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A Highly Facile and Efficient One-Step Synthesis of N^6-Adenosine and N^6-2′-Deoxyadenosine Derivatives

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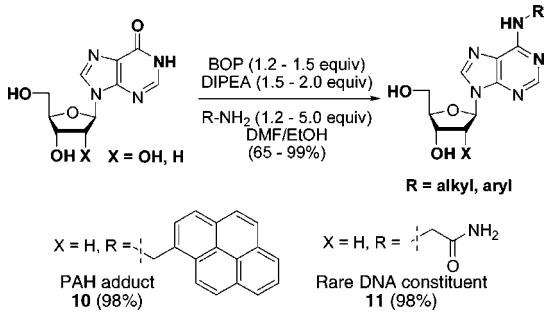
ABSTRACT



A highly facile and efficient one-step synthesis of N^6-adenosine and N^6-2′-deoxyadenosine derivatives has been developed. Treatment of inosine or 2′-deoxyinosine, without protection of sugar hydroxyl groups, with alkyl or arylamines, in the presence of BOP and DIPEA in DMF, led to the formation of N^6-adenosine and N^6-2′-deoxyadenosine derivatives in good to excellent yields. Carcinogenic polyaromatic hydrocarbon (PAH) N^6-2′-deoxyadenosine adduct 10 and a rare DNA constituent 11 were thus synthesized directly from 2′-deoxyinosine both in 98% yield.

Amino heterocycles are common biological and pharmaceutical components the synthesis of which often dictates the success of drug discovery and related research. We have been involved in direct amination of cyclic amide systems (Figure 1), with early emphasis on the synthesis of nucleosides to be reported herein.

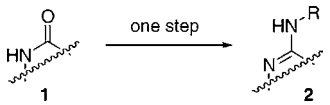


Figure 1. Direct amination of amide systems.

Purine bases play paramount roles in numerous biological processes.[1] Structurally modified purine bases, nucleosides, and nucleotides have drawn considerable attention and led to the discovery of numerous biologically active compounds.[1] N^6-Amino purines are key members of the nucleoside family. The broad spectrum of their functionality has long piqued research interests. However, formation of a C−N bond in such biologically important systems remains challenging. A common approach is S_NAr displacement of amines with C6 halopurines[2] that often require extra steps to synthesize. Since the modern chemistry has not yet rendered syntheses without a protection/deprotection protocol, the typical four-step

(1) Suhadolnik, R. J. *Nucleosides as Biological Probes*; Wiley: New York, 1979.

(2) For representative references, see: (a) Srivastava, P. C.; Robins, R. K.; Meyer, R. B., Jr. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1988; Vol. 1, pp 113−281. (b) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917−2920. (c) Han, S.; Harris, C. M.; Harris, T. M.; Kim, H.-Y. H.; Kim, S. J. *J. Org. Chem.* **1996**, *61*, 174. (d) Nair, V.; Richardson, S. G. *J. Org. Chem.* **1980**, *45*, 3969. (e) Véliz, E. A.; Beal, P. A. *Tetrahedron Lett.* **2000**, *41*, 1695−1697. (f) Véliz, E. A.; Beal, P. A. *J. Org. Chem.* **2001**, *66*, 8592 and references therein. For recent reviews, see: (g) Lakshman, M. K. *J. Organomet. Chem.* **2002**, *653*, 234−251. (h) Hocek, M. *Eur. J. Org. Chem.* **2003**, 245−254.

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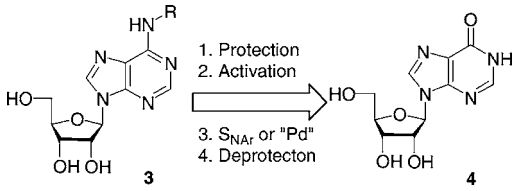


Figure 2. Conventional formation of adenosine derivatives.

