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A Simple Synthesis of Nitriles from Aldoximes[1]

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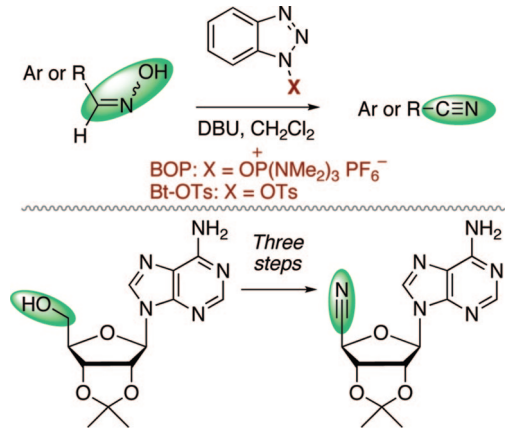

Easily synthesized aldoximes have been converted to the corresponding nitriles under very mild conditions by a simple reaction with 1*H*-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and DBU in CH_2Cl_2, THF, or DMF. As an alternative reagent that eliminates the formation of hexamethylphosphoramide as a byproduct, use of 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt-OTs) and DBU was investigated. Reactions with this reagent also proceeded smoothly and in good yields, although in one case *N*-sulfonylation was observed. An attempt to gain mechanistic insight into the BOP-mediated reaction has been made using $^{31}P\{^1H\}$ NMR. However, no phosphorus-bearing intermediate could be readily observed. Finally, the method has been applied to the synthesis of an antiviral 4′-cyano adenosine analogue from a commercial precursor using a single saccharide protecting group.

Introduction

The cyano moiety is a highly important one not only due to its synthetic value as precursor to other functionalities but also due to its presence in a variety of natural products, pharmaceuticals, and novel materials. Although a plethora of methods are known for access to the cyano functionality,[2,3] dehydration of aldoximes remains a convenient route.[4] Some recently reported methods for aldoxime dehydration involve

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$NaICl_2$/aq NH_3,[5] *N*-chlorosuccinimide and pyridine,[6] W−Sn mixed hydroxide in *o*-xylene at 149 °C,[7] thermal dehydration,[8] reaction with ethyldichlorophosphate/DBU/3 Å MS,[9] use of Silphos [$PCl_{3-n}(SiO_2)_n$] in MeCN,[10] ZnO/AcCl at 80 °C,[11] reaction with chlorosulfonic acid in toluene at 90 °C,[12] use of Ga(III)OAc/MeCN at 85−120 °C,[13] and reaction with dimethylacetylene dicarboxylate and Et_3N.[14]

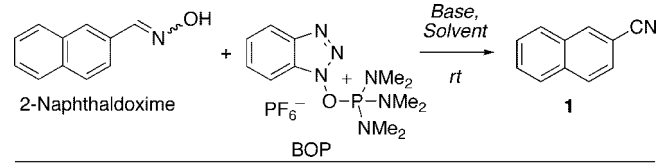
In connection with some on going studies on nucleoside modification, we had reason to examine mild methods for the conversion of aldoximes to nitriles. In this respect, use of PPh_3/I_2 in CH_2Cl_2 has been reported to yield nitriles in high yield and within short reaction times.[15] However, in our hands, a test reaction of 2-naphthaldoxime under these conditions showed incomplete reaction in 5 h, and upon prolonging the reaction time, formation of some 2-naphthaldehyde was also observed (resonance at δ 10.17 ppm in the ^{1}H NMR) in addition to the nitrile. Switching from PPh_3 to hexamethylphosphorus triamide [HMPT, $(Me_2N)_3P$] did not provide a significant improvement, and aldehyde formation was again observed. This led us to question whether the formation of aldehyde could become a complicating problem in the dehydration of other oximes. On the basis of the foregoing, as well as the procedural aspects of several recently described methods and the belief that mild methods would be necessary for relatively fragile substrates, we decided to reinvestigate aldoxime dehydration. This paper reports our results on the development of a new method for the synthesis of nitriles from aldoximes.

