DOI: 10.1002/ejoc.200800752

Synthesis of N^6,N^6-Dialkyladenine Nucleosides Using Hexaalkylphosphorus Triamides Produced in Situ

Mahesh K. Lakshman,*[a] Asad Choudhury,[a][‡] Suyeal Bae,[a] Eliezer Rochttis,[a][‡] Padmanava Pradhan,[a][‡‡] and Amit Kumar[a]

Dedicated to the memory of Dr. John W. Daly (1933–2008)[†]

Keywords: Inosine / Adenosine / Phosphorus triamide / Iodine / Amines

Reactions between secondary amines and phosphorus trichloride (PCl_3) leads to the formation of the corresponding tris(dialkylamino)phosphanes or hexaalkylphosphorus triamides [HAPTs: $(R_2N)_3P$]. Treatment of silyl-protected 2′-deoxyinosine and acetyl-protected inosine with the HAPTs produced in situ, together with iodine (I_2), leads to the formation of N^6,N^6-dialkyladenosine and -2′-deoxyadenosine. In some cases the stoichiometry of the amine is important, as is the use of a tertiary amine base. The effect of amine stoichiometry on the reaction between HAPT and I_2 has been studied by $^{31}P\{^1H\}$ NMR spectroscopy.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

The physiological importance of adenine and modified adenine nucleosides cannot be overstated. Because of this high importance, the adenosine core has been the subject of numerous structural modifications. The emergent compounds have been studied for their wide-ranging effects, such as modulation of A_1, A_2 and A_3 receptors that control important biofunctions,[1] and also as antiviral,[2] anticancer,[3] and antimalarial[4] pharmacophores. The classical method for introducing modifications at the exocyclic amino groups of adenine nucleosides is the S_NAr displacement, in which a leaving group at the purine 6-position is displaced with suitable amines.[5]

One important limitation to the use of S_NAr displacement is the availability of suitable nucleoside derivatives, many of which involve non-trivial synthesis. The most significant problem in these processes is the cleavage of the labile glycosidic bond. Although C-6 sulfonates can be prepared from hypoxanthine nucleosides, competing N-1 and O-6 sulfonylation occurs.[6] In order to circumvent some of the problems associated with access to electrophilic nucleoside precursors, non-aqueous diazotization methods have been developed.[7] Nevertheless, newer and simpler methods are needed for the synthesis of *N*-modified adenine nucleosides.

In this context, the combination of PPh_3/I_2/amine for the introduction of morpholinyl, piperidinyl, and imidazolyl groups at the 6-positions of purine nucleosides has been reported.[8] This reaction presumably proceeds by formation of $[(Ph_3P^+I)I^-]$, which reacts at the amide carbonyl group of the hypoxanthine residue to afford a nucleoside phosphonium salt (Scheme 1). Expulsion of Ph_3PO from this intermediate by the amine then results in the *N*-modified adenine nucleoside. Along the same lines, treatment of hypoxanthine nucleosides with 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and amines has been used to synthesize *N*-substituted adenine nucleosides (Scheme 1).[9] An O-6 phosphonium salt was proposed as the intermediate in these transformations, which undergoes reaction with the amine by displacement of hexamethylphosphoramide [tris(dimethylamino)phosphane oxide or HMPA].[9] We have recently analyzed the mechanism of the reaction between the hypoxanthine core and BOP and have confirmed that in the absence of an amine, a nucleoside phosphonium salt is formed en route to the O^6-(benzotriazol-1-yl) nucleoside derivatives.[10] These new nucleoside derivatives are excellent substrates for modification at C-6. The chemical understanding gained subsequently led to the development of a second-generation synthesis of O^6-(benzotriazol-1-yl)inosine and -2′-deoxy-

---

[a] Department of Chemistry, The City College and The City University of New York,
160 Convent Avenue, New York, NY 10031-9198, U.S.A.
Fax: +1-212-650-6107
E-mail: lakshman@sci.ccny.cuny.edu

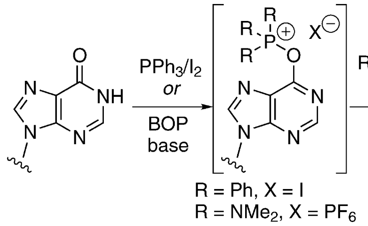
[‡] Undergraduate research participant.

[‡‡] Manager, CCNY high-field NMR facility.

[†] Former laboratory chief (NIDDK) NIH, an exceptional scientist and individual.

Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

inosine through the use of $PPh_3/I_2/HOBt$,[11] as well as polymer-supported reagents for nucleoside modification.[12] As a result of our interest in understanding whether other phosphanes can be utilized for modification of purine nucleosides at C-6, we became involved in the work described here (Scheme 1).



Scheme 1. In situ formation of C-6 phosphonium derivatives and their conversion into adenosine analogues.

Results and Discussion

In our initial experimentation with 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine and the PPh_3/I_2 combination, we quickly discovered that the products were contaminated by the $Ph_3P{=}O$ byproduct and that separation was difficult. Scrutiny of the literature (supporting information to ref.[8b]) indicated a similar problem. We expected that amelioration of this problem could be attained through the use of a polymer-supported phosphane (Figure 1). To our surprise, polymer-supported triphenylphosphane from two different sources[13] proved ineffective for the reaction, and so we focused our attention on the family of the proazaphosphatranes, which have proved to be interesting in other reactions.[14] These compounds (Figure 1) also proved ineffective for conversions, with significant amounts of starting materials left in many instances.

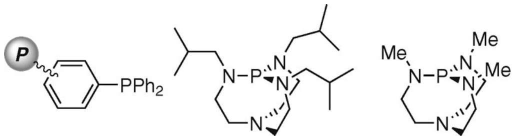
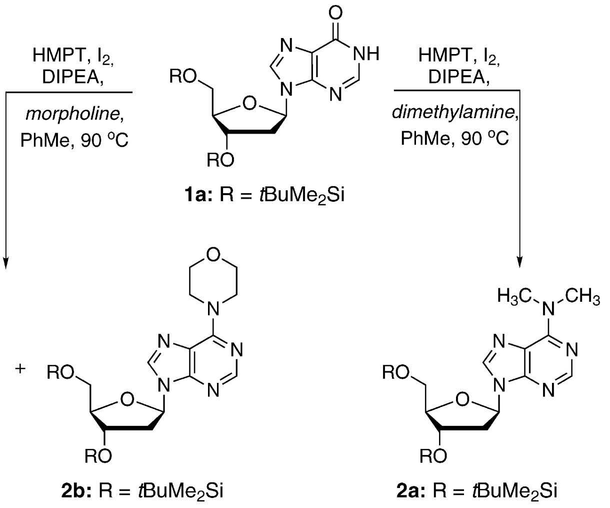


Figure 1. Reagents that were initially tested.

