

Microwave-Assisted Rapid and Regioselective Synthesis of *N*-(alkoxycarbonylmethyl) Nucleobases in Water

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Foi desenvolvido um método fácil e ambientalmente benigno para a preparação de nucleobases *N*-(etioxicarbonilmetil) e *N*-(*iso*-propoxycarbonilmetil), importantes na construção de blocos para Ácidos Nucleicos Peptídicos (ANP). Todas as nucleobases são regioselectivamente alquiladas e os produtos desejados são obtidos com rendimentos moderados a altos, sob irradiação de microondas por 8 minutos em água como solvente e na presença de Et₃N como base

A facile and eco-friendly approach has been developed for the preparation of *N*-(ethoxyxycarbonylmethyl) nucleobases and *N*-(*iso*-propoxycarbonylmethyl) nucleobases, which are important building blocks for Peptide Nucleic Acids (PNA). All the nucleobases are regioselectively alkylated and the desired products are obtained in moderate to high yields under microwave irradiation for 8 min in water as the solvent and in the presence of Et₃N as the base.

Keywords: modified nucleoside, microwave irradiation, water

Introduction

In order to find out effective, selective, nontoxic antiviral and antitumor drugs, modified nucleosides have become of great interest in recent years, due to their intriguing chemical and pharmacological properties.¹ Carbocyclic nucleosides,² acyclic nucleosides,³ 5-substituted pyrimidine nucleosides⁴ and others have been designed and prepared, such as Neplanocin A (**1**), Acyclovir (**2**), and BVDU (**3**) (Figure 1), which exhibited potential biological activities against Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Hepatitis B Virus (HBV) and so on. In 1991, Nielsen and coworkers reported a novel synthetic mimic of DNA in which the sugar-phosphate backbone of natural

nucleic acid was replaced with a polyamide backbone, named Peptide Nucleic Acids (PNA, **4**).⁵ PNA can hybridize to complementary DNA, RNA, or PNA, and exhibit higher thermal stability and better sequence discrimination than DNA. Therefore, PNA has attracted wide attention in medicinal chemistry for the development of biosensors and gene therapeutic drugs, and a number of groups have developed several methods for the preparation of the monomers and submonomers of PNA, including ours.⁶ However, some drawbacks also exist in the reported methods. For example, low yields and poor regioselectivity are frequently encountered. What is more, long reaction time up to 24 h, inert gas atmosphere, harsh reaction conditions, and toxic solvents are usually required, which do not meet the requirement of green chemistry.⁷

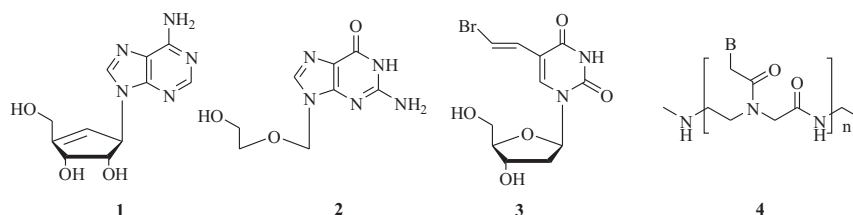


Figure 1. Structures of some modified nucleosides.

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In order to expand our interest in the modification of nucleoside and obtain the submonomers in higher yields under milder reaction conditions in shorter reaction time, we turned our attention to microwave irradiation (MWI).⁸ Microwave assisted organic synthesis has been widely utilized in recent years for the formation of a variety of carbon-carbon and carbon-heteroatom bonds, which usually lead to a remarkable decrease in reaction time, enhancement in yields, easier workup, and better regioselectivity.⁹ However, only a few methods were reported to obtain these modified nucleoside analogues under MWI.¹⁰ Herein, we report a rapid, convenient, and green protocol for the synthesis of the *N*-(ethoxycarbonylmethyl) nucleobases and *N*-(*iso*-propoxycarbonylmethyl) nucleobases, building blocks for Peptide Nucleic Acids.