Results and Discussion

It has been reported that amides can be converted to nitriles via the use of PyBOP and (*i*-Pr)$_2$NEt in CH_2Cl_2 at 40 °C.[16] This led us to consider whether aldoximes, which are generally more acidic than alcohols,[17,18] could undergo dehydrative reactions with commercially available BOP (which is somewhat cheaper than PyBOP) and a base. Herein we report development of a simple dehydration of aldoximes using BOP. During the course of these studies, we have also evaluated the use of a sulfonate ester of HOBt (Bt-OTs) for this oxime to cyanide conversion. Finally, we have used this method as one of three steps in a short and efficient synthesis of adeninyl ribofuranonitrile, a compound that has demonstrated useful antiviral activity.

Our initial work commenced with screening of solvent and base so as to obtain optimal reaction conditions. These early reactions were performed using 2-naphthaldoxime as a representative, electronically unbiased substrate, and 2 molar equiv of BOP. The results are shown in Table 1.

TABLE 1. Initial Experiments on the Dehydration of 2-Naphthaldoxime Using BOP



entry	base, solvent	time (h)	yield[a] (%)
1	2.3 molar equiv of DBU, THF	3.5	91
2	2.3 molar equiv of DBU, DMF	3.5	93
3	2.3 molar equiv of DBU, CH_2Cl_2	1	95
4	2.3 molar equiv of DBU, $CHCl_3$	1	NA[b]
5	2.3 molar equiv (*i*-Pr)$_2$NEt, DMF	19	Inc[c]
6	2.3 molar equiv of (*i*-Pr)$_2$NEt, CH_2Cl_2	20	90
7	no base, CH_2Cl_2	6 days	NR[d]
8	no base, DMF	45	NR[d]

[a] Yield where reported is of isolated and purified product. [b] Although this reaction was complete within 1 h, the reaction was not clean, and therefore, the product was not isolated. [c] The aldoxime was still present although product formation was observed. [d] No product formation was observed, and aldoxime was still present.

From the results in Table 1 it is evident that use of BOP and DBU in CH_2Cl_2 led to fast conversion of the aldoxime and in good yield (entry 3). THF and DMF are also suitable solvents (entries 1 and 2), whereas $CHCl_3$ was inferior in which the reaction did not proceed cleanly. The weaker base (*i*-Pr)NEt_2 also appears to be suitable, although a much slower reaction was observed (entry 6). With this base, DMF proved to be an inferior solvent (entry 5). Presence of the base is important as demonstrated by absence of reaction without added base (entries 7 and 8).

At this point, we wanted to assess the generality of this transformation and subjected a variety of aldoximes (prepared by conventional methods involving the use of $NH_2OH\cdot HCl$ and aqueous Na_2CO_3, K_2CO_3, or NaOH) to the optimized reaction conditions. The results of these reactions are summarized in Table 2. During the course of these experiments, we learned that use of CH_2Cl_2 at elevated temperature led to the formation of a product resulting from the reaction of hydroxybenzotriazole with CH_2Cl_2.[19] Thus, THF is a preferred solvent for reactions at higher temperatures. Some of the nitrile syntheses were therefore performed in THF to assess its general suitability (entries 3, 4, and 7 in Table 2). In one case (entry 5), DMF was used for solubility reasons.

As can be seen from Table 2, reactions with BOP proceeded smoothly. However, we wanted to assess whether the formation of hexamethylphosphoramide [HMPA, $(Me_2N)_3PO$] as byproduct could be eliminated. This would make the reaction more useful for development of biologically important materials. For this we evaluated several options and settled on 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt-OTs) as a potential reagent. Bt-OTs is known in the literature[20] and can be quite readily synthesized[20a] (Scheme 1).