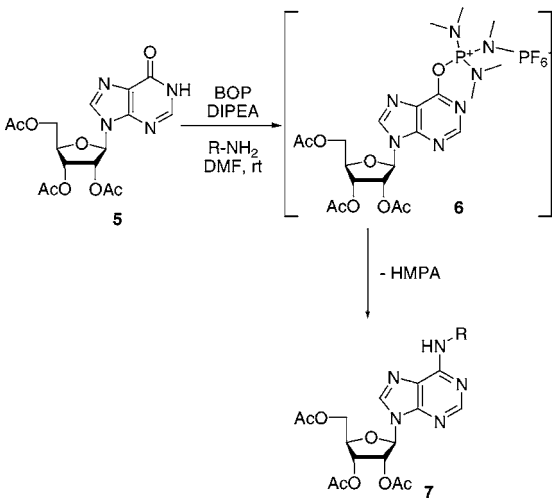
procedure (Figure 2) begins with protection of the sugar moiety followed by halide formation, often under harsh conditions. This transformation can lead to cleavage of the glycosyl bond, so acid-labile protecting groups for the sugar hydroxyl groups must be avoided. Subsequent S_NAr reactions performed with strong nucleophiles such as aliphalic amines[3] are somewhat satisfactory, but reactions with less nucleophilic aromatic amines are often unsuccessful.[2a,4] Lakshman,[5] Johnson,[6] Rizzo,[7] and Harvey[8] have recently applied the Buchwald−Hartwig chemistry to the preparation of carcinogenic N^6-nucleoside adducts. The development of a facile C−N bond-forming reaction would allow an easy access to these biologically important and complex nucleoside systems.[1,5−8]

1-*H*-Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and other phosphonium salts have been used for amide bond formation.[9] It is assumed that the formation of an (acyloxy)phosphonium salt is involved.[9] In our research, we discovered that BOP was suitable for the activation of certain cyclic amide bonds.[10] We reasoned that formation of a phosphonium salt may provide sufficient activation in a nucleoside system as well, thus allowing a C−N bond-forming reaction in such a system. Beal[2e,f] recently reported the synthesis of 6-bromopurine and 6-chloropurine ribosides by treatment of protected nucleosides with NBS or CX_4 with $P(NMe_2)_3$ and a halide source. Robins[11] also reported that treatment of protected inosine and 2′-deoxyinosine derivatives with a cyclic secondary amine or imidazole with $I_2/Ph_3P/EtN(i\text{-}Pr)_2$ in CH_2Cl_2 or toluene under modified Appel combinations[12] gave rise to N^6-substituted purine nucleosides. In addition, Sung[13] and Mansour[14] reported formation of protected C4-(1,2,4-triazol-1-yl) and C4-imidazole uracil derivatives with 4-Cl-$PhOPOCl_2$, respectively.

We were interested in exploring our phosphonium salt mediated C−N bond formation with two goals in mind: (1) to achieve amination with arylamines under mild and non-metal-catalyzed conditions; and (2) to conduct reactions directly with unprotected nucleosides, i.e., **4** to **3** in a single step, a type of transformation that has not been documented.[15]. In this communication, we report a highly facile and convenient one-step synthesis of N^6-adenosine and N^6-2′-deoxyadenosine derivatives including arylamine analogues and carcinogenic amine adducts of 2′-deoxyribonucleosides through phosphonium salt intermediates.

Our work began with screening some common amide coupling activators as well as other reaction conditions[16] and ultimately led to the successful synthesis of adenosine analogue **7a** (Scheme 1). Activation of 2′,3′,5′-tri-*O*-acetyli-

Scheme 1



nosine **5** with BOP reagent (1.2 equiv) in the presence of DIPEA (1.5 equiv) in DMF at room temperature was followed by treatment with benzylamine (1.2 equiv). The desired N^6-benzyladenosine **7a** was formed in near quantitative yield (98%, Table 1). It is our belief that the phosphonium salt **6** was involved in this facile C−N bond-forming process.[17] Subsequent substitution by a variety of amines led to the formation of desired products upon elimination of a molecule of HMPA (Table 1).

