Asian Journal of Chemistry Vol. 20, No. 6 (2008), 4685-4691

Oxidation of the 5'-Position of Adenosine Analogues

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The yield for the oxidation of cordycepin was almost quantitative in reproducible runs. This method for adenosine and its analogues is far more attractive than methodologies using 1-(3-dimethylaminopropyl)-3-ethylcarboiimide (EDC·HCl) and DMSO, dicyclohexyl carboiimide (DCC) and dichloro acetic acid (DCAA) in DMSO, tetra-N-propylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide (NMO), CrO_3 in pyridine, DMSO with trichloroacetic anyhydride or oxidations which proceed through either the oxime or the 1,3-diphenylimidazolidine derivative to furnish the aldehyde.

Key Words: 5'-Hydroxyl oxidation, Periodinane, Purine nucleosides.

INTRODUCTION

Purine and pyrimidine nucleosides bearing functionalities at the 4'α-position have recently been shown to possess antiviral activity[1-4]. Nucleosides such as 4'-cyano-, 4'-azido-, 4'-ethynylthymidine and 4'-ethynyl-2'-deoxycytidine are reported to exhibit potent anti-HIV activity. We have synthesized 4'-C-ethynyl-D-arabinofuranosyl and 4'-C-ethynyl-2'-deoxy-D-ribofuranosyl nucleosides which were shown to act as inhibitors of HIV reverse transcriptase through their triphosphates. Cordycepin (3'-deoxyadenosine) is reported to possess antiviral activity against several RNA viruses[5]. The molecular basis of this antiviral activity is believed to be the inhibition of viral RNA polymerases by cordycepin 5'-triphosphate.

In an effort to synthesize novel cordycepin analogues with functionalized substitution at the 4'-position, we have focused on the utililization of the carboxaldehyde (**1**) as the key intermediate for providing entry to this class of compounds. There are a few examples in the literature of nucleoside

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5'-carboxaldehydes, access to these key intermediates in sugar-modified nucleoside synthesis is exceedingly difficult. This is particularly the case for adenosine analogues. For example, Rosenberg and co-workers[6] noted that oxidation of 2'-deoxy-3'-*o*-*tert*-butyldiphenylsilyl nucleosides and 2',3'-*o*-isopropylidene derivatives of nucleosides worked well under the Swern conditions [DMSO/$COCl_2$] in most cases except for adenosine derivatives. An alternate route to adenosine 5'-carboxalde-hyde proceeds through the 1,3-diphenylimidazolidine or oxime derivatives[7]. However, this procedure is somewhat cumbersome and the yields are modest. Because adenosine 5'-carboxaldehyde derivatives represent attractive intermediates from which many novel adenosine targets can readily be synthesized, we developed a highly efficient procedure for this oxidation and our report communicates these results.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Varian Mercury Plus 400 MHz or Varian Inova 500 MHz NMR spectrometers. High resolution ESI or FAB mass spectral data were obtained through the Nebraska Center for Mass Spectrometry. Column chromatographic separations were carried out using 230-400 mesh silica gel.

2',5'-Di-*o*-(*tert*-butyldimethylsilyl)-3'-deoxyadenosine (3): Adenosine (5.0 g, 18.73 mmol, 1.0 eq) was dissolved in dry pyridine (40 mL). *tert*-Butyldimethylsilyl chloride (TBDMSCl) (8.46 g, 56.19 mmol, 3.0 eq) was added in a single portion. The reaction stirred room temperature for 48 h and was then concentrated *in vacuo*. The residue was partitioned between 150 mL ice-cold 5 % HCl (aq) and 150 mL of CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (aq) (75 mL) and brine (75 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography with a gradient of hexane/EtOAc (4:1 to 2:1 to 3:2 to 1:1 to 1:4 to 100 % EtOAc). Two major fractions were collected which corresponded to the desired 2',5'-di-*o*-(*tert*-butyldimethylsilyl) (2',5'-di-OTBDMS) derivative and the 3',5'-di-OTBDMS isomer produced, respectively, in a ratio of 6:4. The 3',5'-di-OTBDMS derivative was isomerized by stirring with 100 mL of MeOH and 2.5 mL of NEt_3 (2.5 % v/v) at room temperature for 3 h. The reaction mixture was concentrated and purified by flash column chromatography. 2',5'-Di-*o*-(*tert*-butyldimethylsilyl)-3'-deoxyadenosine was obtained in 61 % (5.69 g) overall yield as a white solid. ^1H ($CDCl_3$, 500 MHz): δ 8.34 (s, 1H), 8.22 (s, 1H), 6.16 (bs, 2H, $-NH_2$), 6.12 (d, 1H, J = 5.0 Hz), 4.64 (t, 1H, J = 4.5 Hz), 4.29 (t, 1H, J = 4.0 Hz), 4.21 (q, 1H, J = 2.5, 5.5 Hz), 4.01 (dd, 1H, J = 2.0, 11.5 Hz), 3.85 (dd, 1H, J = 2.0, 11.5 Hz), 2.94 (bs, 1H, OH), 0.95 (s, 9H), 0.83 (s, 9H), 0.14 (d, 6H, J = 8.5 Hz), -0.09 (d, 6H, J = 28 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.7, 153.1,

