Straightforward C-8 Alkylation of 2'(or 3')-Azidoadenosine Derivatives by Utilizing Pd(0) Catalyst and Tetraalkyltin

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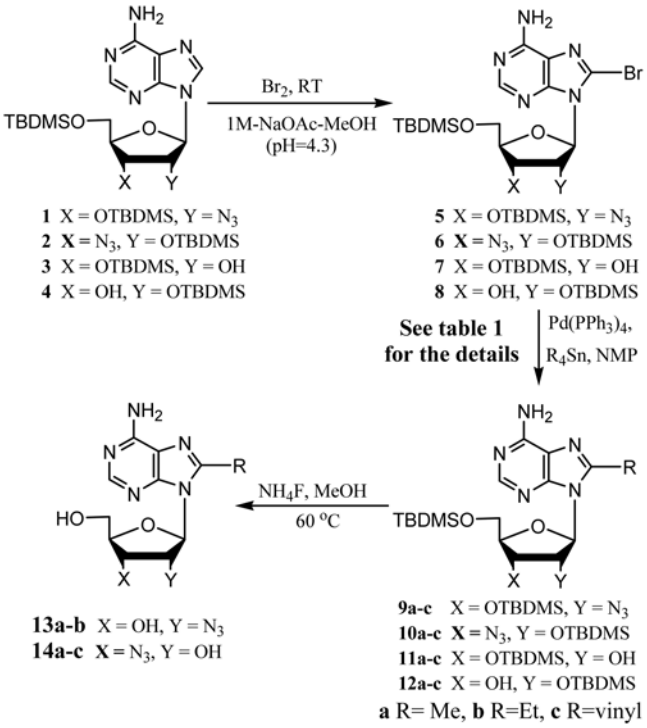
Purine-modified nucleosides are of great interest for their potential utility as synthetic precursors in chemotherapeutic studies such as antiviral agents,[1] for the design of antisense polynucleotides[2] and sequence specific DNA cleaving agents,[2,3] in sequencing DNA,[4] and as biochemical probes, *e.g.* in purine receptor activation.[5] The modification at 8-position of purine moiety is of particular interest, since it could influence strongly syn/anti conformation of the purine base, which could in turn cause significant changes in the interaction between the substrate molecules and active sites of enzymes or receptors.[6] In addition, the introduction of alkyl substituents to purine could afford the desired lipophilicity for cell permeability to adenosine-containing biomolecules such as cyclic-adenosine diphosphoribose (cADPR) and β-NAD$^+$.[7] In our ongoing synthetic efforts to prepare structurally diverse adenosine-containing biomolecules such as cADPR,[8] and enzyme inhibitors against adenosyl-L-homocysteine hydrolase,[9] our work has been extended to the syntheses of both purine- and sugar-modified adenosine derivatives as another potential synthetic intermediates. In the precedent work,[8a] we reported the convenient synthetic route to prepare sugar-modified adenosine derivatives having an azido group (**1**, **2**) and their reductive products at 2' or 3'-position of ribose moiety. This methodology was successfully extended eventually to prepare sugar and base modified adenosine derivatives[8b] **13** and **14** by utilizing Pd(0) catalyzed cross-coupling alkylation reaction with tetraalkyltin reagents starting from the silyl-protected adenosine **3** and **4** (Scheme 1; **3**, **4** => **7**, **8** => **11**, **12** => **13**, **14**).

While the previously reported work is meaningful in terms of the successful 8-alkylation of selectively protected adenosine derivatives (Scheme 1; **7**, **8** => **11**, **12**), the final transformation of compound **11** and **12** to compound **13**, **14** involved rather lengthy steps and furthermore wasted the valuable key intermediates during the multistep reactions. Since we had fair amount stock of compound **1** and **2**,[8a] which are already fully functionalized through several steps starting from **3** and **4**, we decide to apply Pd(0) catalyzed cross-coupling alkylation reaction to those compounds, thereby the key intermediates **13** and **14** for cADPR will be available more conveniently and in better yields.

Now, the introduction of alkyl substituents to 8-position of adenine moiety was accomplished through halogenation followed by palladium catalyzed cross-coupling reaction with tetraalkyltin reagents.[10] Thus, 2' and 3'-azidoadenosine (**1**, **2**) were brominated by usual bromination condition (Br_2, 1 M acetate buffer-MeOH, rt) to provide 8-bromoadenosine derivatives **5** and **6** in high yields (> 90%, Scheme 1).[11] And the next cross coupling reactions were performed in NMP with the variation of concentrations of $Pd(PPh_3)_4$ catalyst and tetraalkyltin (alkyl = methyl, ethyl, and vinyl), and with the variation of temperature (Table 1).[12] While the high reaction temperature around 100 °C is required for the conventional Pd(0) catalyzed cross-coupling reactions,[8b,10] the 8-methylation of the compounds **5** and **6** at this temperature gave a desired products in very poor yields (< 20%) along with the small amount of recovered starting materials. The variation of concentration of Pd(0) catalyst



Scheme 1. Synthesis of 8-alkylsubstituted 2' (or 3')-azidoadenosine derivatives.

Table 1.

