Pergamon

Tetrahedron Letters 42 (2001) 2977–2980

TETRAHEDRON LETTERS

Base-modified nucleosides from carbohydrate derived oxazolidinethiones: a five-step process

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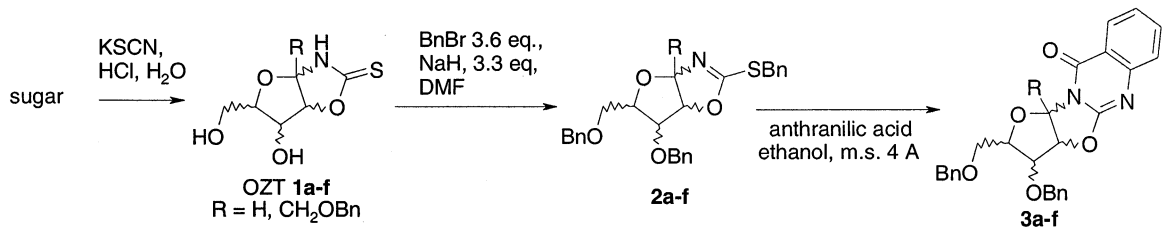
Received 9 February 2001; accepted 3 March 2001

Abstract—Starting from unprotected carbohydrates, base-modified nucleosides could be reached in four steps through the condensation of anthranilic acid with a suitably protected sugar-derived 2-alkylthio-1,3-oxazoline.

Synthetic base-modified nucleosides and nucleotides have an important impact in various fields. Their biological properties have found application in antiviral tools against VZV and HIV,[1] in evaluation and study of DNA damages,[2] as well as in the anti-sense approach and DNA-probe technology with fluorescence properties.[3] Investigations were also undertaken on the physico-chemical parts of DNA base-to-base interactions (hydrogen bonding and stacking).[4] Two general methods for nucleoside preparation have been reported in the literature, one using the glycosylation method[5] which may lead to anomeric selectivity problems, the other based on a multistep process to construct entirely the base from the sugar.[6]

Our convergent approach to artificial nucleoside synthesis involves a sugar derived 1,3-oxazolidine-2-thione (OZT) and anthranilic acid. Condensation reactions of anthranilic acid derivatives have already been explored.[7] Within the frame of a research program centered on the preparation and reactivity of chiral natural OZT, such reactions were developed.[8,9] Application of the process of anthranilic acid condensation with per-benzylated OZT led to new homochiral quinazolinone derivatives. Application of the cyclocondensation process to sugar-derived OZT constitutes a promising extension of this reaction to new base-modified nucleosides.

Preparing the sugar derived OZT **1a–f** is straightforward (Scheme 1).[10] Standard conditions were applied to various series of sugars: D- and L-arabinose, D-xylose, D-ribose (aldopentose series) as well as D-fructose and L-sorbose (hexoketose series). On native or partially protected sugars (1-*O*-benzyl-D-fructose and 1-*O*-benzyl-L-sorbose), the OZT were obtained in one step using potassium thiocyanate in acidic conditions (80–100%). This reaction allowed us to produce diverse OZT **1a–f** in which the configuration of the sugar ring was perfectly defined. A furano-conformation, confirmed by ^{1}H and ^{13}C NMR spectrum[11] and an anomeric configuration controlled by the location of the hydroxyl group on C-2 were observed. In addition, in D-fructo- and L-sorbo-derivatives, known to usually give mix-



Scheme 1.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)00357-4

Table 1. Application of the procedure to aldoses and ketoses

Sugars	R	**2a–f** (%)	**3a–f** (%)
D-Arabinose	H	38	78
L-Arabinose	H	41	79
D-Xylose	H	48	75
D-Ribose	H	42	65
1-*O*-Benzyl-D-fructose	CH_2OBn	64	14
1-*O*-Benzyl-L-sorbose	CH_2OBn	38	16

tures of compounds, the benzyl protection on the first position determined the formation of only one stereoisomer of the four that could be expected from the unprotected sugar.[12]

Prior to cyclocondensation, the OZT has to be activated through *S*-alkylation.[13] This sequence furnishes per-*O*- and -*S*-benzylated compounds **2a–f** in reasonable yields for a two-step sequence (Table 1).

