Microwave-Promoted Michael Addition in Neat Water: A Rapid, Efficient and Green Method for the Preparation of Acyclic Nucleosides

Gui-Rong Qu,* Zhi-Guang Zhang, Ming-Wei Geng, Ran Xia, Lin Zhao, Hai-Ming Guo*

College of Chemistry and Environmental Science, Henan Normal University, Xinxiang 453007, P. R. of China
Fax +86(373)3326336; E-mail: ghm@htu.cn

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Abstract: Syntheses of acyclic nucleosides were achieved in water with the aid of microwave irradiation, providing a rapid, efficient and convenient method for the preparation of acyclic nucleosides in high yields.

Key words: acyclic nucleoside, microwave irradiation (MWI), Michael addition, green solvent

Strong interest in acyclic nucleosides started when Acyclovir (ACV, **1**) was firstly reported as a potent anti-herpes drug in the mid-1970s.[1] A great number of other nucleoside analogues for antiviral chemotherapy belonging to 'open chain' acyclic sugar analogues[2] such as Gencicovir (**2**), and 9-[2-(phosphonylmethoxy)ethyl]adenine (**3**) were substantially found (Figure 1). Many methods were reported to obtain these important nucleoside analogues, including alkylation of the nucleobases with various alkylating agents,[3] Michael addition of purine and pyrimidine to an activated multiple bond.[4] Over the past two decades, microwave irradiation has become a very popular and useful technique in synthetic chemistry.[5] To the best of our knowledge, microwave-promoted Michael addition in neat water has not yet been employed in the synthesis of acyclic nucleosides. Water, a safe and environmentally benign solvent, has attracted much attention in synthetic chemistry recently.[6] It is very cheap, clean, non-toxic and non-flammable, which leads to easier work-up and has great advantages over organic media. Herein, we describe a rapid, efficient and green method for the preparation of a series of acyclic nucleosides using triethylamine (Et_3N) as the base under microwave irradiation in water.

To initiate our study, we examined the ability of microwave promoting the Michael addition of uracil and acrylonitrile in water. The influence of various bases was examined to evaluate their activities as well as their selectivities. The results are summarized in Table 1. When K_2CO_3 was used as a base, Michael addition reaction proceeded smoothly to give the product **6a** in 60% yield (Table 1, entry 1). Uracil was exclusively alkylated at the N-1 position. The site of N-alkylation was characterized by ^1H NMR and ^{13}C NMR spectra analysis.[4g] Potassium hydroxide or magnesium oxide could also be used as the base and no significant changes in yield were observed (entries 2 and 3). However, high yield was obtained by employing 4-dimethylaminopyridine (DMAP) or Et_3N as the base instead of K_2CO_3 (entries 4 and 5). The base was necessary because no reaction happened without base, even prolonging the irradiation time to 15 minutes (entry 6). Finally, Et_3N became the base of the choice because it is very common and inexpensive. Using Et_3N as the base has an additional advantage in that it is unnecessary to neutralize the reaction mixture by diluted HCl, for it can be easily removed in vacuo because of its low boiling point (88.8 °C). Changing irradiation time has some influence on the yield (entries 7–10). As shown in Table 1, when the reaction time was shorter or longer than five minutes, lower yield was obtained and N-3-alkylation product was observed if reaction time was longer than five minutes. Therefore five minutes was the optimized reaction time.

After obtaining the optimized reaction conditions, we applied this procedure to other uracil derivatives (Table 2). Gratifyingly, all the substrates were exclusively alkylated at N-1 position. When the reaction mixtures were cooled to room temperature, **6b** and **6c** could pre-

