Notes

Hydrolysis and Hydrogenolysis of Formamidines: *N,N*-Dimethyl and *N,N*-Dibenzyl Formamidines as Protective Groups for Primary Amines

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Introduction

Protective groups play a pivotal role in the synthesis of complex organic substances.[1] A number of reagents and procedures have been described to specifically protect and deprotect primary amines. *N,N*-Dialkyl formamidines and especially *N,N*-dimethyl formamidines have been widely used as protective groups for the exocyclic amino function of nucleosides.[2−12] Recently, we described the use of *N,N*-dibenzyl formamidine as a primary amine protective group.[13] Our investigations originated from the need to dispose of a protective group that is stable in moderately acidic and basic experimental conditions and that can be removed under neutral conditions. *N,N*-Dibenzyl formamidines fulfill the performance and application criteria, and the masking group can be removed by catalytic hydrogenation with palladium-on-carbon catalysts.

Herein, we describe the results of our investigations concerning the reactivity of *N,N*-dimethyl and *N,N*-dibenzyl formamidines toward hydrolysis and hydrogenolysis reactions.

Results and Discussion

We prepared a series of *N*-alkyl and *N*-aryl *N′,N′*-dimethyl and *N′,N′*-dibenzyl formamidines to study their properties. There are a number of reports in the literature for the preparation of *N′,N′*-dialkyl amidines.[14−16] In the present work, the synthesis of *N′,N′*-dimethyl formamidines was carried out using DMF dimethyl acetal[17−19] and the procedure described by Zemlicka.[12] The synthesis of *N′,N′*-dibenzyl formamidines was carried out according to our previously published procedure.[13]

Hydrolysis Reactions. The mechanism of amidine hydrolysis has been studied in detail elsewhere.[15,20−24] The reaction proceeds via the formation of a hemiorthoamide that can cleave in two different ways (Scheme 1).

Hydrolysis of *N*-alkyl *N′,N′*-dibenzyl formamidines in neutral conditions proceeded in a way different from that of *N′,N′*-dimethyl compounds (Table 1). The reaction essentially goes through *path a* as *N,N*-dibenzyl formamide **5a** is formed during the reaction, whereas only a trace amount of *N*-alkyl formamide **4b** can be detected by ^{1}H NMR (entries 2, 3, 5, and 7). In the case of *N*-alkyl *N′,N′*-dimethyl formamidines, the hydrolysis reaction is much more rapid than with dibenzyl compounds and goes through *path b*. This is clearly evidenced by the production of *N*-alkyl formamide in almost quantitative yield in a few hours at room temperature (entries 1, 4, and 6).[25] The course of the reaction is assumed to be governed by the respective pK_a value of each nitrogen atom in the intermediate hemiorthoamide structure **2**. In that compound, the nitrogen atom bearing three alkyl substituents (N′) is more basic than the disubstituted one (N) as a result of the electron-donating character of the alkyl groups. Thus, the hemiorthoamide evolves toward species **3b**, further yielding the *N*-alkyl formamide **4b**. In the case of *N′,N′*-dibenzyl compounds, because of the small electron-withdrawing character of the two benzyl moieties, the N′ center appears less basic than the N center[26] and the hydrolysis reaction evolves through *path a*, yielding the amine **4a**.

* Tel.: 33 (0)3 88 67 68 57. Fax: 33 (0)3 88 67 88 91. E-mail: lebeau@aspirine.u-strasbg.fr.

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(25) Interestingly, it was recently reported that hydrolysis of dimethyl formamidines in absolute ethanol in the presence of 2 equiv of zinc chloride required 24 h at room temperature to quantitatively afford the corresponding *N*-alkyl formamide: Toste, D.; McNulty, J.; Still, I. W. J. *Synth. Commun.* **1994**, *24*, 1617−1624.
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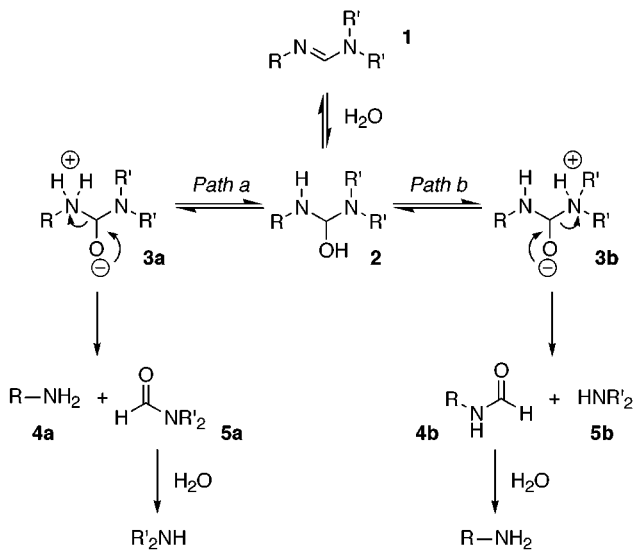
Scheme 1



Hydrolysis of *N*-aryl *N*′,*N*′-disubstituted formamidines is more difficult because of the conjugation between the formamidine double bond and the aromatic cycle. As previously reported, introduction of a phenyl ring on the imino nitrogen of an amidine reduces its basicity by a factor 1000.[27] Consequently, the *N*-aryl formamidine hydrolysis proceeds via *path b* (Scheme 1). The reaction conditions are harsher, and unreacted starting material is recovered in many cases (entries 8−13). In neutral experimental conditions, *N*-aryl *N*′,*N*′-dimethyl formamidines afford the corresponding *N*-aryl formamides (entries 8 and 11), whereas *N*′,*N*′-dibenzyl compounds remain unreacted (entries 9 and 12). Hydrolysis of *N*-aryl *N*′,*N*′-dibenzyl formamidines requires the use of a base and higher temperature (entries 10, 12,[28] and 13). When triethylamine is used, *N*-aryl formamide is obtained (entry 10), whereas potassium hydroxide yields the corresponding aniline without any trace of *N*-aryl formamide (entry 13). In both cases, the hydrolysis is expected to yield the formanilide (Scheme 1, *path b*[29]) and it is likely that, in the presence of potassium hydroxide, it is rapidly hydrolyzed into the corresponding aniline. This is consistent with the results in the literature related to the rate of alkaline hydrolysis of formanilides.[30,31]