We then reasoned that increasing the ease of removal of the resultant phosphane oxide might allow circumvention of the problem. Tris(dimethylamino)phosphane (HMPT) was not only expected to display enhanced nucleophilicity in its reaction with I_2, but the formed HMPA should potentially be removable by washing with water. It was with this in mind that we embarked on subsequent experimentation, the results of which are reported here.

On the basis of the above considerations, we initially subjected 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**1a**) to treatment with HMPT/I_2/morpholine/iPr$_2$NEt (DIPEA) in toluene at 90 °C (Scheme 2). This reaction proceeded smoothly and appeared clean by TLC. However, the ^{1}H NMR spectrum of the product from this reaction was interesting. The signals for the purine, saccharide, and morpholinyl resonances were clearly visible, but there was an additional broad resonance at δ = 3.52 ppm. It was the presence of this signal that led us to doubt the purity of the product obtained.



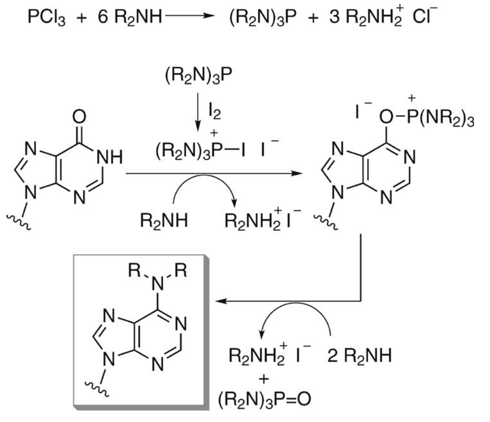
Scheme 2. Initial attempts to convert **1a** into the C-6 morpholinyl and dimethylamino derivatives.

Since *N*,*N*-dimethyladenosine is formed in the reaction between 2′,3′,5′-tri-*O*-acetylinosine, HMPT, and CX_4 (X = Br or Cl),[15] we reasoned that the byproduct obtained in the reaction of **1a** might be the *N*,*N*-dimethyl-2′-deoxyadenosine derivative **2a** (Scheme 2). Competing formation of dimethylamides in HMPT-mediated conversions of 2,2,2-trihaloethyl esters into amides has been reported in the literature.[16] Our next effort was therefore the synthesis of **2a** by simply replacing morpholine with Me_2NH. This reaction proceeded smoothly, affording the *N*,*N*-dimethyl-2′-deoxyadenosine derivative **2a** in good yield. With this authentic **2a** we were able to identify it as the byproduct formed along with the morpholinyl derivative **2b** in the initial reaction with morpholine (pure **2a** displays a broad resonance at δ = 3.52 ppm that sharpens upon heating to 45 °C).

The two experiments above indicated that the HMPT/I_2 combination could be used to produce effective activation of the C-6 amide linkage with no problems associated with product isolation and purification. However, a problem that remained to be solved was the competing formation of **2a**. This reaction could potentially be more significant if amines with nucleophilicities lower than that of dimethylamine were to be used.

At this juncture we reasoned that specific tris(dialkylamino)phosphanes or hexaalkylphosphorus triamides (HAPTs) could potentially be prepared from individual amines and used in combination with I_2 for activation of the C-6 amide carbonyl group. The ensuing nucleoside phosphonium salts could then be subjected to subsequent displacement reactions with the amines used for forming the specific HAPT. In such an event, there would be only one possible amine nucleophile in the reaction.

In this context, HAPT derivatives such as tris(pyrrolidino)- and tris(piperidino)phosphanes have been prepared by treatment of PCl_3 with pyrrolidine and piperidine, respectively.[17] In our experiments, we decided to conduct the entire operation – consisting of: (a) formation of the HAPT, (b) activation of the C-6 amide, and (c) the amination reaction – as a one-pot process without isolation of the individual tris(dialkylamino)phosphanes. We chose secondary amines for the current work for two reasons: primary amines could potentially form polymeric products with PCl_3, and reactions between HAPTs and primary amines could lead to iminophosphoranes $[(R_2N)_3P{=}NR]$.[18] With secondary amines these potentially complicating problems can be avoided. Finally, in initial experiments, we opted to use the secondary amine itself as base. Our overall logic is represented in Scheme 3. As can be seen from this scheme, a total of 9 mol-equiv. of the amine would be needed per mol-equiv. of PCl_3.



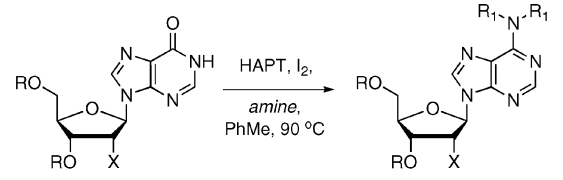
Scheme 3. Plausible synthesis of adenine nucleosides through in situ formation of HAPT $[(R_2N)_3P]$.

On the basis of these considerations, the initial conditions we opted for were 2.6–3.0 mol-equiv. PCl_3/20–30 mol-equiv. secondary amine/2.2 mol-equiv. I_2 with toluene (PhMe) as solvent. Under these conditions, 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**1a**) and 2′,3′,5′-tri-*O*-acetylinosine (**1b**) were converted into a series of *N*,*N*-disubstituted adenine derivatives (Table 1).

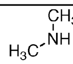
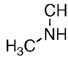
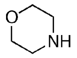
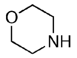
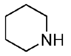
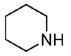
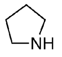
Despite the simplicity of the reaction and the overall reasonable results obtained (Table 1), difficulties were faced in some reactions. For example, the reaction involving pyrrolidine and **1b** did not yield tractable product. This led us to question the underlying reasons, one of which was the possible competitive formation of tetrakis(dialkylamino)phosphonium salts (Scheme 4). Such salts have been described in the literature.[19]

We interpreted this unexpected difficulty as follows. When excesses of fairly nucleophilic amines are utilized, there can be two competing processes: (a) reaction of the nucleoside O-6 with the iodo-HAPT intermediate formed from the reaction between the HAPT and I_2, and (b) reaction between the amine and the iodo-HAPT intermediate produced. It is conceivable that in the present cases the tetrakis(dialkylamino)phosphonium species represents a dead-end intermediate that does not react at the O-6 atom of the nucleoside.

