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Copper-catalyzed N-alkoxyalkylation of nucleobases involving direct functionalization of sp^3 C–H bonds adjacent to oxygen atoms

Rui Huang, Chunsong Xie *, Lin Huang, Jinhua Liu *

College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, PR China

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ABSTRACT

N-Alkoxyalkylation of nucleobases was realized by the copper-catalyzed peroxide-promoted coupling of nucleobases with readily available saturated ethers. Both purines and pyrimidines could be *N*-alkoxyalkylated through this method in moderate to good yields. 2D-NMR revealed that *N*9-alkoxyalkylation preferentially occurred when purines were used in this reaction.

1. Introduction

The N-alkoxyalkylation of nucleobases has received much attention mainly because that *N*-alkoxyalkylated nucleobases are core structures in many biologically active analogues of natural nucleosides.[1] Traditionally, this could be realized by the N-alkoxyalkylation of natural and modified nucleobases taking advantage of *α*-halogenated ethers,[2] *α*-acetoxyl ethers,[3] and alkyl vinyl ethers[4] as alkylating reagents. Although had proven to be efficient, these alkylating partners often needed multistep pre-synthesis, and strong bases, stoichiometric Lewis acids or Bronsted acids were always required in these processes. Recently, Guo et al. had reported a novel method, which directly utilized alkyl ethers to alkylate purines under thermal and irradiation conditions.[5] However, this method still suffered from that the nucleobases were limited to purines, and also that the need of stoichiometric (diacetoxyiodo) benzene as reaction promoter, which would generate iodobenzene byproduct during the reaction. So the development of novel and direct access to *N*-alkoxyalkylated nucleobases, especially from readily available materials and under mild conditions, is still of much significance.

During the past few years, transition metal catalyzed direct functionalization of sp^3 C–H bonds adjacent to heteroatoms had been much studied.[6] Among these, iron and copper-catalyzed direct *α*-C–H activation of saturated ethers had been well investigated.[7] Based on these progresses, we envisioned that the N-alkoxyalkylation of nucleobases could be realized via the coinage-metals catalyzed direct coupling of saturated ethers and nucleobases. In this paper, we will report our findings concerning on this new strategy.

2. Results and discussion

We started our investigation by choosing 2,6-dichloropurine **1a** and THF (tetrahydrofuran) **2a** as model substrates. The subjection of **1a** to react with **2a** in the presence of 10 mol % $CuCl_2$ and 5 equiv TBHP (*tert*-butyl hydroperoxide) at 70 °C for 24 h gave a 38% yield of aimed product **3aa** (Table 1, entry 1). 2D-NMR experiments indicated that the alkoxyalkylation happened regioselectively, affording the *N*9-alkoxyalkylated 2,6-dichloropurine as the major product (see SD for details).

The addition of bidentate nitrogen ligands proved to be advantageous. A higher yield (65%) was obtained when using 2,2′-bipyridyl as the ligand (Table 1, entry 2). Other bidentate nitrogen ligands, such as 1,10-phenanthroline, N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine, N^1,N^2-dimethylethane-1,2-diamine, and ethane-1,2-diamine all gave worse results (Table 1, entries 3–6). $CuCl_2$ had proven to be the best catalyst, and lower yields were given when using other copper complexes, such as $CuBr_2$, $Cu(OAc)_2$, CuCl, CuBr, and CuI (Table 1, entries 7–11). Increasing of the reaction concentration proved to be beneficial, and a 74% yield of **3aa** was provided when conducting the reaction in 2 mL THF (Table 1, entry 12). However, further reducing the volume of the solvent was found to be detrimental with lower yields were produced (Table 1, entries 13–15). TBHP had proven to be the most efficient oxidant, and the reaction was totally halted when using

* Corresponding authors. Tel.: +86 571 28866142; fax: +86 571 28865630; e-mail addresses: chunsongxie@hznu.edu.cn (C. Xie), ljh@hznu.edu.cn (J. Liu).

