Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 7783–7786

Low temperature dehydrogenation of α-indoline nucleosides

Tilak Chandra, Shawn Zou and Kenneth L. Brown*

Department of Chemistry and Biochemistry, Ohio University, Athens, OH 45701-3132, USA

Received 15 July 2004; revised 4 August 2004; accepted 5 August 2004

Abstract—A variety of α-indole nucleosides are easily prepared from α-indoline nucleosides in excellent yield and at moderate temperature using manganese dioxide and molecular sieves in benzene or methylene chloride.

1. Introduction

Semi-synthesis/partial synthesis of cobalamins[1] (vitamin B_{12} derivatives, Fig. 1) modified in the axial base requires the synthesis of the lower axial ligand for the nucleotide loop. Among others, B3-deaza derivatives (Fig. 1) are of interest because they lack the coordinating nitrogen of the axial base but maintain the remaining structural features of the coenzyme. While many B_{12} analogs with altered axial nucleotides can be obtained by 'guided biosynthesis',[2] via fermentation of *Propionibacterium shermanni* on media supplemented with the desired axial base, indoles are not incorporated into the synthesized B_{12} due to their lack of reactivity with the necessary ribosyltransferase, which catalyzes formation of the axial nucleoside.[3] Consequently, the synthesis of such deaza cobalamins requires the development of a robust method for the synthesis of α-indole nucleosides. In previous work[4] we prepared and fully characterized the desired dimethylindoline nucleoside with the α-N-configuration in excellent yield, the most critical step being the coupling of the indoline to the ribose to give the unusual α-N-glycosidic bond configuration. For the semi-synthesis of the indole derivative of cyanocobalamin, we have now prepared the α-indole nucleoside by reacting 1-(5-O-triphenylmethyl-2,3-O-isopropylidene-α-D-ribofuranosyl)5,6-dimethylindoline[4] with manganese dioxide in benzene or methylene chloride in presence of molecular sieves at slightly elevated temperature.

There are few reports of the dehydrogenation of the related β-indoline nucleosides to corresponding β-indole nucleosides. Preobrazhenskaya et al.[5] reported the dehydrogenation of 1-(2,3,5-O-tri-O-benzoyl-β-D-ribofuranosyl)indoline to the corresponding indole nucleoside using manganese dioxide in benzene at reflux for 15 h. However, the α-nucleosides are thermodynamically unstable and may isomerize to the corresponding β-nucleosides. Consequently, harsh reaction conditions for the dehydrogenation of the α-indoline nucleosides are problematic. The desired α-nucleosides do not survive these drastic conditions and undergo polymerization. Dehydrogenation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] does not give the desired nucleosides and gives charred products instead. In view of the above, we have developed a mild, high yield dehydrogenation method for these unstable α-indoline nucleosides using different solvents and molecular sieves. To compare the reactivity of these α-nucleosides, the indole and dimethylindoline bases were also dehydrogenated under similar condition and produce the indoles in similar yields.

The dimethylindoline and indoline nucleosides were prepared in good yield by coupling silylated indoline bases to the protected sugar, 2,3-O-(1-methylethylidene)-5-O-(triphenylmethyl)-D-ribofuranose in presence of 2-fluoro-1-methylpyridinium-*p*-toluenesulfonate[7] as a condensing agent. 1-(5-O-triphenylmethyl-2,3-O-isopropylidene-α-D-ribofuranosyl)indoline, **1**, was dehydrogenated in either benzene or methylene chloride using MnO_2 in presence of type 4 A molecular sieves. The reaction, which was monitored by TLC and NMR, proceeds rapidly and without decomposition or isomerization of

* Corresponding author. Tel.: +1 740 593 1737; fax: +1 740 593 0148; e-mail: brownk3@ohio.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.110

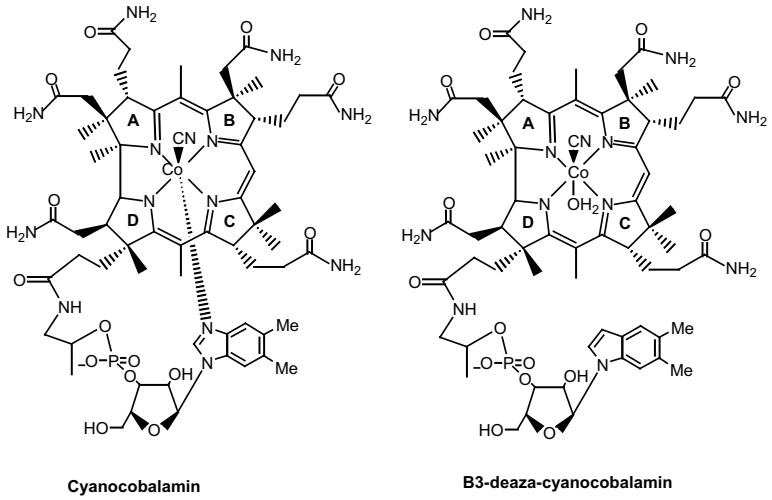


Figure 1.