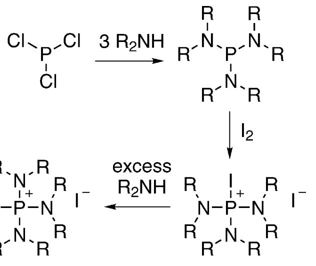
Table 1. Initial reactions of hydroxy-protected 2′-deoxyinosine and inosine with HAPT formed in situ, I_2 and secondary amine.



1a: X = H, R = *t*BuMe$_2$Si
1b: X = OR, R = COCH$_3$
2a–d: X = H, R = *t*BuMe$_2$Si
3a–d: X = OR, R = COCH$_3$

Entry	Substrate	Amine	Substrate/PCl_3/amine/I_2 time	Product yield[a]
1	**1a**		1:3:30:2.2 1 h	**2a** 92%[b]
2	**1b**		1:2.6:22:2.2 2.5 h	**3a** 81%[b]
3	**1a**		1:3:30:2.2 6 h	**2b** 69%
4	**1b**		1:2.6:20:2.2 2 h	**3b** 71%
5	**1a**		1:3:30:2.2 2 h	**2c** 65%
6	**1b**		1:2.6:30:2.2 5 h at r.t. then 15 min at 90 °C	**3c** 76%
7	**1a**		1:3:30:2.2 4 h	**2d** 73%

[a] Yield is of isolated, purified products. [b] Reaction with a 2 M solution of Me_2NH in THF.



Scheme 4. Plausible reaction of HAPT with I_2 and subsequent conversion into a tetrakis(dialkylamino)phosphonium salt.

In order to test this working hypothesis, we conducted two experiments. In one case, piperidine (6 mol-equiv.) was carefully added at 0 °C to a well-stirred solution of PCl_3 in anhydrous toluene. After the mixture had been brought to room temperature and stirred for about 30 min, I_2 (1.2 mol-equiv.) was added. The suspension was stirred at room temperature for about 23 h and then filtered. The filtrate, when concentrated to dryness and analyzed by $^{31}P\{^1H\}$ NMR spectroscopy (Figure 2A), showed a predominant resonance at δ = 26.55 ppm (relative to 85% H_3PO_4 as external reference). A second experiment was conducted in a similar manner with the exception that excess piperidine (30 mol-equiv.) was used. $^{31}P\{^1H\}$ NMR analysis (Figure 2B) showed an entirely different resonance at δ = 20.69 ppm.

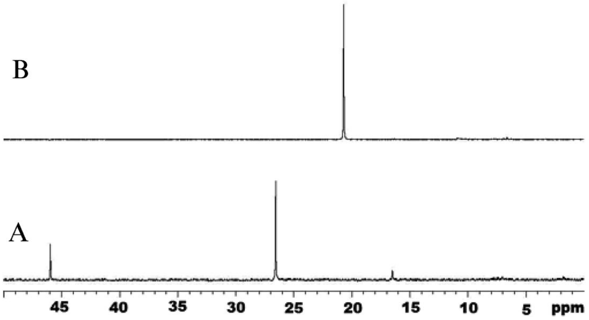
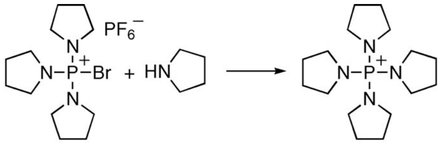


Figure 2. $^{31}P\{^1H\}$ NMR spectra (in $CDCl_3$) of the reaction mixture obtained with (A) PCl_3 + piperidine (6 mol-equiv.) + I_2 (1.2 mol-equiv.), and (B) PCl_3 + piperidine (30 mol-equiv.) + I_2 (1.2 mol-equiv.).

The results clearly indicated the formation of a new phosphorus-containing species when a large excess of piperidine was present. To verify these results further, another experiment was conducted (see scheme above Figure 3). A toluene solution of commercially available bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) was exposed to pyrrolidine (15 mol-equiv.) for about 20 h. The reaction mixture was concentrated to dryness and analyzed by $^{31}P\{^1H\}$ NMR spectroscopy. The initial ^{31}P resonance of PyBroP at δ = 27.93 ppm (Figure 3A) was replaced by new resonances, with the major one at δ = 25.14 ppm (Figure 3B).



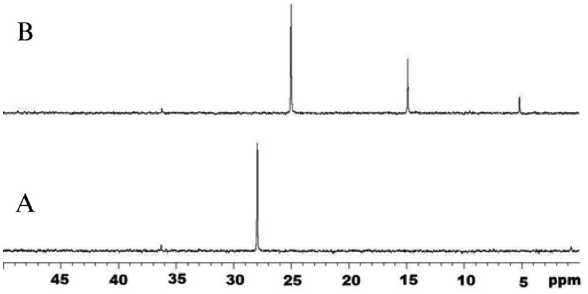
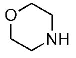
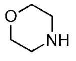
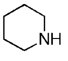
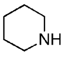
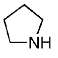
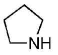


Figure 3. $^{31}P\{^1H\}$ NMR spectra (in $CDCl_3$) of (A) PyBroP and (B) PyBroP + pyrrolidine (15 mol-equiv.). (The PF_6^- resonance is not shown, but it appears at δ = –143.97 ppm in each case.).

Having gained a better understanding of the underlying chemical processes involved in these transformations, we decided to evaluate reactions that only involved stoichiometric ratios of PCl_3 and the secondary amine (PCl_3/amine, 1:6). This should in principle result in the formation of the HAPT and amine hydrochloride. Then, in order to prevent formation of the tetrakis(dialkylamino)phosphonium species, the reaction with the nucleoside was conducted in the presence of a tertiary amine: $i Pr_2NEt$. The tertiary amine not only acts as proton sponge but can also liberate free secondary amine from the initially formed hydrochloride salt for the final displacement step. A brief analysis of solvents [toluene (PhMe), 1,2-dimethoxyethane (DME), and CH_2Cl_2] was also conducted at this stage in order to optimize the reactions. The results of these experiments are shown in Table 2.

Table 2. Modified conditions tested for the synthesis of *N*,*N*-modified adenine nucleoside derivatives.