It was determined that preactivation was not necessary as demonstrated in various C−N bond-forming reactions with

(3) Robins, M. J.; Basom, G. L. *Can. J. Chem.* **1973**, *51*, 3161−3169.
(4) (a) Maruenda, H.; Chenna, A.; Liem, L.-K.; Singer, B. *J. Org. Chem.* **1998**, *63*, 4385−4389. (b) Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090−6091. (c) Lakshman, M. K.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc*. **1991**, *113*, 6589−6594. (d) Lakshman, M. K.; Lehr, R. E. *Tetrahedron Lett*. **1990**, *31*, 1547−1550. (e) Kim, S. J.; Harris, C. M.; Jung, K.-Y.; Koreeda, M.; Harris, T. M. *Tetrahedron Lett.* **1991**, *32*, 6073−6076.
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(6) De Riccardis, F.; Bonala, R. R.; Johnson, F. *J. Am. Chem. Soc*. **1999**, *121*, 10453−10460.
(7) Elmquist, C. E.; Stover, J. S.; Wang, Z.; Rizzo, C. J. *J. Am. Chem. Soc*. **2004**, *126*, 11190−111201.
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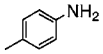
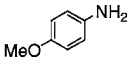
(15) Phosphonium salts of primary and secondary alcohols readily undergo nucleophilic substitutions. (a) Castro, B.; Chapleur, Y.; Gross, B.; Selve, C. *Tetrahedron Lett*. **1972**, 5001−5004. (b) Castro, B.; Selve, C. *Tetrahedron Lett*. **1973**, 4459−4463. (c) Downie, I. M.; Heaney, H.; Kemp, G. *Tetrahedron* **1988**, *44*, 2619−2624 and references therein.
(16) PyBOP and PyBroP were also active towards activation of inosine but less effective. DMF was found to be the best solvent.
(17) The phosphonium salt was observed on LCMS.

Table 1. Amination of Sugar-Protected Inosine

entry	amine	reaction conditions	product (%)
1	Bn-NH_2	rt. < 1 h	**7a** (98)
2		rt, overnight	**7b** (99)
3		"	**7c** (99)
4		"	**7d** (87)
5		"	**7e** (70)
6		rt, overnight then 80 °C. 10 h	**7f** (78)
7		rt, 48 h	**7g** (74*)

a panel of amines (Table 1). With the exception of aromatic amines, all reactions were completed overnight at ambient temperature providing the desired adenosine analogues **7a**−**7e** in good to excellent yields (70−99%). The aromatic amines reacted more slowly as expected. For instance, reaction with *p*-anisidine (Table 1, entry 7) was accomplished at room temperature to produce the desired product **7g** (74% isolated yield and 20% recovered starting material), whereas heating (80 °C, 10 h) was required for the reaction with *p*-toluidine to give the desired product **7f** (Table 1, entry 6).

To perform this reaction on an unprotected system, selective activation is required. We reasoned this was possible due to the much lower pK_a value of the cyclic amide group compared to that of the sugar moiety. We thus began to look into direct amination of unprotected nucleosides (Scheme 2).

Scheme 2

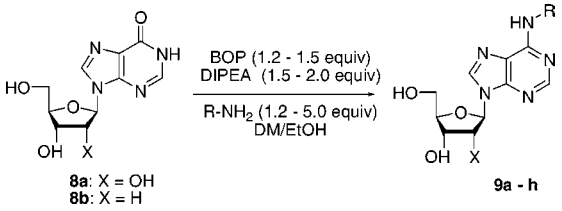
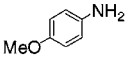
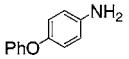
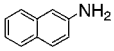
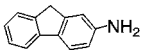


Table 2 demonstrates the high flexibility of this newly discovered C−N bond formation in unprotected nucleoside systems. Compared to protected inosine, reactions of unprotected substrates with aliphatic and aromatic amines require longer reaction times. The slower reaction rate was partially due to the low solubility of inosine in DMF. The reactions with benzylamine (Table 2, entries 1 and 2) were completed at room temperature.[18] The reactions with aromatic amines also proceeded at room temperature; however, heating was required to push the reactions to completion. Nevertheless, all of reactions provided the desired products in good yields. HOBt adduct was also observed by LCMS in these cases and is hypothesized to be an intermediate in the reaction.[19]