Interestingly, Bt-OTs has not found much use in such dehydrative reactions. Application of Bt-OTs in the present cases

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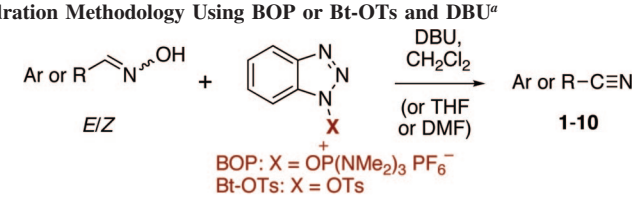
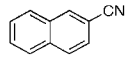
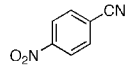
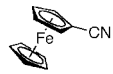
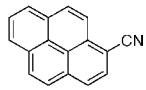
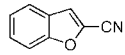
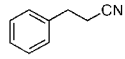
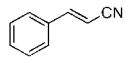
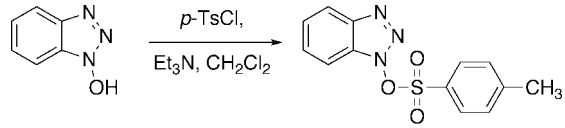
TABLE 2. Generality of the Dehydration Methodology Using BOP or Bt-OTs and DBU[a]



entry	product	reagent	time, temp	CN $\bar{\nu}$	product, yield[b]
1		BOP	45 min, rt	2225 cm^{-1}	**1:** 95%
		Bt-OTs	25 min, rt		**1:** 95%
2		BOP	45 min, rt	2233 cm^{-1}	**2:** 96%
		Bt-OTs	30 min, rt		**2:** 95%
3		BOP[c]	1 h, 50 °C	2224 cm^{-1}	**3:** 84%
		Bt-OTs[c]	30 min, rt		**3:** 80%
4		BOP[c]	1.5 h, rt	2223 cm^{-1}	**4:** 97%
		Bt-OTs[c]	1 h, rt		**4:** 89%
5		BOP[d]	45 min, rt	2213 cm^{-1}	**5:** 96%
		Bt-OTs[d]	30 min, rt		**5:** 90%
6		BOP	45 min, rt	2228 cm^{-1}	**6:** 85%
		Bt-OTs	30 min, rt		**6:** 85%
7		BOP[c]	2 h, rt	2224 cm^{-1}	**7:** 72%
		Bt-OTs[c]	45 min, rt		**7:** 42%
					8: 50%[e]
8		BOP	45 min, rt	2246 cm^{-1}	**9:** 86%
		Bt-OTs	30 min, rt		**9:** 73%
9		BOP	35 min, rt	2216 cm^{-1}	**10:** 92%
		Bt-OTs	20 min, rt		**10:** 92%

[a] Reactions were conducted on a 1 mmol scale except in the case of the pyrene oxime (entry 5) where reaction with Bt-OTs was conducted on a 0.75 mmol scale. [b] Yield of isolated and purified products. [c] Reaction was performed in THF. [d] Reaction was performed in DMF. [e] In this reaction with Bt-OTs, in addition to indole-3-carbonitrile **7**, the 1-(*p*-toluenesulfonyl)indole-3-carbonitrile **8** was also isolated in 50% yield.

SCHEME 1. Synthesis of 1*H*-Benzotriazol-1-yl-4-methylbenzene sulfonate (Bt-OTs)



also resulted in satisfactory conversions to the nitriles, and these results are shown in Table 2 as well. Reaction of the unprotected indole with BOP and DBU produced a very satisfactory return of the nitrile **7** (entry 7). However, reaction of this oxime with Bt-OTs and DBU produced an easily separable product mixture consisting of the carbonitrile **7** (42%) as well as the corresponding *N*-tosyl derivative[21] **8** (50%). Such *N*-sulfonylation has been observed during amide formation.[20d] Interestingly, the aldoxime derived from 3-phenyl-1-propanal also underwent conversion in good yield to the nitrile **9** (entry 8) despite the generally lower acidity of alkyl aldoximes.[17] From the standpoint of functional group compatibility, reactions with BOP are tolerant of the nitro, organometallic, and free amino entities (entries 2, 4, and 7) as well as ortho substituents on an aryl ring. Additionally, it can be reasoned that in cases such as indole carboxaldehyde, protection and dehydration can be effectuated in one step under appropriate conditions using Bt-OTs.

