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Radical Route for the Alkylation of Purine Nucleosides at C6 via Minisci Reaction

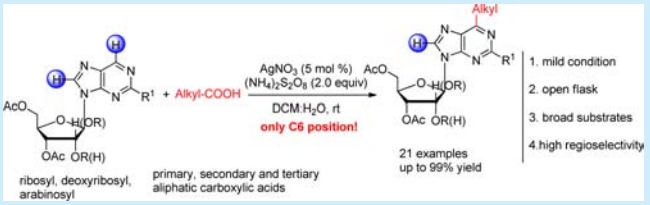
Ran Xia,[†,‡] Ming-Sheng Xie,[‡] Hong-Ying Niu,[‡] Gui-Rong Qu,*[,†,‡] and Hai-Ming Guo*[,†,‡]

[†]School of Environment, Henan Normal University, Xinxiang, Henan Province 453007, China

[‡]Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan Province453007, P. R. China

Supporting Information

ABSTRACT: A highly regioselective Minisci reaction with the decarboxylative alkylation of purine nucleosides under mild conditions was developed. With 5 mol % $AgNO_3$ as a catalyst and $(NH_4)_2S_2O_8$ as an oxidant, a series of purine nucleosides including ribosyl, deoxyribosyl, arabinosyl purine nucleosides worked well with primary, secondary, and tertiary aliphatic carboxylic acids.



Purine bases and nucleosides, as the basic structural units in RNA and DNA, have found broad applications in biological and pharmaceutical chemistry. In particular, C6-alkylated purine analogues possess unique biological effects such as cytostatic,[1] antiviral, and antimicrobial activities[2] or receptor modulation.[3] For example, 6-methylpurine and 6-ethylpurine ribonucleoside (Figure 1, **A** and **B**) have highly

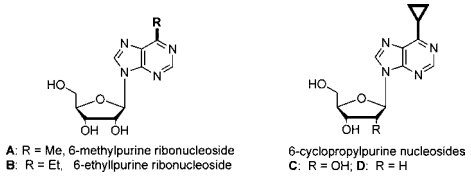
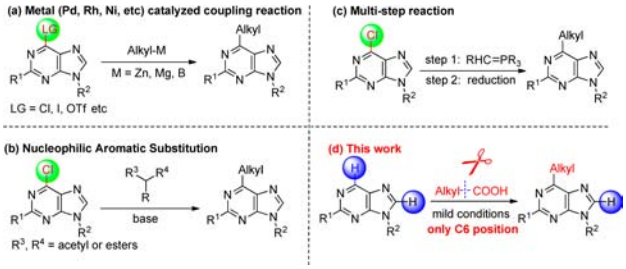


Figure 1. Selected examples of C6-alkylated purine analogues with biological activities.

cytotoxic and antitumor activities,[4] and 6-cyclopropylpurine ribonucleosides (Figure 1, **C** and **D**) exert interesting cytostatic activities.[4] Furthermore, modification of purine derivatives at C6 can adjust the number of hydrogen bonds in the purine moiety[5] and thus improve the biological activities of the purine compounds.[6−8] Therefore, searching for an efficient alkylation method of purine derivatives at C6 is of great interest.

Conventional methods of introducing the alkyl group into C6 of purines include the following: (1) classical metal-catalyzed coupling reactions such as Negishi,[9] Kumada,[10] and Suzuki reactions,[11] which require alkylzinc reagents, Grinard reagents, and alkylboronic reagents, respectively (Scheme 1a); (2) the nucleophilic aromatic substitution (S_NAr) reaction of 6-halopurines with 3-alkylacetylacetone in the presence of base or microwave irradiation (Scheme 1b);[12−14] (3) the displacement of a suitable leaving group on the purines by alkylidenephosphorane (Wittig reagent) and subsequent hydrolysis to give C6-alkylated products (Scheme 1c).[15] Although numerous

Scheme 1. Synthetic Routes to 6-Alkylpurines



efforts have been devoted to the synthesis of 6-alkylpurines and remarkable progress has been made, there are still some problems unsolved. For instance, the current methods suffer from either expensive reagents/catalysts/ligands, harsh reaction conditions, limited substrate scope, low regioselectivities, or multiple-step procedures. Thus, developing an efficient route to obtain C6-alkylated purines from cheap and easily available alkylating reagents under mild condition is challenging and fascinating.