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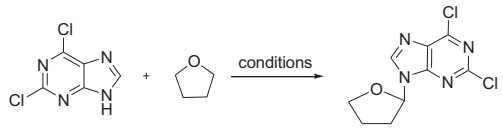
Table 1
The optimization Work[a]



1a **2a** **3aa**

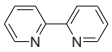
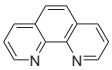
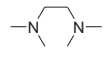
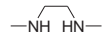
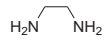
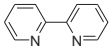
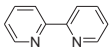
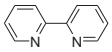
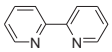
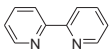
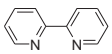
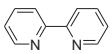
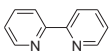
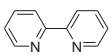
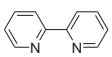
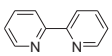
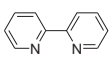
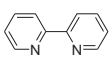
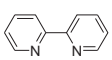
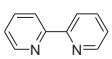
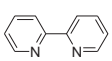
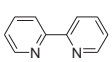
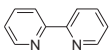
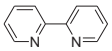
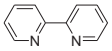
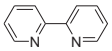
Entry	Catalyst	Ligand	Oxidant	T °C	t (h)	V_{2a} (mL)	Yield %[b]
1	$CuCl_2$	No	TBHP	70	24	6	38
2	$CuCl_2$		TBHP	70	24	6	65
3	$CuCl_2$		TBHP	70	24	6	47
4	$CuCl_2$		TBHP	70	24	6	35
5	$CuCl_2$		TBHP	70	24	6	35
6	$CuCl_2$		TBHP	70	24	6	41
7	$CuBr_2$		TBHP	70	24	6	43
8	$Cu(OAc)_2$		TBHP	70	24	6	59
9	CuCl		TBHP	70	24	6	40
10	CuBr		TBHP	70	24	6	38
11	CuI		TBHP	70	24	6	45
12	**$CuCl_2$**		**TBHP**	**70**	**24**	**2**	**74**
13	$CuCl_2$		TBHP	70	24	1	39
14	$CuCl_2$		TBHP	70	24	0.5	26
15	$CuCl_2$		TBHP	70	24	0.1	20
16	$CuCl_2$		$(t\text{-BuO})_2$	70	24	2	NR
17	$CuCl_2$		$(PhCO_2)_2$	70	24	2	50
18	$CuCl_2$		$PhCO_3t\text{-Bu}$	70	24	2	53
19	$CuCl_2$		H_2O_2	70	24	2	20
20	$CuCl_2$		O_2	70	24	2	NR
21	$CuCl_2$		TBHP	50	24	2	50
22	$CuCl_2$		TBHP	RT	24	2	30
23	$CuCl_2$		TBHP	70	12	2	52
24	$CuCl_2$		TBHP	70	6	2	38

Table 1 (*continued*)

Entry	Catalyst	Ligand	Oxidant	T °C	t (h)	V_{2a} (mL)	Yield %[b]
25	$CuCl_2$		TBHP	70	3	2	29
26	$CuCl_2$		TBHP	70	48	2	74
27[c]	$CuCl_2$		TBHP	70	24	2	73

[a] Reaction conditions: **1a** (1 mmol), catalyst (0.1 mmol), ligand (0.1 mmol), oxidant (5 mmol).
[b] Isolated yield.
[c] 20 mol % $CuCl_2$ and bipyridyl were used.

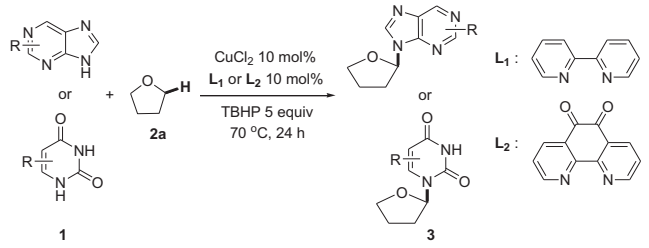
2-(*tert*-butylperoxy)-2-methylpropane or O_2 as the promoter (Table 1, entries 16–20). Moreover, it was found that 70 °C was necessary for the reaction, since lowering the reaction temperature delivered lower yields (Table 1, entries 21 and 22). Furthermore, 24 h had proven to be necessary reaction time, and the yields gradually fell down when shortening the reaction time (Table 1, entries 23–25). However, further elongation of the reaction time seemed to be of no use either, and a comparable yield was afforded when the reaction was conducted for 48 h (Table 1, entry 26). A similar result was also obtained in the case of increasing the loading of the reaction catalyst. When performing the reaction under the circumstance that the catalyst loading was 20%, a comparable yield (73%) was afforded (Table 1, entry 27).