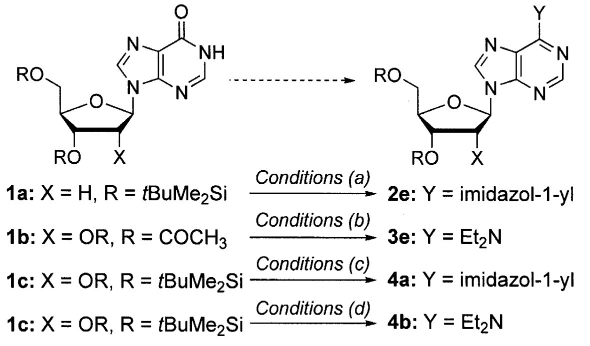
Entry	Substrate	Amine	Substrate/PCl_3/amine/I_2/$i Pr_2NEt$ Solvent, time at temperature	Product yield[a]
1	**1a**		1:3:18:3:9, PhMe, 21 h at r.t.	**2b** 71%
2	**1b**		1:3:18:3:9, PhMe, 24 h at r.t.	**3b** 65%
3	**1b**		1:3:30:2.2:0, CH_2Cl_2, 21 h at r.t.	Inc.[b]
4	**1b**		1:3:18:3:9, PhMe, 21 h at r.t.	**3c** 62%
5	**1b**		1:3:18:3:9, DME, 18 h at r.t.	**3d** 43%
6	**1b**		1:3:18:3:9, DME, 1 h at 85 °C then 4.5 h at r.t.	**3d** 35%[c]

[a] Where reported, yield is of isolated, purified product. [b] Inc. = incomplete reaction, about 80% **1b** remained. [c] About 20% **1b** was still present on workup.

From Table 2 it is clear that in many cases complete reaction can be attained in the presence of the tertiary amine. As can be seen in Entries 1, 2, 4 and 5, complete reaction with the nucleosides can be accomplished in the presence of $i Pr_2NEt$ but with only 18 mol-equiv. of the secondary amine. DME proved to be a good solvent for the reaction between **1b** and pyrrolidine (Entry 5), a reaction that was generally problematic/low-yielding.

As shown in Scheme 5, the imidazol-1-yl nucleoside **2e** can also be synthesized from **1a** by use of PCl_3 (3 mol-equiv.)/imidazole (30 mol-equiv.)/I_2 (2.2 mol-equiv.). The reaction of **1a**, which was conducted in 1,2-dichloroethane (DCE) for better solubility of imidazole, proceeded to completion at room temperature in 72 h (63% yield). In contrast to this successful reaction of disilyl derivative **1a**, the corresponding treatment of triacetate **1b** was unsuccessful. We then investigated the use of Et_2NH as the nucleophile (Scheme 5). In this case, surprisingly, successful reaction was observed with the triacetate **1b** (82% yield of **3e**), but the reaction with the disilyl derivative **1a** was unsuccessful. In contrast, O^6-(benzotriazol-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine underwent smooth reaction with Et_2NH, leading to the diethylamino product.[20]

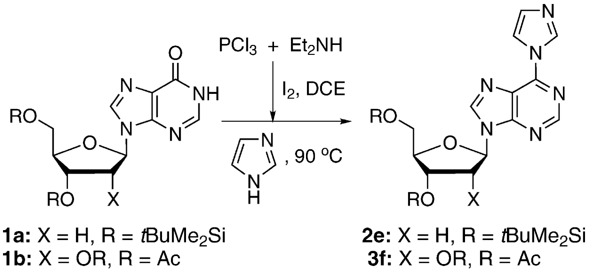
In order to determine what role if any the 2′-substituent plays, we conducted two additional experiments on the trisilyl-protected inosine **1c** (Scheme 5). We chose to conduct



Scheme 5. Synthesis of the C-6 imidazol-1-yl and diethylamino derivatives. Conditions: (a) PCl_3 (3 mol-equiv.)/imidazole (30 mol-equiv.)/I_2 (2.2 mol-equiv.), DCE, room temp.; (b) PCl_3 (3 mol-equiv.)/Et_2NH (30 mol-equiv.)/I_2 (2.2 mol-equiv.), PhMe, room temp.; (c) PCl_3 (3 mol-equiv.)/imidazole (30 mol-equiv.)/I_2 (2.2 mol-equiv.), DCE, 90 °C; (d) PCl_3 (3 mol-equiv.)/Et_2NH (30 mol-equiv.)/I_2 (2.2 mol-equiv.), DCE, 90 °C.

reactions with imidazole (with which **1b** did not yield any product) and Et_2NH (with which **1a** did not yield any product). In these reactions, the imidazolyl product **4a** was obtained in 47% yield within 36 h, and the diethylamino product **4b** was obtained in 81% yield within 8 h. Although we are unable to explain the protecting-group-based differences in reactivity, there appears to be a link between the protecting group on the saccharide and reactivity at the purine. A similar effect has previously been observed in direct displacement reactions at the C-6 position in a purine nucleoside.[21]

Finally, we wanted to assess whether a relatively hindered HAPT such as $(Et_2N)_3P$ and I_2 could be used to activate the C-6 amide carbonyl group with a second nucleophilic amine performing the displacement (Scheme 6). Thus, PCl_3 (3.0 mol-equiv.) was exposed to Et_2NH (9 mol-equiv.) and I_2 (2.2 mol-equiv.) in DCE. Addition of either **1a** or **1b**, imidazole (30 mol-equiv.) and heating at 90 °C then led to formation of the imidazol-1-yl derivative from *both* **1a** and **1b** (67% and 86% product yields, respectively). These results are particularly relevant, as **1b** did not undergo successful reaction when the imidazole/PCl_3/I_2 combination was used for amide carbonyl activation.



Scheme 6. Synthesis of 6-imidazolyl derivatives from disilyl-protected 2′-deoxyinosine and triacetyl-protected inosine through use of PCl_3/Et_2NH/I_2 for amide activation.

Conclusions

Although we and others have developed the use of Pd-catalyzed amination methods for nucleoside modification,[22] the S_NAr displacement approach continues to play an important role. In this paper we have studied the use of tris(dialkylamino)phosphanes (HAPTs) generated in situ for the conversion of protected inosine and 2′-deoxyinosine derivatives into adenosine analogues. In several instances, excess secondary amine can be used for the formation of the HAPT, as well as as a base and nucleophile. However, it appears that the formation of tetrakis(dialkylamino)phosphonium salts can become a competing process with the strongly nucleophilic[23] and sterically less demanding amines. Both silyl and acetyl protecting groups are suitable for these reactions, although some differences in reactivity were observed. In a distantly related reaction, adenine has been produced in 16% yield upon heating of hypoxanthine with $(MeO)_3P=O$ at 100 °C, followed by treatment with NH_4Cl/K_2CO_3 at 100 °C.[24] The leaving group proposed in that reaction was dimethyl phosphate, whereas in the present case a phosphoramide species is the likely leaving group.