On the other hand, the radical process, as a powerful method for alkylation reaction, always proceeds under mild reaction conditions.[16] The only example of radical alkylation for C6-H purines was acomplished with iodoalkane promoted by $FeSO_4$ and *t*-BuOOH under acidic conditions.[17] It is well-known that the Minisci reaction using carboxylic acid as alkyl precursor has the advantages of low cost, effectiveness, and ease of use in organic synthesis;[18] however, its application on the modification of purine is still unexplored. In the context of projects in the modification of purines,[19,20] herein we report the silver-catalyzed radical decarboxylative alkylation of C6-H purine

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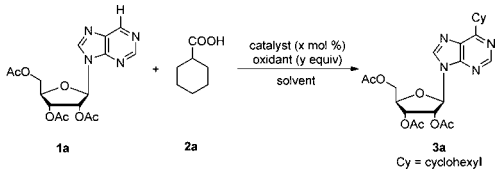
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (x)	oxidant (y)	solvent	temp (°C)	time (h)	yield[b] (%)
1	none	$K_2S_2O_8$ (1.5)	DCM	rt	2	0
2	$FeSO_4$ (10)	$K_2S_2O_8$ (1.5)	DCM	rt	2	0
3	$CuSO_4$ (10)	$K_2S_2O_8$ (1.5)	DCM	rt	2	0
4	CF_3CO_2Ag (10)	$K_2S_2O_8$ (1.5)	DCM	rt	2	25
5	CF_3CO_2Ag (10)	$K_2S_2O_8$ (1.5)	DCM:H_2O (1:1)	rt	2	39
6	CF_3CO_2Ag (10)	$K_2S_2O_8$ (1.5)	DCM:H_2O (1:1)	rt	6	68
7	$AgNO_3$ (10)	$K_2S_2O_8$ (1.5)	DCM:H_2O (1:1)	rt	6	72
8	$AgNO_3$ (10)	$(NH_4)_2S_2O_8$ (2)	DCM:H_2O (1:1)	rt	6	93
9	$AgNO_3$ (5)	$(NH_4)_2S_2O_8$ (2)	DCM:H_2O (1:1)	rt	6	93
10	$AgNO_3$ (2)	$(NH_4)_2S_2O_8$ (2)	DCM:H_2O (1:1)	rt	6	63
11	$AgNO_3$ (5)	none	DCM:H_2O (1:1)	rt	6	0
12	$AgNO_3$ (5)	$(NH_4)_2S_2O_8$ (2)	DCM:H_2O (1:1)	50	6	47

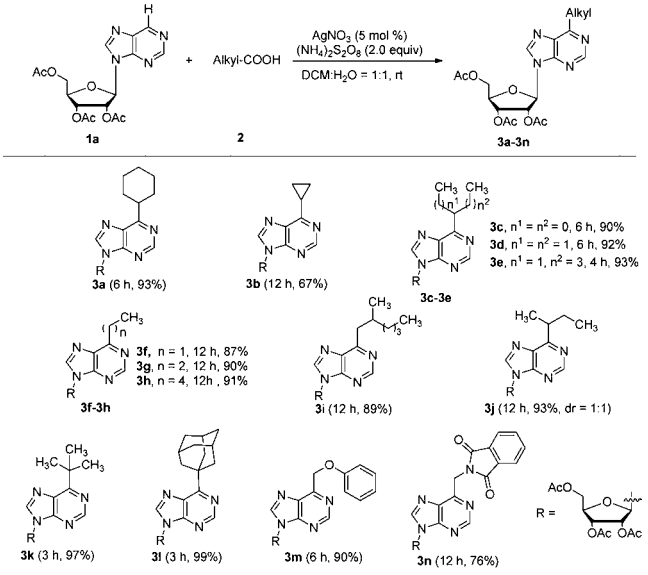
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (2.0 equiv). [b]Isolated yields.

nucleosides with alkyl carboxylic acids under mild conditions (Scheme 1d).