The reactivity of formamidine derivatives of cytidine toward hydrolysis was found to be intermediate between those of *N*-alkyl and *N*-aryl formamidines. This is consistent with the partial aromaticity of cytosine. Thus, the ^4N formamidine-protected cytosine nucleosides are quantitatively deprotected in neutral conditions at 50 °C (entries 14 and 15). The *N*′,*N*′-dialkyl formamidine of adenine and guanosine derivatives (entries 16−19) cannot be deprotected in these conditions, and the recovery of the exocyclic amino function requires the use of potassium hydroxide. In all these cases, as a result of the existence of mesomeric forms of the nucleosides, the hydrolysis reaction proceeds according to *path a* (Scheme 1), except that the N center is not protonated.

Hydrogenolysis Reactions. There are very few reports in the literature on hydrogenolysis of amidines,[32−34] and the reaction has not been investigated for primary amine protection−deprotection purposes so far. We submitted a series of *N*-alkyl and *N*-aryl *N*′,*N*′-dimethyl or *N*′,*N*′-dibenzyl formamidines to a set of different hydrogenolysis conditions to study the scope of the deprotection reaction (Table 2).

Hydrogenolysis of *N*-alkyl formamidines generally lead to a mixture of compounds (entries 1−9). The *N*-alkylamine is obtained together with the *N*-methyl alkylamine and the *N*-alkyl formamide. The ratio between the different constituents of the mixture varies depending on the nature of the two *N*′ substituents (methyl or benzyl groups), on the hydrogen source (H_2, ammonium formate, or cyclohexene), and on the solvent and catalyst used. It is likely that the formamide observed at entries 2 and 3 results from partial hydrolysis of the formamidine during the course of the reaction. This is consistent with the kinetics of the hydrolysis reaction reported in Table 1. More intriguing is the obtaining of alkylamines and *N*-methyl alkylamines. We found only one example in the literature for the reduction of a *N*-alkyl formamide into the corresponding *N*-methyl alkylamine by catalytic hydrogenation.[35] The transformation was described in 1923 and requires very harsh experimental conditions (nickel catalyst, high pressure of hydrogen, 200−210 °C). On the other hand, the obtaining of an alkylamine from its formamide in hydrogenolysis condition has also been reported.[36] However, in that case, the amine probably resulted from the acidic hydrolysis of the formamide. Nevertheless, tentative hydrogenolysis of *N*-(4,4-diethoxybutyl)-formamide in the conditions described at entry 4 did fail, and starting material was quantitatively recovered even after prolonged reaction time. This definitely rules out the formation of the amine and/or methylamine via the reduction or the hydrolysis of the formamide. Though we have no direct experimental evidence of that, it is supposed that the formation of amines results from the preliminary reduction of the imino function in formamidines (Scheme 2). The orientation of the reaction depends on the respective pK_a values of the two nitrogen atoms in the aminal. Thus, the intermediate *N*-hydroxymethylamines **6a** and **6b** can evolve in two different ways. They can eliminate either a formaldehyde molecule to give the corresponding amine or a water molecule to give the imine. That imine can be further hydrogenolyzed and transformed into the *N*-methyl alkylamine.

In the particular case of *N*-aryl formamidines (entries 10 to 19), *N*-methyl arylamines are not observed as side products. This is in agreement with the results of Abrams and Kallen on the formation of *N*-hydroxymethylamines from aromatic exocyclic amines and formaldehyde.[37] They provided evidence that *N*-hydroxymethyl derivatives of

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(28) Because of steric hindrance, 2,6-dimethylaniline derivatives were very resistant to hydrolysis (Table 1, entries 11−13).
(29) In the hydrolysis of *N*-aryl *N*′,*N*′-disubstituted formamidines under basic conditions, the intermediate species **3b** (Scheme 1) is presumably not fully protonated at N′.
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(34) Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5365−5368.
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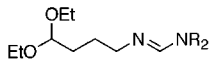
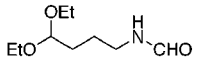
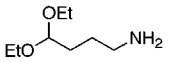
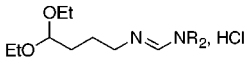
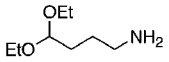
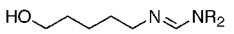
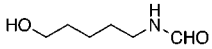
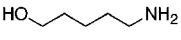
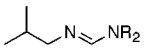
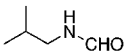
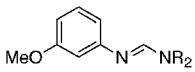
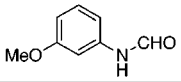
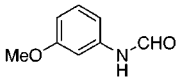
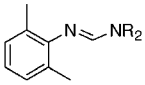
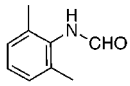
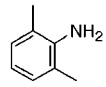
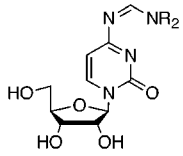
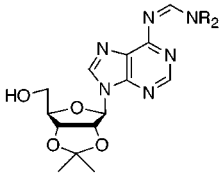
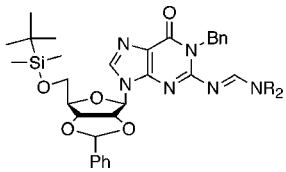
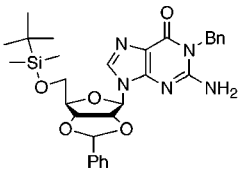
(37) Abrams, W. R.; Kallen, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7777−7789.

