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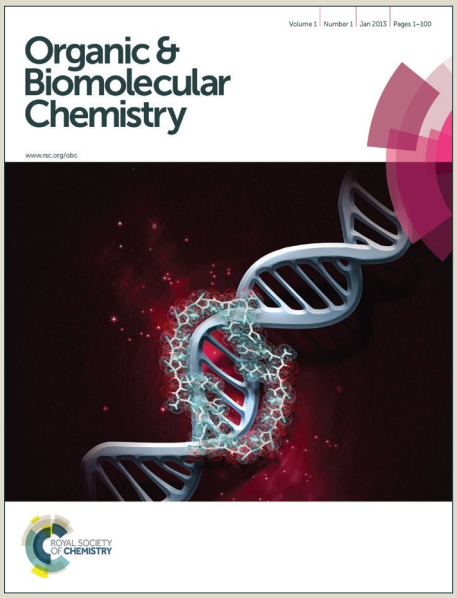

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Synthesis of Cycloalkyl Substituted Purine Nucleosides via a Metal-Free Radical Route

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Abstract: An efficient route to synthesize cycloalkyl substituted purine nucleosides was developed. This metal-free C-H activation was accomplished by *t*BuOO*t*Bu initiated radical reaction. By adjusting the amount of *t*BuOO*t*Bu and reaction time, the selective synthesis of C6-monocycloalkyl or C6,C8-dicycloalkyl substituted purine nucleosides could be realized. Furthermore, uracil and related nucleosides were also suitable substrates, giving the C5-cyclohexyl substituted uracil derivatives in good yields with excellent regioselectivities.

Introduction

In recent years, the humanity infectious diseases, which are caused by viruses, increased progressively because the reproduction and propagation of viruses guest in human beings.[1] Therefore, the modification of purine and pyrimidine analogues have displayed extremely important due to their outstanding antiviral activities.[2] Subsequently, great endeavors have been devoted to search various purine or pyrimidine analogues to study their biological activities.[3] In particular, cycloalkyl substituted purine and pyrimidine derivatives possess unique biological effects, such as antifolate (Figure 1, **A**),[4a] adenosine receptor antagonists (Figure 1, **B**),[4b] cytostatic (Figure 1, **C** and **D**),[4c] against herpes simplex (Figure 1, **E**),[4d] and receptor modulation.[4e-4g] In view of the significant biological activities exhibited by cycloalkyl substituted purine and pyrimidine derivatives, searching for a useful method to construct cycloalkyl substituted purine and pyrimidine analogues is highly desirable.

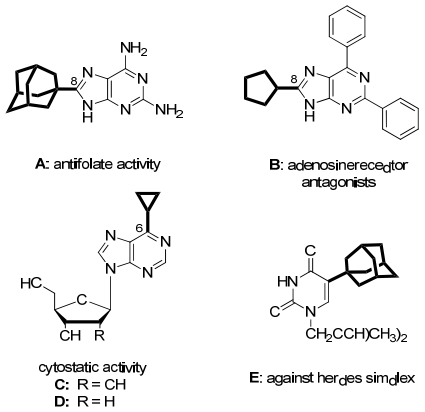
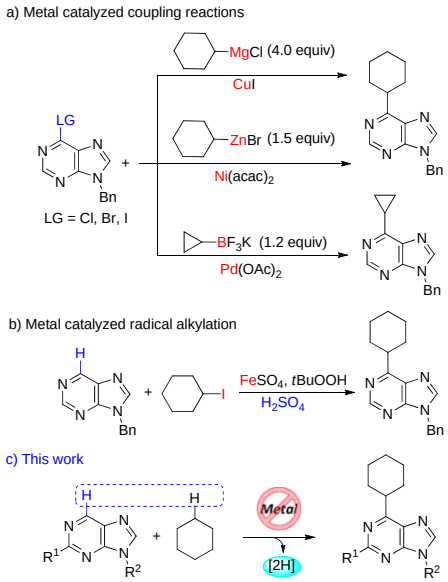


Figure 1. Selected examples of the cycloalkyl substituted purine and pyrimidine analogues with biological activities



Scheme 1. Synthetic routes to cycloalkyl substituted purine derivatives.