Entry	Starting material	Reaction condition			Product/ yield (%)
		Pd(0) catalyst (%)	R_4Sn (equiv.)	Reaction temp. (°C)/time (h)	
1	5	20	R=Me (4)	35/3	**9a** (95)
2	6	20	R=Me (4)	45/2.5	**10a** (80)
3	5	10	R=Et (2)	100/5	**9b** (48)[a]
4	6	15	R=Et (4)	110/4	**10b** (53)
5	5	10-20	R=vinyl (2-6)	30-110	**9c**[b]
6	6	20	R=vinyl (4)	100/0.5	**10c** (13)[c]

[a,b,c]starting material recovered (10, 24, 12 %, respectively)

and tetramethyltin didn't give any positive influence on the yields and product composition. However, to our surprise, the 8-methylation of the compounds **5** and **6** was occurred under much mild conditions (35-45 °C) with excellent yields (**9a**: 95%, **10a**: 80%) (Entry 1 and 2 in Table 1). The breakthrough in 8-methylation encouraged us to apply this mild condition to next 8-ethylation and 8-vinylation. The reactions, however, were disappointingly slow or did not take place at all for ethylation and vinylation, respectively at the reaction temperature spanned over 30-80 °C. Upon raising the reaction temperature to 100-110 °C, only 8-ethyl adensine derivatives (**9b** and **10b**) were obtained in moderate yields (~50%, Entry 3 and 4, Table 1). Under the same reaction condition, the 8-vinyl-2'-azidoadenosine derivative (**10c**) was obtained even in poor yield (13%) along with the small amount of recovered starting material (Entry 6 in Table 1). Several variations for the reaction temperature, time and concentration of catalyst were not productive for the vinylation reaction (Entry 5 in Table 1). After all, the order of reactivity [methyl > ethyl > vinyl] was observed for the 8-alkylation reaction as reported in other literature.[8a,10] These 8-alkylated compounds **9** and **10** were desilylated to already reported azido compounds **13** and **14** with NH_4F/ MeOH at 60 °C with no incident.[13]

In summary, our trial for 8-alkylation of adenosine derivatives showed excellent results in methylation reaction under mild reaction condition, but only moderate results for ethylation. Although, the reaction scope is somewhat limited, this high yielding and yet very convenient methodology to secure valuable key intermediates **13a-b** and **14a-c** starting from the large stock of compounds **1** and **2** would expedite to prepare our dream compounds c-ADPR containing azido group at sugar portion and alkyl group at 8-position of purine base.

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11. **A typical procedure for the 8-bromination.** A solution of **1** (1.3 g, 2.62 mmol) in MeOH (120 mL)/1 M sodium acetate (20 mL) was added bromine (0.28 mL, 5.50 mmol) at rt and stirred for a half hour. The mixture was diluted with 50 mL of saturated sodium metabisulfite solution and stirred until the red color was disappeared. The volatile was evaporated and the resulting aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layer was washed with water (100 mL), dried over $MgSO_4$, and evaporated to give pale yellowish foam. This residue was purified by column chromatography to give **5** as pale yellow solid (1.38 g, 92%). **5**: mp 171-172 °C; ^{1}H-NMR, $CDCl_3$ δ 8.27 (s, 1H, H8), 6.25 (br, 2H, -NH_2), 6.01 (d, 1H, J = 4.8 Hz, H1'), 5.47 (t, 1H, J = 4.8 Hz, H2'), 5.11 (t, 1H, J = 5.2 Hz, H3'), 4.09 (m, 1H, H4'), 3.95 (dd, 1H, J = 5.2, 11.6, H5'a), 3.73 (dd, 1H, J = 4.0, 11.6 Hz, H5'b), 1.03 (s, 9H, Si-*t*-butyl), 0.79 (s, 9H, Si-*t*-butyl), 0.28, 0.26, 0.00, –0.08 (s, 3H for each, four Si-methyl); ^{13}C-NMR δ 154.47, 152. 68, 150.68, 128.26, 120.26, 88.01, 85.19, 72.24, 62.05, 61.34, 25.79, 25.66, 18.16, 18.09, –4.71, –4.93, –5.61, –5.67; TOFMS: *m/z* $(M+H)^+$ 599.
12. **Typical procedure for the 8-alkylation of adenosine derivatives.** To a solution of **5** (0.1 g, 0.166 mmol) and tetrakis(triphenylphosphine)palladium(0) (38 mg, 0.0332 mmol) in 1 mL of *N*-methyl-2-pyrrolidinone (NMP) was added tetramethyltin (0.092 mL, 0.664 mmol) under Ar atmosphere. The mixture was stirred for 3 hours at 35 °C. The mixture was partitioned between EtOAc (50 mL) and water (25 mL). The aqueous layer was extracted with EtOAc once more (50 mL). The combined organic layer was washed with water (50 mL × 2) and brine (50 mL), dried over $MgSO_4$, evaporated to give pale yellow oily residue. The residue was applied to column chromatography (2 × 10 cm) and eluted with EtOAc-hexane (7:3). The appropriate fractions were collected and evaporated to give white solid **9a** (84 mg, 95%), which was desilylated to provide the already reported compound **13a**. **9a**: mp 188-189 °C; ^{1}H-NMR ($CDCl_3$) δ8.28 (s, 1H, H8), 5.85 (d, 1H, J = 4.8 Hz, H1'), 5.67 (br, 2H, -NH_2), 5.50 (t, 1H, J = 4.8 Hz, H2'), 5.08 (t, 1H, J = 5.6 Hz, H3'), 4.08 (m, 1H, H4'), 3.93 (dd, 1H, J = 4.4, 11.2, H5'a), 3.73 (dd, 1H, J = 4.0, 11.6 Hz, H5'b), 2.68 (s, 3H, 8-CH_3), 1.04 (s, 9H, Si-*t*-butyl), 0.79 (s, 9H, Si-*t*-butyl), 0.30, 0.26, 0.00, –0.08 (s, 3H for each, four Si-methyl); ^{13}C-NMR δ 154.50, 1521.99, 150.72, 150.53 (C8, C4), 118.72, 86.45, 84.93, 72.24, 62.40, 61.51, 25.85, 25.65, 18.19, 18.14, 14.54, –4.67, –4.91, –5.60, –5.67; TOFMS: *m/z* $(M+H)^+$: 535.
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