Condensation of the 2-alkylthio-1,3-oxazoline derivatives **2a–f** with anthranilic acid in dry ethanol offers an efficient access to sugar derived quinazolinones **3a–f** mostly in good yields.[14] In the case of D-fructo and L-sorbo derivatives, however, yields were quite poor. Those results might be explained by a steric hindrance of the benzyloxymethyl group attached to the anomeric carbon. Moreover, a competing nucleophilic attack of ethanol providing the corresponding 2-ethoxy-1,3-oxazoline analogs was observed. Improvement of the conditions was investigated using different solvents such as DMF or *tert*-butanol. In aprotic media (DMF), no condensation was detected and in *tert*-butanol only a very slow reaction occurred. Activation was performed through addition of two equivalents of camphorsulfonic acid. In such conditions, cyclocondensations occurred in reasonable yield for D-fructo and L-sorbo derivatives (57 and 70%, respectively).

Some preliminary attempts with other 1,2-aminoaromatic acids were undertaken as a possible extension of the method. We employed the D-xylo-derivative **1c** as a model using the typical procedure.[12] The results (Table 2) showed that the presence of an electron withdrawing group hampered the reaction. The replacement of benzene by a pyridine ring (2-aminonicotinic acid) expectedly did not allow the formation of the desired compound.

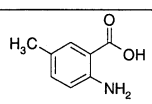
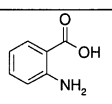
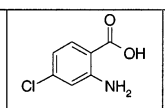
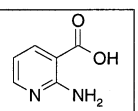
In order to validate our approach to base-modified nucleosides, we have investigated the ring-cleavage of quinazolinones **3**. Inspired by the well documented 2,2′-anhydronucleoside chemistry we have reacted the D-arabino derivative **3a** in basic conditions.[15] This reaction is effective in good yield (67%) and in our case, takes place with no inversion of configuration. We obtained a D-arabino compound **4a**, which incorporates a quinazolinedione system as the base. The 2,2′-anhydronucleoside **3a** was also submitted to acidic conditions to afford **4a** with a better yield of 74%.[16] Further hydrogenolysis of benzyl groups (H_2 and Pd/C) afforded the D-arabinonucleoside analog **5a** with 74% yield (Scheme 2).[17]

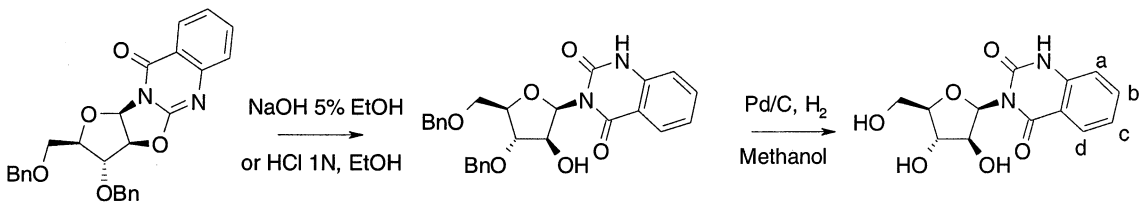
In summary, a concise (five steps) and practical synthesis of base-modified nucleosides has been disclosed starting from native carbohydrates through OZT derivatives. This procedure constitutes an original application of cyclocondensations involving anthranilic acid and analogs. The reaction has been extended with success to different sugar series (pentoses and hexoses) and also to diverse heterocyclic systems. Further exploration of the chemistry is currently performed to obtain D-ribo and 2-deoxy-D-ribo analogs.

Acknowledgements

This work was supported by a TEMPUS-PHARE grant (J.G.) and an MENRT grant (D.G.).

Table 2. Extension to diverse amino-aromatic acids

Aromatic system				
yields	78%	75%	38%	no reaction



3a **4a** **5a**

Scheme 2.