Considering the importance of cycloalkyl substituted purine analogues, numerous routes have been developed to construct this class of heterocyclic compounds (Scheme 1). The classic strategy is metal catalyzed coupling reactions, including:

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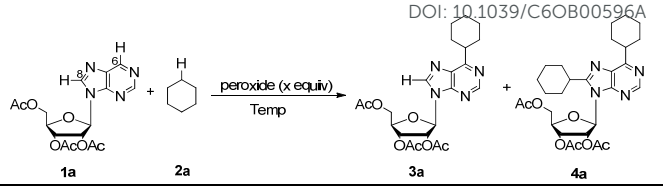
a) Copper mediated reactions of Grignard reagents with 6-halopurines;[5] b) Nickel catalyzed Negishi coupling reactions of organozinc halides with 6-halopurines;[6] c) Palladium catalyzed coupling reactions of alkyl trifluoroborates with 6-halopurines[7] (Scheme 1a). Whereas these reactions always need expensive noble metals which would have residual toxic metals in the final products. Meanwhile, these reactions also need leaving groups at the C6 position of purine derivatives. The only example of radical alkylation for C6-H purines was accomplished with cycloalkyl iodo as an alkylating reagent promoted by $FeSO_4$ and *t*BuOOH under strong acidic conditions.[8] However, the current methods always suffered from either expensive metal catalysts or harsh reaction conditions. In the context of ongoing projects in modifying purine and pyrimidine derivatives,[9,10] thus, we wish to develop a direct method to construct cycloalkyl substituted purine and pyrimidine analogues with metal-free under mild conditions.

Initially, we used 6-*H*-2′,3′,5′-*tri*-*O*-acetylpurine riboside (**1a**) and cyclohexane (**2a**) as model substrates to optimize the reaction conditions (Table 1). When the reaction was conducted with *t*BuOO*t*Bu as a peroxide at 100 °C for 12 h, the reaction did not occur and the substrates **1a** was recovered (entry 1). To our delight, increasing reaction temperature from 100 °C to 120 °C, the C6-monocyclohexyl substituted purine product **3a** was obtained with 24% yield (entry 2). However, a mixture of C6-monocyclohexyl substituted purine **3a** and C6, C8-dicyclohexyl substituted purine **4a** was afforded with 77% total yield when the reaction temperature increased from 120 °C to 140 °C (entry 3). Therefore, how to obtain a single cyclohexyl substituted purine product was the focus for the following optimization of the conditions. When the reaction time was shortened from 12 h to 1 h, the yield of product **3a** was increased from 45% to 56% while the purine **4a** was not formed (entries 3-4). Encouraged by the results, different reaction times were further evaluated. When the reaction was performed for 2 h, the product **3a** was exclusively obtained with 91% yield (entries 4-6). When other peroxides including *tert*-butyl hydroperoxide (TBHP) and dicumyl peroxide (DCP) were evaluated, no better results were obtained (entries 7-8). Thus, the optimal reaction time is 2 h for the selective generation of C6-monocyclohexyl substituted purine **3a**. Subsequently, we wish to realize the selective synthesis of purine **4a**. Then, the amount of peroxide *t*BuOO*t*Bu was examined, and the yield of purine **4a** was increased to 10% yield when 3.0 equiv *t*BuOO*t*Bu was used (entries 9-10). Prolonging the reaction time to 24 h, the yield of product **4a** increased greatly (entries 11-12). Therefore, when the reaction was performed with 3.0 equiv of *t*BuOO*t*Bu at 24 h, the purine **3a** disappeared completely and the C6,C8-dicyclohexyl substituted purine **4a** was obtained with 89% yield (entry 13). Therefore, by adjusting the amount of *t*BuOO*t*Bu and the reaction time, we can realize the selective synthesis of C6-monocyclohexyl or C6,C8-dicyclohexyl substituted purine nucleosides with excellent yields.