In comparison of this method to our recently reported chemistry using O^6-(benzotriazol-1-yl)inosine derivatives,[10–12] this method offers a one-step conversion of hypoxanthine nucleosides into adenosine derivatives, and is particularly useful with cyclic secondary amines. However, the previously reported procedure[10–12] is overall more versatile in terms of the diversity of nucleophiles that can be used for the C-6 functionalization.

Experimental Section

General: Thin layer chromatography was performed on silica plates (250 µm), and column chromatographic purifications were performed on silica gel (200–300 mesh). PhMe was distilled from Na, DCE, iPr_2NEt, and CH_2Cl_2 were distilled from CaH_2, and anhydrous DME was obtained from a commercial supplier. All other reagents were obtained from commercial sources and used without further purification. The conventional numbering system for purine nucleosides is used. ^1H NMR spectra were recorded at 500 MHz and were referenced to the residual protonated solvent. $^{31}P\{^1H\}$ NMR spectra were recorded at 202 MHz and were referenced to 85% H_3PO_4 as external standard. Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are in Hertz. Some representative synthetic procedures are given below. HRMS data is reported for new compounds.

9-[2-Deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(morpholin-4-yl)purine (2b)[10]

With *i*Pr₂NEt and Stoichiometric Morpholine: PCl_3 (43.6 µL, 0.499 mmol) and dry toluene (10.7 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice/water bath to ca. 5 °C. After the mixture had been kept at this temperature for 20 min, morpholine (0.26 mL, 2.99 mmol) was added slowly and dropwise, while the temperature was maintained below 10 °C. The mixture was brought to room temperature and was stirred for 30 min. I_2 (126.7 mg, 0.499 mmol) was added to the reaction mixture, and the stirring was continued at room temperature for 10 min. Disilyl-2′-deoxy-

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

inosine **1a** (80.0 mg, 0.166 mmol) and DIPEA (0.26 mL, 1.49 mmol) were added, and the mixture was stirred at room temperature for 21 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 20% acetone in hexanes afforded the morpholinyl nucleoside **2b** (64.5 mg, 71% yield) as a viscous, pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ = 8.34 (s, 1 H, Ar-H), 8.02 (s, 1 H, Ar-H), 6.46 (t, *J* = 6.8 Hz, 1 H, 1′-H), 4.59 (app. dt, *J* = 6.2, 3.4 Hz, 1 H, 3′-H), 4.29 (br. s, 4 H, 2 OCH_2), 4.00 (app. q, *J* = 3.9 Hz, 1 H, 4′-H), 3.85–3.81 (m, 5 H, 2 NCH_2 and 5′-H), 3.76 (dd, *J* = 11.2, 4.4 Hz, 1 H, 5′-H), 2.59 (app. dt, *J* = 13.6, 6.4 Hz, 1 H, 2′-H), 2.41 (ddd, *J* = 13.6, 5.8, 4.0 Hz, 1 H, 2′-H), 0.90 (s, 18 H, *t*Bu), 0.09, 0.07 (2 s, 12 H, $SiCH_3$) ppm.

With Excess Morpholine: PCl_3 (40.8 µL, 0.468 mmol) and dry toluene (4.0 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice bath to 0 °C. After the mixture had been kept at this temperature for 5 min, morpholine (0.41 mL, 4.68 mmol) was added slowly and dropwise, and a white precipitate formed. The mixture was brought to room temperature and was stirred for 30 min. I_2 (87.1 mg, 0.343 mmol) was added, followed by the addition of disilyl-2′-deoxyinosine **1a** (75.0 mg, 0.156 mmol). The mixture was heated at 90 °C for 6 h. The orange-colored reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 20% acetone in hexanes afforded the morpholinyl nucleoside **2b** (59.2 mg, 69% yield).

9-[2-Deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(imidazol-1-yl)purine (2e)[10]

With Et_2NH and Imidazole: PCl_3 (40.8 µL, 0.468 mmol) and dry DCE (4.0 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice bath to 0 °C. After the mixture had been kept at this temperature for 10 min, Et_2NH (0.144 mL, 1.404 mmol) was added slowly and dropwise, while the temperature was maintained at 0 °C, during which a white precipitate formed. The mixture was brought to room temperature and was stirred for 30 min, during which time the precipitate appeared to dissolve. I_2 (87.1 mg, 0.343 mmol) was added to the reaction mixture, and the stirring was continued at room temperature for 10 min. Disilyl-2′-deoxyinosine **1a** (75.0 mg, 0.156 mmol) and imidazole (318.6 mg, 4.68 mmol) were added, and the mixture was stirred at 90 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 60% EtOAc in hexanes afforded the imizadolyl nucleoside **2e** (56.0 mg, 67% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 9.20 (s, 1 H, Ar-H), 8.80 (s, 1 H, Ar-H), 8.46 (s, 1 H, Ar-H), 8.40 (s, 1 H, Ar-H), 7.27 (s, 1 H, Ar-H), 6.55 (t, *J* = 6.0 Hz, 1 H, 1′-H), 4.59 (app. dt, *J* = 5.6, 4.2 Hz, 1 H, 3′-H), 4.06 (app. q, *J* = 4.2 Hz, 1 H, 4′-H), 3.91 (dd, *J* = 11.4, 3.9 Hz, 1 H, 5′-H), 3.80 (dd, *J* = 11.4, 2.9 Hz, 1 H, 5′-H), 2.65 (app. dt, *J* = 12.7, 6.0 Hz, 1 H, 2′-H), 2.51 (ddd, *J* = 12.7, 5.9, 2.3 Hz, 1 H, 2′-H), 0.92, 0.91 (2 s, 18 H, *t*Bu), 0.11, 0.10 (2 s, 12 H, $SiCH_3$) ppm.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-(morpholin-4-yl)purine (3b)[8b,21]

With *i*Pr_2NEt and Stoichiometric Morpholine: PCl_3 (53.1 µL, 0.61 mmol) and dry toluene (10 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice/water bath to ca. 5 °C. After the mixture had been kept at this temperature for 15 min, morpholine (0.32 mL, 3.66 mmol) was added slowly and dropwise, while the temperature was maintained below 10 °C. The mixture was brought to room temperature and was stirred for 30 min. I_2 (154.4 mg, 0.609 mmol) was added to the reaction mixture, and the stirring was continued at room temperature for 10 min. Inosine triacetate **1b** (80.0 mg, 0.203 mmol) and *i*Pr_2NEt (0.32 mL, 1.84 mmol) were added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 30% acetone in hexanes afforded the morpholinyl nucleoside **3b** (60.9 mg, 65% yield) as a viscous, pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ = 8.34 (s, 1 H, Ar-H), 7.89 (s, 1 H, Ar-H), 6.21 (d, *J* = 5.5 Hz, 1 H, 1′-H), 5.89 (t, *J* = 5.4 Hz, 1 H, 2′-H), 5.64 (dd, *J* = 5.3, 4.6 Hz, 1 H, 3′-H), 4.43 (dd, *J* = 4.6, 2.0 Hz, 1 H, 4′-H), 4.42 (dd, *J* = 12.8, 3.2 Hz, 1 H, 5′-H), 4.36 (dd, *J* = 12.8, 5.2 Hz, 1 H, 5′-H), 4.29 (br. s, 4 H, 2 OCH_2), 3.82 (t, *J* = 4.9 Hz, 4 H, 2 NCH_2), 2.14, 2.13, 2.07 (3 s, 9 H, $OCOCH_3$) ppm.

