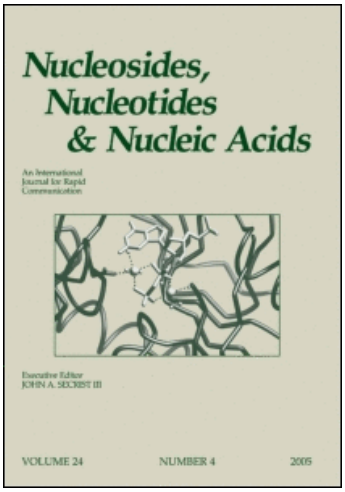


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Stereocontrolled Synthesis of Pyridazine, Pyrazine, and Triazine 2'-DEOXY-β-Nucleosides by Means of Intramolecular Glycosylation

Hideyuki Sugimura[a]; Miho Motegi[a]; Keiko Sujino[a]
[a] The Noguchi Institute, Tokyo, Japan

To cite this Article Sugimura, Hideyuki , Motegi, Miho and Sujino, Keiko(1995) 'Stereocontrolled Synthesis of Pyridazine, Pyrazine, and Triazine 2'-DEOXY-β-Nucleosides by Means of Intramolecular Glycosylation', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 413 — 416
To link to this Article: DOI: 10.1080/15257779508012397
URL: http://dx.doi.org/10.1080/15257779508012397

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 413-416 (1995)

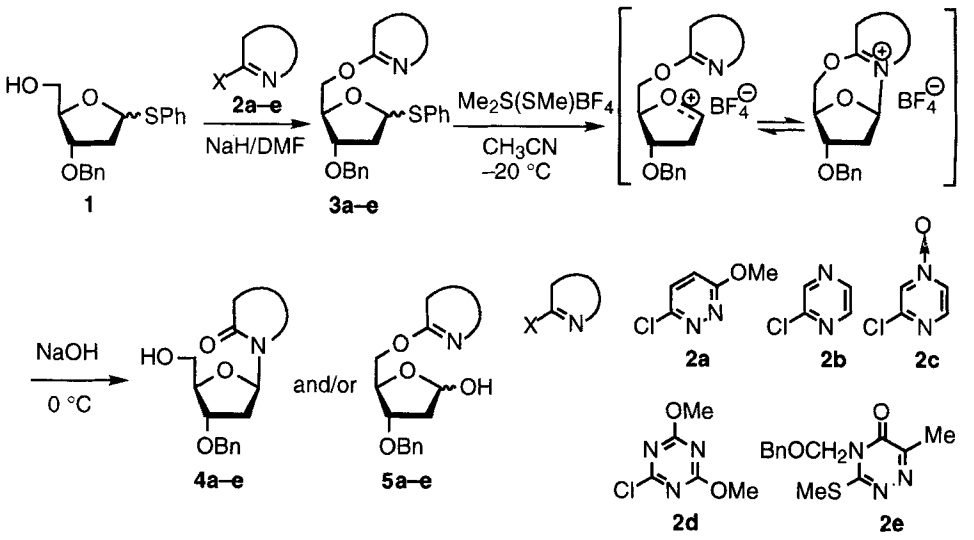
STEREOCONTROLLED SYNTHESIS OF PYRIDAZINE, PYRAZINE, AND TRIAZINE 2'-DEOXY-β-NUCLEOSIDES BY MEANS OF INTRAMOLECULAR GLYCOSYLATION

Hideyuki Sugimura,* Miho Motegi, and Keiko Sujino
The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo 173, Japan

Abstract: The stereocontrolled synthesis of 2'-deoxynucleoside analogs was explored by intramolecular glycosylation of pyridazine, pyrazines and triazines. These heterocycles were temporarily connected to the 5-O position in 1-thioglycoside via ethereal linkage.

The synthesis of base-modified thymidine and 2'-deoxycytidine analogs, in which the pyrimidine base is substituted by other heterocycles such as pyridazines,[1] pyrazines[2] and triazines,[3] is of much interest due to their potential antitumor and antiviral activity. Although a number of approaches to these derivatives have appeared, the stereoselective construction using the coupling reaction of a 2-deoxy sugar residue with a heterocyclic base remains a considerable synthetic challenge. We have recently reported the stereocontrolled synthesis of pyrimidine 2'-deoxy- and 2',3'-dideoxy-β-nucleosides by intramolecular glycosylation.[4,5] In this paper, we extended this method to the stereoselective synthesis of pyridazine, pyrazine and triazine 2'-deoxynucleosides.