From a mechanistic consideration, we wanted to evaluate the course of the dehydration reaction of aldoximes with BOP and DBU. As shown in Scheme 2, there are two mechanistic possibilities. In pathway 1, upon oxime deprotonation by DBU, initial reaction could occur at the phosphorus atom of BOP with the formation of a new phosphonium species. In the alternative pathway 2, an S_N2'-like reaction at the nitrogen atom could result in a direct expulsion of HMPA. Since each pathway involves formation of new phosphorus-containing species, we felt that $^{31}P\{^1H\}$ NMR may prove useful in this assessment.

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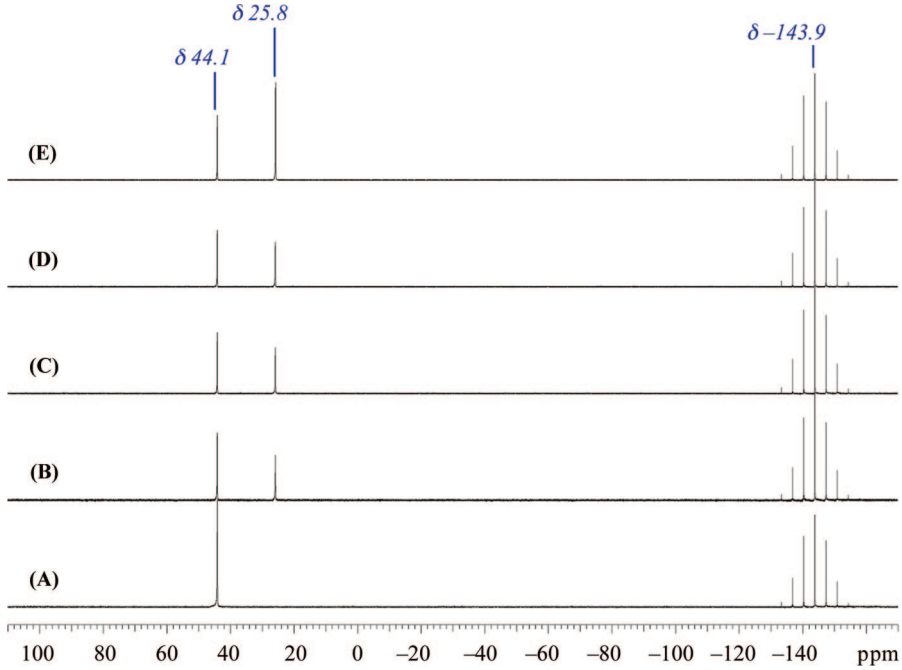
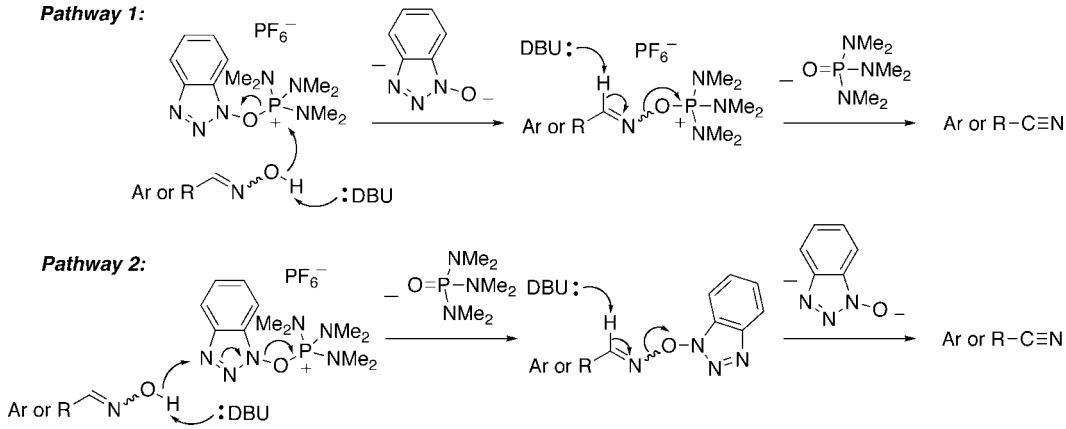
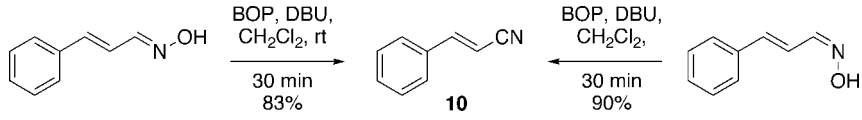