Table 1. Comparison of dehydrogenation of protected nucleoside by using benzene/methylene chloride in presence of MnO_2 and molecular sieves

S. No.	Reactant	Solvent	Rexn. temp (°C)	Time (h)	Yield (%)[a]
1	Indoline nucleoside	Benzene	40–50	1–1.5	90
2	Dimethylindoline nucleoside	Benzene	40–50	1–1.5	94
3	Br-indoline nucleoside	Benzene	40–50	1.5–3	90
4	Indoline nucleoside	Methylene chloride	30–40	2–3	92
5	Dimethylindoline nucleoside	Methylene chloride	30–40	2–3	95
6	Br-indoline nucleoside	Methylene chloride	30–40	2–3	86
7	Indoline base	Benzene	40–50	1–2	90
8	Dimethylindoline base	Benzene	40–50	1–2	91

[a] Isolated yields.

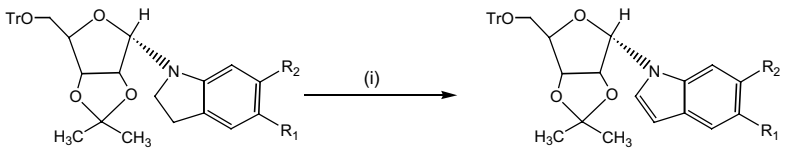
the starting material. Dehydrogenation of dimethylindoline and indoline nucleosides is complete within 1 h in benzene at 40–50 °C whereas the 5-bromoindoline takes 1.5–3.0 h (Table 1). After completion, the reaction mixture was cooled to room temperature and filtered through Celite, and after the usual work up, the solvent was removed under reduced pressure and the product had a clean NMR spectrum without any purification. The crude product was just passed through a small silica gel column to remove the inorganic impurities. The reaction was repeated in methylene chloride at 30–40 °C using MnO_2 and molecular sieves and proceeded smoothly without any decomposition, in 95% yield (dimethylindoline). The reaction proceeds much faster (1–1.5 h) in benzene than methylene chloride. Without molecular sieves, the reaction was sluggish and required higher temperature and more time (Scheme 1).

The structures of the indole nucleosides were confirmed based on previous characterization[4] of the corresponding indoline nucleosides and confirmed by ^{1}H NMR, ^{13}C NMR, high resolution mass spectroscopy, and as well as 2D NMR (COSY and NOESY). The proton spectra of compound **6**[11] showed two sharp singlets at δ 1.384 and δ 1.610 with a separation of 0.22 ppm for the methyl protons of isopropylidene. The anomeric proton was visible at δ 6.854 with a coupling constant of 4.0 Hz, consistent with the α-configuration. The two indole proton showed a strong NOE with one of the isopropylidene methyls, which further supports the α-anomeric configuration (Fig. 2). Other spectroscopic data were compared with literature[8–10] assignments for the α-N-configuration.

2. General method for dehydrogenation of compound 1, 2, and 3

Method a. To a solution of indoline nucleoside **1** (0.700 g, 1.3 mmol) in benzene (20 mL) was added activated manganese(IV) oxide (0.879 g, 10 mmol) and type 4 A molecular sieves (5 g) at room temperature. The reaction mixture was stirred at 40–50 °C for 1–1.5 h and the reaction progress was monitored by TLC and ^{1}H NMR. The reaction mixture was filtered and thoroughly washed with methylene chloride (3 × 10 mL). The solvent was then removed under reduced pressure and the residue was extracted with methylene chloride (100 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was then passed through a small silica gel column and eluted with methylene chloride–hexane (1:1) to give the desired product in 90% isolated yield[11] (Table 1).

Method b. To a solution of nucleoside **1** (0.5 g, 0.93 mmol) in methylene chloride (20 mL) activated manganese(IV) oxide (0.85 g, 9.7 mmol) and type 4 A



1: $R_1 = R_2 = H$
2: $R_1 = R_2 = CH_3$
3: $R_1 = Br$, $R_2 = H$
4: Indoline base
5: dimethylindoline base

6: $R_1 = R_2 = H$
7: $R_1 = R_2 = CH_3$
8: $R_1 = Br$, $R_2 = H$
9: Indole base
10: dimethylindole base

Scheme 1. Reagents and conditions: (i) MnO_2, molecular sieves, benzene, 40–50 °C or MnO_2, molecular sieves, methylene chloride, 30–40 °C.