Initially, we began our study by using 6-*H*-2′,3′,5′-tri-*O*-acetylpurine riboside (**1a**) and cyclohexylcarboxylic acid (**2a**) as model substrates to optimize the reaction conditions (Table 1). With $K_2S_2O_8$ as an oxidant, several catalysts including $FeSO_4$, $CuSO_4$, and CF_3CO_2Ag were tested in DCM at rt for 2 h, and only CF_3CO_2Ag could afford the desired decarboxylative alkylation product **3a** with 25% yield (Table 1, entries 1−4). It is worth mentioning that the alkylation exclusively happened at the C6 position of riboside, which was proved by HSQC, HMBC, and COSY spectra (see the Supporting Information for details). That is to say, the reaction showed high regioselectivity at C6 of riboside. Considering that the poor solubility of $K_2S_2O_8$ in DCM was unfavorable for the reaction, water was added as a cosolvent, and the yield of **3a** was improved to 39% (Table 1, entries 4 and 5). To our delight, the yield of **3a** could reach to 68% when the reaction time was prolonged to 6 h (Table 1, entry 6). Further experiments showed that $AgNO_3$ was better than CF_3CO_2Ag, and $(NH_4)_2S_2O_8$ showed higher efficiency than $K_2S_2O_8$ (Table 1, entries 6−8). When the catalyst loading decreased from 10 to 5 mol %, the yield remained unchanged (Table 1, entries 8 and 9), while further reduction of catalyst loading to 2 mol % led to lower yield (Table 1, entry 10). The oxidant was proved to be crucial for the reaction because no product was obtained in the absence of $(NH_4)_2S_2O_8$ even when excess amounts of $AgNO_3$ were used (Table 1, entry 11). Meanwhile, the yield of **3a** was decreased greatly when the reaction temperature was increased, and room temperature was the better choice (Table 1, entries 9 vs 12).

Under the optimized reaction conditions, a series of carboxylic acids were subjected to the reaction (Scheme 2). To our delight, all primary and secondary acyclic alkyl carboxylic acids gave the corresponding 6-alkylpurine nucleosides in satisfactory yields, and the length of the carbon chain had little impact on the yields (**3a**−**j**). The carboxylic acids with small rings were less reactive than larger ones (**3a** vs **3b**). Surprisingly, when 3-methylbutyric acid **2j** was tested, the product **3j** was obtained with the migration of methyl group form β position to α position (**3j**). For the tertiary alkyl

Scheme 2. Silver-Catalyzed Decarboxylative Alkylation of Various Alkyl Carboxylic Acids[a]



[a]Reaction conditions: **1a** (0.25 mmol), carboxylic acid **2** (2.0 equiv), $AgNO_3$ (5 mol %), $(NH_4)_2S_2O_8$ (2.0 equiv), DCM (1.0 mL), H_2O (1.0 mL), and isolated yields based on **1a**.

carboxylic acids, the catalytic system was highly efficient, affording the desired products with 97−99% yields (**3k**,**l**). Furthermore, the carboxylic acid bearing O or N atom, such as phenoxyacetic acid and phthalimidoacetic acid also furnished the reaction smoothly (**3m**,**n**). In all cases, the reaction exhibited high level of regioselectivities and exclusively occurred on the C6 position of purine nucleosides.

Subsequently, a variety of purine nucleosides were then probed (Scheme 3). Arabinoribosyl purine nucleosides (**1b**,**c**), deoxyribosyl purine nucleoside (**1d**), and ribosyl purine nucleosides (**1e**−**g**) all proceeded well to give the corresponding alkylation products with good to high yields (**4b**−**g**, 76−90%). In addition, benzyl-substituted purine (**1h**) also

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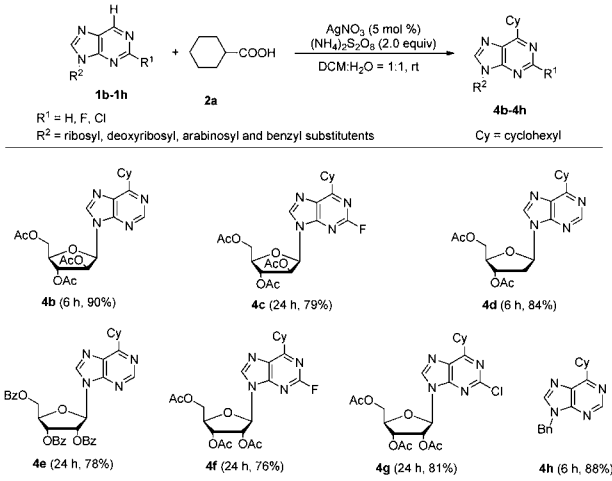
Scheme 3. Scope of Purines for the Silver-Catalyzed Decarboxylative Alkylation[a]