FIGURE 1. Monitoring the course of the reaction between 2-naphthaldoxime, 2 molar equiv of BOP, and 2.3 molar equiv of DBU in CD_2Cl_2 using $^{31}P\{^1H\}$ NMR: (A) naphthaldoxime (0.2 M in CD_2Cl_2) + BOP; (B) 5 min after addition of DBU; (C) 45 min after addition of DBU; (D) 100 min after addition of DBU; and (E) reaction mixture spiked with HMPA (1.0 molar equiv).

SCHEME 2. Two Possible Pathways for the Formation of Nitriles by Dehydration of Aldoximes Using BOP



SCHEME 3. Independent Reactions of *E*- and *Z*-Cinnamaldoximes



Therefore, a series of experiments was undertaken. First, a reaction of 2-naphthaldoxime and DBU was conducted in CH_2Cl_2 in the *absence* of BOP. Consistent with our expectations, no reaction was observed over a 2-h period and only starting material was present, clearly indicating that BOP is necessary for the reaction (which is complete within 1 h in the presence of BOP). Next, a reaction between 2-naphthaldoxime and BOP was conducted in CD_2Cl_2 using DBU, and the reaction was monitored by $^{31}P\{^1H\}$ NMR (Figure 1). In CD_2Cl_2, the phosphonium resonance of BOP appears at δ 44.1 ppm relative to 85% H_3PO_4 as external standard (the PF_6^- septet appears at δ −143.9 ppm). As the reaction progressed, no new discernible signal for a second phosphonium species was observed even at a short reaction time of 5 min, but only formation of HMPA was observed at δ 25.8 ppm (pure HMPA appears at δ 25.4 ppm in CD_2Cl_2). Finally, after 100 min, the reaction mixture was spiked with 1 molar equiv of HMPA. An increase in the signal intensity δ 25.8 ppm was observed, confirming the HMPA resonance.

A second $^{31}P\{^1H\}$ NMR experiment was conducted with *o*-bromobenzaldoxime (see Figure 1 in the Supporting Information). The result was identical to that obtained with 2-naphthaldoxime. Thus, if a phosphonium salt was indeed an intermediate in this reaction as in pathway 1 shown in Scheme 2, it was perhaps a fleeting species and not easily observed via $^{31}P\{^1H\}$ NMR. Carboxylic acids[20c] and amide functionalities of nucleosides[22] have been shown to react with BOP via a phosphonium derivative. On the other hand, the NMR experi-

ment raises the question of the alternate mechanism that causes rapid formation of HMPA without intermediacy of a new phosphonium species, such as pathway 2 in Scheme 2. However, at the present time we have not been able to identify any other reactive intermediate, and the question of the mechanism remains open.

In order to assess whether there is a substantial difference in the relative ease with which *E*- and *Z*-oximes undergo dehydration under the conditions described, we separated the isomeric oximes of cinnamaldehyde (silica gel eluted with 10% EtOAc in hexanes) and characterized each by NMR.[23] Reaction of *E*-isomer with BOP and DBU under the optimized conditions (Scheme 3) led to complete reaction within 30 min and an 83% isolated yield of nitrile **10**. Similar reaction of the *Z*-isomer was also complete within 30 min with a 90% isolated yield of **10**. Thus, it appears that oxime stereochemistry may not have a major influence on the ease of this conversion.

