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An expedient synthesis of N^6-substituted-5′-modified adenosines

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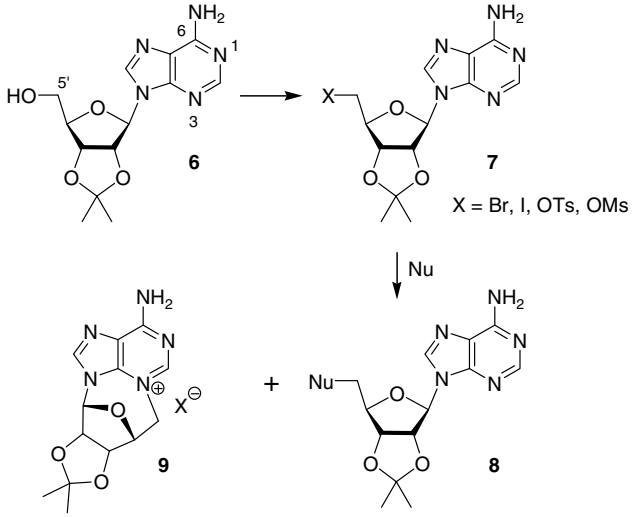
Abstract—Herein we report a short and efficient synthesis of N^6-substituted 5′-modified adenosines, which was achieved in four steps from 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)inosine.

Adenosine analogues which are substituted at N^6 and/or modified at the 5′-position have been the subject of widespread interest. Many N^6-substituted 5′-modified adenosines act as adenosine agonists (e.g., **1**) and the nature of the groups in the N^6 and 5′-positions exhibits a profound influence on receptor affinity and subtype selectivity.[1–3] Certain N^6-substituted 5′-modified adenosines have also been found to be partial agonists at the A_1 and A_3 adenosine receptor subtypes (e.g., compounds **2** and **3**, respectively).[4,5] Compounds of this type have also been used as agents for positron emission topography (PET) imaging of brain A_1 adenosine receptors.[6] Furthermore, 5′-modified adenosines have featured prominently in studies on the biological methylating agent, methyl transferase *S*-adenosyl-L-methionine (SAM). The 5′-aziridine based SAM mimic **4** is one such example.[7] Antibiotics that inhibit *Mycobacterium tuberculosis* have also been identified that possess a heteroatom motif in the 5′-position (e.g., compound **5**).[8]

With the broad scope of application of this class of compounds, an expedient access would be of particular synthetic utility. Many syntheses have been described; typically the 5′-alcohol of an 2′,3′-isopropylidene adenosine is activated as a halide or sulfonate (Scheme 1).[6,9–12] When these intermediates are subjected to substitution conditions, they can undergo an intramolecular cyclisation as N3 displaces the 5′-leaving group.[13,14] This is well documented and reflected in the low to moderate yields reported for this approach. The formation of the cyclonucleoside can be suppressed *via* the withdrawal of



Scheme 1.

electron density from the N3 position, either through the acylation of N^6 or the oxidation of N1 to the corresponding N-oxide.[15,16] Such measures generally elongate the synthesis. An electron-withdrawing group in the 6-position has also been shown to be effective in eliminating unwanted cyclisations of this type.[17,18]

A chloro group can be introduced directly in the 5′-position of unprotected N^6-substituted adenosines via treatment with thionyl chloride ($SOCl_2$) in hexamethylphosphoramide (HMPA). This reaction can be quite low yielding and is not directly applicable in cases where the N^6-substituent is sensitive to the chlorination conditions. Furthermore, subsequent substitution of the chloride is also generally low yielding (<50%)[4], presumably

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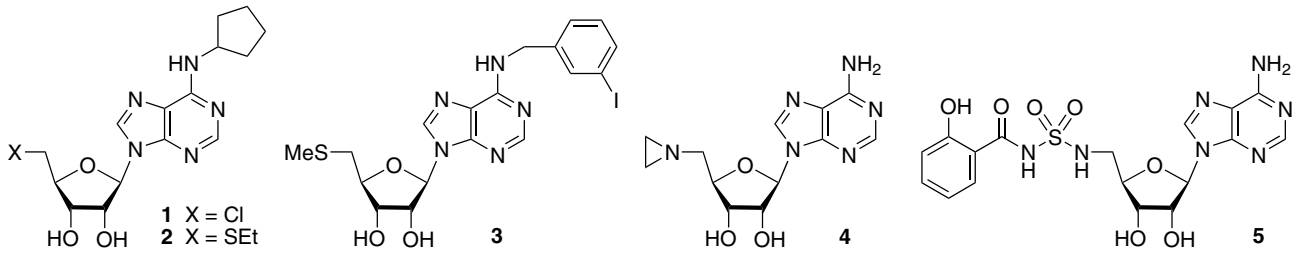


as a result of the competing reactions such as the cyclisation described above. This approach failed completely for amine nucleophiles and an alternative approach involved selective *tert*-butyldimethylsilyl (TBS) protection of the 5′-hydroxyl, benzoyl protection of the 2′- and 3′-hydroxyls, followed by deprotection and tosylation of the 5′-OH prior to reaction with the appropriate amine.[4] Interestingly, the displacement of the tosyl proceeded in good yield (generally >70%) when the 2′,3′-hydroxyl groups were protected as benzoyl esters (in contrast to the 2′,3′-isopropylidene examples).

