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Straightforward C-8 alkylation of adenosine analogues with tetraalkyltin reagents

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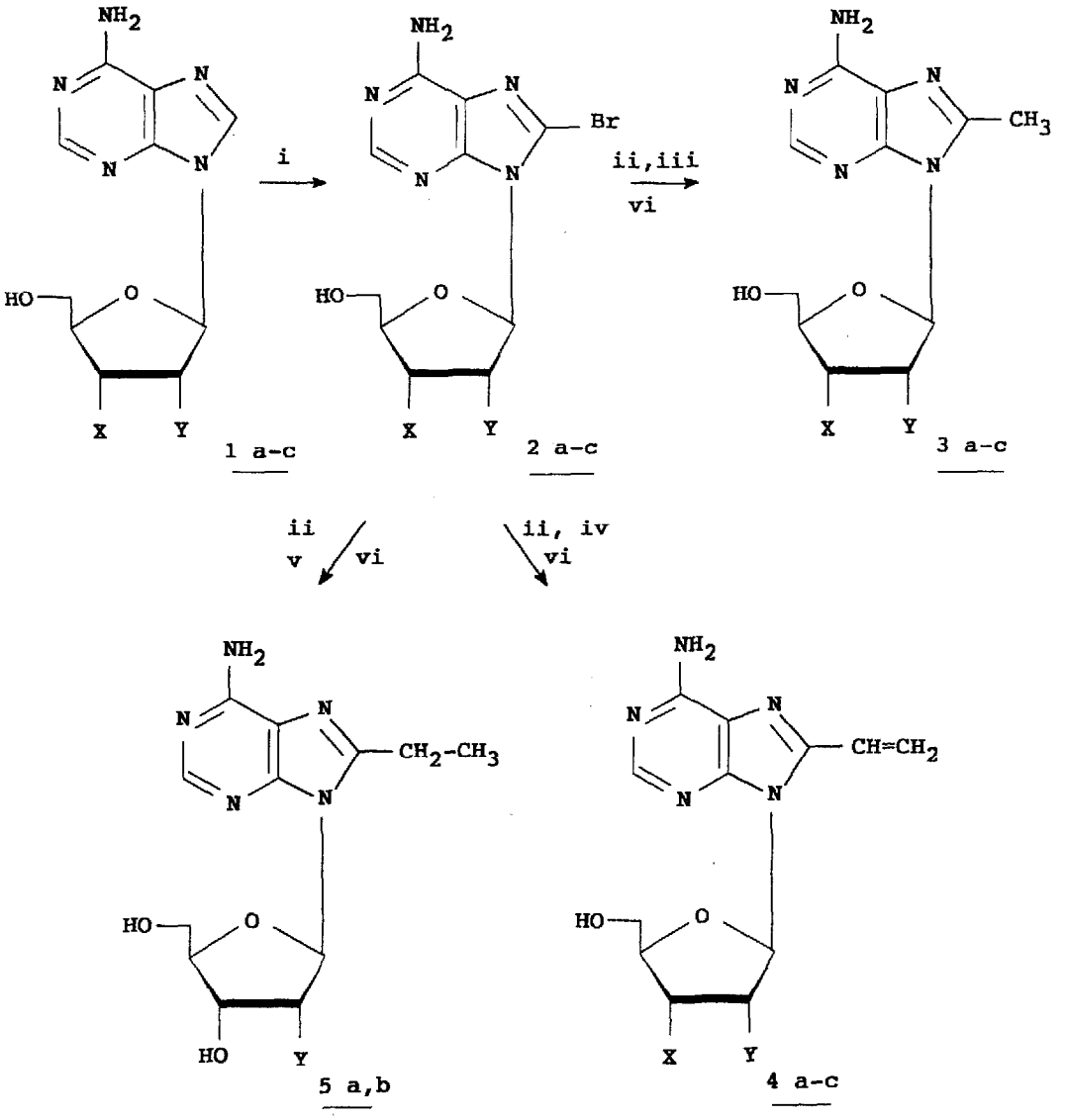
Abstract : A one step synthesis of the 8-methyl-, 8-ethyl -and 8-vinyl derivatives of adenosine, 2'-deoxyadenosine and 2',3'-dideoxyadenosine starting from the readily available 8-bromo congeners is described. This reaction makes use of a transient silylation procedure and a Pd(0) catalysed cross-coupling with tetraorganotin reagents.

As pointed out before on numerous occasions, nucleosides with a modified purine moiety are of interest for their possible biological activity within the context of antiviral therapeutic agents[1-3], for the design of antisense polynucleotides[4] and sequence specific DNA cleaving agents[4,5], in sequencing DNA[6,7] and as purine receptor agonists/antagonists[8]. Modification of the 8-position is of particular interest, because it influences strongly the syn/anti conformation of the purine base.