References

1. (a) McGuigan, C.; Yarnold, C. J.; Jones, G.; Velazquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4479–4484; (b) Brancale, A.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1215–1217.
2. (a) Harwood, E. A.; Hopkins, P. B.; Sigurdsson, S. T. *J. Org. Chem.* **2000**, *65*, 2959–2964; (b) Kotera, M.; Roupioz, Y.; Defrancq, E.; Bourdat, A.-G.; Garcia, J.; Coulombeau, C.; Lhomme, J. *Chem. Eur. J.* **2000**, *6*, 4163–4169.
3. (a) Rösler, A.; Pfleiderer, W. *Helv. Chim. Acta* **1997**, *80*, 1869–1881; (b) Trévisiol, E.; Defrancq, E.; Lhomme, J.; Laayoun, A.; Cros, P. *Eur. J. Org. Chem.* **2000**, 211–217; (c) Jourdan, F.; Ladurée, D.; Robba, M. *J. Heterocycl. Chem.* **1994**, *31*, 305–312; (d) Wang, Z.; Rizzo, C. J. *Org. Lett.* **2000**, *2*, 227–230.
4. (a) Guckian, K. M.; Morales, J. C.; Kool, E. T. *J. Org. Chem.* **1998**, *63*, 9652–9656; (b) Kool, E. T.; Morales, J. C.; Guckian, K. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 990–1009.
5. (a) Jungmann, O.; Pfleiderer, W. *Tetrahedron Lett.* **1996**, *37*, 8355–8358; (b) Sugimura, H.; Osumi, K.; Kodaka, Y.; Sujino, K. *J. Org. Chem.* **1994**, *59*, 7653–7660.
6. (a) Gosselin, G.; Bergogne, M.-C.; De Rudder, J.; De Clercq, E.; Imbach, J.-L. *J. Med. Chem.* **1986**, *29*, 203–213; (b) Mourier, N. S.; Eleuteri, A.; Hurwitz, S. J.; Tharnish, P. M.; Shinazi, R. F. *Bioorg. Med. Chem.* **1999**, *7*, 2759–2766.
7. (a) Sauter, F.; Fröhlich, J.; Blasl, K.; Gewald, K. *Heterocycles* **1995**, *40*, 851–866; (b) Preshad, M.; Chen, L.; Repic, O.; Blacklock, T. J. *Synth. Commun.* **1998**, *28*, 2125–2129.
8. Leoni, O.; Bernardi, R.; Gueyrard, D.; Rollin, P.; Palmieri, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4775–4780.
9. (a) Gueyrard, D.; Grumel, V.; Leoni, O.; Palmieri, S.; Rollin, P. *Heterocycles* **2000**, *52*, 827–843; (b) Gueyrard, D.; Leoni, O.; Palmieri, S.; Rollin, P. *Tetrahedron: Asymmetry* **2001**, *12*, 337–340.
10. Bromund, W.; Herbst, R. M. *J. Org. Chem.* **1945**, 267–276.
11. Davidson, R. M.; Byrd, G. D.; White, E.; Margolis, S. A.; Coxon, B. *Magn. Reson. Chem.* **1986**, *24*, 929–937.
12. (a) Grouiller, A.; Mackenzie, G.; Najib, B.; Shaw, G.; Ewing, D. *J. Chem. Soc., Chem. Commun.* **1988**, 671–672; (b) Lichtenthaler, F. W.; Klotz, J.; Flath, F.-J. *Liebigs Ann. Chem.* **1995**, 2069–2080.
13. **Typical procedure for OZT preparation and benzylation**: D-Arabinose (1 g, 6.67 mmol) and KSCN (1.3 g, 13.4 mmol) were dissolved in cold water and then 37% HCl (1.1 mL) was added. The solution was kept at room temperature for 2 hours then at 55°C overnight. The solution was evaporated and purified over silica gel with ethyl acetate as eluent. The D-arabino-OZT derivative **1a** (1.1 g, 5.75 mmol) was isolated in 86% yield. $[\alpha]_D^{20}$ −52 (*c* 1.07, CH_3OH); ^1H NMR (250 MHz, DMSO) 3.15–3.35 (m, 2H, H-5), 3.84 (t, 1H, $J=6.0$ Hz, H-3), 4.23 (m, 1H, H-4), 4.94 (t, 1H, $J=5.5$ Hz, OH), 5.03 (d, 1H, $J_{1,2}=5.5$ Hz, H-2), 5.69 (d, 1H, $J=4.0$ Hz, OH), 5.78 (d, 1H, $J_{1,2}=5.5$ Hz, H-1), 10.8 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO) 61.4 (C-5), 74.8, 87.4, 89.9, 92.1, 188.9 (CS); ISMS *m/z* 192 $(m+H)^+$.