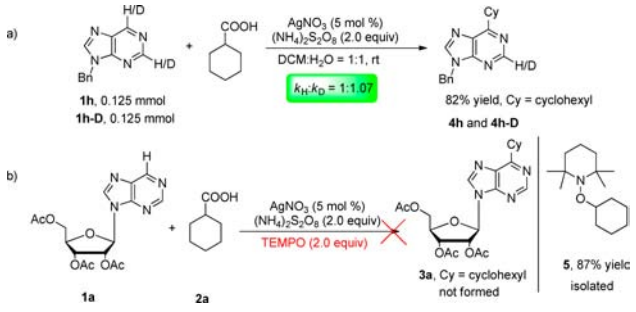


[a]Reaction conditions: **1** (0.25 mmol), **2a** (2.0 equiv), $AgNO_3$ (5 mol %), $(NH_4)_2S_2O_8$ (2.0 equiv), DCM (1.0 mL), H_2O (1.0 mL), room temperature, and isolated yields based on **1**.

proceeded smoothly to afford **4h** with high yield (**4h**, 88% yield). These results showed that this catalytic system could tolerate various substituents at *N*9 in purine derivatives.

Next, some experiments were designed to study the mechanism of the Minisci reaction. First, the kinetic isotope effect (KIE) experiment was performed, and the KIE was determined to be 1.07, which indicated that the C6−H bond breaking event was not the rate-determining step (Scheme 4a).

Scheme 4. (a) Kinetic Isotope Effect (KIE) Experiment; (b) Radical-Trapping Experiments



Next, in the presence of radical scavenger TEMPO, the Minisci reaction was completely inhibited and the radical-trapping byproduct **5** was isolated in 87% yield (Scheme 4b). When other radical precursors such as cyclohexane or cyclopropylboronic acid were tested, the corresponding alkylation products were obtained with good yields, showing good generality of the radical reactions for the functionation of C6-H in purine derivatives (see the Supporting Information for details).

Subsequently, the ^1H NMR studies between $AgNO_3$ and **1a** were carried out, and the downfield shifts of the resonances for the C6-H and C8-H protons of **1a** were observed. Meanwhile, the peak of C6-H became broad and the peak of C8-H was still sharp. However, no change of the C2 proton was found. Thus, we proposed that the C6-H was activated by the Ag(I) cation through the coordination with *N*7 of the purine derivative (Figure 2). On the basis of the above experiments, a proposed

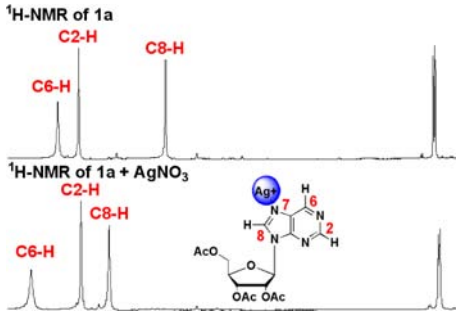
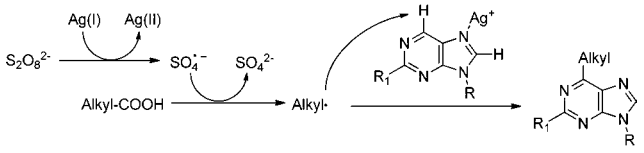


Figure 2. Interaction between **1a** and $AgNO_3$.

mechanism is shown in Scheme 5. First, Ag(I) cation was oxidized to Ag(II) cation by peroxydisulfate ion, and sulfate

Scheme 5. Proposed Mechanism for the Minisci Reaction



radical anion was generated. Subsequently, the aliphatic carboxylic acid was oxidized to alkyl radical by sulfate radical anion. Finally, the alkyl radical reacted with C6-H rather than C8-H to afford the corresponding product through radical substitution reaction.[21c]

In summary, we have developed a highly regioselective Minisci reaction for the synthesis of C6-alkylated purine nucleosides using carboxylic acids as alkylation reagents. A series of purine nucleosides including ribosyl, deoxyribosyl, arabinosyl, and nonsugar purine nucleosides worked well. Moreover, this catalytic system could tolerate a number of readily available primary, secondary, and tertiary aliphatic carboxylic acids. The mechanism studies showed that the alkylation presumably involved the radical process. Further synthetic applications of this reaction to biologically interesting compounds are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, optimization of the reaction conditions, proposed mechanism, copies of all spectra, and full characterization for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: quguir@sina.com.
*E-mail: guohm518@hotmail.com.

Notes

The authors declare no competing financial interest.

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