Results and Discussion

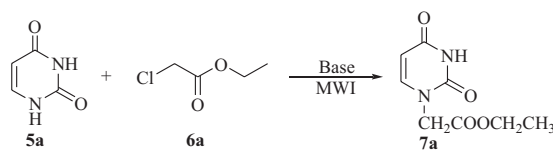
Initially, we selected uracil (**5a**) and ethyl chloroacetate (**6a**) as a model system to investigate the effect of solvents, bases, and irradiation time on the yield. DMF is an excellent solvent to absorb microwave energy and dissolve the nucleobase, for its high polarity. However, dark reaction mixture and poor yield were obtained, indicating side reactions had occurred (entry 1). Using CH₃CN as solvent also did not give rise to high yield, in which uracil had poor solubility, so 52% yield was achieved, associated with *N*³-alkylated product (entry 2). To our surprise, uracil was exclusively alkylated at *N*¹, and **7a** was obtained in satisfactory yield by using water as the solvent in the presence of K₂CO₃ as the

base (entry 3), suggesting this method was highly regioselective. Water is a promising medium to replace volatile organic solvent¹¹ and a good absorber for microwave energy. Water, in combination with microwave irradiation, makes our procedure highly cost-effective and benign to the environment. More importantly, this strategy has been successfully applied to several kinds of reactions.¹²

The influence of base also played an important role in the yield. Lower yield was obtained by using NaOH as the base, maybe the strong base could speed up the hydrolysis of ethyl chloroacetate, especially in boiling water (entry 4). Therefore, weaker bases were employed subsequently. To our delight, obvious changes in yield were observed when DMAP (4-Dimethylaminopyridine) (entry 5), DABCO (1,4-Diazabicyclo[2.2.2]octane) (entry 6), NaHCO₃ (entry 7) and TEA (Triethylamine) (entry 8) were evaluated. At last, TEA became the best of choice because it was very cheap and easily available. It is also worthy to mention that it is unnecessary to neutralise the excess TEA after reaction, since it can be easily removed in vacuum because of its low boiling point (88.8 °C), which could simplify the workup and present an additional synthetic advantage. Changing irradiation time had significant effect on the yield too (entries 8, 9). However, it seemed that the reaction reached the chemical equilibrium after irradiation for 8 min (entry 10), because only slight change in yield was detected when longer reaction time than 8 min was adopted (entry 11).

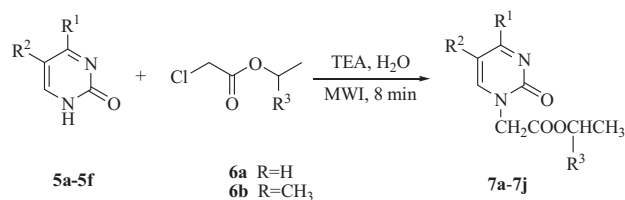
With this promising system in hand, we extended the substrate scope to other uracil derivatives, as outlined in Table 2.

Table 1. Optimization of reaction conditions under MWI^a



Entry	Solvent	Base	Irradiation time / min	Yield / % ^b
1	DMF	K ₂ CO ₃	4	30
2	CH ₃ CN	K ₂ CO ₃	5	52
3	H ₂ O	K ₂ CO ₃	5	60
4	H ₂ O	NaOH	5	47
5	H ₂ O	DMAP	5	65
6	H ₂ O	DABCO	5	67
7	H ₂ O	NaHCO ₃	5	61
8	H ₂ O	TEA	5	68
9	H ₂ O	TEA	7	74
10	H ₂ O	TEA	8	80
11	H ₂ O	TEA	9	79

^aReaction conditions: **5a** (2 mmol), **6a** (6 mmol), base (4 mmol), solvent (5 mL), MWI 250 W (105 °C); ^bIsolated yield after silica gel column chromatography.

Table 2. Microwave-assisted alkylation of uracil derivatives^a

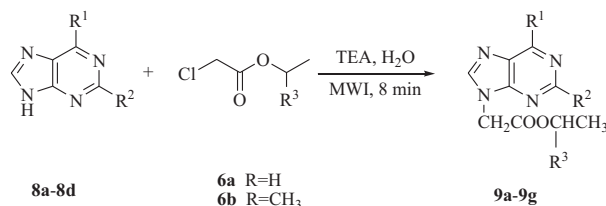
Entry	Uracil derivatives	R ¹	R ²	R ³	Product	Yield / % ^b
1	5a	OH	H	H	7a	80
2	5b	OH	CH ₃	H	7b	76
3	5c	OH	Cl	H	7c	74
4	5d	OH	I	H	7d	77
5	5f	NH ₂	H	H	-	- ^c
6	5e	NHAc	H	H	7e	68
7	5a	OH	H	CH ₃	7f	77
8	5b	OH	CH ₃	CH ₃	7g	70
9	5c	OH	Cl	CH ₃	7h	67
10	5d	OH	I	CH ₃	7i	69
11	5e	NHAc	H	CH ₃	7j	73

Reaction conditions: **5a-5f** (2 mmol), **6** (6 mmol), TEA (4 mmol), H₂O (5 mL), ^aMWI 250 W (105 °C); ^bIsolated yield after silica gel column chromatography; ^cThe desired product was not obtained.