Our strategy is outlined in SCHEME 1. Treatment of the sodium salt of **1** with pyridazine, pyrazine and triazine derivatives, **2a–e**, affords **3a–e** in satisfactory yields. The activation of these thioglycosides with $Me_2S(SMe)BF_4$ leads to oxonium intermediates, which are then converted to quaternary onium salts. Subsequent basic hydrolysis affords the desired β-N-glycosides **4**. The results obtained are summarized in TABLE 1. The reaction of pyridazine derivative **3a** proceeds smoothly to give the desired nucleoside **4a** as the sole product. However, similar glycosylation using pyrazine derivatives **3b** and **3c** results in poor yields probably due to the lability of the oxonium and the quaternary onium intermediates. Unfortunately, the reaction of 1,3,5-triazine derivative **3d** fails to yield the nucleoside product **4d**, instead affording **5d** which can be assumed to result from direct hydrolysis of the oxonium salt. Low nucleophilicity of the triazine seems to be the reason for the production of **5d**. On the other hand, the reaction of 1,2,4-triazine derivative **3e** at –20 °C is complicated by the formation of side-products.



SCHEME 1

TABLE 1.

Heterocyclic compound	Yield of **3** (%)	Reaction time for glycosylation	Yield(s) of **4**(%)	**5** (%)
2a	62	10 min	85	–
2b	85	1.5 h	18	31
2c	85	5 h	12	16
2d	69	5 h	–	88[a]
2e	58	5 h[b]	59[c]	18

[a] Small amounts of unidentified compounds were contained. [b] The reaction was carried out at –78 °C using C_2H_5CN as the solvent. [c] The starting material was recovered in 10% yield.

However, by performing the reaction at –78 °C in propionitrile, the desired 6-azathymidine **4e** is obtained in 59% yield.

EXPERIMENTAL

Heterocyclic compounds **2a**, **2b** and **2d** were purchased and **2c**[3a] and **2e**[6] were prepared according to the literature.

General Procedure for the Intramolecular Glycosylation. The Preparation of 3a–e. To a solution of thioglycoside **1** (1 mmol) in 6 mL of DMF was added NaH (2

mmol) under Ar. The mixture was then stirred at room temperature for 1 h. After the reaction mixture was cooled at –50 °C (for **2a**) or 0 °C (for **2b–e**), a heterocyclic compound (2 mmol) was added and the mixture was allowed to warm to room temperature and stirred overnight. After water was added, the mixture was extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel to give **3**.

The Intramolecular Glycosylation. To a solution of **3** (0.2 mmol) in 50 mL of CH_3CN (C_2H_5CN for **3e**) was added powdered molecular sieves 4A under Ar. After 30 min, the solution was cooled to –20 °C (–78° C for **3e**) and $Me_2S(SMe)BF_4$ (0.22 mmol) was added. The reaction mixture was stirred at the same temperature for an appropriate period (see TABLE 1). 1 M NaOH aq. was added and then the mixture warmed to 0 °C. After 2 h, saturated NH_4Cl aq. was added. The aqueous layer was extracted with $CHCl_3$ and the combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel. The following nucleosides were prepared according to this procedure.

1-(3-*O*-Benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-3-methoxypyridazin-6-one (4a). mp 94–95 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.38 (ddd, 1H, *J*=3.9, 6.8, 13.7 Hz, H-2'), 2.58 (ddd, 1H, *J*=6.5, 6.5, 13.7 Hz, H-2'), 3.12 (br, 1H, OH), 3.68 (d, 1H, *J*=11.7 Hz, H-5'), 3.76 (s, 3H, OMe), 3.87 (dd, 1H, *J*=2.9, 11.7 Hz, H-5'), 4.22 (dd, 1H, *J*=2.9, 6.3 Hz, H-4'), 4.39-4.42 (m, 1H, H-3'), 4.55 (d, 1H, *J*=12.2 Hz, $PhCH_2$), 4.61 (d, 1H, *J*=11.7 Hz, $PhCH_2$), 6.80(t, 1H, *J*=6.6 Hz, H-1'), 6.86 (d, 1H, *J*=9.8 Hz), 6.90 (d, 1H, *J*=9.8 Hz), 7.28-7.36 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$) δ 36.2, 54.5, 63.3, 71.6, 79.2, 85.4, 86.3, 127.2, 127.7, 127.9, 128.5, 133.6, 137.7, 153.5, 159.0; IR (KBr) 3360, 2930, 2860, 1670, 1590, 1290, 1110, 1020 cm^{-1}; Anal Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07%. Found: C, 61.45; H, 6.39%.

1-(3-*O*-Benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazin-2-one (4b). ^{1}H NMR ($CDCl_3$) δ 2.34 (ddd, 1H, *J*=3.3, 6.7, 13.7 Hz, H-2'), 2.55 (br, 1H, OH), 2.65 (ddd, 1H, *J*=3.4, 6.3, 13.7 Hz, H-2'), 3.79 (dd, 1H, *J*=2.9, 11.7 Hz, H-5'), 3.97 (dd, 1H, *J*=2.9, 11.7 Hz, H-5'), 4.26 (t, 1H, *J*=2.9 Hz, H-4'), 4.25-4.32 (m, 2H, H-3', 4'), 4.52 (d, 1H, *J*=11.7 Hz, $PhCH_2$), 4.60 (d, 1H, *J*=11.7 Hz, $PhCH_2$), 6.19 (t, 1H, *J*=6.6 Hz, H-1'), 7.31-7.39 (m, 6H, H-5, aromatic), 7.56 (d, 1H, *J*=3.9 Hz, H-6), 8.11 (d, 1H, *J*=1.5 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 37.8, 62.6, 71.7, 78.3, 86.0, 88.4, 124.1, 124.4, 127.7, 128.1, 128.6, 137.4, 149.6, 155.6.