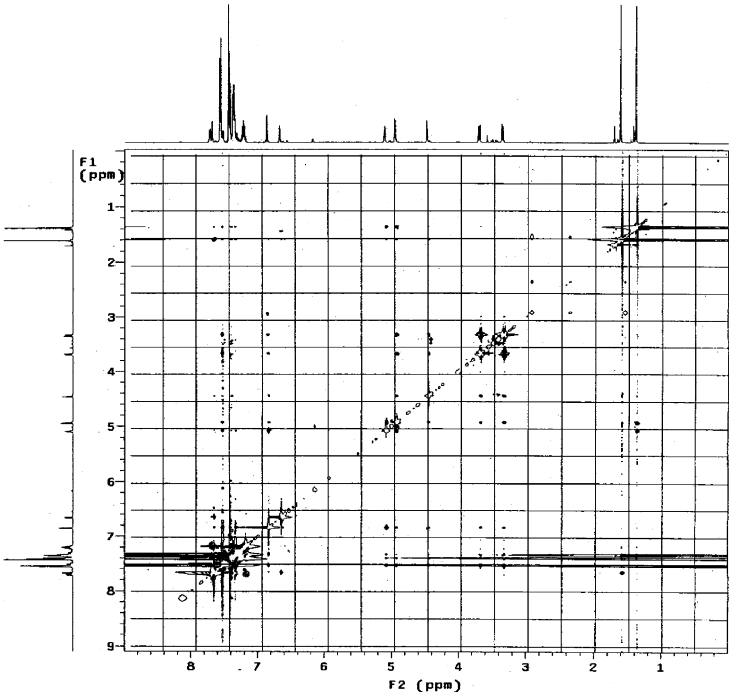


Figure 2. NOESY spectrum of compound **6**.

molecular sieves (5 g) was added and the mixture was heated slowly at 40 °C for 2 h. The progress of the reaction was monitored by TLC. After completion, the mixture was cooled to room temperature, filtered, and washed thoroughly with methylene chloride, and then concentrated under reduced pressure and passed through a small silica gel column to remove the inorganic impurities.

References and notes

1. Brown, K. L.; Zou, X.; Li, J.; Chen, G. *Inorg. Chem.* **2001**, *40*, 5942–5947.
2. Krautler, B.; Konrat, R.; Stupperich, E.; Faber, G.; Gruber, F.; Kratky, C. *Inorg. Chem.* **1994**, *33*, 4128–4139.
3. Cheong, C.-J.; Escalante-Semerena, J. C.; Rayment, I. *J. Biol. Chem.* **2002**, *277*, 41120–41127.
4. Brown, K. L.; Chandra, T.; Zou, S.; Valente, E. J. *Chem. Commun.*, communicated. The indoline nucleosides were synthesized by coupling freshly prepared, silylated dimethylindoline/indoline base to an anomeric mixture of the protected sugar 2,3-O-(1-methylethylidene)5-O-(triphenylmethyl)α/β-D-ribofuranose by using 2-fluoro-1-methylpyridinium-*p*-toluenesulfonate as a condensing agent in 90–96% yield.
5. Preobrazhenskaya, M. N.; Yartseva, I. V.; Ektova, L. V. *Nucleic Acid Chem.* **1978**, *2*, 623–721.
6. Preobrazhenskaya, M. N.; Vigdorchik, M. N.; Suvorov, N. N. *Tetrahedron* **1967**, *23*, 4653–4660.
7. Mukaiyama, T.; Hashimoto, Y.; Hayashi, Y.; Shoda, S. I. *Chem. Lett.* **1984**, 557–560.
8. Tapiero, C.; Imbach, J. L.; Townsend, L. B.; Stuart, T. R. *Nucleic Acid Chem.* **1978**, *2*, 1055.
9. Imbach, J. L.; Barascut, J. L.; Kam, B. L.; Rayner, B.; Tamby, C.; Tapiero, C. *J. Heterocycl. Chem.* **1973**, *10*(6), 1069–1070.
10. Rayner, B.; Tapiero, C.; Imbach, J. L. *Carbohydr. Res.* **1976**, *47*(2), 195–202.
11. *Selected data for* **6**. R_f 0.8; ^{1}H NMR ($CDCl_3$): δ 1.384 (s, 3H, CH_3), 1.610 (s, 3H, CH_3), 3.329 (dd, $J = 3$, 7.5 Hz, 1H, 5′), 3.679 (dd, $J = 2.5$, 7.5 Hz, 1H, 5″), 4.468 (br t, 1H, 4′), 4.937 (d, $J = 6$ Hz, 1H, 3′), 5.086–5.107 (m, 1H, 2′), 6.66 (d, $J = 3.5$ Hz, 1H, indole), 6.854 (d, $J = 4$ Hz, 1H, 1′),

