Ionic liquid-accelerated Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters: a rapid approach to carboacyclic nucleosides synthesis

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Abstract

Ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) efficiently accelerates Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters in the presence of catalytic amount of Cs_2CO_3 under microwave irradiation to give carboacyclic nucleosides in good to high yields and short reaction times.

Keywords: Ionic liquid, Michael addition, nucleobase, Cs_2CO_3, carboacyclic nucleoside, microwave

Introduction

Currently, ionic liquids are the subject of considerable interest as benign reaction media in organic synthesis because of their unique properties, such as non-volatility, non-flammability, recyclability, high thermal stability and ability to dissolve a wide range of materials. During the past decade, a variety of ionic liquids have been demonstrated as efficient and practical alternatives to volatile organic solvents for many important organic reactions, including carbon-carbon, carbon-oxygen, carbon-sulfur carbon-nitrogen and carbon-phosphorus bonds formation.[1]

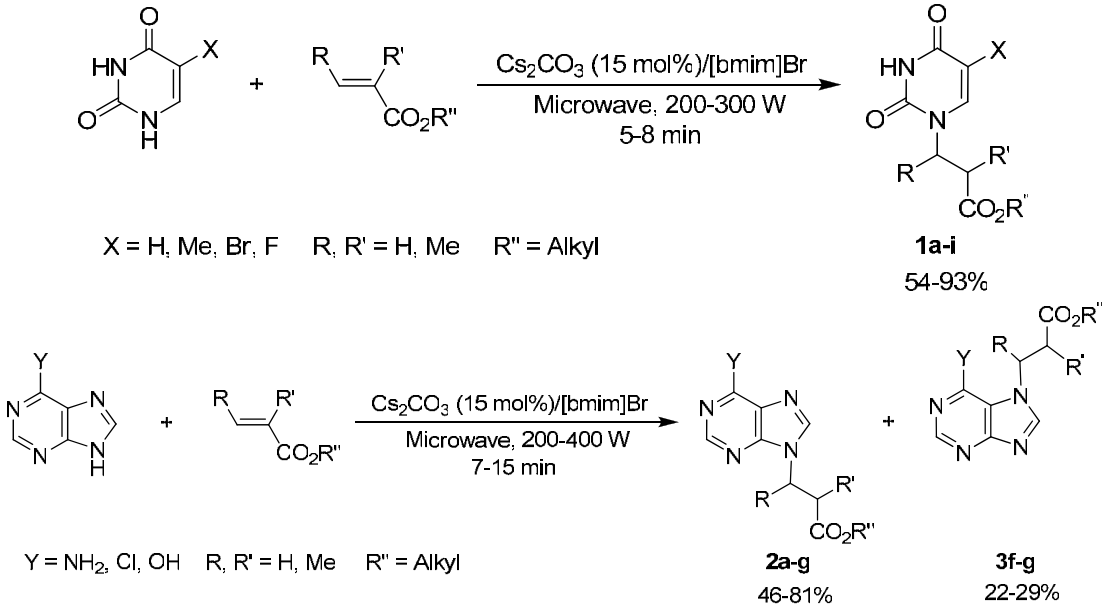
Carboacyclic nucleosides have attracted much interest due to their potential use as antiviral,[2] anticancer,[3] antibiotic,[4] and antipsychotic agents.[5] The aza-Michael addition of nucleobases to electrophilic multiple bonds has been used as a useful route toward carboacyclic nucleosides synthesis.[6-13] Several catalysts have been applied to achieve this transformation, including ZnO-tetrabutylammonium bromide,[6] 1,4-diazabicyclo[2,2,2]octane,[7] *t*-BuOK,[8] NaOEt,[9] PBu_3,[10] enzyme,[11] and [bmim]OH.[12] K_2CO_3 in DMF has been also used for Michael addition of only purine nucleobases to α,β-unsaturated esters as well as acrylonitrile.[13] It is worth noting that the

methods that have been established for the Michael reaction of nucleobases are associated with some drawbacks, such as long reaction time, low yield, low selectivity, the use of expensive catalysts, the use of only unhindered electrophilic alkenes, and no compliance with the green chemistry protocols. Moreover, some methods can be used for Michael reaction of only pyrimidines or only purines.

