (CH_{arom}), 138.7 (C-8), 139.6 (C_{arom}), 149.1 (C-4), 153.0 (C-2), 155.3 (C-6), 168.9 (CO). MS (FAB, GT) 476 $(M+H)^+$, 474 $(M-H)^-$. UV (EtOH 95) $\lambda_{max} = 263$ nm ($\varepsilon_{max} = 16400$). $[\alpha]_D^{20}$ −46.0 (*c* 1.00, $CDCl_3$).

12. *Selected physicochemical data for compound* **6**. Mp 153 °C. ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ 2.13 (s, 3H, CH_3), 3.39 (ddd, $J = 14.6$, 6.1, 4.5 Hz, 2H, H-7′), 4.03 and 4.37 (ABX, $J = 13.4$, 1.6 Hz, 2H, H-5′), 4.08 (br s, 1H, H-3′), 4.22 (d, $J = 2.0$ Hz, 1H, H-4′), 4.75 (s, 1H, H-2′), 5.08 (dd, $J = 6.1$, 4.5 Hz, 1H, H-6′), 5.58 (br d, $J = 8.2$ Hz, 1H, H-5), 5.80 (s, 1H, H-1′), 7.52–7.65 (m, 4H, H_{arom} and H-6), 7.84–7.87 (m, 2H, H_{arom}), 8.97 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 20.6 (CH_3), 59.4 (C-7′), 66.0 (C-5′), 74.8 (C-3′), 77.1 (C-4′), 79.8 (C-2′), 89.7 (C-1′), 95.1 (C-6′), 101.1 (C-5), 128.2 (CH_{arom}), 129.0 (CH_{arom}), 134.0 (C-6), 139.8 (C_{arom}), 139.9 (CH_{arom}), 149.8 (CO), 163.0 (CO), 168.8 (CO). MS (FAB, GT) 453 $(M+H)^+$, 451 $(M-H)^-$. UV (EtOH 95) $\lambda_{max} = 263$ nm ($\varepsilon_{max} = 9200$). $[\alpha]_D^{20}$ −10.0 (*c* 1.00, $CDCl_3$).

13. Sahabuddin, S.; Ghosh, R.; Achari, B.; Mandal, S. B. *Org. Biomol. Chem.* **2006**, *4*, 551–557.

14. (a) Len, C.; Mackenzie, G. *Tetrahedron* **2006**, *62*, 9085–9107; (b) Pathak, T. *Chem. Rev.* **2002**, *102*, 1623–1667; (c) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768.

15. Physicochemical data of compound **9** are in agreement with those reported in the literature: Gosselin, G.; Bergogne, M.-C.; Derudder, J.; De Clercq, E.; Imbach, J.-L. *J. Med. Chem.* **1986**, *29*, 203–213.