Table 1. The optimization of reaction conditions.[a]



1a 2a 3a 4a

Entry	Peroxide	x [equiv]	T [°C]	Time [h]	**3a** Yield [%][b]	**4a** Yield [%][b]
1	*t*BuOO*t*Bu	2.0	100	12	0	0
2	*t*BuOO*t*Bu	2.0	120	12	24	0
3	*t*BuOO*t*Bu	2.0	140	12	45	32
4	*t*BuOO*t*Bu	2.0	140	1	56	0
5	***t*BuOO*t*Bu**	2.0	**140**	**2**	**91**	**0**
6	*t*BuOO*t*Bu	2.0	140	3	85	5
7[c]	TBHP	2.0	140	2	26	0
8	DCP	2.0	140	2	66	0
9	*t*BuOO*t*Bu	1.0	140	2	73	0
10	*t*BuOO*t*Bu	3.0	140	2	83	10
11	*t*BuOO*t*Bu	2.0	140	4	74	20
12	*t*BuOO*t*Bu	2.0	140	24	37	55
13	***t*BuOO*t*Bu**	3.0	**140**	**24**	**0**	**89**

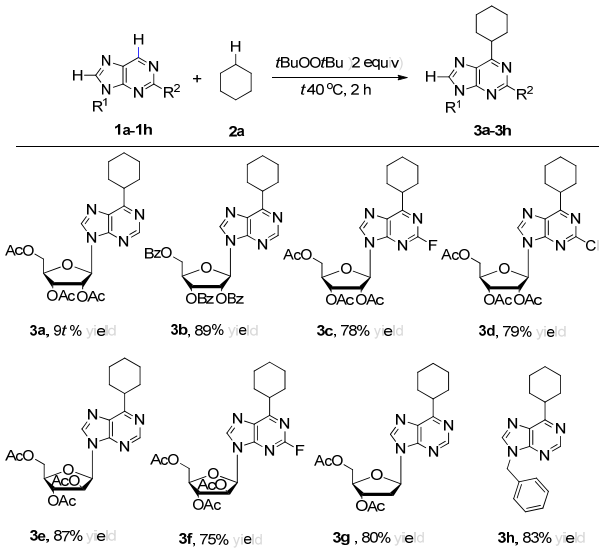
[a] Unless otherwise note, the reaction conditions were: **1a** (0.25 mmol) and **2a** (2.5 mL) under air; [b] Isolated yields based on **1a**; [c] 70% aqueous solution.

Subsequently, the substrate scope of the cycloalkylation reaction was examined under the optimized conditions (Table 1, entry 5) for the selective generation of C6-monocyclohexyl substituted purine derivative. When purine nucleosides bearing different ribosyl substitution were tested, the corresponding C6-monocyclohexyl substituted purine nucleosides were obtained with 78-91% yields (Scheme 2, **3a**-**3d**). To our delight, purine nucleosides containing arabinoribosyl substitutions also were suitable substrates to afford the desired C6-monocyclohexyl substituted purine nucleosides with 75-87% yields (Scheme 2, **3e**-**3f**). In the case of purine nucleosides bearing deoxyribosyl substitution, the reaction proceeded well giving the C6-monocyclohexyl substituted product **3g** in 80% yield (Scheme 2, **3g**). Furthermore, 9-benzyl-9*H*-purine worked well to furnish the target product **3h** in 83% yield (Scheme 2, **3h**).