150.1, 139.0, 119.9, 88.1, 85.4, 76.9, 71.4, 63.3, 26.2, 25.8, 18.7, 18.1, -4.8, -5.3. HRMS (M + H) calcd. for $C_{22}H_{42}N_5O_4Si_2$ 496.27, found 496.27.

The 2',5'-di-OTBDMS adenosine derivative prepared above (5.69 g, 11.49 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (115 mL) and purged with N_2. Next, 4-dimethylaminopyridine (5.61 g, 45.98 mmol, 4.0 eq) was added in a single portion followed by phenoxythiocarbonyl chloride (3.2 mL, 22.99 mmol, 2.0 eq). The reaction mixture was stirred for 18 h at room temperature and was diluted with CH_2Cl_2 (200 mL). The organic phase was washed with water, 1 N HCl (aq), H_2O, $NaHCO_3$ (aq) and NaCl (aq) (200 mL each) and then dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography using a solvent gradient of 4:1 to 2:1 to 1:1 to 3:7 hexane/EtOAc. The product was obtained as an orange foam in 60 % yield (4.33 g). ^{1}H ($CDCl_3$, 500 MHz): δ 8.52 (s, 1H), 8.37 (s, 1H), 7.58 (t, 2H, J = 8.0 Hz), 7.45 (t, 1H, J = 7.0 Hz), 7.25 (d, 2H, J = 8.5 Hz), 6.70 (s, 2H, -NH_2), 6.37 (d, 1H, J = 5.5 Hz), 6.01 (dd, 1H, J = 3.5, 5.0 Hz), 5.12 (t, 1H, J = 5.0 Hz), 4.66 (q, 1H, J = 2.5, 5.5 Hz), 4.22 (dd, 1H J = 2.5, 11.5 Hz), 4.12 (dd, 1H, J = 2.5, 11.5 Hz), 1.12 (s, 9H), 0.98 (s, 9H), 0.32 (d, 6H, J = 5.0 Hz), 0.088 (d, 6H, J = 88.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194., 155.9, 153.5, 153.2, 150.2, 138.6, 129.7, 126.9, 121.9, 119.9, 88.1, 82.8, 81.2, 74.9, 62.9, 26.3, 25.6, 18.6, 18.0, -5.0, -5.2. HRMS (M + H) calcd. for $C_{29}H_{46}N_5O_5SSi_2$ 632.27, found 632.27.

