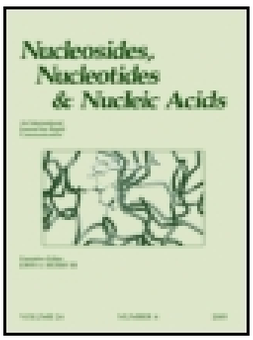

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The Convenient Synthesis of Unsaturated Nucleoside Analogues in Water under Microwave Irradiation

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ABSTRACT

A convenient method for the regioselective synthesis of unsaturated nucleoside analogs in water under microwave irradiation was developed. All pyrimidine and purine nucleoside derivatives were exclusively alkylated at N1 and N9 respectively in good to excellent yields. In addition, this system could tolerate a broad range of functional groups, such as chloro, bromo, iodo, alkyl, amino, and hydroxyl groups. More importantly, the reaction scale could be enlarged to 50 mmol which made this route attractive for industrial application.

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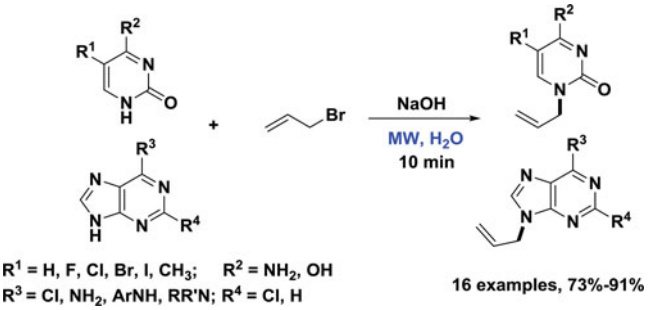
Microwave irradiation; convenient synthesis; unsaturated nucleoside; green solvent

GRAPHICAL ABSTRACT



In recent years, modified nucleoside analogues have become of great interest due to their intriguing biological and pharmacological properties.[1–3] A number of nucleoside drugs exhibiting potent antiviral and antitumor activities have been prepared by modification of the carbohydrate cycles.[4–6] Unsaturated bonds are widely prevalent in carbohydrate cycles of many drugs and bioactive compounds such as neplanocin A,[7] carbovir,[8] entecavir[9] and stavudine (Scheme 1).[10] Furthermore, because the effective participation of arene moieties and *p*-bonds in biological systems, allyl and arylmethyl nucleobases can be proved as vital synthons for the development of new drug molecules.[11]

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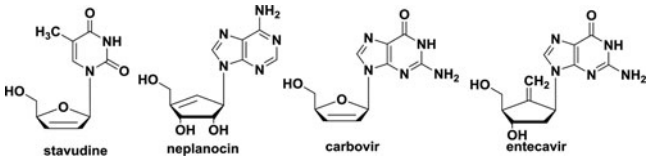
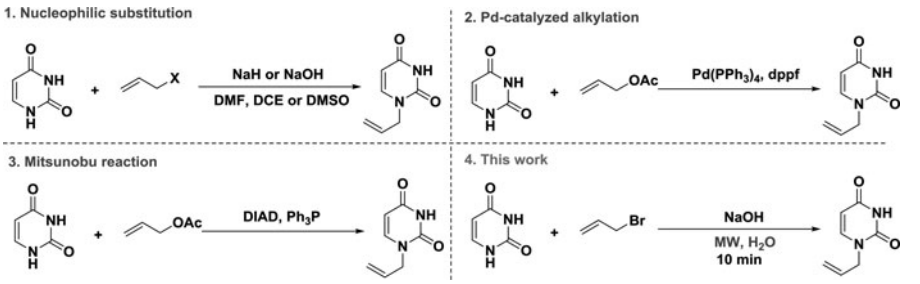
As a result, the development of methods for introducing unsaturated bonds into nucleosides has been the subject of intense research. A variety of direct nucleophilic substitution reactions have been developed for the synthesis of unsaturated nucleoside analogues in the presence of strong bases in organic solvents, such as DMF (N,N-dimethyl-formamide), DCE (1,2-dichloroethane), and DMSO (dimethyl sulfoxide) et al. (route 1, Scheme 2).[12,13] In addition, Mitsunobu reaction[14] and palladium-catalyzed Tsuji–Trost reaction[15] were also available (routes 2–3, Scheme 2). Iodine catalyzed coupling of 2,4-*bis*(trimethylsiloxy) pyrimidines with allyl halides and arylmethyl halides was also employed to afford unsaturated nucleoside analogues.[16,17] Despite these extensive progresses, current methods have significant limitations: some systems utilized strong basic conditions and organic solvents. Others often required toxic and expensive transition metals. Therefore, a green method with a broad substrate scope is highly desirable. Water is cheap, clean, nontoxic, and nonflammable, which leads to easier workup and has attracted much attention in synthetic chemistry recently.[18,19] In the context of ongoing projects on the synthesis of nucleosides,[20–23,5] herein, we reported the synthesis of the simplest unsaturated nucleoside analogs in water under microwave irradiation.