With Excess Morpholine: PCl_3 (42.7 µL, 0.489 mmol) and dry toluene (6 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice bath to 0 °C. After the mixture had been kept at this temperature for 5 min, morpholine (0.33 mL, 3.77 mmol) was added slowly and dropwise, and a white precipitate formed. The mixture was brought to room temperature and was stirred for 30 min. I_2 (0.106 mg, 0.418 mmol) was added, followed by the addition of inosine triacetate **1b** (75.0 mg, 0.19 mmol). The mixture was heated at 90 °C for 2 h 10 min. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 5% MeOH in CH_2Cl_2 gave a slightly impure product that was rechromatographed with 20% acetone in CH_2Cl_2 to yield the morpholinyl nucleoside **3b** (62.7 mg, 71% yield).

2′,3′,5′-Tri-*O*-acetyl-N^6,N^6-diethyladenosine (3e):[21,25] PCl_3 (40.8 µL, 0.468 mmol) and dry toluene (4.0 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice/water bath to 10 °C. After the mixture had been kept at this temperature for 10 min, Et_2NH (0.59 mL, 5.70 mmol) was added dropwise, while the temperature was maintained at 10 °C. A very viscous mixture was formed, and the stirring was continued at room temperature for 30 min. I_2 (106.1 mg, 0.418 mmol) was added to the reaction mixture, and the stirring was continued for 10 min. Inosine triacetate **1b** (75.0 mg, 0.190 mmol) was added, and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 70% EtOAc in hexanes afforded **3e** (69.7 mg, 81% yield) as a light yellow, viscous liquid. ^{1}H NMR ($CDCl_3$): δ = 8.32 (s, 1 H, Ar-H), 7.87 (s, 1 H, Ar-H), 6.21 (d, *J* = 5.7 Hz, 1 H, 1′-H), 5.90 (t, *J* = 5.6 Hz, 1 H, 2′-H), 5.65 (dd, *J* = 5.5, 4.2 Hz, 1 H, 3′-H), 4.43 (dd, *J* = 4.2, 2.0 Hz, 1 H, 4′-H), 4.41 (dd, *J* = 12.7, 3.3 Hz, 1 H, 5′-H), 4.36 (dd, *J* = 12.7, 5.4 Hz, 1 H, 5′-H), 4.17–3.72 (br. s, 4 H, CH_2), 2.13 (s, 6 H, $OCOCH_3$), 2.06 (s, 3 H, $OCOCH_3$), 1.28 (t, *J* = 6.9 Hz, 6 H, CH_3) ppm.

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-(imidazol-1-yl)purine (3f)[8b,21]

With Et_2NH and Imidazole: PCl_3 (42.7 μL, 0.571 mmol) and dry DCE (6.0 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice bath to 0 °C. After the mixture had been kept at this temperature for 10 min, Et_2NH (0.18 mL, 1.74 mmol) was added slowly and dropwise, while the temperature was maintained at 0 °C, and a white precipitate formed. The mixture was brought to room temperature and was stirred for 30 min, during which time the precipitate appeared to dissolve. I_2 (106.2 mg, 0.418 mmol) was added to the reaction mixture, and the stirring was continued at room temperature for 10 min. Inosine triacetate **1b** (75.0 mg, 0.190 mmol) and imidazole (388.4 mg, 5.71 mmol) were added, and the mixture was stirred at 90 °C for 5 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with EtOAc afforded **3f** (76.0 mg, 86% yield) as a light-brown syrup. ^1H NMR ($CDCl_3$): δ = 9.17 (s, 1 H, Ar-H), 8.79 (s, 1 H, Ar-H), 8.39 (s, 1 H, Ar-H), 8.27 (s, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 6.27 (d, *J* = 5.3 Hz, 1 H, 1′-H), 5.97 (t, *J* = 5.4 Hz, 1 H, 2′-H), 5.67 (t, *J* = 5.3 Hz, 1 H, 3′-H), 4.49 (app. q, *J* = 4.1 Hz, 1 H, 4′-H), 4.47 (dd, *J* = 12.7, 3.1 Hz, 1 H, 5′-H), 4.40 (dd, *J* = 12.7, 4.3 Hz, 1 H, 5′-H), 2.17, 2.14, 2.09 (3 s, 9 H, $OCOCH_3$) ppm.

6-(Imidazol-1-yl)-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (4a)

With Excess Imidazole: PCl_3 (33.0 μL, 0.368 mmol) and dry DCE (4.0 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice bath to 0 °C. After the mixture had been kept at this temperature for 10 min, imidazole (249 mg, 3.66 mmol) was added, and a white precipitate formed. The mixture was brought to room temperature and was stirred for 30 min. I_2 (68.1 mg, 0.268 mmol) was added to the reaction mixture, and the stirring was continued at room temperature for 10 min. Trisilylinosine **1c** (75.0 mg, 0.122 mmol) was added, and the mixture was stirred at 90 °C for 36 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 25% EtOAc in hexanes afforded **4a** (38.0 mg, 47% yield) as a white solid. Characterization of this product has been reported previously.[26]