The 2',5'-di-OTBDMS-3'-phenoxythiocarbonyl adenosine derivative prepared above (4.33 g, 6.86 mmol, 1.0 eq) was dissolved in dry toluene (43 mL) in a 250 mL 3-neck round bottom flask and brought to reflux under N_2. A solution of toluene (21.2 mL), AIBN (225 mg, 1.37 mmol, 0.20 eq) and Bu_3SnH (2.8 mL, 10.29 mmol, 1.5 eq) was added *via* syringe over 0.5 h. The reaction mixture was heated under reflux for 6 h and then concentrated. The crude material was subjected to column chromatography using an EtOAc/hexane gradient of 6:4 to 7:3. The product was obtained as an off-white amorphous powder in 85 % yield (2.81 g). ^{1}H ($CDCl_3$, 500 MHz): δ 8.25 (s, 1H), 8.24 (s, 1H), 7.28 (s, 2H, -NH_2), 5.95 (s, 1H), 4.55-4.57 (m, 1H), 4.45-4.49 (m, 1H), 4.02 (dd, 1H, J = 2.0, 11.5 Hz), 3.67 (dd, 1H, J = 2.0, 11.5 Hz), 1.74-2.22 (m, 2H), 0.81 (s, 9H), 0.80 (s, 9H), 0.03 (d, 6H, J = 23.5 Hz), -0.001 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.1, 152.6, 149.1, 138.4, 119.9, 91.7, 81.0, 76.0, 63.6, 33.6, 25.9, 25.6, 18.4, 18.0, -5.0, -5.6. HRMS (M + H) calcd. for $C_{22}H_{42}N_5O_3Si_2$ 480.28, found 480.28.

N^6-Benzoyl-2'-*o*-(*tert*-butyldimethylsilyl)-3'-deoxyadenosine (4): The 2',5'-di-OTBDMS-3'deoxyadenosine **3** (2.54 g, 5.30 mmol, 1.0 eq) was dissolved in dry pyridine (72 mL) and stirred at room temperature under N_2. To this solution was added benzoyl chloride (2.5 mL, 21.21 mmol, 4.0 eq) and the reaction continued to stir for 18 h. The reaction was cooled

to 0 °C in an ice bath and NH_4OH (28 % aq) was slowly added (20 mL). The mixture stirred for 0.5 h at 0 °C. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (350 mL). The organic layer was washed with water, $NaHCO_3$(aq) and brine (175 mL each) and dried over Na_2SO_4 and concentrated. The crude product was subjected to flash column chromatography using a 7 cm diameter column and 12 cm of silica gel. A solvent gradient of 7:3 hexane/EtOAc was used to elute the product. The N^6-benzoylated product was isolated in 95 % (2.61 g) yield as a foam. ^1H ($CDCl_3$, 500 MHz): δ 9.33, (bs, 1H, -NH), 8.78 (s, 1H), 8.54 (s, 1H), 8.02 (d, 2H, *J* = 8.0 Hz, ArH), 7.54-7.60 (m, 1H, ArH), 7.48 (t, 2H, *J* = 8.0 Hz, ArH), 6.08 (d, 1H, *J* = 1.0 Hz), 4.62-4.66 (m, 1H), 4.56-4.61 (m, 1H), 4.13 (dd, 1H, *J* = 2.5, 12.0 Hz), 3.78 (dd, 1H, *J* = 2.5, 12.0 Hz), 2.10-2.28 (m, 1H), 1.88 (dd, 1H, *J* = 2.0, 6.0 Hz), 0.93 (s, 9H) 0.90 (s, 9H), 0.14 (d, 6H, *J* = 10.5 Hz), 0.10 (d, 6H, *J* = 10.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.0, 152.6, 151.3, 149.5, 141.6, 134.1, 132.7, 128.9, 128.0, 123.5, 92.2, 81.6, 77.5, 63.9, 33.9, 26.2, 25.8, 18.7, 18.1, -4.6, -4.9, -5.2, -5.3. HRMS (M + H) calcd. for $C_{29}H_{46}N_5O_4Si_2$ 584.30, found 584.30.