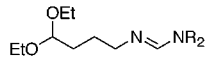
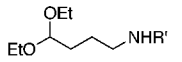
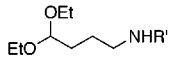
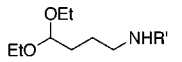
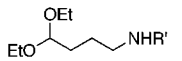
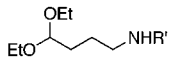
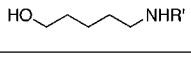
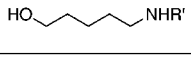
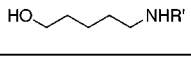
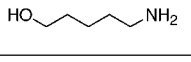
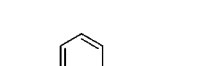
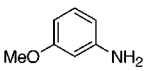
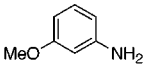
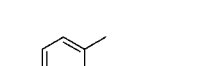
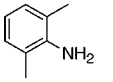
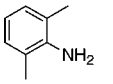
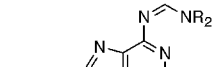
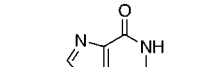
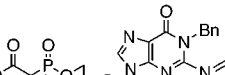
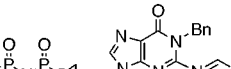
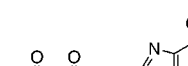
Table 1

Entry	Substrate	R	Experimental conditions	Product (yield, %)
1		Me	*t*-BuOH/H_2O : 3/7, RT, 2 h	 (98)
2		Bn	MeOH/H_2O : 1/1, RT, 34 h	 (76)
3		Bn	MeOH/H_2O : 1/1, RT, 6 days	 (25) Starting material (73)
4		Me	MeOH/H_2O : 4/1, RT, 3 h	 (91)
5		Bn	*t*-BuOH/H_2O : 1/1, RT, 24 h	 (99)
6		Me	MeOH/H_2O : 4/1, RT, 2 h	 (97)
7		Bn	MeOH/H_2O : 4/1, RT, 72 h	 (67) Starting material[a] (29)
8		Me	*t*-BuOH/H_2O : 1/1, RT, 48 h	 (70)[b]
9		Bn	THF/*t*-BuOH/H_2O : 1/5/5, RT, 48 h	Starting material (100)
10		Bn	THF/*t*-BuOH/H_2O/Et_3N : 1/5/5/1 80 °C, 4 h	 (48) Starting material (44)
11		Me	*t*-BuOH/H_2O : 2/1 Et_3N 4 eq., RT, 7 days	 (42) Starting material (58)
12		Bn	*t*-BuOH/H_2O/Et_3N : 6/3/1 80 °C, 24 h	Starting material (100)
13		Bn	*t*-BuOH/H_2O : 2/1 30 eq. KOH, 80 °C, 12 h	 (45) Starting material (52)
14		Me	MeOH/H_2O : 2/1, 50 °C, 36 h	Cytidine (99)
15		Bn	MeOH/H_2O : 2/1, 50 °C, 26 h	Cytidine (99)
16		Me	THF/*t*-BuOH/H_2O : 3/10/2 KOH 4 eq., RT, 8 h	2',3'-*O*-Isopropylidene adenosine (96)
17		Bn	THF/*t*-BuOH/H_2O : 3/10/2 KOH 4 eq., RT, 8 h	2',3'-*O*-Isopropylidene adenosine (77)
18		Me	THF/*t*-BuOH/H_2O : 3/10/2 KOH 4 eq., RT, 3 h	 (87)
19		Bn	THF/*t*-BuOH/H_2O : 3/10/2 KOH 4 eq., RT, 3 h	(72)

[a]The starting compound was not completely soluble.
[b]The reaction was brought to near completion (94%) after 6 days, or increasingthe temperature to 50°C for 16 h.

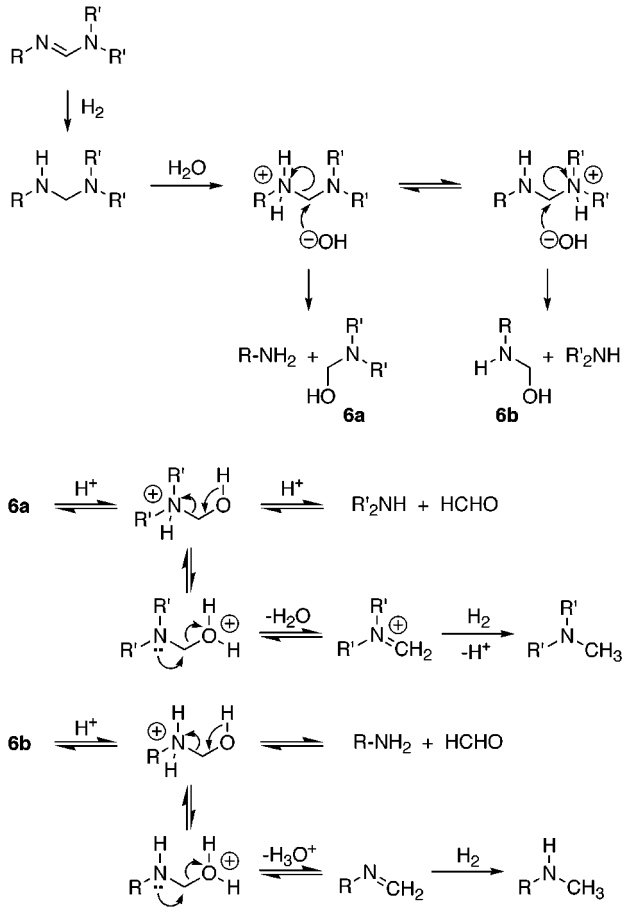
aniline and related compounds are in equilibrium with the amine and formaldehyde and not with the imine. Thus, the hydrogenolysis of a *N*-aryl formamidine is a very clean reaction and affords the corresponding ary-

