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# Intermolecular Hydrogen Abstraction Reaction between Nitrogen Radicals in Purine Rings and Alkyl Ethers: A Highly Selective Method for the Synthesis of N-9 Alkylated Purine Nucleoside Derivatives

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**Abstract:** A highly selective method for the synthesis of N-9 alkylated purine nucleoside derivatives *via* an intermolecular hydrogen abstraction reaction between nitrogen radicals in purine rings and alkyl ethers was developed. Novel purine nucleoside derivatives were obtained with good to high yields in the presence of (diacetoxyiodo)benzene (DIB) and iodine in one-step reaction.

**Keywords:** alkyl ethers; intermolecular hydrogen abstraction reaction; nitrogen radicals; purine nucleoside derivatives

Purine nucleoside derivatives have provided a productive area of chemical and biological research.[1] For example, some purine nucleoside analogues are used as antiviral (AZT, d4T, 3TC, etc.)[1a] and antitumor agents (AraC, FU, etc.).[1b] Furthermore, N-9 substituted purine nucleoside analogues[2] are a very important class of heterocyclic compounds in biology, fulfilling functional roles as nucleic acids, coenzymes, and constituents in metabolic processes, energy storage, and cell signaling.[3]

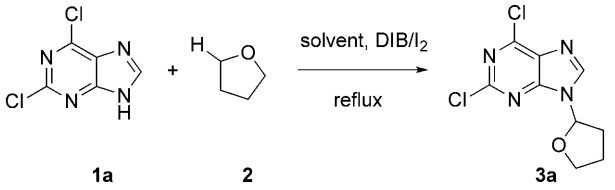
Alkylation is one of the commonly used methods for the synthesis of purine nucleoside derivatives. The most frequently used alkylating agents of purine bases are halogenated compounds,[4] mesylate,[5] and tosylate.[6] But up to now, there is no report on the synthesis of purine nucleoside analogues *via* reaction of the $sp^3$ N–H bond of the purine ring and the $sp^3$ C–H of an alkyl ether. Alkyl ethers are cheaper and more readily available than their corresponding alkyl halides, which makes this procedure much more attractive. At the same time, alkylation of purines is rarely regiospecific, and mixtures of N-9 and N-7 isomers are usually obtained.[7] So selective ways for the alkylation of purine analogues at the N-9 position are highly desirable.

The intramolecular hydrogen abstraction reaction promoted by alkoxy radicals has attracted considerable interest among organic synthetic chemists since it offers the remarkable possibility of carrying out remote free radical functionalizations of unactivated carbons.[8] To the best of our knowledge, there are only few reports on intramolecular hydrogen abstraction reactions by aminyl radicals.[9] However, there is no report on an intermolecular hydrogen abstraction reaction. According to our previous work on the synthesis of purine nucleoside derivatives,[10] we envisioned that the intermolecular hydrogen abstraction reaction between the $sp^3$ N–H bond of the purine ring and the $sp^3$ C–H bond of an alkyl ether could be applied to form purine nucleoside derivatives in a more effective way. Herein, we describe the direct N-9–H alkylation of purines with alkyl ether *via* an intermolecular hydrogen abstraction reaction to give a series of highly selective N-9 substituted purine nucleoside derivatives.

Initially, we investigated the intermolecular hydrogen abstraction reactions between 2,6-dichloropurine and tetrahydrofuran (THF). The solvent effects were examined and the results are shown in Table 1 (entries 1–8). No reaction was observed in DMF, DMSO,

**Table 1.** The alkylation of 2,6-dichloropurine with THF.[a]




1a 2 3a

| Entry | Solvent | DIB/$I_2$ | Yield [%][b] |
|---|---|---|---|
| 1 | DMF[c] | 2/0 | 0 |
| 2 | DMSO[c] | 2/0 | 0 |
| 3 | DCM | 2/0 | 0 |
| 4 | EtOAc | 2/0 | 0 |
| 5 | $C_6H_{12}$ | 2/0 | 10 |
| 6 | $CH_3CN$ | 2/0 | 20 |
| 7 | DCE | 2/0 | 41 |
| 8 | THF | 2/0 | 45 |
| 9 | THF | 2/trace | 94 |
| 10 | DCE | 2/trace | 90 |
| 11 | THF[d] | 2/trace | 50 |
| 12 | THF[e] | 2/trace | 0 |
| 13 | THF | 0/trace | 0 |
| 14 | THF | 1/trace | 35 |
| 15 | THF | 1.5/trace | 68 |

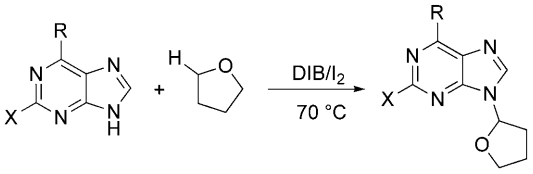
[a] *Reaction conditions:* 2,6-dichloropurine **1a** (1 mmol), THF **2** (2 mmol), solvent (2 mL), reaction time, 3 h.
[b] Isolated yield based on 2,6-dichloropurine.
[c] The reaction temperature was 70 °C.
[d] The reaction temperature was 50 °C.
[e] Room temperature.