To our delight, all the uracil derivatives were exclusively alkylated at N¹, confirmed by HMBC spectra. Treatment of nucleobases with *iso*-propyl chloroacetate (**6b**) under the same conditions as ethyl chloroacetate (**6a**) successfully afforded corresponding products in moderate yields. Substituting 5-*H* in **5a** with Cl, CH₃, or I had little influence on the yield, indicating the substituent-effect was not obvious (entries 1-4, 7-10).¹³ It was necessary to protect the exocyclic amino group of cytosine (**5f**, entry 5), because more than three spots were detected by TLC. As a result, N⁴-acetyl cytosine (**5e**) was utilized as the precursor of cytosine in order to prevent side reactions,

and then alkylation of **5e** as described above afforded **7e** and **7j** in 68% and 73% yield (entries 6 and 11), respectively.

Application of this procedure to a series of purine derivatives also proved to be successful. The desired products in moderate to high yields were also obtained, as described in Table 3. Gratifyingly, this method gave N⁹-alkylated products, uncontaminated with N⁷-alkylated products. Maybe N⁹ position has higher electron density than N⁷. As was expected, the replacement of **6a** with **6b** resulted in minor changes in yields. It could be concluded that the alkyl side chains in chloroacetate could not

Table 3. Alkylation of purine derivatives in the presence of TEA under MWI^a

Entry	Purine derivatives	R ¹	R ²	R ³	Product	Yield / % ^b
1	8a	Cl	H	H	9a	72
2	8b	Cl	Cl	H	9b	70
3	8c	NH ₂	H	H	9c	- ^c
4	8d	benzylamino	H	H	9d	78
5	8a	Cl	H	CH ₃	9e	69
6	8b	Cl	Cl	CH ₃	9f	74
7	8d	benzylamino	H	CH ₃	9g	81

^aReaction conditions: **8a-8d** (2 mmol), **6** (6 mmol), TEA (4 mmol), H₂O (5 mL), MWI 250 W (105 °C); ^bIsolated yield after silica gel column chromatography; ^cOnly trace amount of **9c** was obtained.

influence their electrophilic reactivities. When 2-*H* in **8a** was substituted by Cl, only neglectable variations in yield were detected (entries 1, 2 and 5, 6). The exocyclic amino group of adenine was also necessary to protect (entry 3),¹⁴ because only trace amount of desired product was obtained. Treatment of 6-chloro purine with benzyl amine under the same conditions as we reported⁸ afforded *N*⁶-benzylamino purine (**8d**) in 86% yield. Then alkylation of it as described above gave rise to **9d** and **9g** in 76% and 80% yields, respectively (entries 4 and 7).

Finally, the formation of **7a** and **9a** was conducted in a pre-heated oil bath (105 °C) under the identical conditions as the microwave method in order to evaluate the effectiveness of our method in comparison with conventional heating method, as shown in Table 4. It had been found that the reaction proceeded with only 12% yield of **7a** and 16% yield of **9a** after 8 min, 52% and 56% after 6 h, demonstrating clearly that our method is superior to the conventional method.

Table 4. Yields of **7a** and **9a**, obtained by the conventional heating method

Product	time / min	Yield / % ^a	time / h	Yield / % ^a
7a	8	12	6	52
9a	8	16	6	56

^aIsolated yield after silica gel column chromatography.

Conclusions

In conclusion, we have developed a rapid, facile, and environmentally benign protocol for the preparation of *N*-(alkoxycarbonylmethyl) nucleobases, which are important building blocks for PNA. All the products are achieved in moderate to high yields, as well as high regioselectivity, assisted by MWI in water as the solvent. Our method has several advantages in terms of yields, mild reaction conditions, short reaction time, and lack of side products. Extension of this method to synthesize other submonomers of PNA is currently in progress in our laboratory.

Experimental

All reagents and solvents were purchased from commercial sources and used without further purification. The nucleobases were a gift from Xinxiang Tuoxin Biochemical Technology & Science Co. Ltd, P. R. China.

Melting points were determined with an XRC-1 micro melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded in DMSO-*d*₆ solutions on a Bruker DPX-400 spectrometer (at 400 MHz and 100 MHz, respectively) using TMS as internal

standard. Chemical shifts (δ) were expressed in ppm and coupling constants (*J*) were given in Hz. Mass spectra were taken with a JEOL JMS-DX302 mass spectrometer. Elemental analyses were performed on an EA-1110 (CE Instruments) instrument. All reactions were performed in a commercially available single-mode microwave apparatus equipped with a high sensitivity IR sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, P. R. China).