Table 2

Entry	Substrate	R	Experimental conditions	Product (yield, %)
1		Me	MeOH, RT, H_2 (60 psi) Pd/C-Pd(OH)$_2$/C : 1/1, 5 h	 R' = H (69) R' = Me (28)
2		Me	MeOH, 65 °C, HCO_2NH_4 Pd/C, 12 h	 R' = H (26) R' = CHO (35) R' = Me (11) Starting material (23)
3		Me	*i*-PrOH, cyclohexene : 1/1, 65 °C Pd/C-Pd(OH)$_2$/C : 1/1, 13 h	 R' = H (4) R' = CHO (69) Starting material (18)
4		Bn	THF/*t*-BuOH/H_2O : 1/7/7, RT H_2 (15 psi), Pd(OH)$_2$/C, 24 h	 R' = H (38) R' = Me (43)
5		Bn	MeOH/H_2O : 1/1, 65 °C HCO_2NH_4, Pd(OH)$_2$/C, 14 h	 R' = H (63) R' = Me (14)
6		Me	MeOH, RT, H_2 (70 psi) Pd/C-Pd(OH)$_2$/C, 14 h	 R' = H (42) R' = Me (40)
7		Bn	MeOH, RT, H_2 (70 psi) Pd(OH)$_2$/C, 7 h	 R' = H (48) R' = Me (44)
8		Bn	*t*-BuOH/H_2O : 1/1, 65 °C HCO_2NH_4, Pd(OH)$_2$/C, 6 h	 R' = H (26) R' = Me (71)
9		Bn	THF/MeOH : 1/9, 65 °C HCO_2NH_4, Pd(OH)$_2$/C, 4 h	 (98)
10		Me	*t*-BuOH/H_2O : 2/1, RT H_2 (65 psi), Pd(OH)$_2$/C, 12 h	 (98)
11		Bn	*t*-BuOH/H_2O : 2/1, RT H_2 (55 psi), Pd(OH)$_2$/C, 5 h	 (90)
12		Me	MeOH/H_2O : 1/1, RT, H_2 (70 psi) Pd/C-Pd(OH)$_2$: 1/1, 60 h	 (86)
13		Bn	MeOH/H_2O : 9/1, RT, H_2 (70 psi) Pd/C-Pd(OH)$_2$: 1/2, 64 h	 (83)
14		Me	MeOH/H_2O : 1/1, RT, H_2 (70 psi) Pd(OH)$_2$/C, 14 h	2',3'-*O*-Isopropylidene adenosine (98)
15		Bn	*t*-BuOH/H_2O : 1/1, RT H_2 (70 psi), Pd(OH)$_2$/C, 24 h	2',3'-*O*-Isopropylidene adenosine (99)
16		Me	*t*-BuOH/H_2O : 1/1, RT, H_2 (40 psi) Pd/C-Pd(OH)$_2$/C : 1/1, 20 h	Guanosine (98)
17		Bn	*t*-BuOH/H_2O : 1/1, RT, H_2 (40 psi) Pd/C-Pd(OH)$_2$/C : 1/1, 20 h	Guanosine (99)
18		Bn	*t*-BuOH/H_2O : 1/1, RT, H_2 (70 psi) Pd/C-Pd(OH)$_2$: 1/1, 24 h	 (94)
19		Bn	*t*-BuOH/H_2O : 1/1, RT, H_2 (70 psi) Pd/C-Pd(OH)$_2$/C : 1/1, 24 h	 (91)

lamine in almost quantitative yield. Cytidine derivatives described in Table 1 were not submitted to hydrogenolysis reaction conditions as the double bond in cytosine would not be preserved. To complete our observations,

Scheme 2



we have to mention that we did not find any significant difference in the kinetics of the hydrogenolysis of *N*-aryl *N*′,*N*′-dimethyl and *N*′,*N*′-dibenzyl formamidines.

Conclusion

We have investigated the properties of a series of differently substituted formamidines in hydrolytic and hydrogenolytic experimental conditions. We have outlined structural features related to the imino nitrogen substituent and to the two amino substituents orienting the course of the hydrolysis and hydrogenolysis reactions. *N*-Alkyl *N*′,*N*′-dimethyl formamidines provide an easy access to the corresponding formamide by neutral hydrolysis, whereas in the dibenzyl series, the same formamidines are readily transformed into the primary amine. Both types of compounds lead to a mixture of alkylamine and *N*-methyl alkylamine when submitted to hydrogenation. Aryl formamidines are more resistant to hydrolysis and often require basic conditions to afford the corresponding primary amine. On the other hand, their hydrogenolysis quantitatively restores the aromatic exocyclic primary amine. This definitely appears to be of special interest in the field of oligonucleotide chemistry, as it provides an alternative to the hydrolysis under basic conditions that is incompatible with many substrates.

Experimental Section

General methods were previously reported elsewhere.[38] All compounds were purified to homogeneity, and analytical samples showed one spot when checked by HPTLC (Merck $60F_{254}$ or RP-$18F_{254s}$). All the yields indicated refer to pure isolated compounds.

Typical Procedure for the Preparation of Dimethyl Formamidines. The primary amine (1 mmol) is stirred for 5 h at room temperature in *N*,*N*-dimethyl formamide dimethyl acetal (0.5 mL, 3.7 mmol).[39] The reaction mixture is reduced in vacuo, and the amino-protected compound is purified by chromatography on silica gel.