With the optimal condition in hand, we next studied the scope of the reaction and the results were summarized in Table 2. Various substituted purines **1b**–**e** were subjected to the reaction and gave the expected nucleoside analogues **3ba**–**ea** in moderate yields (Table 2, entries 2–5). A variety of groups, such as Cl and Boc were well tolerated, allowing the further conversion of these nucleoside analogues. Inspired by the elegant findings on the ligand-promoted copper-catalyzed aerobic C–H functionalization reported by Stahl and co-workers,[8] we found that in the course of our experiment using **1e** as the nucleobase, switching the ligand to more electron-poor bidentate nitrogen ligand 1,10-phenanthroline-5,6-dione $\mathbf{L_2}$ was somewhat beneficial with a slightly higher yield (55%) being delivered. Similar results were also obtained in the case of pyrimidine derivatives **1f** and **1g** (Table 2, entries 6 and 7). When using Boc protected thymine **1f** as the substrate, a moderate yield (50%) was produced under the standard condition. After increasing the catalyst loading to 20%, just a slightly higher yield (54%) was provided. When changing the ligand to $\mathbf{L_2}$, a 58% yield could be obtained even though the catalyst loading was 10%. Analogously, in the case of cytosine derivative **1g**, a slightly higher yield (40%) was produced when using $\mathbf{L_2}$ than $\mathbf{L_1}$. Although the exact reason for this ligand effect remained unclear at present, we inferred that the lowering of the electron density on ligand nitrogens would lead to an increase of the oxidation capacity of the catalytically active metal center toward the peroxides.

In addition, we also examined the reaction of free natural nucleobases, such as cytosine **1h** with **2a**. Just a trace amount of desired product **3ha** could be detected. Instead, the 4-amino alkoxyalkylated product **3ha′** was produced in a 45% yield (Scheme 1). Still, this transformation is of significance due to that the *N*4-alkoxyalkyalted pyrimidines have been found to have interesting biological activities.[9]

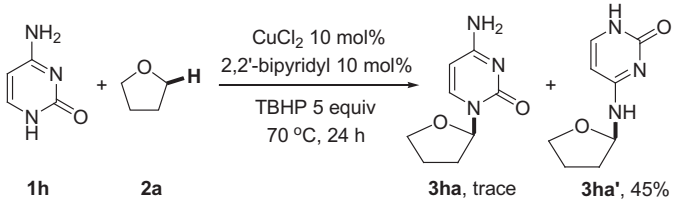
After surveying various nucleobases, we turned our attention to test various ethers. Pleasingly, various saturated ethers had proven to be reliable reactants as illustrated in Table 3. When using 1-butoxybutane **2b**, tetrahydro-*2H*-pyran **2c**, and dioxane **2d** to react with 2,6-dichloropurine **1a**, a variety of *N*-alkoxyalkylated products **3ab**–**ad** were produced in moderate yields (Table 3,

Table 2
The coupling of THF with Nucleobases[a]



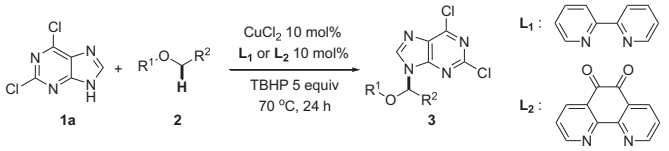
Entry	Nucleobase	Product	Yield %[b]
1	1a	3aa	74
2	1b	3ba	65
3	1c	3ca	51
4	1d	3da	55
5	1e	3ea	50 55[d]
6	1f	3fa	50 54[c] 58[d]
7	1g	3ga	35 40[d]

[a] Reaction conditions: **1** (1 mmol), **2a** (2 mL), $CuCl_2$ (0.1 mmol), $\mathbf{L_1}$ (0.1 mmol), TBHP (5 mmol).
[b] Isolated yields.
[c] 20 mol % $CuCl_2$ and bipyridyl were used.
[d] $\mathbf{L_2}$ instead of $\mathbf{L_1}$ was used.



Scheme 1. The N-alkoxyalkylation of free cytosine.