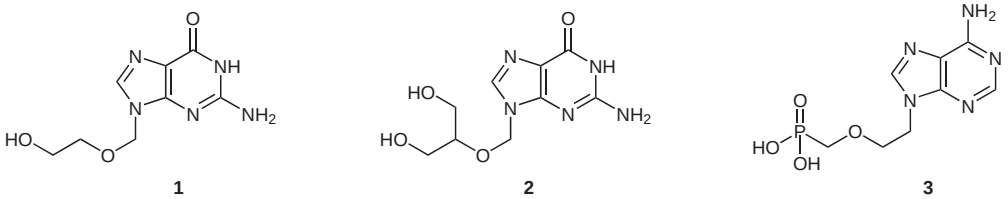

Figure 1 Structures of some acyclic nucleosides

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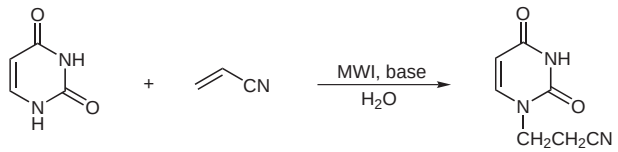
Table 1 Optimization of Reaction Conditions under Microwave Irradiation[a]



4a **5** **6a**

Entry	Base	Irradiation time (min)	Yield (%)[b]
1	K_2CO_3	5	60
2	KOH	5	54
3	MgO	5	62
4	DMAP	5	83
5	Et_3N	5	82
6	Base-free	15	No reaction
7	Et_3N	4	69
8	Et_3N	4.5	74
9	Et_3N	6	81
10	Et_3N	7	78

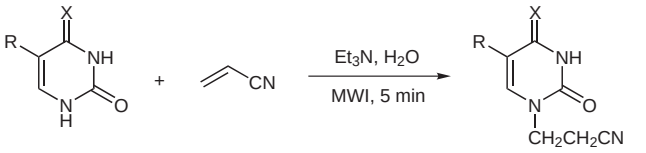
[a] Reaction conditions: uracil (2 mmol), acrylonitrile (6 mmol), base (6 mmol), H_2O (5 mL), MWI 250 W (100 °C).
[b] Isolated yields based on nucleobase.

cipitate from the reaction mixtures in high purities and yields. But as far as **6a**, **6d**, and **6e** were concerned, no precipitate appeared, even if the reaction mixtures were put into refrigerator for two hours. After volatilization of the solvents in vacuo, the solid residues were subjected to column chromatographic purification to provide **6a**, **6d**, and **6e**, as pure compounds in high yields. Interestingly, when H-5 in **4a** was replaced with Cl, CH_3, or I, only a negligible difference was observed in the yield[7] (entries 2–4). No obvious change in yield was detected as 4-oxo was substituted with 4-thio (entry 5).

We have also extended this reaction to some cytosine derivatives that provided compounds **8a**–**d** in high yields (Table 3). Firstly, cytosine derivative **7a** was selected as a nucleobase, and the exocyclic amino group of **7a** was protected as an acetamide. The reaction proceeded smoothly to provide the product **8a** in 83% yield (entry 1). More interesting is that cytosine with the free exocyclic amino group could also give rise to the product **8b** in 83% yield (entry 2). This implied that our method has high regioselectivity. The reaction could also proceed with the H-5 position substituted by F or Br. High regioselectivity and high yields were also obtained (entries 3 and 4).

Applying this procedure to a series of purine derivatives, the desired products were also obtained in moderate to high yields (Table 4). To our delight, it is also unnecessary to protect the exocyclic amino group in purine. The most probable reason was their relatively weak nucleophilic character according to previous observations.[8] The

Table 2 Michael Addition of Uracil Derivatives to Acrylonitrile[a]

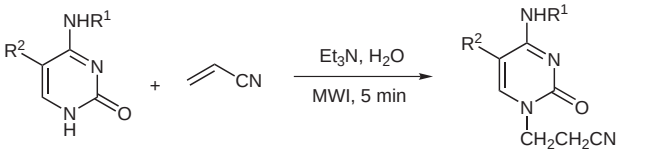


4a–e **5** **6a–e**

Entry	R	X	Product	Yield (%)[b]
1	H	O	**6a**	82
2	Cl	O	**6b**	78
3	I	O	**6c**	72
4	Me	O	**6d**	82
5	H	S	**6e**	74

[a] Reaction conditions: nucleobases (2 mmol), **5** (6 mmol), H_2O (5 mL), Et_3N (6 mmol), MWI 250 W (100 °C).
[b] Isolated yields based on nucleobases.