Typical Procedure for the Preparation of Dibenzyl Formamidines. Dimethyl formamide dimethyl acetal (1 mmol) and dibenzylamine (3 mmol) are refluxed in dry acetonitrile for 20 h. The reaction mixture is evaporated to dryness, and traces of remaining DMF dimethyl acetal are removed by two successive addition/evaporation steps with toluene. The crude residue is dissolved in anhydrous CH_3CN and added to the primary amine (0.4 mmol) in CH_3CN.[40] The resulting solution is stirred at room temperature until the amine has completely disappeared when checked by TLC. The solvent is removed in vacuo, and the amino-protected compound is purified by chromatography on silica gel.

***N*′-(4,4-Diethoxy-butyl)-*N*,*N*-dimethyl-formamidine** (Table 1, entry 1; yield: 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25 (s, 1H); 4.51 (t, J = 5.1, 1H); 3.75−3.36 (m, 4H); 3.27 (t, J = 6.3, 2H); 2.81 (s, 6H); 1.70−1.62 (m, 4H); 1.25 (t, J = 6.9, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.78; 102.84; 60.65; 55.83; 36.93; 31.15; 27.71; 15.19. IR (neat) ν 2974; 2926; 2873; 1655. MS (CI/NH_3): 217 $[M + H]^+$.

***N*′-(4,4-Diethoxy-butyl)-*N*,*N*-dibenzyl-formamidine** (Table 1, entry 2; yield: 75%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.62 (s, 1H); 7.33−7.12 (m, 10H); 4.53 (t, J = 5.1, 1H); 4.31 (s, 4H); 3.85−3.40 (m, 4H); 3.34 (t, J = 5.9, 2H); 1.70−1.62 (m, 4H); 1.25 (t, J = 6.9, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.54;137.61; 128.75; 128.32; 127.97; 127.68; 127.04; 102.82; 60.63; 55.77; 50.03; 31.14; 27.56; 15.23. IR (neat) ν 2972; 2928; 2871; 1649. MS (CI/NH_3): 369 $[M + H]^+$.

***N*′-(4,4-Diethoxy-butyl)-*N*,*N*-dibenzyl-formamidine hydrochloride** (Table 1, entry 3; this compound is obtained by bubbling HCl gas in a solution of *N*′-(4,4-diethoxy-butyl)-*N*,*N*-dibenzyl-formamidine in ether; yield: 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.55 (s, 1H); 7.30−7.10 (m, 10H); 4.65−4.55 (m, 4H); 4.43 (t, J = 5.1, 1H); 3.85−3.40 (m, 6H); 1.72 (m, 2H); 1.58 (m, 2H); 1.16 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.60; 132.85; 128.75; 128.26; 102.26; 61.15; 45.52; 29.99; 25.31; 15.09. IR (neat) ν 3030; 2972; 2877; 1692.

***N*′-(5-Hydroxy-pentyl)-*N*,*N*-dimethyl-formamidine** (Table 1, entry 4; yield: 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (s, 1H); 3.53 (t, J = 6.2, 2H); 3.15 (t, J = 6.6, 2H); 2.76 (s, 6H); 1.60−1.38 (m, 4H); 1.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.91; 62.04; 55.86; 37.03; 32.35; 31.07; 23.23. IR (neat) ν 2930; 2859; 1646. MS (CI/NH_3): 159 $[M + H]^+$; 176 $[M + NH_4]^+$.

***N*′-(5-Hydroxy-pentyl)-*N*,*N*-dibenzyl-formamidine** (Table 1, entry 5; yield: 78%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.72 (s, 1H); 7.42−7.20 (m, 10H); 4.38 (s, 4H); 3.65 (t, J = 6.4, 2H); 3.38 (t, J = 6.6, 2H); 1.67−1.62 (m, 4H); 1.25 (q, J = 7.0, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.80; 137.12; 128.46; 127.74; 127.27; 126.90; 62.39; 55.20; 55.17; 32.30; 31.78; 23.14. IR (neat) ν 3028; 2929; 2858; 1646. MS (CI/NH_3): 328 $[M + NH_4]^+$.

***N*′-Isobutyl-*N*,*N*-dimethyl-formamidine** (Table 1, entry 6; yield: 99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (s, 1H); 3.03 (d, J = 4.5, 2H); 2.83 (s, 6H); 1.73 (h, J = 4.5, 1H); 0.89 (d, J = 4.5, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.80; 64.29; 37.00, 30.36; 20.31. IR (neat) ν 2960; 2872; 1667. MS (CI/NH_3): 129 $[M + H]^+$.

***N*′-Isobutyl-*N*,*N*-dibenzyl-formamidine** (Table 1, entry 7; yield: 81%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (s, 1H); 7.45−7.20 (m, 10H); 4.38 (s, 4H); 3.19 (d, J = 6.8, 2H); 1.87 (h, J = 6.8, 1H); 0.96 (d, J = 6.8, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.84; 137.70; 136.98; 129.03; 128.40; 127.99; 127.77; 127.13; 64.24; 56.35; 50.14; 30.42; 20.46. IR (neat) ν 2957; 2866; 1649. MS (CI/NH_3): 281 $[M + H]^+$.

(38) Lebeau, L.; Oudet, P.; Mioskowski, C. *Helv. Chim. Acta* **1991**, *74*, 1697−1706.

(39) Hindered primary amines required prolonged reaction time at higher temperature (50−60 °C).

(40) The reaction can be run in anhydrous DMF with a comparable yield and without any formation of *N*, *N*-dimethyl formamidine.