Table 3
The N-alkoxyalkylation of 2,6-dichloropurine[a]

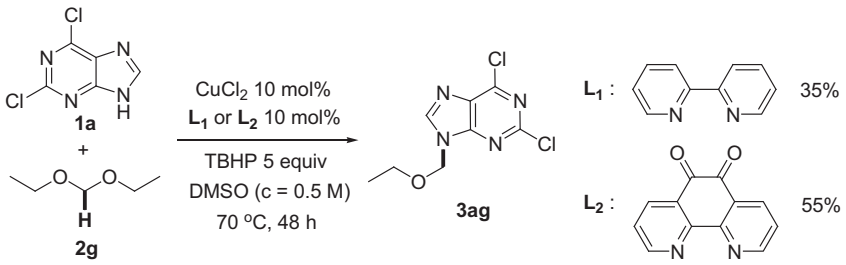


Entry	Ether	Product	Yield %[b]
1	2b	3ab	35 43[c] 52[d]
2	2c	3ac	58
3	2d	3ad	35 43[c] 51[d]
4	2e	3ae	76
5	2f	3af	70[e]

[a] Reaction conditions: **1a** (1 mmol), **2** (2 mL), $CuCl_2$ (0.1 mmol), $\mathbf{L_1}$ (0.1 mmol), TBHP (5 mmol).
[b] Isolated yields.
[c] 20 mol % $CuCl_2$ and bipyridyl were used.
[d] $\mathbf{L_2}$ instead of $\mathbf{L_1}$ was used.
[e] The diastereoselectivity was nearly 1:1.

entries 1–3). Once again, for the substrates that led to low yields (**2b** and **2d**), we tested the reaction with 20% catalyst loading or changing the ligand to $\mathbf{L_2}$, and found that the yields increased gradually. When using the unsymmetrical ether like isochroman **2e** as the alkylating component, a good yield (76%) of regioselective C–H functionalization product **3ae** was produced with the C–N bond forming at the more acidic methylene position (Table 3, entry 4). Interestingly, unsymmetrical dialkyl ether, such as tetrahydro-2-methylfuran **2f** was also proven to be a reliable reaction partner with **1a**, producing the regioselective nucleosidation product **3af** in a 70% yield and 1:1 diastereoselectivity (Table 3, entry 5). This is of much significance due to that this kind of 5′-substituted products represent structurally ubiquitous scaffolds in many useful nucleoside analogues.[10]

Besides these, we also conducted the reaction between 2,6-dichloropurin **1a** and diethoxymethane **2g**, and surprisingly found that a *N*-ethoxymethylated nucleobase **3ag** was produced in a 35% yield (Scheme 2). After changing the reaction ligand to $\mathbf{L_2}$, a higher yield (55%) was obtained. Although did not get our anticipated product, we still believed that this reaction was noteworthy, since it offered a good pathway for the synthesis of nucleoside analogues bearing an unsymmetrical dialkyl ether moiety.[11] Moreover, the fact



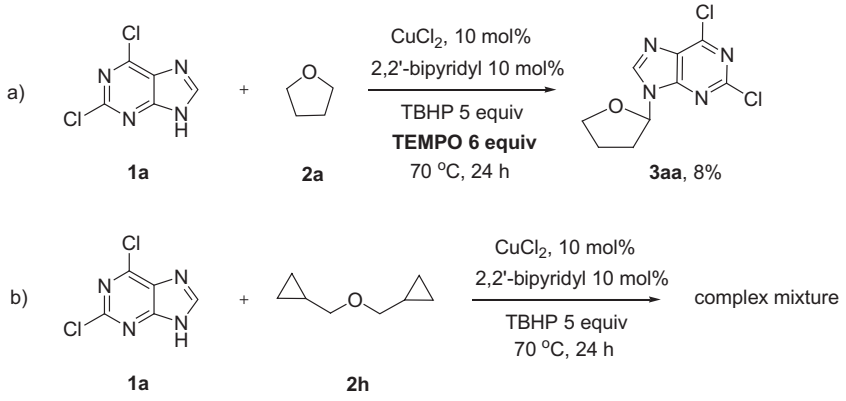
Scheme 2. The N-ethoxymethylation of **1a**.