Table 3 Michael Addition of Uracil Derivatives to Acrylonitrile[a]



7a–d **5** **8a–d**

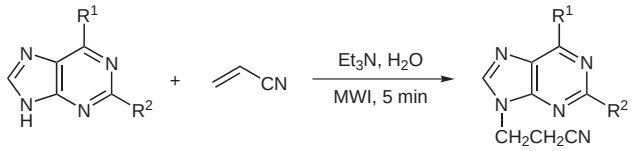
Entry	R^1	R^2	Product	Yield (%)[b]
1	Ac	H	**8a**	83
2	H	H	**8b**	83
3	H	F	**8c**	84
4	H	Br	**8d**	80

[a] Reaction conditions: nucleobases (2 mmol), **5** (6 mmol), H_2O (5 mL), Et_3N (6 mmol), MWI 250 W (100 °C).
[b] Isolated yields based on nucleobase.

adenine derivatives that were substituted by 6-benzyl and 6-hydroxyethyl (**9f**–**i**), which behaved as Ca^{2+} antagonists, selective A1 agonists and pharmacological tools,[9] were also alkylated exclusively at N-9 (entries 6–9). It is also worthy of mention that the hydroxyl group in **9g**–**i** was not alkylated. Another method was employed to prove that the substrates **9g**–**i** were alkylated at N-9.[10] HMBC spectra also ascertained that the site of alkylation was N-9 and not N-7 or another position.

In order to check the generality of our method, other Michael acceptors were investigated. Treatment of 6-chloropurine with methyl acrylate, ethyl acrylate, *tert*-butyl acrylate under the similar conditions as mentioned above successfully gave rise to the corresponding products **12a**–**c** in high yields and regioselectivity. The results are summarized in Table 5. It could be concluded that the length of alkoxy group (OR) in acrylate has little influence on the result of reaction.

Table 4 Michael Addition of Various Purine Derivatives to Acrylonitrile[a,11]

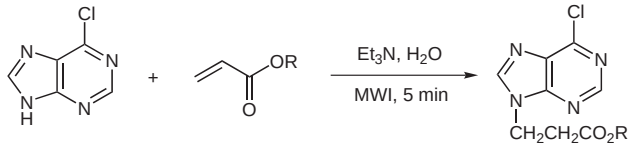


9a–i **5** **10a–i**

Entry	R^1	R^2	Product[12]	Yield (%)[b]
1	Cl	H	**10a**	82
2	NH_2	H	**10b**	84
3	Cl	NH_2	**10c**	86
4	NH_2	Cl	**10d**	77
5	NH_2	F	**10e**	80
6	Benzyl amino	H	**10f**	74
7	$HOCH_2CH_2NH$	H	**10g**	78
8	$HOCH_2CH_2NH$	Cl	**10h**	73
9	$HOCH_2CH_2NH$	NH_2	**10i**	76

[a] Reaction conditions: nucleobase (2 mmol), **5** (6 mmol), H_2O (5 mL), Et_3N (6 mmol), MWI 250 W (100 °C).
[b] Isolated yields based on nucleobase.

Table 5 Michael Addition of 6-Chloropurine to Acrylate[a]



9a **11a–c** **12a–c**

Entry	R	Product	Yield (%)[b]
1	Me	**12a**	79
2	Et	**12b**	83
3	*t*-Bu	**12c**	76

[a] Reaction conditions: 6-chloropurine (2 mmol), **11** (6 mmol), H_2O (5 mL), Et_3N (6 mmol), MWI 250 W (100 °C).
[b] Isolated yields based on **9a**.