General procedure for the synthesis of 1-(ethoxycarbonylmethyl) uracil (7a)

To a mixture of uracil (2 mmol, 0.224 g) and TEA (0.56 mL, 4 mmol) in neat water (5 mL), ethyl chloroacetate (0.65 mL, 6 mmol) was added. Then the mixture was irradiated under reflux at 250 W (105 °C) for 8 min. Subsequently, the reaction mixture was concentrated to dryness under reduced pressure and the residue was purified by column chromatography (EtOAc-EtOH 95:5) to afford **7a** in 80% yield.

The preparation of N⁶-benzylamino purine (8d)

Benzylamine (12 mmol) was added to a stirred suspension of 6-chloropurine (5 mmol) in water (10 mL) in a 50 mL round-bottomed flask. After vibration, the flask was moved into microwave oven and irradiated at 200 W for 10 min. After the reaction completed, the solvent and excess benzylamine were removed in vacuum. The crude product was purified by column chromatography using ethyl acetate as eluent to afford **8d** in 84% yield.

1-(Ethoxycarbonylmethyl) uracil (7a)

White crystals; mp 135-136 °C; ¹H NMR: δ 1.22 (t, 3H, *J* 7.2, CH₃), 4.165 (q, 2H, *J* 7.2, OCH₂), 4.508 (s, 2H, NCH₂), 5.608 (d, 1H, *J* 8, 5-H), 7.612 (d, 1H, *J* 8, 6-H), 11.317 (s, 1H, 3-H).

1-(Ethoxycarbonylmethyl) thymine (7b)

Colorless needle crystals; mp 170-171 °C; ¹H NMR: δ 1.22 (t, 3H, *J* 7.2, CH₂CH₃), 1.771 (s, 3H, 5-CH₃), 4.163 (q, 2H, *J* 7.2, OCH₂), 4.465 (s, 2H, NCH₂), 7.492 (s, 1H, 6-H), 11.31 (s, 1H, 3-H).

5-Chloro-1-(ethoxycarbonylmethyl) uracil (7c)

Pale yellow crystals; mp 168-170 °C; ¹H NMR: δ 1.21 (t, 3H, *J* 7.2, CH₃), 4.161 (q, 2H, *J* 7.2, OCH₂), 4.508 (s, 2H, NCH₂), 8.157 (s, 1H, 6-H), 11.985 (s, 1H, 3-H); ¹³C NMR: δ 14.16 (CH₃), 48.89 (NCH₂), 61.51 (OCH₂),

106.45 (5-C), 143.27 (6-C), 150.23 (2-C), 159.58 (4-C), 167.97 (C=O); HR-MS calc. for $C_8H_9ClN_2O_4$ 232.0251, found 232.0243; Anal. calc. for $C_8H_9ClN_2O_4$ for C 41.31, H 3.90, N 12.04; found C 41.26, H 3.78, N 12.12.

1-(Ethoxycarbonylmethyl)-5-iodo uracil (7d)

White powder; mp 158-160 °C; 1H NMR: δ 1.207 (t, 3H, J 7.2, CH_3), 4.154 (q, 2H, J 7.2, OCH_2), 4.501 (s, 2H, NCH_2), 8.204 (s, 1H, 6-H), 11.787 (s, 1H, 3-H).

N⁴-Acetyl-1-(ethoxycarbonylmethyl) cytosine (7e)

Colorless crystals; mp 190-191 °C; 1H -NMR: δ 1.217 (t, 3H, J 7.2, CH_2CH_3); 2.117 (s, 3H, $COCH_3$), 4.161 (q, 2H, J 7.2, OCH_2), 4.621 (s, 2H, NCH_2), 7.189 (d, 1H, J 7.2, 5-H), 8.044 (d, 1H, J 7.2, 6-H), 10.816 (s, 1H, 3-H).

1-(Iso-propoxycarbonylmethyl) uracil (7f)

Colorless crystals; mp 134-135 °C; 1H NMR: δ 1.203 (t, 6H, J 7.2, CH_3), 4.465 (s, 2H, NCH_2), 4.953 (m, 1H, OCH), 5.608 (q, 1H, J 8 and 2, 5-H), 7.616 (d, 1H, J 8, 6-H), 11.366 (s, 1H, 3-H).