7.18–7.25 (m, 2H, Ar, indole), 7.35–7.43 (m, 9H, Ar, trityl), 7.51 (d, $J = 6.5$ Hz, 1H, indole), 7.54 (d, 6H, trityl), 7.67 (d, $J = 3.0$ Hz, 1H, indole), 7.704 (d, $J = 7.5$ Hz, 1H, indole); ^{13}C NMR ($CDCl_3$): δ 24.42 (CH_3), 26.00 (CH_3), 65.97 (CH_2, 5′), 80.44 (C2′), 81.39 (C4′), 82.61 (C3′), 87.11 (1′), 87.71 (Cquat), 102.41 (C3 indole), 109.02 (CH, indole), 113.25 (Cquat), 119.92 (C2, indole), 120.98 (Cquat), 121.66 (CH, indole), 126.97 (Cquat), 127.02 (Cquat), 127.36 (CH), 127.89 (CH), 128.09 (CH), 128.59 (CH), 128.71 (CH), 136.03 (CH), 143.40 (Cquat); MS (FAB) *m/z*: 532 (M^+ +1), 243; HRMS: *m/z*: 532.2488 (calcd for $C_{35}H_{34}NO_4$: 532.2486) (M+H); IR (KBr cm^{-1}): 2902, 2362, 1495, 1462, 1383, 1318, 1220, 1117, 1081, 996, 749, 706. *Selected data for* **7**. The dimethylindoline nucleoside, **7**, was similarly dehydrogenated as described for the indole nucleoside **6**. Yield: 95%, white foam, ^{1}H NMR ($CDCl_3$): δ 1.365 (s, 3H, CH_3), 1.646 (s, 3H, CH_3), 2.327 (s, 3H, CH_3, Ar), 2.357 (s, 3H, CH_3, Ar), 3.334 (m, 2H, CH_2, 5 and 5″), 4.351–4.377 (m, 1H, 4′), 4.826–4.847 (m, 1H, 3′), 4.929–4.949 (m, 1H, 2′), 6.076 (d, $J = 3.5$ Hz, 1H, 1′), 6.369 (d, $J = 2.5$ Hz, 1H, indole), 7.072 (d, $J = 3.5$ Hz, 1H, indole), 7.242–7.295 (m, 9H, trityl), 7.387 (s, 1H, Ar), 7.401 (s, 1H, Ar), 7.46 (d, $J = 6$ Hz, 6H, trityl); ^{13}C NMR ($CDCl_3$): δ 20.00 (CH_3), 20.60 (CH_3), 25.47 (CH_3), 27.34 (CH_3), 63.70 (CH_2, 5′), 81.05 (C3′), 83.77 (C4′), 84.29 (C2′), 86.92 (Cquat), 91.26 (C1′), 102.60 (CH), 110.63 (CH), 114.41 (Cquat), 121.05 (CH), 123.72 (CH), 127.08 (CH), 127.85 (CH), 127.85 (CH), 128.71 (CH), 128.90, 131.13 (Cquat), 134.60 (Cquat), 143.59 (Cquat); MS (FAB) *m/z*: 560 (M^+ +1), 459, 443, 374, 341, 313, 244, 243; HRMS: *m/z*: 560.2800 (calcd for $C_{37}H_{38}NO_4$: 560.2854) (M+H); IR (KBr cm^{-1}): 2946, 2376, 2338, 1472, 1458, 1380, 1279, 1211, 1081, 761, 703, 674. *Selected data for* **8**. Yield: 90%, white foam, ^{1}H NMR ($CDCl_3$): δ 1.364 (s, 3H, CH_3), 1.638 (s, 3H, CH_3), 3.33 (dd, $J = 3.9$, 6.5 Hz, 1H, CH_2, 5′), 3.42 (dd, $J = 3.9$, 6.5 Hz, 1H, 5″), 4.364–4.388 (m, 1H, 4′), 4.847–4.878 (m, 1H, 3′), 4.909–4.929 (m, 1H, 2′), 6.02 (d, $J = 3.3$ Hz, 1H, 1′), 6.41 (d, $J = 2.8$ Hz, 1H, indole), 7.24 (d, 1H, indole), 7.26–7.30 (m, 9H, trityl), 7.38 (s, 1H, indole), 7.41 (d, $J = 6$ Hz, 6H, trityl), 7.47 (d, 2H, indole), 7.74 (d, 1H, indole); MS (FAB) *m/z*: 612 (M^+ +1), 613, 615, 616, 611, 548, 447, 394, 337, 245, 244, 243, 197, 149; HRMS: *m/z*: 610.1593 (calcd for $C_{35}H_{33}NO_4Br$: 610.1591) (M+H).