We now report a short synthetic access into 5′-deoxy-5′-modified-N^6-substituted adenosines through a novel protection and chlorination strategy (Scheme 2).

Our approach begins with TBS protected inosine (**10b**) which is obtained in excellent yield (94%) from commercially available inosine, **10a**. Heating **10b** in neat $SOCl_2$ for 1–2 h, followed by addition of DMF and further reflux, gives the difunctionalized material, **12**, in very good yield (78%) as a stable crystalline solid.[19] This reaction proceeds initially through the intermediate, **11**, which is the isolated product when the reaction is ceased prior to the addition of DMF.

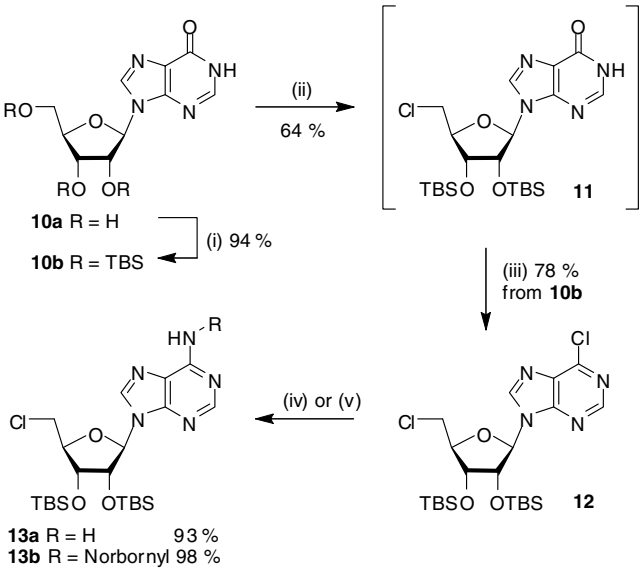
The addition of DMF after 1 h is an important feature of this reaction. In the absence of DMF, the 5′-chloro inosine analogue **11** was obtained in 64% yield. As expected, DMF was required for chlorination of the 6-position. Interestingly, when DMF was added at the beginning of the reaction, a complex mixture of products was obtained. Based on this observation, it appears that it is necessary to ensure that the chlorination of the 5′-position is complete prior to the introduction of a 6-chloro group.

Amination of the 6-position proceeds in excellent yield (**13a**, 93%) via our previously reported method.[17] (±)-*endo*-Norborn-2-yl amine hydrochloride was incorporated in nearly quantitative yield (98%) in refluxing *t*-BuOH in the presence of Hünigs base [$N(i\text{-}Pr)_2Et$] to give **13b** as a mixture of diastereomers. We then utilized **13b** as a synthetic platform to obtain a range of 5′-deoxy-5′-modified-N^6-(*endo*-norborn-2-yl)adenosines. The regioselectivity of the substitutions was confirmed by analysis of the aromatic region of both the ^1H and ^{13}C NMR. Negligible changes in the chemical shifts were observed for the 5′-methylene.

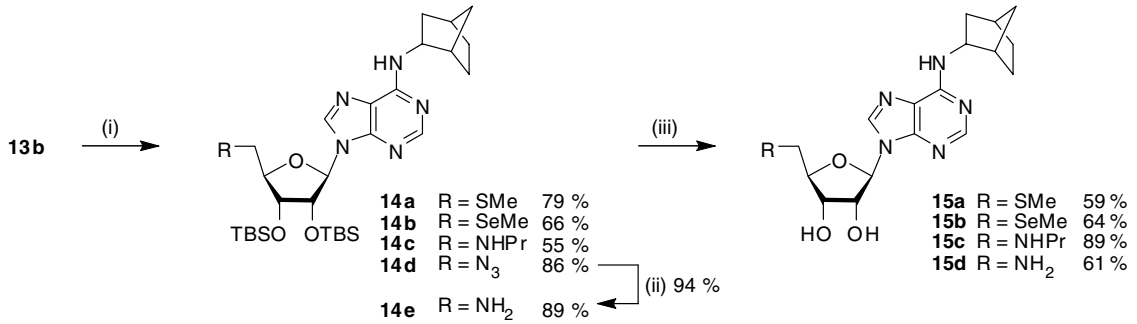
Typically, the desired 5′-modification is achieved using an excess of the appropriate nucleophile. Temperature and solvents employed were dependent on the reactivity of the given nucleophile and its mode of generation.