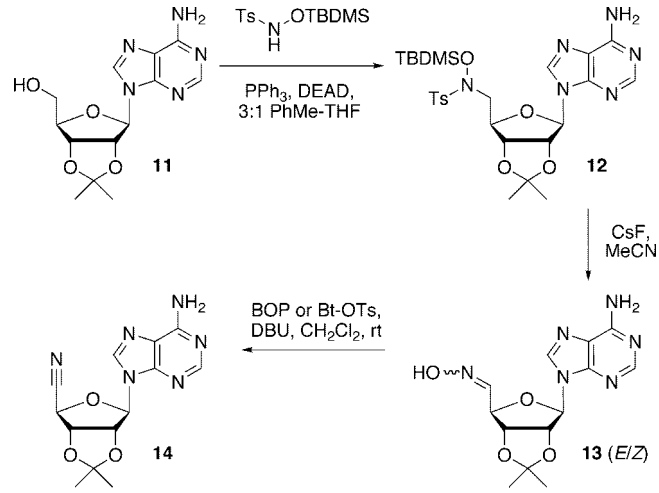
As a final stage in the development of this method, we were interested in assessing its utility for the transformation of relatively sensitive molecules. Thus, we chose to synthesize adeninyl ribofuranonitrile from the commercially available 2′,3′-acetonide of adenosine using minimal protecting groups. Adenyl ribofuranonitrile has shown promising acvitity agains vesicular stomatitis virus (VSV, EC_{50} 1.2 μg/mL) and human cytomegalovirus (HCMV, EC_{50} 1.4 μg/mL).[24]

Although the *E*/*Z* 5′-carbaldoximes derived from adenosine are known compounds,[25] their synthesis posed some challenges. For instance, the exocyclic amino group needed protection and oxidation of the 5′-hydroxyl group had to be performed via a *N*,*N*′-diphenylethylenediamino derivative that yielded the aldehyde hydrate upon hydrolysis. This aldehyde hydrate had to be azeotroped with benzene prior to synthesis of the oxime mixture.[26]

On the basis of these considerations, we opted for a completely different route shown in Scheme 4. Relying on the recently reported *O*-(*tert*-butyldimethylsilyl)-*N*-tosylhydroxylamine as a convenient reagent for synthesis of oximes,[23] the 5′-hydroxyl group of commercially available **11** was converted to the *N*-tosyl-*O*-silylhydroxylamine via a Mitsunobu reaction, to give **12** in 81% yield. This step can be readily accomplished without protection of the exocyclic amino group.[27]

Next, fluoride-mediated desilylation of **12** led to the *E*/*Z* mixture of oximes **13** (80% yield), via the anticipated expulsion of *p*-toluenesulfinate and tautomerization of the incipient nitroso nucleoside. Comparison of the NMR data of this product mixture to reported data[25] confirmed the formation of **13**. Finally, exposure of **13** to 2 molar equiv of BOP and 2.3 molar equiv of DBU in CH_2Cl_2 at room temperature led to the formation of the ribofuranonitrile **14** in 95% yield within 45 min. Alternatively, the use of 2.0 molar equiv of Bt-OTs and 2.3 molar equiv of DBU in CH_2Cl_2 also led to the formation of **14** in 93% yield, within 35 min at room temperature. Both reactions proceeded

SCHEME 4. Short Synthesis of Adeninyl Ribofuranonitrile Using a Single Protecting Group



smoothly, and in the case of the nucleoside no *N*-sulfonylation was observed with Bt-OTs. Compound **14** has previously been synthesized from the adeninyl methyl ribofuranuronate via the amide in 46% yield.[28]

Conclusions

In summary, we have developed a mild and efficient conversion of aldoximes to nitriles via the use of BOP or Bt-OTs as dehydrating agent in the presence of a base such as DBU. These reactions proceed in CH_2Cl_2 at room temperature in almost all cases tested. THF and DMF are also suitable solvents when elevated temperature is necessary or for solubility reasons. Using this dehydration reaction as one step in a three-step sequence, we have developed a new approach to adeninyl ribofuranonitrile (as its 2′,3′-acetonide) requiring a minimal protecting group strategy. In principle, simple cleavage of the acetonide should yield the fully deprotected compound. The approach described should prove useful for modification of other nucleoside derivatives as well. Finally, we believe that the strategy utilizing the Mitsunobu reaction for oxime synthesis[23] in combination with this new dehydration method will prove to be of use in the synthesis of a wide range of organic nitriles.