Cesium carbonate is a commercially available, heterogeneous, reusable and environmentally benign basic reagent that has been used in various organic transformations, such as *N*3-alkylation of *N*1-substituted pyrimidine nucleobases,[14] *N*-arylation of nucleobases,[15] *N*-alkylation of diethyl acetamidomalonate,[16] *O*-alkylation of alcohols,[17] diarylation of ketones,[18] *S*-alkylation of thiols,[19] synthesis of calix[8]crowns by direct alkylation of *p-tert*-butylcalix[8]arene,[20] and synthesis of nucleoside antibiotic Ascamycin.[21]

The application of microwave technology in organic synthesis has been explored extensively within the last decade. Microwave irradiation has been demonstrated to be as an efficient technique for various organic reactions instead of using conventional heating.[21] This technique often leads to a remarkable decrease in reaction times, increased yields, easier workup, matches with the green chemistry protocols, and may enhance the regio- and stereoselectivity of reactions.[22]

Considering the above facts, and in continuation of our previous studies on nucleoside chemistry,[6,7,14,15,23] we report here an efficient green method for the synthesis of *N*-alkyl nucleobases (carboacyclic nucleosides) via microwave-assisted Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters using catalytic amount of Cs_2CO_3 in [bmim]Br (Scheme 1).



Scheme 1. Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters.

Results and Discussion

We have found previously Cs_2CO_3 acts as an efficient basic reagent for *N*3-alkylation of *N*1-substituted pyrimidines,[14] and *N*-arylation of nucleobases.[15] Moreover, this base has been frequently applied for alkylation reactions.[16-21] These subjects encouraged us to use this base as catalyst for *N*-alkylation of nucleobases via Michael addition reaction. Therefore, firstly we used different amounts of Cs_2CO_3 to accomplish Michael addition of uracil (2 mmol) to *n*-butyl acrylate (2.1 mmol) in [bmim]Br (0.5 g) under microwave irradiation (200 W, max. 110 ºC) to provide compound **1b** (Scheme 1). The results are summarized in Table 1. As it can be seen from Table 1, the reaction proceeded efficiently in the presence of 15 mol% of Cs_2CO_3 at 200 W of microwave power and the desired Michael adduct was obtained in 93% yield after 5 min. We also examined the Michael reaction in the presence of other basic catalysts (Table 1). The results showed that the catalysts K_2CO_3, basic Al_2O_3, CaO and MgO afforded lower yields and longer reaction times in comparison to Cs_2CO_3. Furthermore, we extended this reaction to adenine as a purine nucleobase that gave carboacyclic nucleoside **2b** at 200 W of microwave power (max. 140 ºC) in 81% yield within 8 min (Scheme 1). Considering the excellent results obtained from Cs_2CO_3, we applied this catalyst for all other reactions.

Table 1. The influence of different molar ratios of Cs_2CO_3 to substrate as well as other basic catalysts on the reaction of uracil with *n*-butyl acrylate in [bmim]Br under microwave irradiation

Entry	Catalyst (mol%)	Time (min)	Yield[a] (%)
1	Cs_2CO_3 (10)	7	88
2	Cs_2CO_3 (15)	5	93
3	Cs_2CO_3 (20)	5	90
4	Cs_2CO_3 (35)	4	84
5	K_2CO_3 (15)	8	79
6	Basic Al_2O_3 (15)	15	54
7	CaO (15)	15	48
8	MgO (15)	20	32

[a]Isolated yield.