The N^6-benzoyl-2',5'-di-OTBDMS-3'-deoxyadenosine prepared above (2.38 g, 4.59 mmol, 1.0 eq) was dissolved in THF (54 mL). The solution was cooled to 0 °C with a FLEX-COOL machine (EtOH bath). To this solution was carefully added a mixture of TFA (13.4 mL, 174.26 mmol, 38 eq) and water (13.4 mL). This reaction mixture was stirred at 0 °C for 24 h. The reaction mixture was neutralized with $NaHCO_3$ (aq) (200 mL) very carefully while stirring at 0 °C. The mixture was diluted with EtOAc (200 mL), washed with brine (100 mL) and dried over Na_2SO_4. The organic phase was concentrated in vacuo to give 1.84 g (96 % yield) of a foamy product. ^1H ($CDCl_3$, 500 MHz): δ 9.75 (bs, 1H, -NH), 8.89 (s, 1H), 8.41 (s, 1H), 8.18 (d, 2H, *J* = 8.52 Hz, ArH), 7.72 (t, 1H, *J* = 7.5 Hz, ArH), 7.60-7.75 (m, 2H, ArH), 5.95 (d, 1H, *J* = 4.0 Hz), 5.02-5.10 (m, 1H), 4.64-4.70 (m, 1H), 4.17 (d, 1H, *J* = 13.0 Hz), 3.74 (d, 1H), 2.56-2.66 (m, 1H), 2.18-2.28 (m, 1H), 0.96 (s, 9H), 0.09 (s, 3H), 0.002 (d, 3H, *J* = 2.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.1, 152.3, 150.8, 150.0, 142.5, 133.7, 132.8, 128.8, 128.1, 123.9, 93.2, 81.0, 75.2, 63.9, 34.4, 25.6, 17.9, -5.0, -5.1. HRMS (M + H) calcd. for $C_{23}H_{32}N_5O_4Si$ 470.22, found 470.22.

5-(6-*N*-Benzoylamino-9*H*-purin-9-yl)-tetrahydro-4'-*o*-(*tert*-butyldimethylsilyl)furan-2-carb-aldehyde (1): The N^6-benzoylated-2'-OTBDMS-3'-deoxyadenosine derivative prepared above (1.77 g, 3.77 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (35 mL) and stirred at 0 °C in an ice bath. To this solution was added Dess-Martin periodinane (2.40 g, 5.66 mmol, 1.5 eq) in one portion and the reaction stirred at 0 °C for 1 h. The reaction was quenched at 0 °C by stirring with a solution of $Na_2S_2O_3$ (6.8 g in 40 mL water) and $NaHCO_3$ (saturated, aq, 40 mL) for 10 min to destroy

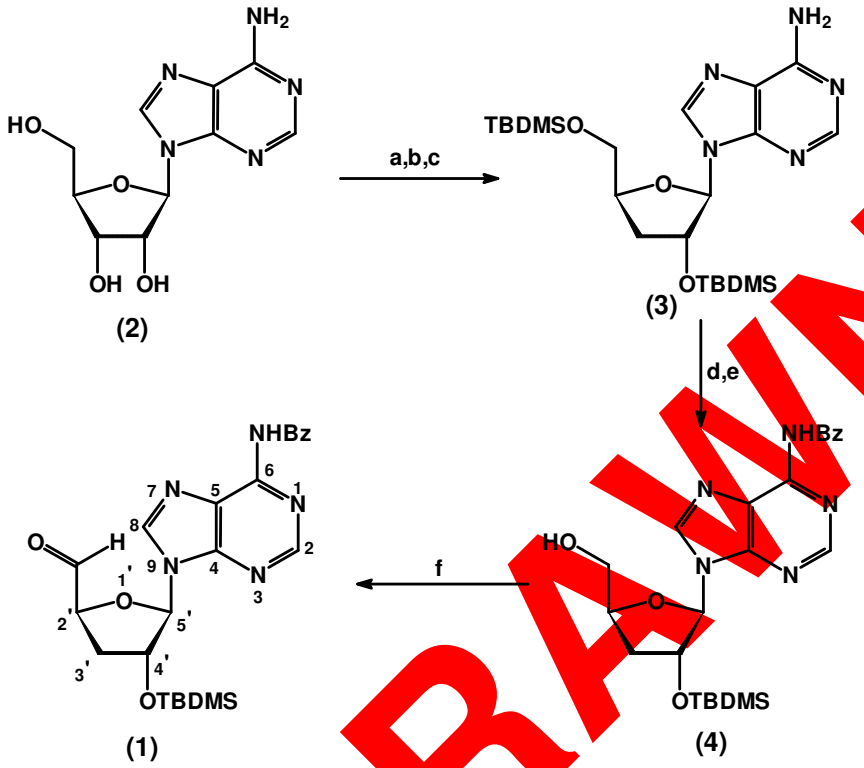
any unreacted Dess-Martin reagent. The reaction mixture was poured into a separatory funnel and extracted with EtOAc (3 × 80 mL). The organic layers were pooled and washed with brine (80 mL), dried over $MgSO_4$ and concentrated to give 1.73 g (98 %) of almost pure (> 98 %) product which was isolated as a foam. ^{1}H ($CDCl_3$, 500 MHz): δ 9.82 (s, 1H, -CHO), 9.03 (bs, 1H,-NH), 8.71 (s, 1H), 8.21 (s, 1H), 7.97 (d, 2H, *J* = 7.5 Hz, ArH), 7.40-7.60 (m, 3H, ArH), 5.98 (d, 1H, *J* = 2.0 Hz), 4.95-5.00 (m, 1H), 4.82 (t, 1H, *J* = 8.5 Hz), 2.23-2.42 (m, 2H), 0.83 (s, 9H), 0.03 (d, 3H, *J* = 4.5 Hz), 0.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 164.7, 152.4, 151.2, 149.8, 141.6, 133.5, 132.8, 128.8, 128.1, 124.0, 93.6, 84.2, 75.5, 35.2, 25.6, 17.9, -4.8, -5.0. HRMS (M + H) calcd. for $C_{23}H_{30}N_5O_4Si$ 468.20, found 468.20.