1-(Iso-propoxycarbonylmethyl) thymine (7g)

White powder; mp 159-160 °C; 1H NMR: δ 1.203 (t, 6H, J 7.2, $CH(CH_3)_2$), 1.757 (d, 3H, J 0.4, 5- CH_3), 4.42 (s, 2H, NCH_2), 4.949 (m, 1H, OCH), 7.497 (d, 1H, J 0.4, 6-H), 11.352 (s, 1H, 3-H); ^{13}C NMR: δ 12.03 (5- CH_3), 21.67 ($CH(CH_3)_2$), 48.74 (NCH_2), 69.06 (OCH), 108.65 (5-C), 141.78 (6-C), 151.09 (2-C), 164.47 (4-C), 167.88 (C=O); HR-MS calc. for $C_{10}H_{14}N_2O_4$: 226.0954, found: 226.0948; Anal. calc. for $C_{10}H_{14}N_2O_4$: C 53.09, H 6.24, N 12.38; found: C 52.98, H 6.19, N 12.31.

5-Chloro-1-(iso-propoxycarbonylmethyl) uracil (7h)

Colorless column crystals; mp 176-177 °C; 1H NMR: δ 1.212 (d, 6H, J 6, CH_3), 4.467 (s, 2H, NCH_2), 4.959 (t, 1H, J 6, OCH), 8.15 (s, 1H, 6-H), 11.961 (s, 1H, 3-H); ^{13}C NMR: δ 21.64 ($CH(CH_3)_2$), 49.05 (NCH_2), 69.36 (OCH), 106.42 (5-C), 143.3 (6-C), 150.23 (2-C), 159.6 (4-C), 167.46 (C=O); HR-MS calc. for $C_9H_{11}ClN_2O_4$: 246.0407, found: 246.0396; Anal. calc. for $C_9H_{11}ClN_2O_4$: C 43.83, H 4.50, N 11.36; found: C 43.70, H 4.45, N 11.30.

5-Iodo-1-(iso-propoxycarbonylmethyl) uracil (7i)

Colorless column crystals; mp 220-221 °C; 1H NMR: δ 1.212 (d, 6H, J 6.4, CH_3), 4.463 (s, 2H, NCH_2), 4.955 (m, 1H, OCH), 8.205 (s, 1H, 6-H), 11.77 (s, 1H, 3-H); ^{13}C NMR: δ 21.66 ($CH(CH_3)_2$), 48.87 (NCH_2), 68.24 (OCH), 69.27 (5-C), 150.26 (6-C), 150.81 (2-C), 161.17 (4-C), 167.58 (C=O); HR-MS calc. for $C_9H_{11}IN_2O_4$: 337.9763,

found: 337.9755; Anal. calc. for $C_9H_{11}IN_2O_4$: C 31.97, H 3.28, N 8.29; found: C 31.89, H 3.20, N 8.25.

N⁴-acetyl-1-(iso-propoxycarbonylmethyl) cytosine (7j)

Colorless column crystals; mp 176-178 °C; 1H NMR: δ 1.207 (d, 6H, J 6.4, $CH(CH_3)_2$), 2.102 (s, 3H, $COCH_3$), 4.579 (s, 2H, NCH_2), 4.952 (m, 1H, OCH), 7.19 (d, 1H, J 7.2, 5-H), 8.045 (d, 1H, J 7.2, 6-H), 10.877 (s, 1H, NH); ^{13}C NMR: δ 21.67 ($CH(CH_3)_2$), 24.5 ($COCH_3$), 50.96 (NCH_2), 69.01 (OCH), 95.29 (5-C), 150.79 (6-C), 155.34 (2-C), 163.12 (4-C), 167.57 (C=O), 171.11 (CCH_3); HR-MS calc. for $C_{11}H_{15}N_3O_4$: 253.1063, found: 253.1051; Anal. calc. for $C_{11}H_{15}N_3O_4$: C 52.17, H 5.97, N 16.59; found: C 52.11, H 5.91, N 16.64.

6-Chloro-9-(ethoxycarbonylmethyl) purine (9a)

Colorless sheet crystals; mp 97-98 °C; 1H NMR: δ 1.215 (t, 3H, J 7.2, CH_3), 4.189 (q, 2H, J 7.2, OCH_2), 5.721 (s, 2H, NCH_2), 8.683 (s, 1H, 2-H), 8.978 (s, 1H, 8-H).

2, 6-Dichloro-9-(ethoxycarbonylmethyl) purine (9b)

White powder; mp 112-113 °C; 1H NMR: δ 1.235 (t, 3H, J 7.2, CH_3), 4.214 (q, 2H, J 7.2, OCH_2), 5.248 (s, 2H, NCH_2), 8.706 (s, 1H, 8-H).

