Addition of Purines to *N*-Boc Imines Generated in Situ in Water: Efficient Synthesis of Novel Acyclic Purine Azanucleosides

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Abstract: A mild, efficient and highly regioselective addition of purine derivatives to *N*-Boc imines generated in situ in water was developed for the first time. A wide range of novel acyclic purine azanucleosides were synthesized in moderate to high yields through this transformation. This methodology was also appropriate for some other N-heterocycles.

Key words: addition, nucleobases, sulfones, imines, nucleosides

Purines play important roles in regulation of many biological processes. Modification of purine nucleoside has provided plenty of biologically active compounds, some of which exhibit remarkable antiviral (ACV, ganciclovir etc.)[1] or anticancer (F-araA, araG, etc.)[2] properties. However, their clinical application can be sometimes limited by the toxic side effects or emergence of drug resistance.[3] Therefore, much attention is still focused on the synthesis of novel purine nucleoside analogues.

Acyclic azanucleosides represent a unique kind of unnatural nucleosides. Owing to their various potent pharmaceutical activities, synthesis and application of acyclic azanucleosides has attracted much attention.[4–6] Up to now, there are mainly two classes of acyclic azanucleosides. One class is the amino acid or peptide derivatives of pyrimidines.[4] The other is the aza-analogues of ganciclovir/penciclovir or acyclovir.[5] Many efficient processes have been developed to prepare these acyclic azanucleosides and their biological activities have been extensively studied. However, to the best of our knowledge, synthesis of acyclic purine azanucleosides via amidoalkylation of purines has not been systematically researched. Meanwhile, alkylation of purine analogues is rarely regiospecific and often provides the mixtures of N-9 and N-7 isomers.[7] Therefore selective methods for the amidoalkylation of purines at the N-9 position are highly desirable.

Most of the aliphatic enolizable aldehyde derived imines are unstable and even hard to isolate, thus resulting in a considerable limitation to the generality of their application. Gratifyingly, this problem can be circumvented by in situ generation of *N*-acylimines from bench stable α-amido sulfones[8] and this strategy has been carried out in a broad scope of reactions to construct numerous compounds.[9] Herein, we report a remarkably mild, efficient and highly N-9 regioselective addition of purine derivatives to *N*-Boc-α-amido sulfones, through which a wide variety of novel acyclic purine azanucleosides were synthesized in good yields for the first time.

First, we investigated the addition of 2,6-dichloropurine (**1a**) to *N*-Boc imine generated in situ from α-amido sulfone **2a** in several organic solvents at room temperature, employing 1.5 equivalents of Na_2CO_3 as the base. As shown in Table 1, when toluene, Et_2O or EtOH were employed as the solvents, almost no reaction was observed (Table 1, entries 1–3). When CH_2Cl_2 and DMF were used as the solvents, poor yields were obtained (Table 1, entries 4 and 5; 28% and 21%, respectively). When THF was used as the solvent, the yield increased to 88% (Table 1, entry 6), but many side products were produced in this reaction medium. Finally, we tried to perform the reaction in neat water. To our delight, the reaction proceeded smoothly to give product **3a** in excellent yield of 97% (Table 1, entry 7). It is significant because we have found such a 'green' process to provide novel valuable acyclic purine azanucleosides. Furthermore, it is noteworthy that 2,6-dichloropurine was absolutely regioselectively alkylated at N-9 position rather than at N-7 position in this transformation. The site of N-alkylation was determined by assigned HMBC spectra analysis (see the supporting information). Afterwards, we examined the effects of various bases and found that Na_2CO_3 was ideal for this reaction.

Having established the optimal reaction conditions, we applied this transformation to a number of purine derivatives with various substituents. As indicated in Table 2, 6-chloropurine derivatives **1a**, **1c** and **1d** underwent the reaction to give the desired products in excellent yields irrespective of the substituents on C2 in purines (Table 2, entries 1, 3 and 4). 6-Unsubstituted purine derivatives **1b** and **1e** resulted in slightly inferior yields of the corresponding products (Table 2, entries 2 and 5). Meanwhile, reaction of 2-chloro-6-methoxypurine (**1f**) only afforded the product in poor yield after 30 hours (Table 2, entry 6). It seems that electron-withdrawing substituent on C6 in purine derivatives accelerates the reaction. On the other hand, electron-donating substituent on C6 in purine derivatives hinders the reaction. Whereas the substituents on C2 position in purine derivatives have little influence on

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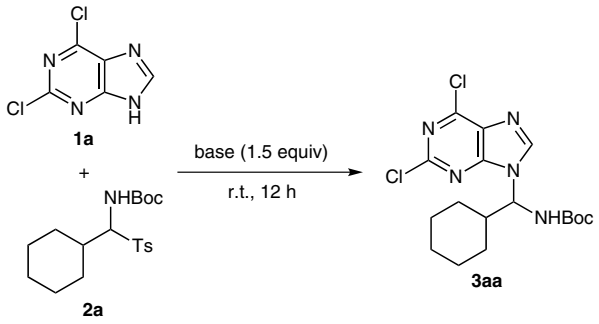
the result of the reaction. 6-Chloro-7-deazapurine (**1g**) exhibited lower activity to provide the product in moderate yield after a prolonged reaction time (Table 2, entry 7).