that this reaction could proceed in DMSO indicated that the use of ether as reaction solvent was not a necessity in the reaction.[12]

3. Mechanistic consideration

The exact reaction pathway of this reaction seems to be complicated and still remains unclear at this moment. To gain some clues for the reaction mechanism, we conducted the radical inhibition experiment by employing TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) as the radical scavenger, and found that the reaction was partially suppressed affording the *N*-alkoxyalkyl 2,6-dichloropurine **3aa** in a 8% yield (Scheme 3a). This implied that the carbon radical might

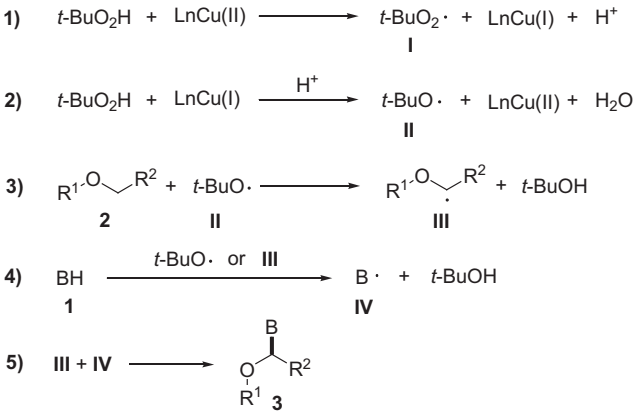
Based on these results, a plausible mechanism was proposed as depicted in Scheme 4. As an initial of the cascade events, the single electron transfer (SET) of Cu(II) complex with TBHP generated active Cu(I) species. Then the SET between Cu(I) and TBHP produced the *tert*-butoxyl radical **II** and regenerated the Cu(II) species.[15] Subsequently, hydrogen atom abstraction of ethers **2** by **II** would happen, generating the alkyl radical **III**.[16] Next, nucleobases **1** would be converted into radical specie **IV** by reacting with **II** or **III**. Finally, the coupling of **III** and **IV** would take place, giving the *N*-alkoxyalkylated nucleobases **3** as the reaction product.[5]



Scheme 3. The mechanism experiment.

be involved in the reaction, and a completely copper-mediated inner-sphere mechanism seemed to be unlikely for this reaction. In addition, we had also performed a radical clock experiment by using ((cyclopropylmethoxy)methyl)cyclopropane **2h** as the substrate, but got a quite complex reaction system, which was unable to give anything valuable for the reaction mechanism (Scheme 3b).

However, there were still some results should be noted in the experiment. First, the *N*9-alkoxyalkylated 2,6-dichloropurine **3aa** was site selectively formed. This was quite different with the classic glycosidation that was believed to proceed through ionic mechanisms, since most of them produced both *N*7 and *N*9-alkoxyalkylated products.[13] In contrary, this selectivity was quite consistent with the reported DIB/I_2 promoted N-alkylation of purines, which was assumed to operate through an intermolecular hydrogen abstraction procedure.[5] Second, the unactivated pyrimidines **1f** and **1g** were proven to be competent substrates in the reaction, delivering the regioselectively *N*-alkoxyalkylated products without any O-alkoxyalkylation happened. Due to the low nucleophilicity and low acidity of these cyclic amide substrates, the direct nucleophilic attack or the formation of nucleophilic amido anions via deprotonation seemed unlikely.[14]



Scheme 4. Proposed mechanism.

4. Conclusion

In summary, we have disclosed a novel access to *N*-alkoxyalkylated nucleobases by direct coupling of saturated ethers with

nucleobases. This copper-catalyzed sp^3 C–H functionalization involved transformation shows general tolerance to a variety of functionalities, furnishing various purine, and pyrimidine nucleoside analogues in moderate to good yields. In the whole of this reaction, no wasteful byproduct except H_2O and *t*-BuOH is generated, making this method quite attractive for its economical and environmental significance. Further application of this nucleoside analogue synthesis in a variety of pharmaceuticals and biomedical reagents is currently ongoing in our laboratory.