Experimental Section

Most of the cyano compounds listed in Table 2 are commercially available. Characterization of cyanoferrocene[29] and 1-cyanopyrene[30] have been reported in the literature.

General Procedure for Nitrile Synthesis Using BOP. In an oven-dried, two-necked, 50 mL round-bottomed flask, equipped with a stirring bar was placed a solution of the oxime (1.0 mmol) and BOP (2.0 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 min, and then DBU (2.3 mmol) was added dropwise to the stirring mixture over 2 min. The reaction mixture became a clear homogeneous solution after addition of DBU. The reaction was monitored by TLC, and upon complete consumption of the starting material the mixture was diluted with EtOAc and washed with water (2×) followed by brine.

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The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography. [*Deviation from this procedure:* (a) THF or DMF was appropriately substituted as reaction solvent when needed, e.g., in the reactions with *o*-bromobenzaldoxime, ferrocene carbaldoxime, and pyrene-1-carbaldoxime.]

General Procedure for Nitrile Synthesis Using Bt-OTs. Into an oven-dried, two-necked, 50 mL round-bottomed flask equipped with a stirring bar was placed a solution of the oxime (1.0 mmol) and Bt-OTs (2.0 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 min, and then DBU (2.3 mmol) was added dropwise to the stirring mixture over 2 min. The reaction was monitored by TLC, and upon complete consumption of the starting material the reaction mixture was diluted with EtOAc and washed with water (2×) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography. [*Deviation from this procedure:* (a) the reaction was conducted with 0.75 mmol of pyrene-1-carbaldoxime, (b) THF or DMF was appropriately substituted as reaction solvent when needed, e.g., in the reactions with *o*-bromobenzaldoxime, ferrocene carbaldoxime, and pyrene-1-carbaldoxime.]

5′-Deoxy-5′-[*N*-(*tert*-butyldimethylsilyloxy)-*N*-(*p*-toluenesulfonyl)]-amino-2′,3′-*O*-(isopropylidene)adenosine (12). In a 100 mL oven-dried, round-bottomed flask equipped with a stirring bar were placed 2′,3′-*O*-(isopropylidene)adenosine **11** (0.75 g, 2.44 mmol), *O*-(*tert*-butyldimethylsilyl)-*N*-tosylhydroxylamine (TsNHOTBDMS, 1.10 g, 3.65 mmol), and PPh_3 (1.28 g, 4.88 mmol). Anhydrous toluene (12 mL) and THF (4 mL) were added, and the reaction mixture was cooled to 0 °C with stirring. DEAD (576 μL, 3.66 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. After 5 h, TLC showed complete consumption of the starting material. The reaction mixture was diluted with EtOAc and washed with saturated aq $NaHCO_3$ followed by water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product was loaded onto a silica gel column using CH_2Cl_2 and eluted with 15% EtOAc in CH_2Cl_2 followed by 40% EtOAc in CH_2Cl_2. Compound **12** was obtained as white, foamy solid (1.163 g, 81% yield). R_f (50% EtOAc in CH_2Cl_2) = 0.16. ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.58 (d, 2H, Ar-H, J = 8.2), 7.27 (d, 2H, Ar-H, J = 8.2), 6.03 (d, 1H, H-1′, J = 1.7), 5.94 (br s, 2H, NH_2), 5.56 (dd, 1H, H-2′, J = 6.3, 1.7), 5.15 (dd, 1H, H-3′, J = 6.3, 2.7), 4.50 (dt, 1H, H-4′, J = 6.9, 2.7), 3.43 (m, 1H, H-5′), 2.91 (m, 1H, H-5′), 2.41 (s, 3H, *p*-toluyl CH_3), 1.58 and 1.38 (2s, 6H, isopropylidine CH_3), 0.89 (s, 9H, *t*-Bu), 0.34, 0.24 (2s, 6H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 155.8, 153.1, 149.3, 145.0, 140.5, 129.9, 129.5, 120.5, 114.3, 91.8, 84.3, 84.1, 83.6, 58.0, 27.2, 26.2, 25.6, 21.8, 18.5, −4.1, −4.3. HRMS (ESI) calcd for $C_{26}H_{39}N_6O_6SSi$ $[M + H]^+$ 591.2421, found 591.2427.