Table 1 Screening of Solvents and Bases in the Addition of 2,6-Dichloropurine (**1a**) to *N*-Boc Imine Generated from α-Amido Sulfone **2a**

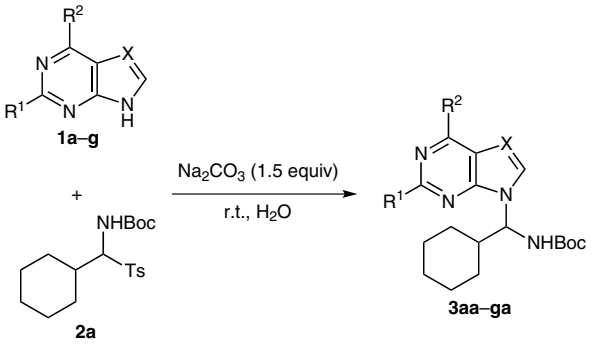


Entry[a]	Solvent	Base	Yield (%)[b]
1	toluene	Na_2CO_3	<5
2	Et_2O	Na_2CO_3	<5
3	EtOH	Na_2CO_3	<5
4	CH_2Cl_2	Na_2CO_3	28
5	DMF	Na_2CO_3	21
6	THF	Na_2CO_3	88
7	H_2O	Na_2CO_3	97
8	H_2O	Li_2CO_3	62
9	H_2O	K_2CO_3	60
10	H_2O	Cs_2CO_3	51
11	H_2O	NaOH	61
12	H_2O	KOH	47
13	H_2O	NaOAc	33
14	H_2O	KF	45

[a] Unless indicated otherwise, the reaction was conducted with 2,6-dichloropurine (**1a**; 0.24 mmol), α-amido sulfone **2a** (0.20 mmol) and base (0.30 mmol) in corresponding solvent (2.0 mL) at r.t.
[b] Isolated yield.

Furthermore, the generality of α-amido sulfones was also investigated. Various α-amido sulfones were subjected to the reaction with 2,6-dichloropurine. The results are summarized in Table 3. As can be seen in Table 3, the yields were highly dependent on the size of the R group in α-amido sulfones. When R was ethyl, propyl, *i*-propyl, *i*-butyl or cyclohexyl, the reaction gave the corresponding products with excellent yields (Table 3, entries 1 and 4–7). When R was H or methyl, the reactions generated some unidentified side products. Therefore, the yields of the desired products decreased obviously (Table 3, entries 2 and 3). When R was a larger substituent such as hexyl,

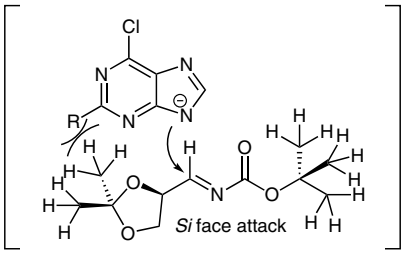
Table 2 Addition of Various Purine Derivatives to *N*-Boc Imine Generated from α-Amido Sulfone **2a**[10,11]



Entry[a]	X	R^1	R^2	**3**	Time (h)	Yield (%)[b]
1	N	Cl	Cl	**3aa**	12	97
2	N	H	H	**3ba**	18	82
3	N	H	Cl	**3ca**	12	94
4	N	NH_2	Cl	**3da**	12	95
5	N	Cl	H	**3ea**	18	78
6	N	Cl	OMe	**3fa**	30	51
7	C	H	Cl	**3ga**	24	62

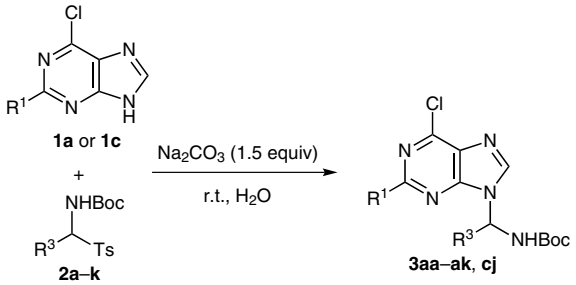
[a] Unless indicated otherwise, the reaction was conducted with purine derivatives **1** (0.24 mmol), α-amido sulfone **2a** (0.20 mmol) and Na_2CO_3 (0.30 mmol) in H_2O (2.0 mL) at r.t.
[b] Isolated yield.