    Compound **1a** (0.657 g, 3.42 mmol) was dissolved in DMF and cooled under argon in an ice–water bath. NaH (0.45 g, 60%, 11.3 mmol) was added. After a few minutes, benzyl bromide (1.34 mL, 11.3 mmol) was added dropwise over a 10 min period. The mixture was left overnight at room temperature, then diluted with water and extracted with ethyl acetate. The organic phase was washed twice with water, brine and was then dried with $MgSO_4$. After evaporation, the residue was purified on silica gel to furnish the per-benzylated oxazoline **2a** (0.695 g, 1.5 mmol). $[\alpha]_D^{20}$ −71 (*c* 1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 3.20 (dd, 1H, $J_{5a,5b}=10$ Hz, $J_{5a,4}=7$ Hz, H-5a), 3.40 (dd, 1H, $J_{5b,4}=5.5$ Hz, H-5b), 4.04 (m, 1H, H-3), 4.19 (s, 2H, CH_2Ph), 4.23 (m, 1H, H-4), 4.36 (d, 1H, $J=12.1$ Hz, CH_2Ph), 4.43 (d, 1H, $J=12.1$ Hz, CH_2Ph), 4.49 (d, 1H, $J=12.1$ Hz, CH_2Ph), 4.55 (d, 1H, $J=12.1$ Hz, CH_2Ph), 4.85 (dd, 1H, $J_{1,2}=6$ Hz, $J_{2,3}=1$ Hz, H-2), 6.01 (d, 1H, $J_{1,2}=6$ Hz, H-1), 7.10–7.30 (m, 15H, H-arom); ^{13}C NMR (63 MHz, $CDCl_3$) 36.1 (CH_2S-), 69.4 (CH_2), 71.6 (CH_2), 73.1 (C-5), 81.9 (C-3), 85.4 (C-4), 88.1 (C-2), 100.7 (C-1), 126.4, 126.7, 127.0, 127.5, 127.7, 127.8, 128.2, 128.3, 128.4, 128.9, 136.4, 136.9, 137.5, 137.8, 138.8, 169.2; ISMS *m/z* 462 $(m+H)^+$.
14. **Typical procedure for condensation**: Compound **2a** (0.2 g; 0.43 mmol) was dissolved in dry ethanol in the presence of 3 Å molecular sieves. Anthranilic acid (0.071 g, 0.52 mmol) was added and the solution heated under reflux for 24 h. The mixture was then evaporated, extracted with CH_2Cl_2, washed twice with saturated $NaHCO_3$, dried over $MgSO_4$ and purified by silica gel flash chromatography. The D-arabino-quinazolinone derivative **3a** (0.155 g, 0.34 mmol) was isolated in 79% yield. $[\alpha]_D^{20}$ −191 (*c* 0.59, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 3.34 (m, 2H, H-5), 4.16 (d, 1H, $J=12.5$ Hz, CH_2Ph), 4.22 (d, 1H, $J=12.5$ Hz, CH_2Ph), 4.42 (m, 1H, H-4), 4.57 (d, 1H, $J=12$ Hz, CH_2Ph), 4.63 (d, 1H, $J=12$ Hz, CH_2Ph), 5.22 (d, 1H, $J_{1,2}=6$ Hz, H-3), 6.57 (d, 1H, $J_{1,2}=6$ Hz, H-1), 7.01–7.04 (m, 2H, H-arom), 7.17–7.20 (m, 3H, H-arom), 7.31–7.37 (m, 6H, H-arom), 7.48 (d, 1H, $J=7.2$ Hz, H-quinazolinone), 7.66 (m, 1H, H-quinazolinone), 8.22 (m, 1H, H-quinazolinone); ^{13}C NMR (63 MHz, $CDCl_3$) 69.1, 72.6, 73.5, 83.6, 85.4, 86.0, 87.7, 119.0 (C-1), 125.0, 126.4, 127.3, 127.9, 128.0, 128.2, 128.4, 128.5, 128.8, 135.2, 136.5, 137.2, 149.2 (C=N), 154.7 (CO); ISMS *m/z* 457 $(m+H)^+$.
15. Schinadzi, R. F.; Chen, M. S.; Prusoff, W. H. *J. Med. Chem.* **1979**, *22*, 1273–1277.
16. The D-arabino-quinazolinone derivative **3a** was dissolved in ethanol then NaOH 5% was added and the solution was stirred at room temperature for 7 days. The solution was evaporated, extracted with ethyl acetate, washed with water until neutral and then dried over $MgSO_4$. The quinazolinedione **4a** was isolated in 67% yield. $[\alpha]_D^{20}$ −85 (*c* 0.65, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 3.53 (s, 1H, OH), 3.74 (dd, 1H, $J_{5a,5b}=10.4$ Hz, $J_{4,5a}=3.0$ Hz, H-5a), 3.89 (dd, 1H, $J_{4,5b}=8.0$ Hz, H-5b), 4.12 (ddd, 1H, $J_{3,4}=7.5$ Hz, $J_{4,5b}=8.0$ Hz, $J_{4,5a}=3.0$ Hz, H-4), 4.29 (dd, 1H, $J_{2,3}=5.5$ Hz, $J_{3,4}=7.5$ Hz, H-3), 4.52–4.72 (m, 4H, H-2, CH_2Ph), 4.85 (d, 1H, $J=11.5$ Hz, CH_2Ph), 6.78 (d, 1H, $J_{1,2}=8.0$ Hz, H-1), 6.93 (d, 1H, $J_{a,b}=8.0$ Hz, Ha), 7.12 (t, 1H, $J_{c,b}=J_{c,d}=8.0$ Hz, Hc), 7.24–7.47 (m, 10H,