1′-Adenin-9-yl-2′,3′-*O*-(isopropylidene)-β-D-ribofuranurononitrile (14). Step 1. Compound **12** (1.32 g, 2.22 mmol) was dissolved in anhydrous CH_3CN (22 mL), and CsF (0.674 g, 4.44 mmol) was added. The reaction mixture was stirred at 60 °C for 1.5 h, at which time TLC showed complete consumption of the starting material. Saturated aq NH_4Cl was added to the cooled reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with water followed by brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was loaded onto a dry-packed silica gel column and eluted using 30% acetone in hexanes. Compound **13** (*E*/*Z* mixture) was obtained as white powder (0.569 g, 80% yield). R_f (4% MeOH in CH_2Cl_2) = 0.03. HRMS calcd for $C_{13}H_{17}N_6O_4$ $[M + H]^+$ 321.1311, found 321.1311. The NMR data for this *E*/*Z* mixture has been reported.[25] The ^{1}H NMR spectrum of this mixture is furnished in the Supporting Information.

Step 2 Using BOP. In an oven-dried, 50 mL, two-necked, round-bottomed flask equipped with a stirring bar was placed a solution of **13** (0.320 g, 1.0 mmol) and BOP (0.885 g, 2.0 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 min, and then DBU (344 μL, 2.30 mmol) was added dropwise over 2−3 min to the stirring solution. The reaction mixture became clear after addition of DBU. After 45 min TLC showed complete consumption of the starting material. The reaction mixture was diluted with EtOAc and washed with water (2×) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using 2% EtOH in CH_2Cl_2 as eluting solvent (the chromatography was repeated a second time). Compound **14** obtained as white solid (0.288 g, 95% yield).

Step 2 Using Bt-OTs. In an oven-dried, 50 mL, two-necked, round-bottomed flask equipped with a stirring bar was placed a solution of **13** (0.277 g, 0.864 mmol) and Bt-OTs (0.500 g, 1.73 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 5 min, and then DBU (297 μL, 1.99 mmol) was added dropwise over 2 min to the stirring solution. The reaction mixture became clear after addition of DBU. After 35 min, TLC showed complete consumption of the starting material. The reaction mixture was diluted with EtOAc and washed with water (2×) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using 2% EtOH in CH_2Cl_2 as eluting solvent (the chromatography was repeated a second time). Compound **14** was obtained as a white solid (0.246 g, 93% yield). R_f (4% MeOH in CH_2Cl_2) = 0.27. ^{1}H NMR ($CDCl_3$): δ 8.39 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 6.20 (s, 1H, H-1′), 5.83 (d, 1H, H-2′, J = 5.7), 5.79 (dd, 1H, H-3′, J = 5.7, 1.4), 5.64 (br s, 2H, NH_2), 4.98 (d, 1H, H-4′, J = 1.4), 1.58 and 1.43 (2s, 6H, isopropylidine CH_3). ^{13}C NMR ($CDCl_3$): δ 155.8, 153.5, 149.7, 140.1, 120.2, 116.2, 115.0, 92.0, 84.9, 84.1, 75.5, 26.7, 25.2. HRMS (ESI): calcd for $C_{13}H_{15}N_6O_3$ $[M + H]^+$ 303.1206, found 303.1207.

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Supporting Information Available: ^{1}H NMR spectra of carbonitriles **1**−**10** shown in Table 2 as well as those of **12**−**14** and COSY spectra of **12** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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