6-Benzylamino-9-(ethoxycarbonylmethyl) purine (9d)

White powder; mp 182-183 °C; 1H NMR: δ 1.224 (t, 3H, J 7.2, CH_3), 4.182 (q, 2H, J 7.2, OCH_2), 4.77 (br s, 2H, $PhCH_2$), 5.078 (s, 2H, NCH_2), 7.197-7.375 (m, 5H, Ph), 8.137 (s, 1H, 8-H), 8.2 (s, 1H, 2-H), 8.251 (s, 1H, NH).

6-Chloro-9-(iso-propoxycarbonylmethyl) purine (9e)

Colorless sheet crystals; mp 142-144 °C; 1H NMR: δ 1.216 (d, 6H, J 6, CH_3), 4.983 (m, 1H, OCH), 5.234 (s, 2H, NCH_2), 8.684 (s, 1H, 8-H), 8.792 (s, 1H, 2-H); ^{13}C NMR: δ 21.61 ($CH(CH_3)_2$), 45 (NCH_2), 69.76 (OCH), 130.65 (5-C), 148.08 (8-C), 149.33 (4-C), 152 (6-C), 152.33 (2-C), 166.97 (C=O); HR-MS calc. for $C_{10}H_{11}ClN_4O_2$: 254.0571, found: 254.0561; Anal. calc. 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 22.08.

2,6-Dichloro-9-(iso-propoxycarbonylmethyl) purine (9f)

Yellow powder; mp 109-110 °C; 1H NMR: δ 1.227 (d, 6H, J 6, CH_3), 4.997 (m, 1H, OCH), 5.207 (s, 2H, NCH_2), 8.701 (s, 1H, 2-H); ^{13}C NMR: δ 21.6 ($CH(CH_3)_2$), 45.18 (NCH_2), 69.9 (OCH), 130.29 (5-C), 149.02 (8-C), 150.07 (4-C), 151.47 (6-C), 153.74 (2-C), 166.67 (C=O); HR-MS calc. for $C_{10}H_{10}Cl_2N_4O_2$: 288.0181, found: 288.0169; Anal. calc. for $C_{10}H_{10}Cl_2N_4O_2$: C 41.54, H 3.49, N 19.38; found: C 41.46, H 3.45, N 19.46.

*N*⁶-benzylamino-9-(iso-propoxycarbonylmethyl) purine (**9g**)

Colorless sheet crystals; mp 179–180 °C; ¹H NMR: δ 1.218 (d, 6H, *J* 6, CH₃), 4.723 (br s, 2H, PhCH₂), 4.969 (m, 1H, OCH), 5.037 (s, 2H, NCH₂), 7.186–7.358 (m, 5H, Ph), 8.135 (s, 1H, 8-H), 8.191 (s, 1H, 2-H), 8.318 (s, 1H, NH); ¹³C NMR: δ 21.66 (CH(CH₃)₂), 42.83 (PhCH₂), 44.26 (NCH₂), 69.35 (OCH), 117.4 (5-C), 126.76 (Ph), 127.32 (Ph), 128.35 (Ph), 140.3 (8-C), 141.4 (4-C), 152.73 (2-C), 154.57 (6-C), 167.58 (C=O); HR-MS calc. for C₁₇H₁₉N₅O₂: 325.1539, found: 325.1525; Anal. calc. for C₁₇H₁₉N₅O₂: C 62.75, H 5.89, N 21.52; found: C 62.68, H 5.80, N 21.60.

Acknowledgments

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Supplementary Information

General procedure, characterization of all compounds and ¹H NMR, ¹³C NMR of selected compounds, are available free of charge at <http://jbcbs.sbg.org.br>, as PDF file.