Scheme 1. The selected nucleoside drugs with unsaturated bonds.



Scheme 2. The routes to unsaturated nucleoside analogues.

Results and discussion

To initiate our study, we conducted the reaction of uracil and ally bromide in water under microwave irradiation. The influence of various bases was examined to evaluate their activities as well as selectivities. The results are summarized in Table 1. When DMF or acetonitrile was used as solvent, NaH or NaOH as base, the reaction proceeded smoothly to give the product **3a** in 36–56% yield (Table 1, entries 1–4). The base was necessary in water because no reaction happened without the

Table 1. Optimization of reaction conditions.[a]

Entry	Solvent	Base	Reaction time/min	Yield/%[b]
1	DMF	NaH	5	56
2	DMF	NaOH	5	36
3	CH_3CN	NaH	5	56
4	CH_3CN	NaOH	5	42
5	H_2O	Free	5	0
6	H_2O	Et_3N	5	35
7	H_2O	DIPEA	5	39
8	H_2O	DMAP	5	45
9	H_2O	K_2CO_3	5	51
10	H_2O	NaOH	5	57
11	H_2O	NaOH	5	78
12	**H_2O**	**NaOH**	**10**	**80**
13	H_2O	NaOH	15	79
14	H_2O	NaOH	20	77
15[c]	H_2O	NaOH	120	68

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (0.6 mmol), solvent (2 mL), MW 0–400 W (100°C);
[b]isolated yields;
[c]heated in oil bath at 100°C.

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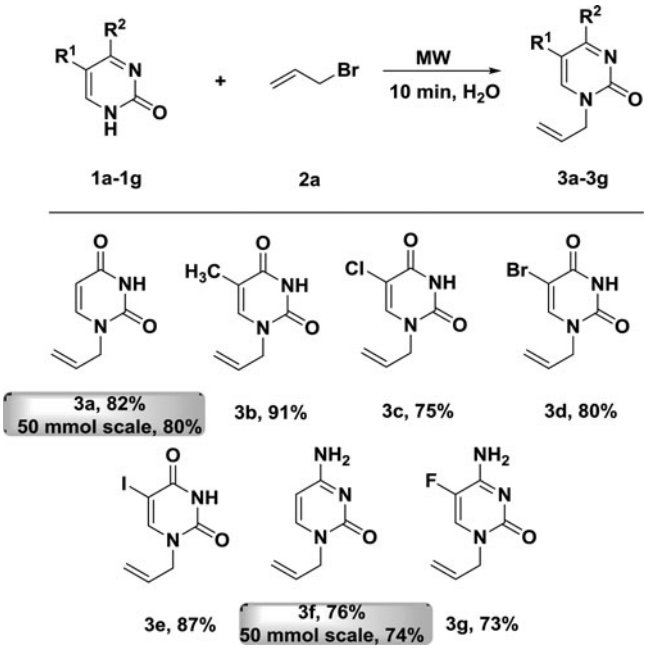
base (entry 5). However, lower yields were obtained when employing DMAP (4-dimethylaminopyridine), Et_3N or K_2CO_3 as the bases in water (entries 6–9). Changing reaction time had some influence on the yields (entries 11–14). When the reaction time was shorter or longer than 10 minutes, lower yield was obtained. Therefore 10 minutes was the best choice. To verify the microwave effects, we conducted the reaction in oil bath under the same reaction conditions. The reaction proceeded for 120 minutes and the product was isolated in lower yield of 68%, which showed the positive effects of microwave irradiation.