Alkylation at the 8-position of purine nucleosides has been accomplished through bromination[9] followed by nucleophilic displacement and further functionalization[10-12]. However, this is a low yielded and time consuming approach. Lithiation of the C-8 position of hydroxy protected purine nucleosides with lithium diisopropylamide[13] followed by reaction with suitable electrophiles therefore was an improvement over the former approach. Palladium catalysed introduction of alkynes[14,15], or of a vinyl or allyl moiety on purine derivatives halogenated at the 2, 6 or 8 position, has been described on several occasions (e.g. ref. 16-18). A recent report also described the C-8 alkylation of 2'-deoxy and 2',3'-dideoxypurine nucleosides[19] starting from the less readily accesible 8-iodoadenosine derivative. Here, only allylation and vinylation were reported on TBDMSi protected nucleosides. Isolation of the deprotected analogues seems to be problematic.

We here report a straightforward C-8 alkylation procedure, amenable for the synthesis of as well adenosine as 2'-deoxy and 2',3'-dideoxyadenosine analogues starting from the easily available 8-bromoadenine derivatives. The C-8 brominated derivatives[9,20] therefore are protected *in situ* by refluxing with hexamethyldisilazane (HMDS) or BSA. Pd(0) catalysed cross coupling with tetraorganotin reagents is followed by treatment with potassium carbonate in methanol, yielding the deprotected C-8 alkylated nucleosides.

In extension of our work with 5-iododeoxyuridine[21], the Pd(0) catalysed cross-coupling reaction with tetraorganotin reagents[22] was first tested on TBDMSi protected 8-iodoadenosine[19]. These reactions went straightforward and besides vinylation, the 8-methyl and 8-ethyladenosine analogues could be obtained. Only allylation went sluggish and together with the 8-allyl derivative also the isomerised 8-(ß-methyl)vinyl, the debrominated product and the starting 8-bromo derivative were isolated from the reaction mixture. Although the synthesis is straightforward, deprotection and isolation



1a-5a X=Y=OH 1b-5b X=OH, Y=H
1c-4c X=Y=H

i) Br_2, acetate buffer pH=4.3; ii) HMDS; iii) $(CH_3)_4Sn$ $Pd(PPh_3)_4$, NMP; iv) $(CH_2{=}CH)_4Sn$, $Pd(PPh_3)_4$, NMP; v) $(CH_3CH_2)_4Sn$, $Pd(PPh_3)_4$, NMP; vi) K_2CO_3, CH_3OH.

of the analogues was met with difficulties. These problems were solved making use of 8-bromoadenosine which is also much easier to obtain than its 8-iodo counterpart. Following acetylation (to facilitate isolation of the alkylated analogues), cross coupling reaction in NMP under $Pd(PPh_3)_4$ catalysis went equally well and only required a slightly higher temperature. The acetyl groups could be removed under alkaline conditions but side reactions occurred with the allyl and vinyl moieties. However, refluxing 8-bromoadenosine with HMDS yielded the *in situ* protected nucleoside. After carrying out the coupling reaction, the trimethylsilyl ethers allowed extraction of the reaction products in ethyl acetate, and facilitated removal of NMP by washing with water. Dissolution in MeOH and reaction with potassium carbonate cleaved the silyl ethers and allowed easy isolation of the alkylated analogues.

In a typical reaction procedure 1.04 g (3 mmol) of 8-bromoadenosine (**2a**) and 10 mL HMDS were refluxed in 20 mL anhydrous dioxane for 8 h. The volatiles were removed in vacuo and the residue was coevaporated with anhydrous toluene and dissolved in 6 mL N-methyl-pyrrolidinone. Tetrakistriphenylphosphine palladium (0) (348 g, 0.3 mmol) and 0.84 mL (6 mmol) of tetramethyltin were added. The mixture was heated at 110°C for 14 h and was partitioned between 100 mL EtOAc and 50 mL of water. The organic phase was washed with water (3x50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was dissolved in 50 mL MeOH, 0.5 g K_2CO_3 were added and the mixture was stirred 4 h at room temperature. After addition of 2 g of silica gel, the mixture was evaporated and the residue was put on top of a small silica gel column and elution with CH_2Cl_2-MeOH 9:1 afforded 625 mg (2.22 mmol, 74%) of **3a**.