References

- Bisacchi, G. S.; Singh, J.; Godfrey, J. D.; Kissick, T. P.; Mitt, T.; Malley, M. F.; Di Marco, J. D.; Gougoutas, J. Z.; Mueller, R. H.; Zahler, R.; *J. Org. Chem.* **1995**, *60*, 2902; Ewing, D.; Glacon, V.; Mackenzie, G.; Postel, D.; Len, C.; *Tetrahedron Lett.* **2002**, *43*, 3503; Paoli, M. L.; Piccini, S.; Rodriguez, M.; Sega, A.; *J. Org. Chem.* **2004**, *69*, 2881; Boesen, T.; Madsen, C.; Pedersen, D. S.; Nielsen, B. M.; Petersen, A. B.; Petersen, M. A.; Munck, M.; Henriksen, U.; Nielsen, C.; Dahl, O.; *Org. Biomol. Chem.* **2004**, *2*, 1245; Robins, M. J.; Hatfield, P. W.; *Can. J. Chem.* **1982**, *60*, 547; Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G.; *J. Org. Chem.* **1999**, *64*, 28; Geen, G. R.; Kincey, P. M.; *Tetrahedron Lett.* **1992**, *33*, 4609; Garg, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C.; *Chem. Rev.* **1999**, *99*, 3525; Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y.; *Chem. Rev.* **2003**, *103*, 1875.
- Haines, D. R.; Tseng, C. K. H.; Marquez, V. E.; *J. Med. Chem.* **1987**, *30*, 943; Theil, F.; Ballschuh, S.; Flatau, S.; Janta-Lipinski, M.; Matthes, E.; *Bioorg. Med. Chem.* **1998**, *6*, 701; Li, F.; Brogan, J. B.; Gage, J. L.; Zhang, D.; Miller, M. J.; *J. Org. Chem.* **2004**, *69*, 4538.
- Kumar, R.; Nath, M.; Tyrrell, D. L. J.; *J. Med. Chem.* **2002**, *45*, 2032; Amblard, F.; Nolan, S. P.; Gillaizeau, I.; Agrofoglio, L.A.; *Tetrahedron Lett.* **2003**, *44*, 9177; Suwiński, J.; Walczak, K.; *Synthesis* **2001**, 225; Jeffery, A. L.; Kim, J.-H.; Wiemer, D. F.; *Tetrahedron* **2000**, *56*, 5077; Nguyen, C.; Ruda, G. F.; Schipani, A.; Kasinathan, G.; Leal, I.; Musso-Buendia, A.; Kaiser, M.; Brun, R.; Ruiz-Perez, L. M.; Sahlberg, B.-L.; Johansson, N. G.; Gonzalez-Pacanowska, D.; Gilbert, I. H.; *J. Med. Chem.* **2006**, *49*, 4183.
- Sajiki, H.; Yamada, A.; Yasunaga, K.; Tsunoda, T.; Amer, M. F. A.; Hirota, K.; *Tetrahedron Lett.* **2003**, *44*, 2179; Petricci, E.; Radi, M.; Corelli, F.; Botta, M.; *Tetrahedron Lett.* **2003**, *44*, 9181; Larock, R. C.; Wang, Y.; Dong, X.; Yao, T.; *Tetrahedron* **2005**, *61*, 11427; Asakura, J.; Robins, M. J.; *J. Org. Chem.* **1990**, *55*, 4928; Ali, H.; Ahmed, N.; Tessier, G.; Lier, J. E.; *Bioorg. Med. Chem. Lett.* **2006**, *16*, 317; De Clercq, E.; Descamps, J.; Balzarini, J.; Giziewicz, J.; Barr, P. J.; Robins, M. J.; *J. Med. Chem.* **1983**, *26*, 661.
- Nielsen, P. E.; Egholm, M.; Berg, R. H.; Buchardt, O.; *Science* **1991**, *254*, 1497; Nielsen, P. E.; *Acc. Chem. Res.* **1999**, *32*, 624; Hyrup, B.; Egholm, M.; Nielsen, P. E.; Wittung, P.; Norden, B.; Buchardt, O.; *J. Am. Chem. Soc.* **1994**, *116*, 7964; Dueholm, K. L.; Egholm, M.; Behrens, C.; Christensen, L.; Hansen, H. F.; Vulpius, T.; Petersen, K. H.; Berg, R. H.; Nielsen, P. E.; Buchardt, O.; *J. Org. Chem.* **1994**, *59*, 5767; Egholm, M.; Buchardt, O.; Nielsen, P. E.; Berg, R.H.; *J. Am. Chem. Soc.* **1992**, *114*, 1895.
- Kosynkina, L.; Wang, W.; Liang, T.C.; *Tetrahedron Lett.* **1994**, *35*, 5173; Thomson, S. A.; Josey, J. A.; Cadilla, R.; Gaul, M. D.; Hassman, C. F.; Luzzio, M. J.; Pipe, A. J.; Reed, K. L.; Ricca, D. J.; Wiethe, R. W.; Noble, S.A.; *Tetrahedron* **1995**, *51*, 6179; Hudson, R. H. E.; Viirre, R. D.; McCourt, N.; Tse, J.; *Nucleosides, Nucleotides, Nucleic Acids* **2003**, *22*, 1029; Sood, G.; Schwalbe, C. H.; Fraser, W.; *Acta Crystallogr.* **1998**, *54*, 1907; Hudson, R. H. E.; Li, G.; Tse, J.; *Tetrahedron Lett.* **2002**, *43*, 1381; Qu, G.-R.; Li, Y.; Han, S.-H.; *J. Chem. Res.* **2005**, 167; Will, D. W.; Breipohl, G.; Langner, D.; Knolle, J.; Uhlmann, E.; *Tetrahedron* **1995**, *51*, 12069; Gasser, G.; Belousoff, M. J.; Bond, A. M.; Spiccia, L.; *J. Org. Chem.* **2006**, *71*, 7565.
- Anastas, P. T.; Warner, J. C.; *Green Chemistry: Theory and Practice*, Oxford University Press: Oxford, 1998.
- Qu, G.-R.; Han, S.-H.; Zhang, Z.-G.; Geng, M.-W.; Xue, F.; *Can. J. Chem.* **2006**, *84*, 819; Qu, G.-R.; Geng, M.-W.; Han, S.-H.; Zhang, Z.-G.; Xue, F.; *Chin. Chem. Lett.* **2006**, *17*, 1149; Qu, G.; Han, S.; Zhang, Z.; Geng, M.; Xue, F.; *J. Braz. Chem. Soc.* **2006**, *17*, 915.
- Khalafi-Nezhad, A.; Soltani Rad, M. N.; Hakimelahi, G. H.; *Helv. Chim. Acta* **2003**, *86*, 2396; Kappe, C.O.; *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; Varma, R.S.; *Green Chem.* **1999**, *1*, 43; Loupy, A.; *Microwaves in Organic Synthesis*, Wiley-VCH: Weinheim, 2002, p.147; Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gumb, A.; *Green Chem.* **2004**, *6*, 128; Cao, Y.-J.; Lai, Y.-Y.; Cao, H.; Xing, X.-N.; Wang, X.; Xiao, W.-J.; *Can. J. Chem.* **2006**, *84*, 1529.