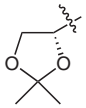
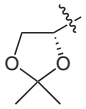
benzyl or 2,2-dimethyl-1,3-dioxolanyl, the reaction could not complete so as to give the product in moderate yields (Table 3, entries 8–10). Reaction of 2,6-dichloropurine and chiral α-amido sulfone **2j** afforded the product with moderate yield and low diastereoselectivity. Meanwhile, when less hindered 6-chloropurine (**1c**) reacted with **2j**, good yield as well as high diastereoselectivity were obtained (Table 3, entry 11). It is noteworthy that the yield and diastereoselectivity were influenced significantly by the size of the substituent at C-2 on purine ring. This can be explained by a proposed reaction model as outlined in Scheme 1. Purine attacks (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde derived imine from *Si* face which is sterically more accessible. Meanwhile, the substituent at C-2 on purine ring has steric influence on the methyl group of imine. Small substituent such as H at C-2 exhibits little steric hindrance and provides the desired product with high yield and diastereoselectivity (Table 3, entry 10). In contrast, larger group such as chloride makes it too difficult for the purine to reach the imine and thus gives the poor result (Table 3, entry 11). Owing to the instability of *N*-(α-amido)nucleobases, we could not deprotect the acetonide functional group in compounds **3aj** and **3cj**. Finally, the reaction of aryl α-amido sulfone was also investigated. However, the reaction proceeded sluggishly to provide the product in poor yield (Table 3, entry 12).



Scheme 1 Model for diastereoselective addition of purines to (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde derived imine

Table 3 Addition of Purine Derivative **1a** or **1c** to *N*-Boc Imines Generated from α-Amido Sulfones **2a**–**2k**



Entry[a]	R^1 (**1**)	R^3 (**2**)	**3**	Time (h)	Yield (%)[b]
1	Cl (**1a**)	*c*-hexyl (**2a**)	**3aa**	12	97
2	Cl (**1a**)	H (**2b**)	**3ab**	18	72
3	Cl (**1a**)	Me (**2c**)	**3ac**	18	74
4	Cl (**1a**)	Et (**2d**)	**3ad**	12	87
5	Cl (**1a**)	Pr (**2e**)	**3ae**	12	91
6	Cl (**1a**)	*i*-Pr (**2f**)	**3af**	12	95
7	Cl (**1a**)	*i*-Bu (**2g**)	**3ag**	12	90
8	Cl (**1a**)	*n*-hexyl (**2h**)	**3ah**	24	71
9	Cl (**1a**)	Bn (**2i**)	**3ai**	18	81
10	Cl (**1a**)	 (**2j**)	**3aj**	24	68 (dr =3.8:1)
11	H (**1c**)	 (**2j**)	**3cj**	24	85 (dr =14.6:1)
12	Cl (**1a**)	Ph (**2k**)	**3ak**	30	40

[a] Unless indicated otherwise, the reaction was conducted with purine derivative (0.24 mmol), α-amido sulfone **2a** (0.2 mmol) and Na_2CO_3 (0.3 mmol) in H_2O (2.0 mL) at r.t.
[b] Isolated yield.

Intrigued by our above described results, some N-heterocycles such as imidazole, 1*H*-benzo[*d*]imidazole and 1*H*-benzo[*d*][1,2,3]triazole were chosen as the nucleophiles to probe whether the addition could be easily accessed. The results are shown in Figure 1. As expected, these reactions also proceeded smoothly to give the corresponding products in high yields.

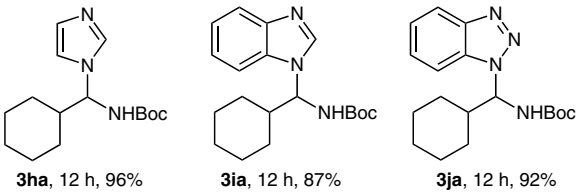


Figure 1 Products of addition of selected N-heterocycles to *N*-Boc imine generated in situ from α-amido sulfone **2a**

In summary, we have developed a remarkably mild, efficient and highly regioselective addition of purine derivatives to *N*-Boc imines generated in situ in water for the first time. The reactions proceeded in aqueous medium at room temperature without any catalyst. A wide range of novel acyclic purine azanucleosides were synthesized in moderate to high yields through this transformation. In addition, this methodology was also appropriate for some N-heterocycles. Further investigation of synthetic and biological utility of these products is ongoing in our laboratory.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **General Procedure for Addition of Purines 1 with α-Amido Sulfones 2**:
N-Boc α-amido sulfone (0.2 mmol, 1.0 equiv), Na_2CO_3 (0.3 mmol, 1.5 equiv), and H_2O (2 mL) were put in a 10-mL glass vial equipped with a small magnetic stirring bar. To the solution was added purine derivative (0.24 mmol, 1.2 equiv). After stirring for the stipulated time at r.t., the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 25 mL, for **3aa**–**3ak**, **3ca** and **3cj**) or $CHCl_3$ (3 × 25 mL, for **3ba**, **3da**, **3ea**, **3fa** and **3ga**). The organic layers were combined, dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel flash chromatography (EtOAc–hexanes, 1:5) to give the pure product.

(11) ***tert*-Butyl Cyclohexyl (2,6-Dichloro-9*H*-purin-9-yl)methylcarbamate (3aa)**:
yield: 97%; white solid; mp 182.7–183.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 8.83 (br, 1 H), 5.63–5.69 (m, 1 H), 2.33 (br, 1 H), 1.65–2.02 (m, 4 H), 1.37 (s, 9 H), 0.83–1.36 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 152.6, 152.4, 151.8, 145.7, 131.3, 81.3, 69.4, 40.1, 29.4, 29.1, 28.1, 25.7, 25.2, 25.1. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{23}Cl_2N_5NaO_2$: 422.1121; found: 422.1138.