Table 1. Synthesis of 8-Alkylated Derivatives of Adenosine (**1a**), 2'-Deoxyadenosine (**1b**) and 2',3'-Dideoxyadenosine (**1c**)

Starting material	Product (b)	Reaction temp. (time)	Yield % (a)	M.P. (°C)	UV (MeOH) λ_{max} (ϵ)
2a (c)	**3a**	110°C (14 h)	74	207-208	261 (14700)
2a	**4a**	110°C (14 h)	70	245(dec)	229 (22500) 294 (12600)
2a	**5a**	130°C (16 h)	80	251	262 (14400)
2b	**3b**	110°C (2 h)	92	169	261 (15500)
2b	**4b**	110°C (14 h)	75	slow dec.	230 (23000) 294 (12600)
2b	**5b**	130°C (14 h)	87	216	262 (14700)
2c (d)	**3c**	110°C (3 h)	72	185	261 (15400)
2c	**4c**	110°C (14 h)	65	>280	229 (23300) 294 (12100)

(a) Isolated yield after chromatography
(b) Besides mp and UV, characterized by ^1H and ^{13}C NMR and mass spectra
(c) Synthesized according to ref. 9
(d) Synthesized according to ref. 20

All other reactions were carried out at the indicated temperature (Table I). Allylation is met with difficulties due to isomerization and reduction. The synthesis of 8-ethyl-2',3'-dideoxyadenosine also is low yielded due to instability of the nucleoside at elevated temperature.

In summary, a straigthforward C-8 alkylation procedure has been developped starting from the easily available 8-bromoadenosine, 8-bromo-2'-deoxyadenosine and 8-bromo-2',3'-dideoxyadenosine. Methylation, ethylation and vinylation proceed equally well by cross-coupling reaction with the respective tetraalkyltin reagents. Only *in situ* protection with trimethylsilyl groups is necessary to facilitate isolation of the desired compound.

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REFERENCES

1. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911-1915.
2. De Clercq, E. *Adv. Drug Res.* **1988**, *17*, 1-20.
3. De Clercq, E. *Chapter 5. Viral DNA synthesis as target for the antiviral action of nucleoside analogues in Antiviral Drugs, Basic and Therapeutic Aspects, p. 47-72.* Calio, R. and Nisticof, G. Ed.; Pythagora Press Rome, Milan. 1989.
4. Oligodeoxynucleotides. *Antisense Inhibitors of Gene Expression. Topics in Molecular and Structural Biology, Volume 12*; Cohen, J.S. Ed.; The Macmillan Press Ltd.: London. 1989.
5. Dreyer, G.B.; Dervan, P.B. *Proc. Natl. Acad. Sci. USA* **1985**, 968-972.
6. Hobbs, F.W. *J. Org. Chem.* **1989**, *54*, 3420-3422.
7. Prober, J.M.; Trainor, G.L.; Dam, R.J.; Hobbs, F.W.; Robertson, C.W.; Zagursky, R.J.; Cocuzza, A.J.; Jensen, M.; Baumeister, K. *Science* **1987**, *238*, 336-341.
8. Jacobson, K.A. *Chapter 12.10. Adenosine (P_1) and ATP (P_2) Receptors, p. 601-642. Membranes and Receptors. Comprehensive Medicinal Chemistry, Volume 3*; Emmett J.C. Volume Ed.; Pergamon Press : Oxford, UK. 1990.
9. Ikehara, M.; Kaneko, M. *Tetrahedron* **1970**, *26*, 4251-4259.
10. Sarfati, S.R.; Pochet, S.; Guerreiro, C.; Namane, A.; Huynh-Dinh, T.; Igolen, J. *Tetrahedron* **1987**, *43*, 3491-3497.
11. Matsuda, A., Nomoto, Y.; Ueda, T. *Chem. Pharm. Bull.* **1979**, *27*, 183-187.
12. Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1984**, *33*, 3263-3270.
13. Hayakawa, H.; Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 72-79.
14. Koyama, S.; Kumazawa, Z.; Kashimura, N. *Nucleic Acids Res. Symposium Series.* **1982**, *11*, 41-44.
15. Matsuda, A.; Shinozaki, M.; Miyasaka, T.; Machida, H.; Abiru, T. *Chem. Pharm. Bull.* **1985**, *33*, 1766-1769.
16. Nair, V.; Buenger, G.S. *J. Am. Chem. Soc.* **1989**, *111*, 8502-8504.
17. Nair, V. *Nucleosides & Nucleotides* **1989**, *8*, 699-708.
18. Nair, V.; Purdy, D.F. *Tetrahedron* **1991**, *47*, 365-382.
19. Moriarty, R.M.; Epa, W.R.; Awasthi, A.K. *Tetrahedron Lett.*, **1990**, *31*, 5877-5880.
20. Van Aerschot, A.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1743-1749.
21. Herdewijn, P.; Kerremans, L.; Wigerinck, P.; Vandendriessche, F.; Van Aerschot, A. *Tetrahedron Lett.* **1991**, *32*, 4397-4400.
22. Stille, J.K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524.

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