We also investigated the Michael reaction between uracil and *n*-butyl acrylate using Cs_2CO_3 in several ionic liquids, including [bmim]Br, [bmim]Cl, [bmim]BF_4 and [bmim]PF_6 under microwave irradiation (200 W, max. 110 ºC) (Table 2). As Table 2 indicates, higher yields and shorter reaction times were obtained in [bmim]Br and [bmim]Cl. However, [bmim]Br was applied as solvent for all reactions, because, the preparation of this ionic liquid was easier in comparison with the other.

Table 2. The Michael addition of uracil to *n*-butyl acrylate using Cs_2CO_3 in different ionic liquids promoted by microwave irradiation

Entry	Ionic Liquid	Time (min)	Yield[a] (%)
1	[bmim]Br	5	93
2	[bmim]Cl	5	86
3	[bmim]BF_4	7	69
4	[bmim]PF_6	7	73

[a]Isolated yield.

To compare the efficiency of ionic liquid versus the conventional solvents, we examined the model reaction in some conventional solvents. Thus, a mixture of uracil (2 mmol), Cs_2CO_3 (15 mol%) and *n*-butyl acrylate (2.1 mmol) was irradiated in a microwave oven (200 W, max. 110 ºC) in several conventional solvents (5 mL) (Table 3). As it is shown in Table 3, higher yield and shorter reaction time were observed in [bmim]Br with respect to the conventional solvents. Therefore, ionic liquid is an essential factor to promote the Michael reaction.

Table 3. Comparative the Michael addition of uracil to *n*-butyl acrylate using Cs_2CO_3 in conventional solvents versus [bmim]Br under microwave irradiation (200 W, max. 110 ºC)

Entry	Solvent	Time (min)	Yield[a] (%)
1	[bmim]Br	5	93
2	DMF	17	54
3	DMSO	12	62
4	*o*-Xylene	20	21
5	Solvent-free	20	17

[a]Isolated yield.

We also studied the effectiveness of microwave heating in comparison to conventional heating on the Michael reaction. For this purpose, compounds **1b** as well as **2b** were also prepared via Michael addition of uracil as well as adenine to *n*-butyl acrylate in the presence of Cs_2CO_3 in [bmim]Br under thermal conditions. The results are displayed in Table 4. Clearly, the microwave procedure is more efficient. It must be mentioned that increasing the reaction temperature or the reaction times under the conventional heating did not improve the reaction yields.

Table 4. Comparative synthesis of compounds **1b** and **2b** using conventional heating versus the microwave method (200 W)

Compound	Temperature[a] (ºC)	Conventional Heating		Microwave Irradiation	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1b	110	240	54	5	93
2b	140	360	46	8	81

[a]Temperature in microwave and thermal conditions. [b]Isolated yield.

To realize the generality and scope of this method, different pyrimidine and purine nucleobases were introduced to structurally diverse α,β-unsaturated esters (Table 5). As Table 5 indicates, all reactions proceeded efficiently and the desired Michael adducts were obtained in good to high yields and short reaction times. It has been observed that the bulkiness of alkoxy group (-OR) in the α,β-unsaturated esters affected slightly on the Michael reactions. The bulkier alkoxy groups afforded lower yields and longer reaction times (Table 5, entries 1-4 and 10-12). The structure of α,β-unsaturated esters had significant effect on the reaction. When nucleobases were reacted with sterically hindered α,β-unsaturated esters such as ethyl methacrylate and ethyl crotonate, the reaction yields decreased (Table 5, entries 5, 6, 13 and 14). Moreover, higher microwave power was applied in these cases. The presence of substituents (Me, Br and F) on 5-position of the pyrimidine nucleobases had no significant effect on the reaction results (Table 5, entries 7-9). When adenine was used in the Michael reaction, exclusively *N*9-alkylated products were produced (Table 5, entries 10-14). However, Michael reactions of 6-chloropurine and hypoxanthine gave *N*7-isomers beside *N*9-ones in low yields (Table 5, entries 15 and 16).