***N′*-(3-Methoxy-phenyl)-*N,N*-dimethyl-formamidine** (Table 1, entry 8; yield: 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.85 (s, 1H); 7.45−7.09 (m, 1H); 6.50−6.45 (m, 3H); 3.65 (s, 3H); 2.86 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.80; 153.14; 152.81; 129.02; 112.79; 107.70; 106.29; 54.48; 39.47; 34.02. IR (neat) ν 2913; 1638; 1589. MS (CI/NH_3): 179 $[M + H]^+$.

***N′*-(3-Methoxy-phenyl)-*N,N*-dibenzyl-formamidine** (Table 1, entry 9; yield: 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.98 (s, 1H); 7.82−7.20 (m, 14H); 6.80−6.62 (m, 3H); 4.74 (s, 2H); 4.35 (s, 2H); 3.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.37; 154.46; 154.23; 137.90; 130.66; 129.65; 129.08; 128.59; 114.38; 109.54; 108.05; 56.22; 54.57; 48.45. IR (neat) ν 3028; 2922; 1633; 1591. MS (CI/NH_3): 331 $[M + H]^+$; 348 $[M + NH_4]^+$.

***N′*-(2,6-Dimethyl-phenyl)-*N,N*-dimethyl-formamidine** (Table 1, entry 11; yield: 73%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (s, 1H); 7.05 (d, J = 7.5, 2H); 6.84 (t, J = 7.5, 1H); 3.01 (s, 6H); 2.17 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.12; 153.00; 149.94; 129.61; 127.65; 121.82; 37.01; 18.61. IR (neat) ν 2918; 1645. MS (CI/NH_3): 177 $[M + H]^+$.

***N′*-(2,6-Dimethyl-phenyl)-*N,N*-dibenzyl-formamidine** (Table 1, entry 12; yield: 93%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H); 7.46−7.30 (m, 10H); 7.10 (d, J = 7.3, 2H); 6.92 (t, J = 7.3, 1H); 4.54 (s, 4H), 2.32 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.06; 149.74; 137.29; 129.53; 128.57; 127.79; 127.39; 122.05; 53.00; 48.45; 18.81. IR (neat) ν 3028; 2914; 1640; 1590. MS (CI/NH_3): 329 $[M + H]^+$.

^{4}*N*-Dimethylaminomethylene cytidine (Table 1, entry 14; yield: 99%). ^{1}H NMR (DMSO-d_6/CD_3OD 1/3, 300 MHz) δ 8.71 (s, 1H); 8.26 (d, J = 7.1, 1H); 6.16 (d, J = 7.1, 1H); 5.93 (d, J = 1.5, 1H); 4.15 (m, 2H); 4.05 (m, 1H); 3.83 (AB part of ABX systtem, $\Delta\nu$ = 18.0, J_{AB} = 12.4, J_{AX} = 2.6, J_{BX} = 3.0, 2H); 3.25 (s, 3H); 3.16 (s, 3H). ^{13}C NMR (DMSO-d_6/CD_3OD 1/3, 75 MHz) δ 173.26; 159.92; 158.27; 144.09; 103.49; 92.20; 58.88; 76.29; 70.60; 61.76; 41.95; 35.69. IR (KBr) ν 2942; 1655; 1626; 1598. MS (CI/NH_3): 299 $[M + H]^+$.

^{4}*N*-Dibenzylaminomethylene cytidine (Table 1, entry 15; yield: 81%). ^{1}H NMR ($CDCl_3$/CD_3OD 2/1, 200 MHz) δ 9.10 (s, 1H); 8.18 (d, J = 7.3, 1H); 7.42−7.10 (m, 10H); 6.18 (d, J = 7.3, 1H); 5.76 (d, J = 2.2, 1H); 4.72 (s, 2H); 4.58 (s, 2H); 4.35−4.05 (m, 3H); 3.85 (AB part of ABX system, $\Delta\nu$ = 18.0, J_{AB} = 12.6, J_{AX} = 2.2, J_{BX} = 2.6, 2H). ^{13}C NMR ($CDCl_3$/CD_3OD 2/1, 50 MHz) δ 172.04; 158.84; 156.81; 142.58; 134.58; 134.29; 128.63; 128.43; 128.08; 127.93; 127.62; 127.13; 102.96; 92.16; 84.31; 74.69; 68.54; 60.08; 54.61; 49.65. IR ($CHCl_3$) ν 2928; 1651; 1573. MS (CI/NH_3): 451 $[M + H]^+$; 468 $[M + NH_4]^+$.

2′,3′-*O*-Benzylidene-5′-*O*-*tert*-butyldimethylsilyl-^{1}*N*-benzyl-^{2}*N*-dibenzylamino-methylene guanosine (Table 1, entry 19; 2 diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 and 8.86 (2s, 1H); 7.89 and 7.83 (2s, 1H); 7.60−7.15 (m, 20H); 6.28 and 6.21 (2d, J = 4.1, 1H); 6.18 and 6.02 (2s, 1H); 5.57 (s, 2H); 5.32 and 5.20 (2dd, J = 4.1, 9.5, 1H); 5.08 and 4.99 (2dd, J = 4.0, 9.5, 1H); 4.63 and 4.61 (2s, 2H); 4.54 and 4.39 (2m, 1H); 4.35 and 4.30 (2s, 2H); 3.85 (m, 2H); 0.88 and 0.86 (2s, 9H); 0.07, 0.06, 0.04, and 0.02 (4s, 6H). ^{13}C NMR (DMSO-d_6/$CDCl_3$ 1/2, 50 MHz) δ 158.12; 157.99; 157.05; 147.51 and 147.55; 138.55; 136.36−134.64 (m); 129.83−125.92 (m); 120.36 and 120.26; 107.49 and 104.25; 89.67 and 89.06; 85.96 and 85.73; 85.29 and 84.68; 82.69 and 81.77; 63.46 and 63.25; 54.76; 48.30 and 48.20; 45.33; 25.89; 18.35; −5.41 and −5.54. IR (neat) ν 3031; 2928; 1688. MS (CI/NH_3): 800 $[M + NH_4]^+$.