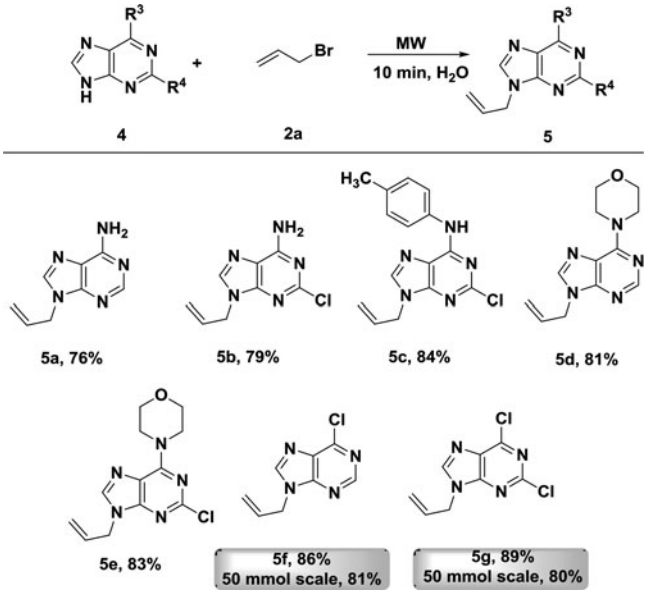
After obtaining the optimized reaction conditions, we examined the scope of pyrimidine derivatives using **2a** as the alkylating donor (Scheme 3). The uracil and cytosine derivatives could be alkylated in perfect regioselectivity to yield the desired unsaturated nucleoside analogues **3a**–**3g** in up to 91% yield. The pyrimidine bearing different functional groups at C5 such as hydrogen, methyl, fluoro, chloro, and bromo or iodo groups all furnished the target products in good yields (73–91%). When H atom was substituted with methyl group in C5, the yield was enhanced (**3a** versus **3b**). When H atom at C5 was substituted with fluoro group, a slightly reduced yield could be observed (**3f** versus **3g**). The electron-withdrawing groups at C5 had negative effects on the yields compared to electron-donating groups (**3a** versus **3c–3e**). The cytosine derivatives gave lower yields compared to the uracil derivatives (**3a** versus **3f**). To our delight, it is unnecessary to protect the exocyclic amino group in cytosines (**3f–3g**), because the alkalinity of NH at *N*9 was stronger than exocyclic amino group. More importantly, **3a** and **3f** could be got at 50 mmol scales with maintained yields and the products could be purified by recrystallization rather than time-consuming chromatography.

Next, we applied this procedure to a series of purine derivatives and the desired products alkylated at *N*9 position were also obtained in moderate to good yields (Scheme 4, 76–89%). Remarkably, several functional groups such as chloro, amino, morpholinyl, and phenyl amine were tolerated well under the reaction conditions.



Scheme 3. Alkylation of ally bromide with pyrimidine derivatives.

It is also worthy of mentioning that the exocyclic amino groups in **5a**–**5b** were not alkylated (**5a**–**5b**). When the hydrogen at C2 was replaced by a chloride, the yield increased slightly (**5a** versus **5b, 5d** versus **5e**, and **5f** versus **5g**). Furthermore, we synthesized **5f** and **5g** at 50 mmol scales through easy workup process and the yields were maintained.