RESULTS AND DISCUSSION

Our successful Dess-Martin oxidation of adenosine or its derivatives (*e.g.*, cordycepin) depends on a judicious selection of protecting groups for both the hydroxyl groups and the N^6-position of the nucleobase. For example, for the synthesis of 3'-deoxyadenosine 5'-carboxaldehyde intermediate (**1**), we devised an efficient protection-deprotection strategy as shown in **Scheme-I**. Adenosine (**2**) was converted in three steps to compound **3**[8,9] by selective 2',5'-disilylation (61 % yield), followed by treatment with phenyl chlorothionoformate and 4-dimethylaminopyridine (DMAP) in dichloromethane (60 % yield)[10] and subsequent Barton radical deoxygenation reaction at C-3 (85 % yield)[11]. Compound **3** can be deprotected to cordycepin and this approach represents an excellent method to produce gram quantities of this antiviral compound.

It was found that the order of the next two steps was very important in terms of yield. The N^6-position of intermediate **3** was first protected using benzoyl chloride in pyridine (95 % yield)[12]. Selective 5'-desilylation was subsequently accomplished using TFA-H_2O-THF (1:1:4) (96 % yield)[13]. Finally, Dess-Martin periodinane was used to oxidize the 5'-hydroxyl group to the aldehyde **1** (98 % yield)[14]. Compound **1** can be deprotected in almost quantitative yield. Although several other oxidation conditions were explored, including EDC·HCl and DMSO[15], DCC and DCAA in DMSO[16], TPAP and NMO[17], CrO_3 in pyridine and DMSO with trichloroacetic anyhydride[18], only the Dess-Martin periodinane oxidation in CH_2Cl_2 proceeded with high efficiency.

In summary, N^6-benzoyl-2'-O-(*tert*-butyldimethylsilyl)-3'-deoxy-4'-formyladenosine **1** can be synthesized in an efficient and facile manner using a judicious protecting group strategy and the Dess-Martin periodinane for the oxidation step. The more robust benzamide and *tert*-butyldimethyl silyl ether protections are far superior for this oxidation than the acetyl protecting group. The aldehyde produced is a key intermediate is useful in the synthesis of many 4'-substituted adenosine nucleosides of antiviral interest.



Scheme-I: Reagents and conditions: (a) TBDMSCl, pyridine, room temperature, 48 h; (b) PhOC(S)Cl, DMAP, CH_2Cl_2, room temperature, 6 h; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 4 h; (d) 1. BzCl, pyridine, room temperature, 2 h. 2. NH_4OH (28 %, aq.), 0 °C, 0.5 h; (e) TFA-H_2O (1:1), THF, 0 °C, 5 h; (f) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 2 h.

ACKNOWLEDGEMENTS

Genesen Labs Ltd. acknowledges the support of this research from IIT, Powai, Mumbai, India for providing NMR spectra.

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(*Received*: 6 September 2007; *Accepted*: 10 March 2008) AJC-6442