1-(3-*O*-Benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazin-2-one 4-Oxide (4c). ^{1}H NMR ($CDCl_3$) δ 2.23 (ddd, 1H, *J*=6.8, 6.8, 13.7 Hz, H-2'), 2.44 (br, 1H, OH), 2.67 (ddd, 1H, *J*=3.9, 6.4, 13.7 Hz, H-2'), 3.80 (d, 1H, *J*=11.7 Hz, H-5'), 3.99 (d, 1H, *J*=11.7 Hz, H-5'), 4.22–4.31 (m, 2H, H-3', 4'), 4.52 (d, 1H, *J*=11.7Hz, $PhCH_2$), 4.60 (d, 1H,

J=11.7 Hz, $PhCH_2$), 6.28 (t, 1H, *J*=6.4 Hz, H-1'), 7.07 (dd, 1H, *J*=2.0, 6.3 Hz), 7.28–7.40 (m, 5H, aromatic), 7.54 (d, 1H, *J*=2.0 Hz), 7.90 (d, 1H, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 38.6, 62.2, 71.7, 77.9, 85.7, 86.9, 121.4, 127.7, 128.1, 128.6, 129.1, 137.3, 157.0.

3'-*O*-Benzyl-3-benzyloxymethyl-6-azathymidine (4e). ^1H NMR ($CDCl_3$) δ 2.91 (s, 3H, Me), 2.23 (ddd, 1H, *J*=2.4, 6.8, 13.7 Hz, H-2'), 2.76 (ddd, 1H, *J*=7.3, 7.3, 13.7 Hz, H-2'), 3.59 (dd, 1H, *J*=1.4, 12.2 Hz, H-5'), 3.70 (ddd, 1H, *J*=2.4, 12.2, 12.2 Hz, OH), 3.89 (d, 1H, *J*=12.2Hz, H-5'), 4.18 (d, 1H, *J*=2.9 Hz, H-4'), 4.48 (ddd, 1H, *J*=2.4, 2.9, 6.8 Hz, H-3'), 4.55 (s, 2H, $PhCH_2$), 4.70 (s, 2H, $PhCH_2$), 5.32 (d, 1H, *J*=10.3Hz), 5.36 (d, 1H, *J*=10.3 Hz), 6.67 (t, 1H, *J*=7.3 Hz, H-1'), 7.25–7.40 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$) δ 16.8, 34.6, 63.0, 71.8, 72.1, 79.4, 80.0, 83.5, 86.2, 127.6, 127.7, 127.9, 128.4, 128.5, 137.4, 137.7, 143.7, 148.8, 156.0.

Acknowledgment. Financial support by a Grant-in-Aid for Encouragement of Young Scientists (No. 05740444 to K. S.) from the Ministry of Education, Science and Culture, Japan is gratefully acknowledged.

REFERENCES

1. (a) Katz, D. J.; Wise, D. S.; Townsend, L. B. *J. Med. Chem.* **1982**, *25*, 813–821 (b) Katz, D. J.; Wise, D. S.; Townsend, L. B. *J. Heterocyclic Chem.* **1983**, *20*, 369–379 (c) Kasnar, B.; Wise, D. S.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *Nucleosides & Nucleotides* **1994**, *13*, 459–479.
2. (a) Berkowitz, P. T.; Bardos, T. J.; Bloch, *J. Med. Chem.* **1973**, *16*, 183–184 (b) Bobek, M.; Bloch, A.; Berkowitz, P.; Bardos, T. J. *J. Med. Chem.* **1977**, *20*, 458–460 (c) Bobek, M.; Tuntiwachwuttikul, P.; Ismail, M. M.; Bardos, T. J. *Nucleosides & Nucleotides* **1991**, *10*, 1657–1665.
3. (a) Skulnick, H. *J. Org. Chem.* **1978**, *43*, 3188–3194 (b) Shiau, G. T.;Prusoff, W. H. *Carbohydr. Res.* **1978**, *62*, 175–177 (c) Mitchell, W. L.; Ravenscroft, P.; Hill, M. L.; Knutsen, L. J. S.; Judkins, B. D.; Newton, R. F.; Scopes, D. I. C. J. *Med. Chem.* **1986**, *29*, 809–816 (d) Basnak, I.; Coe, P. L.; Walker, R. T. *Nucleosides & Nucleotides* **1994**, *13*, 163–175.
4. Sujino, K.; Sugimura, H. *Chem. Lett.*, **1993**, 1187–1190.
5. Sujino, K.; Sugimura, H. *Tetrahedron Lett.*, **1994**, *35*, 1883–1886.
6. Jung, M. E.; Castro, C. *J. Org. Chem.* **1993**, *58*, 807–808.