Table 5. Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters in the presence of Cs_2CO_3 in [bmim]Br promoted by microwave irradiation

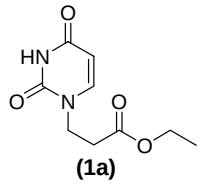
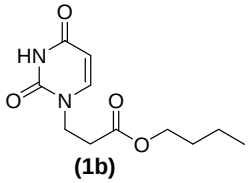
Entry	Product	MW Power (W)	T (º C)	Time (min)	Yield[a] (%)
1[b]	 **(1a)**	200	110	5	90
2[c]	 **(1b)**	200	110	5	93

Table 5. Continued

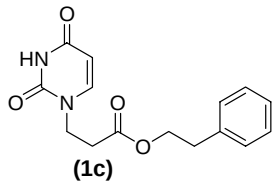
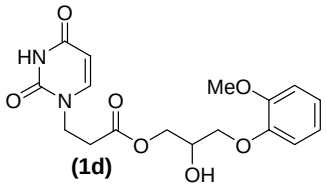
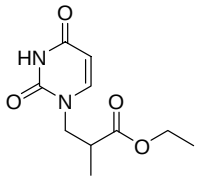
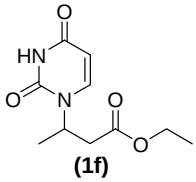
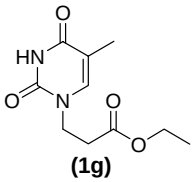
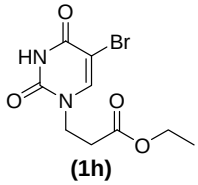
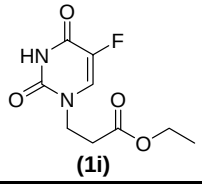
Entry	Product	MW Power (W)	T (º C)	Time (min)	Yield[a] (%)
3[c]	 **(1c)**	200	110	6	87
4[c]	 **(1d)**	200	110	8	84
5[b]	 **(1e)**	300	130	5	67
6[b]	 **(1f)**	300	140	6	54
7[b]	 **(1g)**	200	110	5	87
8[b]	 **(1h)**	200	110	5	88
P9[b]	 **(1i)**	200	110	5	91

Table 5. Continued

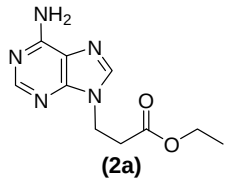
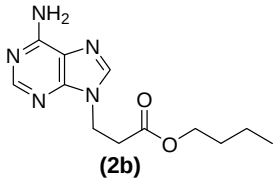
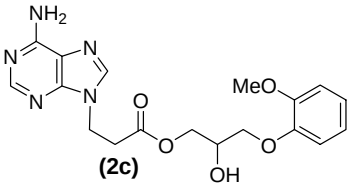
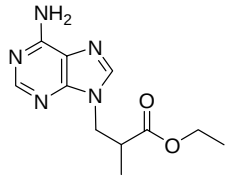
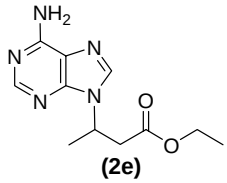
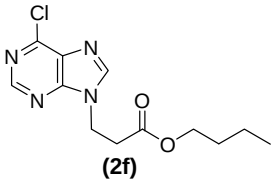
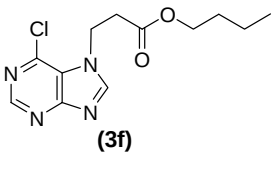
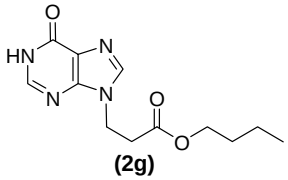
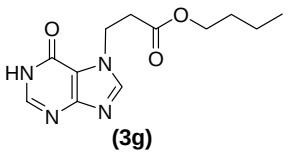
Entry	Product	MW Power (W)	T (° C)	Time (min)	Yield[a] (%)
10[b]	 **(2a)**	200	110[d]	15	76
11[c]	 **(2b)**	200	140	8	81
12[c]	 **(2c)**	200	140	9	73
13[b]	 **(2d)**	300	140	10	59
14[b]	 **(2e)**	400	140	12	46
15[c]	 **(2f)**  **(3f)**	200	130	7	64 29