5. Experimental

5.1. General

All the reactions were carried out under air atmosphere in oven-dried flasks. THF was distilled from Na using benzophenone as indicator. Protected nucleobases **1c**, **1d**, **1f**, and **1g** were synthesized according to reference methods.[17–19] 1,10-Phenanthroline-5,6-dione **L2** was prepared by the reference method.[20] Other materials were purchased from commercial sources, and used without additional purification. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz. Mass spectroscopy data were collected on a HRMS-ESI or HRMS-EI instrument.

5.2. General procedure of the alkylation reaction

Into an oven-dried flask, nucleobase (1.0 mmol), $CuCl_2$ (0.1 mmol), ligand (0.1 mmol), and TBHP (5–6 M in decane, 5.0 mmol) were added in ether (2 mL) at room temperature. The mixture was allowed to react at 70 °C for 24 h. After the completion of the reaction, the mixture was filtered through a pad of Celite, and the filtrate was concentrated until the solvent was completely removed. The residue was then separated on a silica gel column, and gave the final product.

*5.2.1. 2,6-Dichloro-9-(tetrahydrofuran-2-yl)-9H-purine (**3aa**).*[5] Yellow powder, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.23 (s, 1H), 6.32 (t, J=4.2 Hz, 1H), 4.21 (dd, J=14.4, 7.8 Hz, 1H), 4.10 (dd, J=16.0, 7.6 Hz, 1H), 2.56 (m, 2H), 2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 152.1, 151.6, 144.1, 131.4, 86.7, 70.1, 32.7, 24.2. HRMS (EI) calcd for $C_9H_8Cl_2N_4O$: $[M]^+$ 258.0075; found, 258.0079.

*5.2.2. 6-Chloro-9-(tetrahydrofuran-2-yl)-9H-purine (**3ba**).*[5] Yellow powder, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.75 (s, 1H), 8.24 (s, 1H), 6.36 (dd, J=5.6, 2.6 Hz, 1H), 4.32 (dd, J=10.8, 6.6 Hz, 1H), 4.11 (dd, J=10.8, 7.8 Hz, 1H), 2.59 (m, 2H), 2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 151.0, 150.9, 143.4, 132.4, 86.6, 69.9, 32.5, 24.2. HRMS (ESI) calcd for $C_9H_9ClN_4O$: $[M+H]^+$ 225.0538; found, 225.0546.

*5.2.3. 6-(Di(tert-butyloxycarbonyl)amino)-9-(tetrahydrofuran-2-yl)-9H-purine (**3ca**).*[5] Yellow powder, 51% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.75 (s, 1H), 6.41 (dd, J=6.4, 3.6 Hz, 1H), 4.16 (dd, J=14.8, 7.6 Hz, 1H), 3.94 (dd, J=14.4, 7.0 Hz, 1H), 2.44–2.55 (m, 2H), 2.23 (m, 1H), 2.06 (m, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.9, 150.5, 150.2, 142.9, 129.5, 86.2, 83.7, 69.8, 32.4, 27.8, 24.3. HRMS (ESI) calcd for $C_{19}H_{27}N_5O_5$: $[M+H]^+$ 406.2085; found, 406.2094.

*5.2.4. 4-(Di(tert-butyloxycarbonyl)amino)-6-chloro-9-(tetrahydrofuran-2-yl)-9H-purine (**3da**).* White powder, 55% yield. Mp 215–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.24 (s, 1H), 6.30 (dd, J=6.0, 2.4 Hz, 1H), 4.29 (dd, J=14.4, 6.4 Hz, 1H), 4.08 (dd, J=13.0, 7.4 Hz, 1H), 2.47–2.60 (m, 2H), 2.12–2.19 (m, 2H), 1.45 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 151.6, 151.0, 150.6, 144.4, 130.7, 86.8, 83.6, 70.0, 32.5, 27.9, 24.2. HRMS (EI) calcd for $C_{19}H_{26}ClN_5O_5$: $[M]^+$ 439.1622; found, 439.1635.

*5.2.5. 4-Chloro-7-(tetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidine (**3ea**).* Brown oil, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.64 (s, 1H), 7.37 (d, J=4.4 Hz, 1H), 6.62 (d, J=4.0 Hz, 1H), 6.53 (dd, J=6.8, 3.6 Hz, 1H), 4.21–4.27 (m, 1H), 4.01–4.07 (m, 1H), 2.46–2.55 (m, 1H), 2.25–2.42 (m, 1H), 2.12–2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 150.6, 150.5, 126.2, 118.2, 99.9, 85.3, 69.3, 32.5, 24.7. HRMS (ESI) calcd for $C_{10}H_{10}ClN_3O$: $[M+H]^+$ 224.0580; found, 224.0592.