H-arom.), 7.53 (t, 1H, $J_{b,a}=J_{b,c}=7.0$ Hz, Hb), 7.91 (d, 1H, $J_{d,c}=8.0$ Hz, Hd), 9.64 (s, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$) 70.9 (C-5), 72.2 (CH_2Ph), 73.2 (CH_2Ph), 78.8 (C-2), 79.1 (C-4), 82.0 (C-1), 85.8 (C-3), 114.4 (C), 115.1 (Ca), 123.4 (Cc), 127.6, 127.8, 127.6, 127.8, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 135.4 (Cd), 137.9 (C), 138.3 (C), 151.9, (CO), 163.1 (CO); ISMS m/z 457 (m–H_2O+H)$^+$, 475 (m+H)$^+$, 497 (m+Na)$^+$.

17. The D-arabinoquinazolinedione **4a** (0.1 g, 0.021 mmol) was dissolved in methanol, then Pd/C (10%, 0.2 g) was added and the mixture stirred overnight under H_2 at room temperature. After completion, the solution was filtrated over Celite and was washed with pyridine to afford pure **5a** (0.46 mg, 0.016 mmol) with 74% yield. $[\alpha]_D^{20}$ −27 (*c* 1, pyridine); ^{1}H NMR (250 MHz, DMSO–D_2O) 3.55–3.68 (m, 3H, H-5a, H-5b and H-4), 4.18–4.28 (m, 2H, H-2 and H-3), 6.55 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 7.16 (m, 2H, Ha and Hc), 7.59 (dt, 1H, $J_{b,a}=J_{b,c}=8.0$ Hz, $J_{b,d}=1.5$ Hz, Hb), 7.85 (d, 1H, $J_{d,c}=8.0$ Hz, Hd); ^{13}C NMR (63 MHz, DMSO–D_2O) 62.1 (C-5), 76.2 (C-2 or 3), 76.9 (C-2 or 3), 81.4 (C-1), 83.0 (C-4), 114.2 (C), 115.4 (C_a), 122.9 (C_c), 127.8 (C_d), 135.6 (C_b), 139.9 (C), 150.4 (CO), 162.5 (CO); ISMS m/z 295 (m+H)$^+$, 317 (m+Na)$^+$.