In conclusion, we have developed a green, rapid, and operationally simple method for regioselective Michael additions for preparation of acyclic nucleosides in neat water under microwave irradiation. All of the products were obtained in moderate to high yields. Pyrimidine and purine derivatives were exclusively alkylated at N-1 and N-9, respectively. This method also has the practical advantage that the protection of hydroxyl and amino groups is not necessary.

Extension of this strategy to other Michael acceptors such as α,β-unsaturated esters and diethyl vinylphosphonate for the synthesis of acyclic nucleoside analogues, which may represent a new class of drugs and tools for chemical biology, is currently in progress in our laboratories.

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(11) **General Procedure for the Michael Addition of Uracil to Acrylonitrile.**

To a mixture of uracil (2 mmol, 0.224 g) and Et_3N (0.85 mL, 6 mmol) in neat H_2O (5 mL), acrylonitrile (6 mmol, 0.4 mL) was added. Then the mixture was put into the cavity of a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity infrared sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, P. R. of China) and irradiated at 250 W (internal temperature: 100 °C) for 5 min. After completion of the reaction, the mixture was concentrated to dryness under reduced pressure and the residue was purified by column chromatography using EtOAc–cyclohexane (9:1) as the eluent to afford **6a** in 82% yield.

(12) Compound **6e**: yield 74%; yellow crystals; mp 164–165 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.940 (t, 2 H, *J* = 6.4 Hz), 3.982 (t, 2 H, *J* = 6.4 Hz), 6.318 (d, 1 H, *J* = 7.2 Hz), 7.606 (d, 1 H, *J* = 7.2 Hz) 12.766 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.07, 44.46, 112.86, 118.65, 141.39, 148.63, 191.05 ppm. IR (KBr): 3188, 3102, 3073, 3042, 2965, 2926, 2252, 1681, 1622, 1451, 1355, 1317, 1255, 1149, 1094, 866, 855, 638 cm^{-1}. HRMS: *m/z* calcd for $C_7H_7N_3OS$: 181.0310; found: 181.0320. Anal. Calcd for $C_7H_7N_3OS$: C, 46.40; H, 3.89; N, 23.19. Found: C, 46.37; H, 3.85; N, 23.11.

Compound **8d**: yield 80%; white powder; mp 226–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.920 (t, 2 H, *J* = 6.4 Hz), 3.928 (t, 2 H, *J* = 6.4 Hz), 6.993 (s, 1 H), 7.842 (s, 1 H), 8.147 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.14, 45.07, 85.98, 118.82, 147.05, 154.52, 162.81 ppm. IR (KBr): 3364, 3107, 2963, 2945, 2247, 1674, 1650, 1500, 1438, 1410, 1377, 1333, 1280, 1207, 1099, 1028, 988, 824, 778, 653, 628 cm^{-1}. HRMS: *m/z* calcd for $C_7H_7BrN_4O$: 241.9803; found: 241.9810. Anal. Calcd for $C_7H_7BrN_4O$: C, 34.59; H, 2.90; N, 23.05. Found: C, 34.54; H, 2.85; N, 22.97.

Compound **10c**: yield 86%; white powder; mp 220 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.145 (t, 2 H, *J* = 6.4 Hz), 4.354 (t, 2 H, *J* = 6.4 Hz), 6.980 (s, 2 H), 8.181 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.17, 39.26, 118.62, 123.65, 143.23, 150.01, 154.37, 160.20 ppm. IR (KBr): 3494, 3291, 3168, 3155, 3113, 2961, 2947, 2927, 2246, 1631, 1568, 1520, 1481, 1418, 1363, 1326, 1172, 905, 867, 781, 636 cm^{-1}. HRMS: *m/z* calcd for $C_8H_7ClN_6$: 222.0421; found: 222.1410. Anal. Calcd for $C_8H_7ClN_6$: C, 43.16; H, 3.17; N, 37.75. Found: C, 43.14; H, 3.14; N, 37.69.