*5.2.6. tert-Butyl 2,3-dihydro-3-(tetrahydrofuran-2-yl)-5-methyl-2,6-dioxopyrimidine-1(6H)-carboxylate (**3fa**).* White powder, 58% yield. Mp 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.58 (m, 1H), 6.64 (dd, J=8.0, 4.4 Hz, 1H), 4.33 (dd, J=15.2, 6.8 Hz, 1H), 3.93 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 2.22 (m, 1H), 1.99 (m, 1H), 1.93 (d, J=1.2 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 148.6, 147.8, 133.5, 111.6, 86.5, 85.1, 70.6, 28.8, 27.8, 26.5, 13.2. HRMS (EI) calcd for $C_{14}H_{20}N_2O_5$: $[M]^+$ 296.1372; found, 296.1372.

*5.2.7. 4-(Di(tert-butyloxycarbonyl)amino)-1-(tetrahydrofuran-2-yl)-2-oxopyrimidine (**3ga**).* Pale yellow powder, 40% yield. Mp 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.73 (d, J=7.6 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 6.00 (dd, J=6.0, 2.4 Hz, 1H), 4.23 (m, 1H), 4.03 (m, 1H), 2.47 (m, 1H), 2.14 (m, 1H), 2.02 (m, 1H), 1.79 (m, 1H), 1.56 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 154.4, 149.7, 142.6, 95.6, 88.9, 84.8, 70.5, 33.2, 27.7, 23.4. HRMS (ESI) calcd for $C_{18}H_{27}N_3O_6$: $[M+H]^+$ 382.1973; found, 382.1980.

*5.2.8. 4-(Tetrahydrofuran-2-ylamino)pyrimidin-2(1H)-one (**3ha′**).* White powder, 45% yield. Mp 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47 (d, J=8.0 Hz, 1H), 6.02 (dd, J=6.4, 3.6 Hz, 1H), 5.70 (d, J=6.8 Hz, 1H), 4.21 (m, 1H), 3.99 (m, 1H), 2.43 (m, 1H), 2.12 (m, 1H), 2.01 (m, 1H), 1.83 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3, 141.9, 94.8, 90.3, 80.9, 66.8, 30.8, 24.2. HRMS (EI) calcd for $C_8H_{11}N_3O_2$: $[M]^+$ 181.0851; found, 181.0855.

*5.2.9. 9-(1-Butoxybutyl)-2,6-dichloro-9H-purine (**3ab**).*[5] Pale yellow powder, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.29 (s, 1H), 5.79 (dd, J=7.2, 6.0 Hz, 1H), 3.49 (m, 1H), 3.30 (m, 1H), 2.13 (m, 1H), 1.92 (m, 1H), 1.47–1.57 (m, 4H), 1.29–1.38 (m, 4H), 0.97 (t, J=7.6 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 153.1, 151.8, 143.6, 130.7, 85.6, 69.7, 38.4, 31.2, 19.1, 18.1, 13.7, 13.5. HRMS (EI) calcd for $C_{13}H_{18}Cl_2N_4O$: $[M]^+$ 316.0858; found, 316.0856.

*5.2.10. 2,6-Dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**3ac**).*[5] Pale yellow powder, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.34 (s, 1H), 5.77 (dd, J=10.8, 2.4 Hz, 1H), 4.19 (m, 1H), 3.78 (m, 1H), 2.18 (m, 1H), 2.09 (m, 1H), 1.98 (m, 1H), 1.72–1.86 (m, 2H), 1.67–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 152.2, 151.7, 143.7, 130.8, 82.5, 68.9, 32.0, 24.7, 22.5. HRMS (EI) calcd for $C_{10}H_{10}Cl_2N_4O$: $[M]^+$ 272.0232; found, 272.0236.