10. Le, H. P.; Muller, C. E.; *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6139; Peyrottes, S.; Gallier, F.; Bejaud, J.; Perigaud, C.; *Tetrahedron Lett.* **2006**, *47*, 7719; Guezguez, R.; Bougrin, K.; El Akri, K.; Benhida, R.; *Tetrahedron Lett.* **2006**, *47*, 4807; Paolini, L.; Petricci, E.; Corelli, F.; Botta, M.; *Synthesis* **2003**, 1039; Varma, R. S.; Lamture, J.B.; Varma, M.; *Tetrahedron Lett.* **1993**, *34*, 3029; Khalafi-Nezhad, A.; Zarea, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A.; *Synthesis* **2005**, 419; Lanver, A.; Schmalz H.-G.; *Molecules* **2005**, *10*, 508; Khalafi-Nezhad, A.; Soltani Rad, M.N.; Khoshnood, A.; *Synthesis* **2004**, 583.
11. Kormos, C. M.; Leadbeater, N. E.; *Synlett* **2006**, 1663; Gellis, A.; Boufatah, N.; Vanelle, P.; *Green Chem.* **2006**, *8*, 483; Miyazawa, A.; Saitou, K.; Tanaka, K.; Gadda, T. M.; Tashiro, M.; Prakashb, G. K. S.; Olah, G.A.; *Tetrahedron Lett.* **2006**, *47*, 1437; Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C.M.; *Tetrahedron Lett.* **2006**, *47*, 217; Sharma, A.; Kumar, V.; Sinha, A.K.; *Adv. Synth. Catal.* **2006**, *348*, 354; Ju, Y.; Kumar, D.; Varma, R.S.; *J. Org. Chem.* **2006**, *71*, 6697; Paul, S.; Gupta, M.; Singh, P. P.; Gupta, R.; Loupy, A.; *Synth. Commun.* **2005**, *35*, 325.
12. Li, C. J.; Chan, T. H.; *Organic Reactions in Aqueous Media*, John Wiley: New York, 1997; Ju, Y.; Varma, R. S.; *Org. Lett.* **2005**, *7*, 2409; Li, C.-J.; *Chem. Rev.* **2005**, *105*, 3095; Surendra, K.; Krishnaveni, N. S.; Sridhar, R.; Rao, K.R.; *J. Org. Chem.* **2006**, *71*, 5819; Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H.; *Tetrahedron* **2006**, *62*, 3949; Barnard, T. M.; Vanier, G. S.; Collins, M. J.; *Org. Process Res. Dev.* **2006**, *10*, 1233.
13. Khalafi-Nezhad, A.; Zare, A.; Parhami, A.; Soltani Rad, M. N.; Nejabat, G. R.; *Can. J. Chem.* **2006**, *84*, 979.
14. Davies, R. G.; Gibson, V. C.; Hursthouse, M. B.; Light, M. E.; Marshall, E. L.; North, M.; Robson, D. A.; Thompson, I.; White, A. J. P.; Williams, D. J.; Williams, P. J.; *J. Chem. Soc., Perkin Trans. 1*, **2001**, 3365.

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