Scheme 4. Alkylation of various purine derivatives with allyl bromide.

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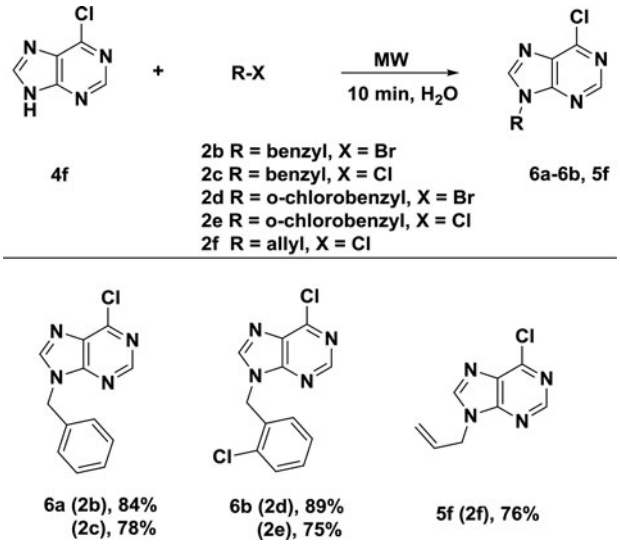
In order to check the generality of our method, other alkylation donors were investigated. Treatment of 6-chloropurine with allyl chloride, benzyl bromide, and *o*-chloro-benzyl bromide under the optimized conditions as mentioned above gave the corresponding products **6a–6b** and **5f** in good yields and good regioselectivity. The results are summarized in Scheme 5. The alkylation donors containing bromide usually gave the desired products in good yields (**6a**, **6b**, and **5f**) whereas the bromide alkylation donors were more costly.



Scheme 5. Alkylation of 6-chloropurine with alkyl halides.

Conclusion

In conclusion, we developed a convenient method for the synthesis of unsaturated nucleoside analogues in water under microwave irradiation. All of the products were obtained in good to excellent yields. Pyrimidine and purine derivatives were exclusively alkylated at *N*1 and *N*9, respectively. This method also had the practical advantage that the protection of hydroxyl and amino groups was unnecessary. Extension of this strategy to a new class of drugs and tools for chemical biology is currently in progress in our laboratories.

Experimental

General

Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 MHz spectrometer for ^{1}H NMR,

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100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to tetramethylsilane as internal standard, residual $CHCl_3$ (DMSO) for ^{1}H or ^{13}C NMR spectroscopy. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). High resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-TofMS/MS system. The reaction was carried out in the single-mode MAS-II microwave reactor (real-time monitoring and control of the reaction temperature by infrared temperature measurement, accuracy $\pm$ 1°C) produced by Sineo Microwave Chemical Technology Co. Ltd. For column chromatography silica gel (200–300 mesh) was used as the stationary phase. All reactions were monitored by thin-layer chromatography. All reagents and solvents were purchased from commercial sources and purified commonly before used.

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General procedures

The procedure for uracil with ally bromide at 0.5 mmol scale (3a). To a mixture of uracil (0.056 g, 0.5 mmol) and NaOH (0.014 g, 0.6 mmol) in neat H_2O (2 mL), allyl bromide (0.052 mL, 0.6 mmol) was added. Then the mixture was put into the microwave reactor and irradiated at 0–400 W (internal temperature: 100°C) for 10 minutes. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography using EtOAc-cyclohexane (9:1) as the eluent to afford **3a**, yield 82%.

The procedure for uracil with ally bromide at 50 mmol scale (3a). To a mixture of uracil (5.6 g, 50 mmol) and NaOH (1.44 g, 60 mmol) in neat H_2O (200 mL), allyl bromide (5.2 mL, 60 mmol) was added. Then the mixture was put into the microwave reactor and irradiated at 0–400 W (internal temperature: 100°C) for 10 minutes. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was recrystallized from ethanol to afford **3a**, yield 80%.

Characterization of Compounds, see the supporting information.

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