2′,3′,5′-Tri-*O*-(*tert*-butyldimethylsilyl)-*N*^{6},*N*^{6}-diethyl-2′-deoxyadenosine (4b): PCl_3 (33.0 μL, 0.368 mmol) and dry toluene (4.0 mL) were placed under nitrogen in a clean, dry, round-bottomed flask containing a stirring bar, and the mixture was cooled in an ice/water bath to 10 °C. After the mixture had been kept at this temperature for 10 min, Et_2NH (0.38 mL, 3.67 mmol) was added dropwise, while the temperature was maintained at 10 °C. A very viscous mixture was formed, and the stirring was continued at room temperature for 30 min. I_2 (68.1 mg, 0.268 mmol) was added to the reaction mixture, and the stirring was continued for 10 min. Trisilylinosine **1c** (75.0 mg, 0.123 mmol) was added, and the mixture was stirred at 90 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 15 mL), followed by brine (15 mL). The organic layer was separated and dried with Na_2SO_4, and the solvents were evaporated to dryness. Chromatographic purification on silica gel with 20% EtOAc in hexanes afforded **4b** (67.0 mg, 81% yield) as a light-yellow, viscous oil. ^1H NMR ($CDCl_3$): δ = 8.29 (s, 1 H, Ar-H), 7.94 (s, 1 H, Ar-H), 6.00 (d, *J* = 5.5 Hz, 1 H, 1′-H), 4.79 (app. t, *J* = 5.0 Hz, 1 H, 2′-H), 4.33 (app. t, *J* = 3.7 Hz, 1 H, 3′-H), 4.10 (app. q, *J* = 4.5, 3.5 Hz, 1 H, 4′-H), 4.02 (dd, *J* = 11.5, 5.0 Hz, 1 H, 5′-H), 4.02–3.92 (br. s, 4 H, CH_2), 3.76 (dd, *J* = 11.5, 3.5 Hz, 1 H, 5′-H), 1.27 (t, *J* = 7.0 Hz, 6 H, CH_3), 0.93, 0.78 (2 s, 27 H, *t*Bu), 0.10, –0.05, –0.02 (3 s, 18 H, $SiCH_3$) ppm. HRMS: calcd. for $C_{32}H_{63}N_5O_4Si_3$ $[M]^+$ 665.4188; found 665.4201.

Supporting Information (see footnote on the first page of this article): Copies of ^1H NMR spectra of compounds **2a**–**e**, **3a**–**f**, **4b**, and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-*N*^{6},*N*^{6}-diethyl-2′-deoxyadenosine.

Acknowledgments

This work was partially supported by the National Science Foundation (grant CHE-0640417) and a Professional Staff Congress CUNY-39 award. E. R. was supported through Research Experience for Undergraduates supplements from the National Science Foundation (grant CHE-0314326). Acquisition of a mass spectrometer was funded by the National Science Foundation (grant CHE-0520963). Infrastructural support was provided by the National Institutes of Health Research Centers in Minority Institutions (grant G12 RR03060).

---

[1] For some examples, see: a) T. D. Ashton, S. P. Baker, S. A. Hutchinson, P. J. Scammells, *Bioorg. Med. Chem.* **2008**, *16*, 1861–1873; b) L. Cappellacci, P. Franchetti, P. Vita, R. Petrelli, A. Lavecchia, B. Costa, F. Spinetti, C. Martini, K.-N. Klotz, M. Grifantini, *Bioorg. Med. Chem.* **2008**, *16*, 336–353; c) T. D. Ashton, K. M. Aumann, S. P. Baker, C. H. Schiesser, P. J. Scammells, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6779–6784; d) L. K. Jeong, S. A. Choe, P. Gunaga, H. O. Kim, H. W. Lee, S. K. Lee, D. K. Tosh, A. Patel, K. K. Palaniappan, Z.-G. Gao, K. A. Jacobson, H. R. Moon, *J. Med. Chem.* **2007**, *50*, 3159–3162; e) H. Adachi, K. K. Palaniappan, A. A. Ivanov, N. Bergman, Z.-G. Gao, K. A. Jacobson, *J. Med. Chem.* **2007**, *50*, 1810–1827; f) R. Volpini, D. Dal Ben, C. Lambertucci, S. Taffi, S. Vittori, K.-N. Klotz, G. Cristalli, *J. Med. Chem.* **2007**, *50*, 1222–1230; g) M. P. Gonzalez, C. Teran, M. Teijeira, A. M. Helguera, *Curr. Med. Chem.* **2006**, *13*, 2253–2266.

[2] For some examples, see: a) M. A. Peterson, P. Ke, H. Shi, C. Jones, B. R. McDougall, W. E. Robinson Jr, *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 499–519; b) S. Zhou, J. Zemlicka, E. R. Kern, J. C. Drach, *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 231–243; c) S. Zhou, E. R. Kern, E. Gullen, Y.-C. Cheng, J. C. Drach, S. Tamiya, H. Mitsuya, J. Zemlicka, *J. Med. Chem.* **2006**, *49*, 6120–6128; d) Y.-h. Koh, J. H. Shim, J. Z. Wu, W. Zhong, Z. Hong, J.-L. Girardet, *J. Med. Chem.* **2005**, *48*, 2867–2875; e) S. F. Wnuk, E. Lewandowska, P. R. Sacasa, L. N. Crain, J. Zhang, R. T. Borchardt, E. De Clercq, *J. Med. Chem.* **2004**, *47*, 5251–5257; f) D. F. Smee, R. W. Sidwell, *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 375–383; g) M. I. Nieto, O. Caamano, F. Fernandez, M. Gomez, J. Balzarini, E. De Clercq, *Nucleosides Nucleotides Nucleic Acids* **2002**, *21*, 243–255.

[3] For some examples, see: a) S. Sinha, R. Srivastava, B. Prusty, B. C. Das, R. K. Singh, *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 773–777; b) E.-J. Lee, H.-Y. Min, H.-J. Chung, E.-J. Park, D.-H. Shin, L. S. Jeong, S. K. Lee, *Biochem. Pharmacol.* **2005**, *70*, 918–924; c) M. Panjehpour, F. Karami-Tehrani, *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1502–1509; d) D. A. Carson, D. B. Wasson, E. Beutler, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 2232–2236; e) L. F. Christensen, A. D. Broom, M. J. Robins, A. Bloch, *J. Med. Chem.* **1972**, *15*, 735–739.

[4] For some examples, see: a) C. Herforth, J. Wiesner, P. Heidler, S. Sanderbrand, S. Van Calenbergh, H. Jomaa, A. Link, *Bio-*

org. Med. Chem. **2004**, *12*, 755–762; b) P. H. Heidler, C. Herforth, A. Link, *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 977–979; c) C. Herforth, J. Wiesner, S. Franke, A. Golisade, H. Jomaa, A. Link, *J. Comb. Chem.* **2002**, *4*, 302–314.