2′,3′-*O*-Benzylidene-5′-*O*-*tert*-butyldimethylsilyl-^{1}*N*-benzyl guanosine (Table 1, entry 19, product; yield: 91%; 2 diastereomers). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77 and 7.73 (2s, 1H); 7.60−7.15 (m, 5H); 6.12 and 5.98 (2s, 1H); 6.11 and 6.05 (2d, J = 2.5, 1H); 5.25 (m, 3H); 5.11 (m, 3H); 4.49 and 4.36 (2m, 1H); 3.81 (m, 2H); 0.91 and 0.88 (2s, 9H); 0.07, 0.06, 0.05 (3s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.07; 153.32; 148.23; 136.05; 135.80; 134.93; 129.92−126.56 (m); 117.98; 107.56; 104.24; 89.78 and 89.12; 86.37 and 85.26; 84.34; 82.49 and 80.82; 63.36 and 63.25; 44.87; 25.86; 18.31; −5.45 and −5.52. IR (neat) ν 2951; 2927; 2854; 1690; 1630. MS (CI/NH_3): 593 $[M + NH_4]^+$.

2′,3′-*O*-Isopropylidene-^{6}*N*-dimethylaminomethylene adenosine (Table 1, entry 16; yield: 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.81 (s, 1H); 8.37 (s, 1H); 7.98 (s, 1H); 5.87 (d, J = 4.6, 1H); 5.22 (dd, J = 4.6, 5.8, 1H); 5.10 (dd, J = 1.5, 5.8, 1H); 4.42 (dd, J = 1.5, 1.8, 1H); 3.75 (AB part of ABX system, $\Delta\nu$ = 19.0, J_{AX} = 1.8, J_{BX} = 2.6, J_{AB} = 12.4, 1H); 3.16 (s, 3H); 3.14 (s, 3H); 1.55 (s, 3H); 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.90; 158.29; 151.88; 149.82; 141.25; 126.70; 113.93; 93.43; 85.78; 83.01; 81.36; 62.82; 41.13; 34.84; 27.19; 24.91. IR (neat) ν 2987; 2935; 1633; 1566. MS (CI/NH_3): 363 $[M + H]^+$.

2′,3′-*O*-Isopropylidene-^{6}*N*-dibenzylaminomethylene adenosine (Table 1, entry 17; yield: 87%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.37 (s, 1H); 8.55 (s, 1H); 7.96 (s, 1H); 7.42−7.10 (m, 10H); 5.89 (d, J = 5.0, 1H); 5.22 (dd, J = 5.0, 5.6, 1H); 5.10 (d, J = 5.6, 1H); 4.87 (s, 2H); 4.53 (m, 1H); 4.43 (s, 2H); 4.10−3.70 (m, 2H); 1.63 (s, 3H); 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.37; 158.97; 151.98; 150.17; 141.46; 135.36; 134.96; 128.84; 128.22; 127.99; 127.74; 127.65; 126.79; 113.82; 94.12; 85.90; 82.86; 81.59; 63.28; 54.54; 47.66; 27.53; 25.13. IR (neat) ν 2932; 1554. MS (CI/NH_3): 515 $[M + H]^+$, 532 $[M + NH_4]^+$.

2′,3′-*O*-Benzylidene-^{2}*N*-dimethylaminomethylene guanosine (Table 2, entry 16; yield: 85%; 2 diastereomers). ^{1}H NMR (CD_3OD, 200 MHz) δ 8.62 and 8.58 (2s, 1H); 8.07 and 8.05 (2s, 1H); 7.60−7.39 (m, 5H); 6.23 (d, J = 2.9, 0.5H); 6.20 (d, J = 3.3, 0.5H); 6.19 and 6.03 (2s, 1H); 5.44−5.36 (m, 1H); 5.22−5.10 (m, 1H); 4.47 (m, 0.5H); 4.35 (m, 0.5H); 3.82−3.74 (m, 2H); 3.14 and 3.13 (2s, 3H); 3.08 and 3.07 (2s, 3H). ^{13}C NMR (CD_3OD, 50 MHz) δ 158.32; 157.08; 149.68; 138.05; 136.05; 135.91; 129.73−126.49 (m); 120.37; 120.29; 107.38; 104.00; 91.01; 89.82; 85.69; 84.97; 83.87; 82.92; 80.35; 62.30; 62.07; 41.31; 34.98. IR (KBr) ν 2930; 1679; 1632. MS (CI/NH_3): 427 $[M + H]^+$, 444 $[M + NH_4]^+$.

2′,3′-*O*-Benzylidene-^{2}*N*-dibenzylaminomethylene guanosine (Table 2, entry 17; yield: 99%; 2 diastereomers). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.89 and 8.87 (2s, 1H); 7.81 and 7.76 (2s, 1H); 7.60−7.25 (m, 15H); 6.02 (d, J = 5.8, 1H); 6.22 and 6.04 (2s, 1H); 5.37 (m, 1H); 5.17 (m, 1H); 4.75−4.40 (m, 5H); 3.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.69; 157.76; 157.16; 149.24; 137.92 and 137.79; 136.11 and 135.83; 134.99 and 134.63; 129.67, 128.80, and 128.62; 128.37, 128.31, and 128.12; 127.73, 126.42 and 126.29; 121.37 and 121.29; 107.40 and 104.10; 91.61 and 90.28; 85.27 and 84.92; 83.78 and 83.55; 83.06 and 80.23; 62.48 and 62.16; 54.81; 47.77. IR (neat) ν 3029; 2926; 1685; 1615. MS (CI/NH_3): 579 $[M + NH_4]^+$.