Compound **10d**: yield 77%; pale yellow powder; mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.141 (t, 2 H, *J* = 6.4 Hz), 4.412 (t, 2 H, *J* = 6.4 Hz), 7.821 (s, 2 H), 8.211 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.58, 39.79, 118.19, 118.65, 141.61, 150.94, 153.53, 157.25 ppm. IR (KBr): 3494, 3418, 3308, 3148, 3087, 3070, 3021, 2979, 2936, 2930, 2860, 2257, 1654, 1597, 1570, 1515, 1479, 1449, 1423, 1409, 1360, 1311, 1257, 644 cm^{-1}. HRMS: *m/z* calcd for $C_8H_7ClN_6$: 222.0421; found: 222.0411. Anal. Calcd for $C_8H_7ClN_6$: C, 43.16; H, 3.17; N, 37.75. Found: C, 43.13; H, 3.11; N, 37.70.

Compound **10g**: yield 78%; white powder; mp 144–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.166 (t, 2 H, *J* = 6.4 Hz), 3.605 (s, 4 H), 4.455 (t, 2 H, *J* = 6.4 Hz), 4.712 (s, 1 H), 7.514 (s, 1 H), 8.184 (s, 1 H), 8.230 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.18, 42.84, 59.99, 118.24, 119.07, 140.44, 149.18, 152.58, 154.83 ppm. HRMS: *m/z* calcd for $C_{10}H_{12}N_6O$: 232.1072; found: 232.1081. Anal. Calcd for $C_{10}H_{12}N_6O$: C, 51.72; H, 5.21; N, 36.19. Found: C, 51.70; H, 5.15; N, 36.11.

Compound **10h**: yield 73%; white powder; mp 152–154 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.134 (t, 2 H, *J* = 6.4 Hz), 3.498–3.597 (m, 4 H), 4.414 (t, 2 H, *J* = 6.4 Hz), 4.771 (t, 1 H, *J* = 5.2 Hz), 8.169 (s, 1 H), 8.208 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.39, 42.90, 45.28, 59.46, 60.67, 118.37, 141.14, 149.78, 153.45, 155.38 ppm. HRMS: *m/z* calcd for $C_{10}H_{11}ClN_6O$: 266.0683; found: 266.0692. Anal. Calcd for $C_{10}H_{11}ClN_6O$: C, 45.04; H, 4.16; N, 31.51. Found: C, 45.02; H, 4.15; N, 31.48.

Compound **10i**: yield 76%; white powder; mp 163–164 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.087 (t, 2 H, *J* = 6.4 Hz), 3.572 (s, 4 H), 4.254 (t, 2 H, *J* = 6.4 Hz), 4.707 (s, 1 H), 5.852 (s, 2 H), 6.958 (s, 1 H), 7.747 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.97, 38.47, 42.66, 60.35, 113.39, 118.38, 136.95, 151.28, 155.20, 160.35 ppm. HRMS: *m/z* calcd for $C_{10}H_{13}N_7O$: 247.1182; found: 247.1174. Anal. Calcd for $C_{10}H_{13}N_7O$: C, 48.58; H, 5.30; N, 39.65. Found: C, 48.51; H, 5.21; N, 39.55.

Compound **12b**: yield 83%; pale yellow crystals; mp 72–74 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.094 (t, *J* = 6.8 Hz, 3 H), 3.014 (t, *J* = 6.8 Hz, 2 H), 4.013 (q, *J* = 7.2 Hz, 2 H), 4.532 (t, *J* = 6.8 Hz, 2 H), 8.689 (s, 1 H), 8.783 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.04, 33.36, 60.47, 130.98, 147.78, 149.09, 151.58, 152.08, 170.54 ppm. HRMS: *m/z* calcd for $C_{10}H_{11}ClN_4O_2$: 254.0571; found: 254.0562. Anal. Calcd for $C_{10}H_{11}ClN_4O_2$: C, 47.16; H, 4.35; N, 22.00. Found: C, 47.08; H, 4.29; N, 21.91.