Introduction of a 5′-methylthio moiety (Scheme 3, **14a**) was achieved overnight at ambient temperature using an excess of sodium methanethiolate (NaSMe). This gave the desired product in a 79% yield. The 5′-azidoanalogue (**14d**) was also obtained in very good yield, 86%, by treating **13b** with an excess of sodium azide (NaN_3) in DMF at 90 °C. Hydrogenolysis (H_2, 10% Pd/C) of **14d** in THF then gives **14e** in excellent yield, 89%. The introduction of azide and its subsequent reduction is a high yielding method for the preparation of 5′-deoxy-5′-aminoadenosines. An alternative approach which employs amine nucleophiles directly can be low yielding as evidenced by the reaction of compound **13b** with neat *n*-$PrNH_2$. This reaction afforded the expected substitution product **14c** in a modest yield of 55% along with a significant amount of recovered starting material (35%). Methyl selenide was also introduced in good yield (**14b**, 66%) *via in situ* reduction of dimethyldiselenide (Me_2Se_2) by $NaBH_4$ in EtOH, followed by refluxing in the presence of **13b**.

The removal of the TBS groups was achieved *via* warming the protected compound in dry MeOH in the presence of a large excess of NH_4F (~10 M equiv). Yields



Scheme 2. Reagents and conditions: (i) TBSCl, imidazole, DMF, rt; (ii) $SOCl_2$, 79 °C; (iii) cat. DMF, $SOCl_2$, 79 °C; (iv) NH_3, *t*-BuOH, sealed tube, 85 °C; (v) (±)-*endo*-norborn-2-yl amine·HCl, $N(i\text{-}Pr)_2Et$, *t*-BuOH, 83 °C.



Scheme 3. Reagents and conditions: (i) for **14a**, NaSMe, DMF, rt; for **14b**, Me_2Se_2, $NaBH_4$, EtOH, 78 °C; for **14c**, *n*-$PrNH_2$, sealed tube, 60–70 °C; for **14d**, NaN_3, DMF, 90 °C; (ii) H_2, Pd/C, THF, rt; (iii) NH_4F, MeOH, 50–60 °C.

up to 89% of the 5′-deoxy-5′-modified-N^6-(*endo*-norborn-2-yl)adenosine were obtained.

Despite the propensity of activated 5′-modified compounds to cyclise with the N3-position of the purine, there was no indication of this occurring. This may well be a result of the bulky 2′- and 3′-TBS protecting groups destabilising the *syn*-conformation required for N3 to displace the 5′-chloro, thereby favouring an intermolecular reaction with the nucleophile. Even weaker nucleophiles (selenides or 1 ° amines) were incorporated in over 50% yield.

We have demonstrated a novel route for the synthesis of 5′-deoxy-5′-modified-N^6-substituted adenosines from an easily accessible 5′,6-dichloropurine riboside **12** which is produced in two steps from the commercially available and relatively inexpensive starting material, inosine. The applicability of this reagent has been demonstrated by the synthesis of a number of N^6-substituted 5′-modified adenosines.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.bmcl.2006.06.019.

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19. 5′-Deoxy-5′-chloro-9-(2,3-bis-*O*-TBS-β-D-ribofuranosyl)-6-chloropurine (**12**). Protected inosine (**10b**, 611 mg, 1.00 mmol) was refluxed in $SOCl_2$ (3.0 mL, 41 mmol) for 1 h. DMF (0.1 mL, 94 mg, 1.29 mmol, 1.3 equiv) was added and the reaction mixture was heated at reflux for a further 2 h. The resultant orange solution was added to a mixture of EtOAc (50 mL) and satd $NaHCO_3$/ice (~50 mL) and allowed to gradually partition between the layers. The mixture was separated and the aqueous layer extracted with EtOAc (50 mL). The combined organic phase was dried ($MgSO_4$), filtered and reduced in vacuo to give an opaque yellow oil which was taken up in MeOH, addition of H_2O crashes out 416 mg (0.78 mmol, 78%) of the title compound, **12**, as an off-white solid (mp 88–89 °C, recrystallised MeOH/H_2O). ^{1}H NMR δ 8.76 (s, H-2/8, 1H), 8.40 (s, H-8/2, 1H), 5.99 (d, J = 4.3 Hz, H-1′, 1H), 4.97 (dd, J = 4.3 and 3.8 Hz, H-2′, 1H), 4.38–4.36 (m, H-3′, H-4′, 2H), 4.04 (dd, J = 12.0 and 4.8 Hz, H-5a′/b′, 1H), 3.76 (dd, J = 12.0 and 3.3 Hz, H-5b′/a′, 1H), 0.96 (s, *t*-Bu, 9H), 0.83 (s, *t*-Bu, 9H), 0.15 (s, CH_3, 3H), 0.13 (s, CH_3, 3H), 0.01 (s, CH_3, 3H), −0.18 (s, CH_3, 3H). ^{13}C NMR δ 151.8, 151.4, 151.0, 144.6, 132.6, 90.1, 83.7, 74.2, 72.3, 43.4 25.8, 25.6, 18.0, 17.8, −4.4, −4.7, −4.7, −5.0. HRMS (ESI) calcd 555.1752 for $(M+Na)^+$. Found 555.1743.