DCM, and EtOAc (entries 1–4). The reaction gave a low yield in cyclohexane presumably due to the poor solubility of the starting material (entry 5). A higher yield was obtained in $CH_3CN$, but the result was still unsatisfactory (entry 6). THF, which is relatively inexpensive and easy to handle, was thus chosen as the solvent for further optimization, although 1,2-dichloroethane (DCE) could give the same result (entries 7 and 8). When a trace of iodine was present in the reaction mixture, a 94% yield was obtained (entry 9), and DCE also gave a similarly surprising result (entry 10). The yield decreased with the reduction temperature, and when the reaction was conducted at room temperature, product **3a** was not observed (entries 9, 11 and 12). And it was obvious that a sufficient amount of DIB was necessary for this reaction (entries 13–15).

Under the optimized reaction conditions, various purines were employed as substrates, and representative results are listed in Table 2. Various 6-halopurine derivatives could react with THF smoothly in good to high yields (entries 1–5). Purine derivatives with nitrogen-containing substituent at the C-6 position could also afford the desired products in good yields (entries 6–8). When the H at C-2 was replaced by a halogen atom (Cl or F), the yield increased slightly (entries 1, 3, 4 and 6). 2-Chloro-6-dimethylaminopurine (**1h**), which was difficult to dissolve in THF, was conducted in DCE to increase the solubility (entry 8).

As shown in Table 3, several other alkyl ethers were subjected to the alkylation reactions of 2,6-dichloropurine **1a** under the optimized reaction condi-

**Table 2.** Direct alkylation of various purines with THF.[a]




1a – 1j 2 3a – 3j

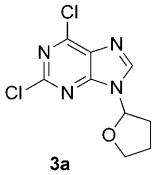
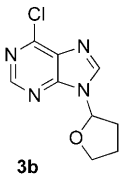
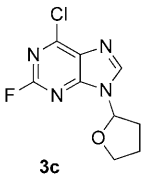
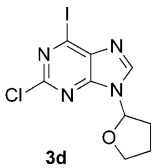
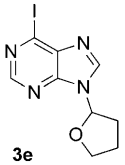
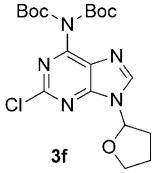
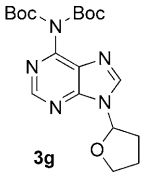
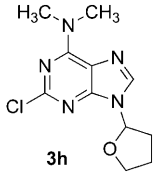
| Entry | Product | Yield [%][b] |
|---|---|---|
| 1 |  3a | 94 |
| 2 |  3b | 84 |
| 3 |  3c | 91 |
| 4 |  3d | 89 |
| 5 |  3e | 85 |
| 6 |  3f | 84 |
| 7 |  3g | 80 |

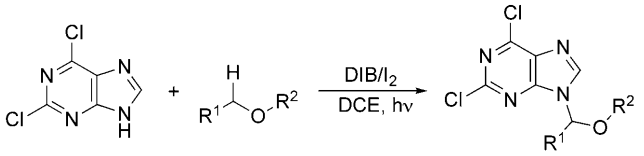
  

**Table 2.** (Continued)

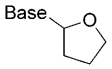
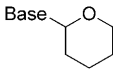
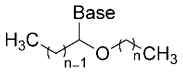
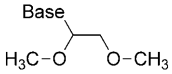
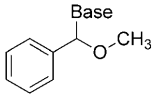
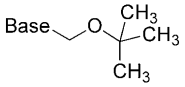
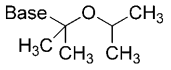
| Entry | Product | Yield [%][b] |
|---|---|---|
| 8 |  **3h** | 75[c] |

[a] *Reaction conditions:* **1** (1 mmol), DIB (2 mmol), $I_2$ (trace), THF (2 mL), 70 °C, 3 h.
[b] Isolated yield based on **1**.
[c] DCE as solvent.