Next, various cycloalkanes were employed to construct C6-monocycloalkyl substituted purine nucleosides (Scheme 3). Under the optimized conditions (Table 1, entry 5), the cycloalkylation reactions worked well with different size of rings in cycloalkanes, including cyclopentane (**2b**), cycloheptane (**2c**), and cyclooctane (**2d**) (Scheme 3, **3a**-**3c**). In the case of decahydronaphthalene (**2d**), an inseparable mixture was obtained (Scheme 3, **3d**). When 1-adamantane (**2e**) was used, the corresponding C6-monocycloalkyl

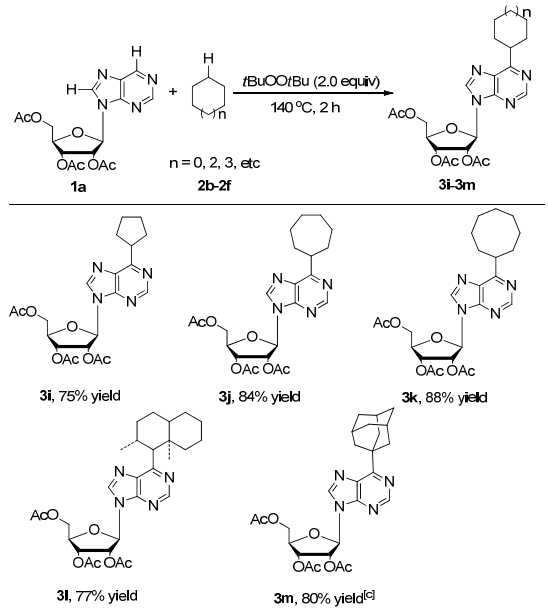
substituted purine nucleoside **3e** was obtained with 80% yield (Scheme 3, **3e**).

Scheme 2. Substrate scope of purine derivatives for the C6-monocycloalkylation.[a,b]



[a] Reaction conditions: **1** (0.25 mmol), *t*BuOO*t*Bu (0.5 mmol) and **2a** (2.5 mL) under air; [b] The yield referred to isolated yield based on substrate **1**.

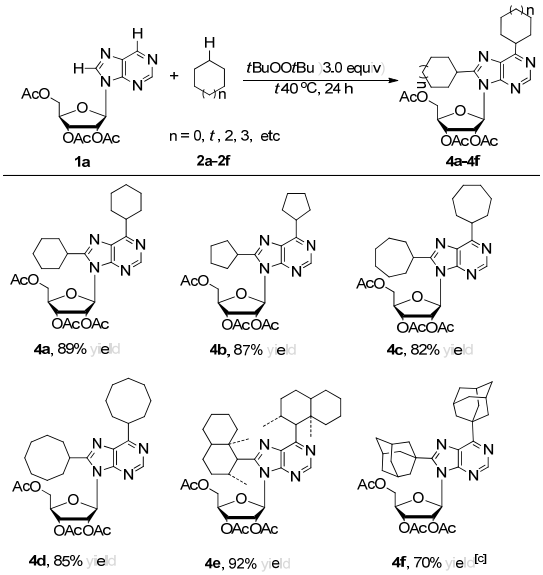
Scheme 3. The C6-monocycloalkylation of **1a** with various cycloalkanes [a,b]



[a] Reaction conditions: **1a** (0.25 mmol), *t*BuOO*t*Bu (0.5 mmol) and **2** (2.5 mL) under air; [b] The yield referred to isolated yield based on substrate **1a**. [c] Benzene (2.0 mL), **2f** (1.25 mmol).