2′,3′-*O*-Benzylidene-5′-*O*-(benzyloxy-benzyloxycarbonyl-methyl-phosphinoyl)-^{1}*N*-benzyl-^{2}*N*-dibenzylaminomethylene guanosine (Table 2, entry 18; 4 diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 and 8.53 (2s, 1H); 7.80, 7.78, 7.77 and 7.74 (4s, 1H); 7.60−7.15 (m, 30H); 6.22, 6.19 and 6.12 (3d, J = 2.6, 1H); 6.15, 6.14, 5.97 and 5.94 (4s, 1H); 5.55 (AB system, $\Delta\nu$ = 9.0, J_{AB} = 14.7, 2H); 5.38, 5.30 and 5.21 (3dd, J = 2.6, 6.4, 1H); 5.15−4.85 (m, 5H); 4.75−4.10 (m, 7H); 2.99, 2.98 and 2.95 (3d, J = 21.4, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.25 and 165.14; 158.05; 157.28; 147.52; 138.22; 136.75−135.01 (m); 129.86−126.50 (m); 120.47; 107.72 and 104.41; 89.14, 88.98 and 88.79; 85.09 and 84.93; 83.83, 83.71, and 82.64; 81.92 and 80.65; 68.51 and 67.52; 65.22; 54.69; 48.41; 45.50; 34.24 (d, J = 135.8). ^{31}P NMR ($CDCl_3$, 121 MHz) δ 21.72; 21.70; 21.67; 21.64. IR (neat) ν 3062; 3090; 2924; 1689; 1612; 1573.

5′-*O*-(Carboxymethyl-hydroxy-phosphinoyl) guanosine bistriethylammonium salt (Table 2, entry 18, product; yield: 94%). ^{1}H NMR (D_2O, 300 MHz) δ 8.00 (s, 1H); 5.74 (d, J = 6.0, 1H); 4.32 (dd, J = 3.0, 4.6, 1H); 4.15 (m, 1H); 3.99 (m, 2H); 2.96 (q, J = 9.2, 12H); 2.73 (d, J = 21.7, 2H); 1.02 (t, J = 9.2, 18H). ^{13}C NMR (D_2O, 75 MHz) δ 174.27; 158.99; 154.03; 151.88; 137.70; 116.22; 86.79; 84.13 (d, J = 7.8); 73.81; 70.58; 64.04 (d, J = 5.3); 46.78; 37.01 (d, J = 121.4); 8.34. ^{31}P NMR (D_2O, 0.5 M Et_3N, 121 MHz) δ 18.20. IR (neat) ν 3422 (b); 3135; 2975; 2938. HRMS: calcd for $C_{12}H_{15}N_5O_9P$ 404.0607, found 404.0633 $[M - H]^-$.

2′,3′-*O*-Benzylidene-5′-*O*-(*N*-benzyl-*P,P′,P′*-tribenzyl imidodiphosphate)-^{1}*N*-benzyl-^{2}*N*-dibenzylaminomethylene guanosine (Table 2, entry 19; 4 diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 and 8.83 (2s, 1H); 7.80, 7.77, 7.74, and 7.72 (4s, 1H); 7.60−7.15 (m, 40H); 6.16 and 6.15 (2d, J = 1.9, 0.5H), 6.08 and 6.07 (2d, J = 3.0, 0.5H); 6.09, 5.89, and 5.86 (3s, 1H); 5.55 (AB system, $\Delta\nu$ = 10.5, J_{AB} = 13.9, 2H); 5.17 (m, 1H); 5.05−4.31 (m, 14H); 4.25−3.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.07; 158.06; 157.20; 147.54; 138.25 and 137.84; 136.52, 135.67, 135.55, 135.41, 135.28, 135.03, 134.98, and 134.90; 129.86−126.49 (m); 120.50; 107.66, 104.36, and 104.31; 88.65 and 88.45; 84.87 and 84.72; 83.70, 83.42, and 82.24; 82.10, 81.98, and 80.61; 69.19; 69.07; 68.98 and 68.88; 66.13 and 66.04;

54.62; 50.81; 48.32; 45.46. ^{31}P NMR ($CDCl_3$, 121 MHz) δ 4.71 (AB system, $\Delta\nu = 65.3$, $J_{AB} = 20.4$); 4.67 (AB system, $\Delta\nu = 67.8$, $J_{AB} = 20.4$); 4.66 (AB system, $\Delta\nu = 54.4$, $J_{AB} = 20.7$); 4.56 (AB system, $\Delta\nu = 59.9$, $J_{AB} = 20.4$). IR (neat) ν 3031; 2926; 1691; 1612; 1573.

5′-*O*-Imidodiphosphate guanosine (Table 2, entry 19, product; yield: 91%). ^{1}H NMR (D_2O, 0.5 M Et_3N, 300 MHz) δ 8.00 (s, 1H); 5.83 (d, $J = 5.4$, 1H); 4.60 (dd, $J = 5.1, 5.4$, 1H); 4.53 (dd, $J = 4.6, 5.1$, 1H); 4.23 (m, 1H); 4.06 (m, 2H). ^{13}C NMR (D_2O, 0.5 M Et_3N, 75 MHz) δ 158.15; 154.38; 152.97; 137.35; 117.58; 87.66; 84.66; 74.15; 70.20; 64.06; 46.78; 10.64. ^{31}P NMR (D_2O, 0.5 M Et_3N, 121 MHz) δ 3.73 (d, $J = 3.6$, 1P); −0.09 (d, $J = 3.6$, 1P). HRMS: calcd for $C_{10}H_{15}N_6O_{10}P_2$ 441.0325, found 441.0329 $[M-H]^-$.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of all compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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