[5] For some representative examples on the use of S_NAr chemistry, see: a) L. S. Jeong, D. Z. Jin, H. O. Kim, D. H. Shin, H. R. Moon, P. Gunaga, M. W. Chun, Y.-C. Kim, N. Melman, Z.-G. Gao, K. A. Jacobson, *J. Med. Chem.* **2003**, *46*, 3775–3777; b) Y. Choi, C. George, P. Strazewski, V. E. Marquez, *Org. Lett.* **2002**, *4*, 589–592; c) S. Chaturvedi, M. K. Lakshman, *Carcinogenesis* **1996**, *17*, 2747–2752; d) S. J. Kim, H. K. Jajoo, H.-Y. Kim, L. Zhou, P. Horton, C. M. Harris, T. M. Harris, *Bioorg. Med. Chem.* **1995**, *3*, 811–822; e) V. Samano, R. W. Miles, M. J. Robins, *J. Am. Chem. Soc.* **1994**, *116*, 9331–9332; f) M. Lakshman, R. E. Lehr, *Tetrahedron Lett.* **1990**, *31*, 1547–1550; g) R. Cosstick, M. E. Douglas, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1035–1040; h) J. F. Gerster, R. K. Robins, *J. Am. Chem. Soc.* **1965**, *87*, 3752–3759; i) *Nucleosides and Nucleotides* (Ed.: L. B. Townsend), Plenum Press, New York, **1988**, vol. 2, chapter 2, pp. 113–281.

[6] C. R. Allerson, S. L. Chen, G. L. Verdine, *J. Am. Chem. Soc.* **1997**, *119*, 7423–7433.

[7] a) P. Francom, M. J. Robins, *J. Org. Chem.* **2003**, *68*, 666–669; b) P. Francom, Z. Janeba, S. Shibuya, M. J. Robins, *J. Org. Chem.* **2002**, *67*, 6788–6796.

[8] a) J. Zlatko, X. Lin, M. J. Robins, *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 137–147; b) X. Lin, M. J. Robins, *Org. Lett.* **2000**, *2*, 3497–3499.

[9] Z.-K. Wan, E. Binnun, D. P. Wilson, J. Lee, *Org. Lett.* **2005**, *7*, 5877–5880.

[10] S. Bae, M. K. Lakshman, *J. Am. Chem. Soc.* **2007**, *129*, 782–789.

[11] S. Bae, M. K. Lakshman, *J. Org. Chem.* **2008**, *73*, 1311–1319.

[12] S. Bae, M. K. Lakshman, *J. Org. Chem.* **2008**, *73*, 3707–3713.

[13] Polymer-supported phosphanes from Lancaster and Strem were tested.

[14] a) J. G. Verkade, P. B. Kisanga, *Aldrichim. Acta* **2004**, *37*, 3–14; b) J. G. Verkade, P. B. Kisanga, *Tetrahedron* **2003**, *59*, 7819–7858.

[15] E. A. Véliz, P. A. Beal, *Tetrahedron Lett.* **2000**, *41*, 1695–1697.

[16] J. J. Hans, R. W. Driver, S. D. Burke, *J. Org. Chem.* **1999**, *64*, 1430–1431.

[17] a) J. L. Bolliger, O. Blacque, C. M. Frech, *Angew. Chem. Int. Ed.* **2007**, *46*, 6514–6517; b) J. L. Bolliger, O. Blacque, C. M. Frech, *Angew. Chem.* **2007**, *119*, 6634–6637; c) D. J. Dellinger, D. M. Sheehan, N. K. Christensen, J. G. Lindberg, M. H. Caruthers, *J. Am. Chem. Soc.* **2003**, *125*, 940–950; d) L. A. Hussain, A. J. Elias, M. N. S. Rao, *Tetrahedron Lett.* **1988**, *29*, 5983–5986.

[18] a) I. D. Cunningham, M. Woodfall, *J. Org. Chem.* **2005**, *70*, 9248–9256; b) T. Rodima, V. Mäemets, I. Koppel, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2637–2644.

[19] a) R. Schwesinger, R. Link, P. Wenzl, S. Kossek, *Chem. Eur. J.* **2006**, *12*, 438–445; b) R. Schwesinger, R. Link, P. Wenzl, S. Kossek, M. Keller, *Chem. Eur. J.* **2006**, *12*, 429–437.

[20] **3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-N^6,N^6-diethyl-2′-deoxyadenosine:** O^6-(Benzotriazol-1-yl)-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (59.8 mg, 0.100 mmol) and Et_2NH (41.4 µL, 0.400 mmol) in dry DME (1.0 mL) were placed in a clean, dry reaction vial containing a stirring bar. The reaction mixture was flushed with nitrogen and was stirred at room temperature for 23 h. The reaction mixture was directly loaded onto a bed of SiO_2, and the product was eluted with EtOAc. The silylated N^6,N^6-diethyl-2′-deoxyadenosine derivative was obtained as a clear gum (54.7 mg, quantitative yield). R_f (20% EtOAc in hexanes) = 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (s, 1 H, Ar-H), 7.96 (s, 1 H, Ar-H), 6.44 (t, J = 6.6 Hz, 1 H, 1′-H), 4.60 (m, 1 H, 3′-H), 4.00 (m, 1 H, 4′-H), 3.98 (br. signal, 4 H, CH_2), 3.81 (dd, J = 11.1, 4.8 Hz, 1 H, 5′-H), 3.75 (dd, J = 11.1, 3.5 Hz, 1 H, 5′-H), 2.63 (m, 1 H, 2′-H), 2.40 (ddd, J = 13.1, 6.0, 3.6 Hz, 1 H, 2′-H), 1.28 (t, J = 7.0 Hz, 6 H, CH_3), 0.91, 0.90 (2 s, 18 H, *t*Bu), 0.10, 0.07, 0.06 (3 s, 12 H, $SiCH_3$) ppm. HRMS: calcd. for $C_{26}H_{49}N_5O_3Si_2$ $[M]^+$ 535.3374; found 535.3378.

[21] E. A. Véliz, P. A. Beal, *J. Org. Chem.* **2001**, *66*, 8592–8598.

[22] For a review, see: M. K. Lakshman, *Curr. Org. Synth.* **2005**, *2*, 83–112.

[23] F. Brotzel, Y. C. Chu, H. Mayr, *J. Org. Chem.* **2007**, *72*, 3679–3688.

[24] I. M. Lagoja, P. Herdewijn, *Chem. Biodiv.* **2005**, *2*, 923–927.

[25] T. Endo, J. Zemlicka, *J. Org. Chem.* **1979**, *44*, 3652–3656.

[26] a) P. Lagisetty, L. M. Russon, M. K. Lakshman, *Angew. Chem. Int. Ed.* **2006**, *45*, 3660–3663; b) P. Lagisetty, L. M. Russon, M. K. Lakshman, *Angew. Chem.* **2006**, *118*, 3742–3745.

Received: July 30, 2008
Published Online: November 25, 2008