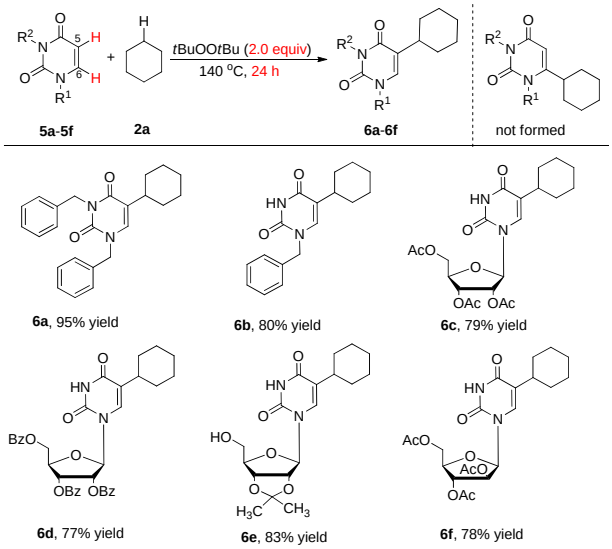
Then, the substrate scope of the cycloalkylation reaction was evaluated to afford C6,C8-dicycloalkyl substituted purine nucleosides under the optimized conditions (Table 1, entry 13). When different size of rings in cycloalkanes were examined, the corresponding C6,C8-dicycloalkyl substituted purine nucleosides were obtained with 82-89% yield (Scheme 4, **4a**-**4d**). When decahydronaphthalene (**2d**) was used, an inseparable mixture also was formed (Scheme 4, **4e**). In the case of 1-adamantane (**2e**), the C6,C8-dicycloalkyl substituted purine nucleoside **4f** was afforded with 70% yield (Scheme 4, **4f**).

Scheme 4. The C6,C8-dicycloalkylation of **1a** with various cycloalkanes [a,b]



[a] Reaction conditions: **1a** (0.25 mmol), *t*BuOO*t*Bu (0.75 mmol) and **2** (2.5 mL) under air; [b] The yield referred to isolated yield based on substrate **1a**. [c] Benzene (2.0 mL), **2f** (2.5 mmol).

Scheme 5. The cycloalkylation of uracils derivatives **5** with cyclohexane **2a**.[a,b]



[a] Reaction conditions: **5** (0.25 mmol), *t*BuOO*t*Bu (0.50 mmol) and **2a** (2.50 mL) under air and the isolated yields were given.

After a variety of cycloalkylated purine derivatives were obtained, uracil and related nucleosides were evaluated in the cycloalkylation reactions.[11] As shown in Scheme 5, *N*1 or *N*3

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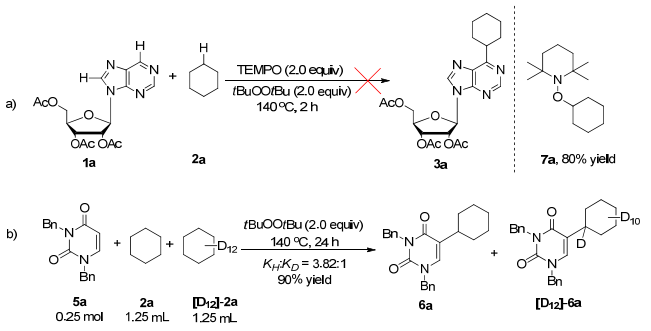
alkyl-substituted uracil derivatives could afford C5-cyclohexyl substituted uracil products **6a**-**6b** with 80-95% yields, while the C6-cyclohexyl substituted uracil products were not formed (Scheme 5, **6a**-**6b**). To our delight, uracil nucleosides bearing *N*1-substitutions such as ribosyl and arabinoribosyl groups all furnished the corresponding C5-cyclohexyl substituted uracil nucleosides with good yields (Scheme 5, **6c**-**6f**). It is worth mentioning that the cycloalkylation reactions could tolerate free hydroxyl and amino groups (Scheme 5, **6b**-**6f)**. In all the case, the cycloalkylation reactions exclusively afforded the C5-cyclohexyl substituted uracil derivatives.

Subsequently, some experiments were performed to evaluate the mechanism of the cycloalkylation reaction. First, when the TEMPO, a radical scavenger, was added, the cycloalkylation reaction was completely inhibited. The radical trapping by-product **7a** was isolated in 80% yield, which indicated that a radical process was involved in the cycloalkylation reaction (Scheme 6a). Next, when the crude product of the reaction was analyzed by GC-MS spectra, the dimerization and three-component coupling products of cyclohexane were detected, which proved the existence of a cyclohexyl radical in the cycloalkylation reaction (see supporting information for detail). Besides, the kinetic isotope effect experiment was performed and a significant isotope effect was observed with K_H/k_D = 3.82, which suggested that the C-H bond cleavage of cyclohexane is the rate-determining step (Scheme 6b).[9e]