*5.2.11. 2,6-Dichloro-9-(1,4-dioxan-2-yl)-9H-purine (**3ad**).* Yellow powder, 51% yield. Mp 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.55 (s, 1H), 6.02 (dd, J=5.6, 2.8 Hz, 1H), 4.21 (dd, J=12.4, 3.2 Hz, 1H), 4.05 (dd, J=11.2, 5.2 Hz, 1H), 3.87–3.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 152.8, 152.1, 144.4, 130.6, 77.7, 68.3, 66.3, 64.2. HRMS (ESI) calcd for $C_9H_8Cl_2N_4O_2$: $[M+H]^+$ 275.0097; found, 275.0101.

*5.2.12. 2,6-Dichloro-9-(isochroman-1-yl)-9H-purine (**3ae**).* Yellow powder, 76% yield. Mp 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.83 (s, 1H), 7.40 (t, J=6.8 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.27 (t, J=7.6 Hz, 1H), 7.22 (s, 1H), 6.97 (d, J=8.0 Hz, 1H), 4.10 (m, 1H), 3.94 (m, 1H), 3.12 (m, 1H), 2.98 (dt, J=16.8, 4.0 Hz, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 153.5, 153.5, 152.0, 144.8, 135.1, 130.9, 129.7, 129.5, 129.3, 127.4, 126.5, 79.2, 61.3, 27.6. HRMS (EI) calcd for $C_{14}H_{10}Cl_2N_4O$: $[M]^+$ 320.0232; Found, 320.0234.

*5.2.13. 2,6-Dichloro-9-(tetrahydro-5-methylfuran-2-yl)-9H-purine (**3af**).* Yellow oil, 70% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.80 (s, 1H), 6.36 (dd, J=6.8, 4.4 Hz, 1H), 6.25 (dd, J=6.8, 3.2 Hz, 1H), 4.52 (m, 1H), 4.20 (m, 1H), 2.44–2.62 (m, 4H), 2.30 (m, 1H), 2.14 (m, 1H), 1.87 (m, 1H), 1.65 (m, 1H), 1.31 (d, J=6.0 Hz, 3H), 1.22 (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.2, 153.0, 152.3, 152.2, 151.4, 150.2, 147.1, 146.8, 131.6, 131.5, 86.0, 85.6, 78.4, 77.3, 32.5, 31.9, 31.6, 21.1, 20.9. HRMS (EI) calcd for $C_{10}H_{10}Cl_2N_4O$: $[M]^+$ 272.0232; found, 272.0229.

5.3. Representative procedure of the N-alkoxyalkylation reaction using DMSO as solvent

Into an oven-dried flask, 2,6-dichloropurine **1a** (1.0 mmol), diethoxymethane **2h** (4 mmol), $CuCl_2$ (0.1 mmol), ligand (0.1 mmol), and TBHP (5–6 M in decane, 5.0 mmol) were added in DMSO (2 mL) at room temperature. The mixture was allowed to react at 70 °C for 48 h. After the completion of the reaction, the mixture was filtered through a pad of Celite. The filtrate was partitioned by EtOAc (10 mL) and brine (10 mL). After separation of the aqueous layer, the organic layer was washed twice by brine (10 mL). Then the organic layer was dried with Na_2SO_4, and further concentrated until the solvent was completely removed. The residue was finally separated on a silica gel column and afforded the final product.

*5.3.1. 2,6-Dichloro-9-(ethoxymethyl)-9H-purine (**3ag**).* White powder, 55% yield. Mp 125–127 °C. ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.27 (s, 1H), 5.64 (s, 2H), 3.59 (q, J=7.2 Hz, 2H), 1.20 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 153.4, 152.0, 145.8, 130.6, 73.3, 66.0, 14.8. HRMS (ESI) calcd for $C_8H_8Cl_2N_4O$: $[M+H]^+$ 247.0148; found, 247.0159.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.020.

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12. One of the reviewers suggested that this reaction was an oxonium process and advised us optimize the common Lewis acids for the reaction. However, we conducted this reaction under various Lewis acid conditions, such as $SnCl_4$, TMSOTf, $BF_3{\cdot}Et_2O$, $FeCl_3$ and ZnI_2, finding no products was provided with the nucleobases were destroyed or fully recovered. A possible reason for these results was that the unsilylated purine could form complexes with Lewis acids, and thereof hampered the reaction. Detailed results could be found in SD (Table S1).
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