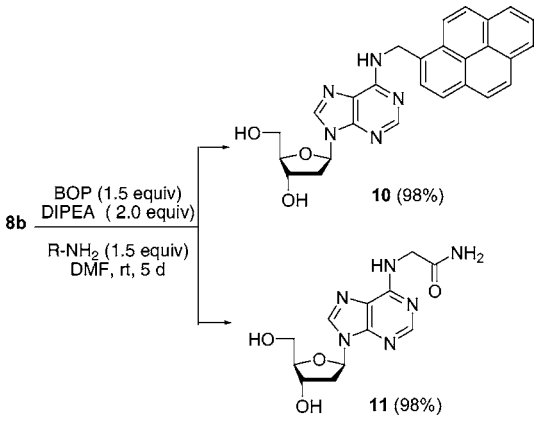
Table 2. Amination of Sugar-Unprotected Inosine and 2′-Deoxyinosine

entry	X	amine	method	product	yield (%)
1	OH	Bn-NH_2	**A**	**9a**	99
2	H	"	**A**	**9b**	99
3	OH		**B**	**9c**	91
4	OH		**B**	**9d**	74[a]
5	OH		**B**	**9e**	81[a]
6	OH		**B**	**9f**	85
7	OH		**B**	**9g**	65[a]
8	OH		**B**	**9h**	72[a]

[a] Method A: BOP (1.2 equiv), DIPEA (1.5 equiv), R-NH_2 (1.2 equiv), rt. Method B: BOP (1.5 equiv), DIPEA (2.0 equiv), R-NH_2 (5.0 equiv), rt, overnight, then 60 or 80 °C. [b]Yield after recrystallization or HPLC purification.

With this facile and efficient methodology in hand, we sought to demonstrate its utility in the synthesis of biologically important nucleosides. Polycyclic aromatic hydrocarbons (PAH) are potent mutagens and carcinogens that pose synthetic challenges.[4c,6−8] We felt that our chemistry could aid the synthesis of these compounds. Therefore, we chose to resynthesize compounds **10**[8b] and **11**[20] that were previously reported in the literature (Scheme 3).

Scheme 3



1-Methylpyrene is a common environmental pollutant.[21] Its dA adduct **10** was synthesized in three steps from a

chlorofuranose (33% overall),[8b] and the dA adduct **11**, a rare DNA constituent, was synthesized through a six-step sequence (34% overall).[20] In our hands, treatment of 2′-deoxyinosine with BOP in the presence of DIPEA at ambient temperature, followed by addition of 1-pyrenemethylamine, led to the formation of the desired products **10**[8b] in just one step in 98% yield (Scheme 3). Similarly, the reaction with glycinamide gave **11**[20] also in 98% yield (Scheme 3).

(18) **Representative Procedure.** To a solution of (−)-inosine (268 mg, 1.0 mmol) and BOP (530.7 mg, 1.2 mmol) in DMF (5 mL) was added DIPEA (0.261 mL, 1.5 mmol), followed by addition of benzylamine (0.131 mL, 1.2 mmol) at room temperature under the nitrogen. The reaction mixture was stirred overnight (∼16 h) at room temperature. The solvent was removed under vacuum, and the crude product was purified on a silica gel column eluted with 0−15% MeOH in DCM to give the desired product **9a** as a white solid (355 mg, 99+%). All products in both Table 1 and Table 2 have been fully characterized.

(19) Mechanistic studies are underway. For work on BtH, see: Katritzky, R. A.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555−2581 and references therein.

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(21) (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University Press: Cambridge, England, 1991. (b) Glatt, H.; Seidel, A.; Harvey, R. G.; Coughtrie, M. W. H. *Mutagenesis* **1994**, *9*, 553−557.

In summary, a highly facile and efficient one-step, phosphonium salt mediated C−N bond-forming reaction was developed for the synthesis of N^6-adenosine and N^6-2′-deoxyadenosine derivatives with both aliphatic and aromatic amines. The one-step synthesis of PAH adduct **10** and DNA constitutent **11** demonstrated the clear advantage of this new methodoloy over the existent procedures. Further studies to broaden its generality and applicability to many other heterocyclic systems are underway, and results will be reported later.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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