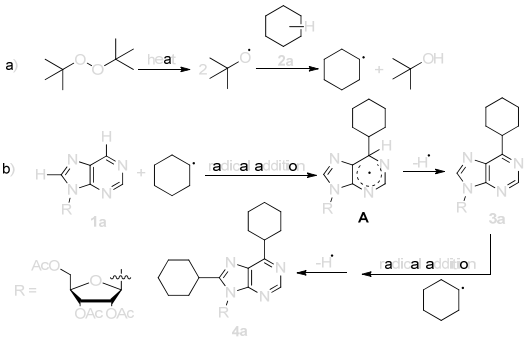
Based on the above experiments, a plausible mechanism for the cycloalkylation reaction was proposed (Scheme 7).[12] In the initiation step, the *tert*-butoxy radical was generated from *t*BuOO*t*Bu by heat. Then, the cyclohexyl radical was formed by the hydrogen abstraction between *tert*-butoxy radical and cyclohexane (Scheme 7a). Subsequently, the radical addition of cyclohexyl radical to C6 position of purine nucleoside **1a** afforded the intermediate **A**, followed by hydrogen abstraction with other radical to produce C6-monocyclohexyl substituted product **3a**. By prolonging the reaction time and increasing the amount of peroxide *t*BuOO*t*Bu, the radical addition of cyclohexyl radical to C6-monocyclohexyl substituted purine nucleoside **3a** occurred, and the C6,C8-dicyclohexyl substituted purine nucleoside **4a** was formed via hydrogen abstraction reaction (Scheme 7b).

Conclusions

We have developed a metal-free strategy for the synthesis of cycloalkyl substituted purine and pyrimidine nucleosides. By adjusting the amount of *t*BuOO*t*Bu and reaction time, the selective synthesis of C6-monocycloalkyl or C6,C8-dicycloalkyl substituted purine nucleosides could be realized. Meanwhile, a variety of purine nucleosides containing ribosyl, arabinoribosyl, and deoxyribosyl substitutions worked well with different size of rings in cycloalkanes, affording the corresponding products with good results (19 examples, 70-92% yields). Furthermore, uracil and related nucleosides also were suitable substrates, giving the C5-cyclohexyl substituted uracil derivatives in good yields with excellent regioselectivities (6 examples, 77-95% yields).



Scheme 6. a) The radical trapping experiment; b) The kinetic isotope effect (KIE) experiment



Scheme 7. The proposed mechanism for the cycloalkylation reaction.

Experimental Section

Monocycloalkylation reaction of 6-*H*-2',3',5'-tri-O-acetylpurine riboside (1a) with cyclohexane (2a)

A reaction vessel was charged with 6-*H*-2',3',5'-*tri*-*O*-acetylpurine riboside (**1a**, 94.5 mg, 0.25 mmol), *t*BuOO*t*Bu (0.095 mL, 0.5 mmol) and cyclohexane (2.5 mL). Then, the reaction vessel was sealed and the resulting solution was stirred at 140 °C for 2 h. After cooling to room temperature, the resulting mixture was removed in vacuo and the residue was purified by column chromatography (SiO_2, petro ether/ethyl acetate = 1:2) to give **3a** with 91% yield.

Dicycloalkylation reaction of 6-*H*-2',3',5'-tri-O-acetylpurine riboside (1a) with cyclohexane (2a)

A reaction vessel was charged with 6-*H*-2',3',5'-*tri*-*O*-acetylpurine riboside (**1a**, 94.5 mg, 0.25 mmol), *t*BuOO*t*Bu (0.143 mL, 0.75 mmol) and cyclohexane (2.5 mL). Then, the reaction vessel was sealed and the resulting solution was stirred at 140 °C for 24 h. After cooling to room temperature, the resulting mixture was removed in vacuo and the residue was purified by column chromatography (SiO_2, petro ether/ethyl acetate = 2:1) to give **4a** with 89% yield.

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