**Table 3.** Direct alkylation of 2,6-dichloropurine with various alkyl ethers.[a]

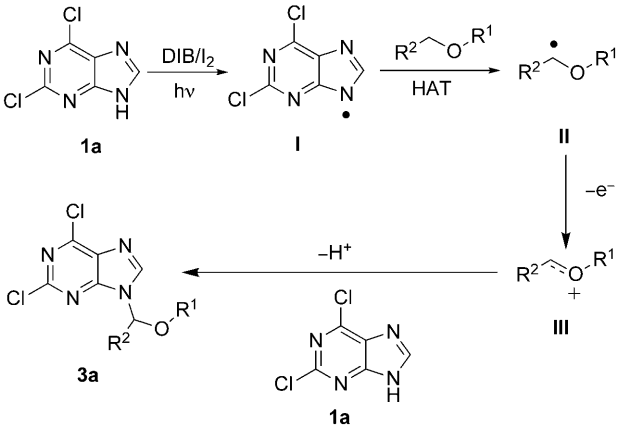


**1a** **4a – 4h** **5a – 5h**

| Entry | Product | | Yield [%][b] |
|---|---|---|---|
| 1 |  | **3a** | 94 |
| 2 |  | **5a** | 85 |
| 3 |  | n = 1 **5b**<br>n = 2 **5c**<br>n = 3 **5d** | 96<br>82<br>60 |
| 4 |  | **5e** | 80 |
| 5 |  | **5f** | 72 |
| 6 |  | **5g** | 43[c] |
| 7 |  | **5h** | 0 |

[a] *Reaction conditions:* 2,6-dichloropurine (1 mmol), alkyl ether (1 mL), DCE (1 mL), DIB (2 mmol), $I_2$ (trace), under nitrogen and irradiation with a 200-W tungsten filament lamp at 70 °C for 4.5 h.
[b] Isolated yield based on 2,6-dichloropurine.
[c] $I_2$ (1 equiv.) was used.

tions shown in Table 1 (entry 10), and to get better results, the reaction was irradiated with a 200-W tungsten filament lamp. Cyclic ether compounds, either five- or six-membered ring, could react well (entries 1 and 2). The straight chain ethers (**4b**–**4d**) afforded the corresponding products **5b**, **5c** and **5d** in moderate to high yields (entry 3), and the yield decreased obviously with the increase of the carbon number of the chain ethers. Methyl ethers gave low yields (entries 4 and 5). It should be noted that the reaction only occurred at the carbon atom of the methylene unit instead of the methyl group on dimethoxyethane and benzyl methyl ether to afford the products **5e** and **5f**. Methyl *tert*-butyl ether (MTBE) could not give the desired product **5g** until 1 equiv. $I_2$ was added, but the yield was low (entry 6). Because of steric hindrance, we did not obtain the desired products from diisopropyl ether (entry 7).



**Scheme 1.** Mechanism of the alkylation reaction between 2,6-dichloropurine and THF.

A possible mechanism[11] of the direct alkylation reaction is depicted in Scheme 1. The N-radical **I** was generated by homolytic fragmentation of a hypothetical iodoamide formed *in situ* by the reaction of amide with DIB and iodine under irradiation with a 200-W tungsten filament lamp at 70 °C. The C-radical **II**, which was initially formed by hydrogen atom transfer (HAT) to the electrophilic N-radical **I**, could be subsequently oxidized by the excess reagent present in the reaction medium to an oxocarbenium ion **III**, which was then trapped by the nucleophilic purine N-9 position.

In summary, we have developed a novel and efficient method for the preparation of purine nucleoside analogues from purine bases and a series of ethers *via* intermolecular hydrogen abstraction reaction between $sp^3$ C–H and $sp^3$ N–H bonds. And the alkylation exclusively occurred on the N-9 position of purine analogues. Compared to previously known approaches, the simplicity of this procedure and the generally satisfactory regioselectivities and yields make this method particularly attractive. The presence of a diverse range of substituents and functional groups in the purines also opens an opportunity to acquire many other derivatives from these initial purines. Further developments might find other applications of

this method in the production of fine chemicals for the pharmaceutical industry.

## Experimental Section

### Typical Experimental Procedure for Intermolecular Hydrogen Abstraction Reaction between N-Radicals in Purine Rings and Alkyl Ether

Purine **1a** (1 mmol) was put in a 10-mL glass vial equipped with a small magnetic stirring bar. To this were added 2 mL THF, trace iodine and 2 equiv. DIB. The mixture was stirred in an oil heating bath at 70 °C for 3 h. Then the vial was cooled to room temperature. After evaporation of the solvent, the crude product was purified by column chromatography over silica gel using EtOAc/petroleum ether (v/v = 1:4) as the eluent, to give **3a**.

**2,6-Dichloro-9-(tetrahydrofuran-2-yl)-9*H*-purine (3a):** White powder, mp 97–99 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 8.20 (s, 1H), 6.30–6.27 (m, 1H), 4.31–4.26 (m, 1H), 4.10–4.04 (m, 1H), 2.55–2.50 (m, 2H), 2.18–2.11 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 152.7, 152.0, 151.6, 143.9, 131.4, 86.7, 70.1, 32.6, 24.0; HR-MS: *m/z* = 259.0149, calcd. for $C_9H_9Cl_2N_4O$ [M + H$^+$]: 259.0153.

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