Table 5. Continued

Entry	Product	MW Power (W)	T (º C)	Time (min)	Yield[a] (%)
16[c]	 **(2g)**	200	140	8	69
	 **(3g)**				22

[a]Isolated yield. [b]In this reaction, the ester/nucleobase ratio (mol/mol) was 1.15/1. [c]In this reaction, the ester/nucleobase ratio (mol/mol) was 1.05/1. [d]This reaction was performed at 110 ºC because of lower boiling point of the corresponding α,β-unsaturated ester, ethyl acrylate.

The interesting behavior of [bmim]Br/Cs_2CO_3 system lies in the fact that it can be re-used after simple washing with Et_2O, rendering thus process more economical. The yields of compound **1b** (model compound) in the 2nd and 3rd uses of the [bmim]Br/Cs_2CO_3 were almost as high as in the first use.

To compare the efficiency and capacity of the present method with the reported methods for the Michael reaction of nucleobases, we have tabulated the results of some these methods in the synthesis of carboacyclic nucleosides **1b**, **1e, 1f, 2b, 2d** and **2e** in Table 6. As it is clear from Table 6, our method have significantly improved Michael addition of pyrimidine nucleobases to sterically hindered α,β-unsaturated esters as well as Michael reaction between purines with either unhindered or hindered α,β-unsaturated esters.

Conclusions

In summary, Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters can be effectively performed in ionic liquids under microwave irradiation. This new method for the synthesis of carboacyclic nucleosides has the advantage of high yield, high selectivity, short reaction time, generality, ease of product isolation, potential for recycling of ionic liquid as well as catalyst, and compliance with the green chemistry protocols.

Table 6. Comparative synthesis of compounds **1b**, **1e**, **1f**, **2b**, **2d** and **2e** using the reported methods versus our method

Compound	Cai et al.[11]		Khalafi-Nezhad et al.[7]		Zare et al.[6]		Present Method	
	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1b	720	44	6	85	25	93	5	93
1e	-	-	10	40	20	48	5	67
1f	-	-	9	27	15	41	6	54
2b	-	-	8	73	20	74	8	81
2d	-	-	12	38	15	37	10	59
2e	-	-	10	24	20	29	12	46

Experimental Section

General Procedures. All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those in the authentic samples. The reactions were carried out using laboratory microwave oven (MW 3000, Landgraf Company, Germany). The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for Michael addition of nucleobases to α,β-unsaturated esters in ionic liquids

To a well-ground mixture of nucleobase (2 mmol) and Cs_2CO_3 (0.098 g, 0.3 mmol) in a microwave vessel was added [bmim]Br (0.5 g) and α,β-unsaturated ester (2.1 to 2.3 mmol) (Table 4), and mixed carefully with a small rod. The resulting mixture was irradiated in a microwave oven for the powers, the temperatures and the times reported in Table 4. Afterward, the reaction mixture was cooled to room temperature and was extracted with Et_2O (3×50 mL). The organic extracts were then combined. After removal of the solvent, the crude product was purified by column chromatography on silica gel eluted with EtOAc/*n*-hexane. After isolation of the product and evaporating of the remaining Et_2O in ionic liquid, the ionic liquid containing the catalyst (Cs_2CO_3/[bmim]Br) was used for next run under identical reaction conditions.

Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1a). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a colorless solid; mp 77-79 °C (Lit.[6] mp 77-79 °C); ^{1}H NMR ($CDCl_3$): δ 1.25 (3H, t, J = 7.0 Hz, CH_3), 2.74 (2H, t, J = 6.0

Hz, O=CCH$_2$), 3.85 (2H, t, *J* = 6.0 Hz, NCH$_2$), 4.11 (2H, q, *J* = 7.0 Hz, OCH$_2$), 5.64 (1H, d, *J* = 7.9 Hz, H$_5$ of uracil), 7.26 (1H, d, *J* = 7.9 Hz, H$_6$ of uracil), 10.19 (1H, s, NH).

Butyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1b). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a colorless solid; mp 62-64 °C (Lit.[6] mp 61-63 °C); ^{1}H NMR (CDCl$_3$): δ 0.92 (3H, t, *J* = 6.8 Hz, CH$_3$), 1.35 (2H, m, CH$_3$C*H*$_2$), 1.56 (2H, m, CH$_3$CH$_2$C*H*$_2$), 2.72 (2H, t, *J* = 5.9 Hz, O=CCH$_2$), 3.80 (2H, t, *J* = 5.9 Hz, NCH$_2$), 4.09 (2H, t, *J* = 6.9 Hz, OCH$_2$), 5.66 (1H, d, *J* = 7.9 Hz, H$_5$ of uracil), 7.25 (1H, d, *J* = 7.9 Hz, H$_6$ of uracil), 10.22 (1H, s, NH).

Phenethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1c). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a pale yellow buff (Lit.[6] buff); ^{1}H NMR (CDCl$_3$): δ 2.71 (2H, t, *J* = 5.8 Hz, O=CCH$_2$), 2.86 (2H, t, *J* = 7.0 Hz, PhCH$_2$), 3.81 (2H, t, *J* = 5.8 Hz, NCH$_2$), 4.32 (2H, t, *J* = 7.0 Hz, OCH$_2$), 5.60 (1H, d, *J* = 7.9 Hz, H$_5$ of uracil), 7.11-7.25 (6H, complex, H$_1$-H$_5$ of phenyl group and H$_6$ of uracil), 10.26 (1H, s, NH).

2-Hydroxy-3-(2-methoxyphenoxy)propyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1d). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a pale yellow oil; IR (neat): 3468, 3170, 3063, 2972, 1732, 1684, 1647 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.75 (2H, t, *J* = 5.9 Hz, O=CCH$_2$), 3.66 (3H, s, CH$_3$), 3.81-3.92 (5H, m), 4.15-4.26 (3H, m), 5.63 (1H, d, *J* = 8.0 Hz, H$_5$ of uracil), 6.71-6.79 (4H, m), 7.20 (1H, d, *J* = 8.0 Hz, H$_6$ of uracil), 10.25 (1H, s, NH); ^{13}C NMR (CDCl$_3$): δ 55.9, 65.4, 68.3, 70.8, 36.6, 45.9, 102.3, 112.3, 114.6, 121.2, 122.0, 145.0, 147.5, 149.7, 151.6, 164.0, 170.6; MS (*m/z*): 364 (M$^+$); Anal. calcd. for C$_{17}$H$_{20}$N$_2$O$_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.25; H, 5.70; N, 7.49.

Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methylpropanoate (1e). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a pale yellow oil (Lit.[7] oil); ^{1}H NMR (CDCl$_3$): δ 1.16-1.21 (6H, m, CH$_2$C*H*$_3$ and CHC*H*$_3$), 2.95 (1H, m, O=CCH), 3.64 (1H, m, one H of NCH$_2$), 3.82 (1H, m, one H of NCH$_2$), 4.12 (2H, q, *J* = 7.0 Hz, OCH$_2$), 5.63 (1H, d, *J* = 7.9 Hz, H$_5$ of uracil), 7.22 (1H, d, *J* = 7.9 Hz, H$_6$ of uracil), 10.22 (1H, s, NH).

Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)butanoate (1f). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a pale yellow solid; mp 115-117 °C (Lit.[7] mp 116-118 °C); ^{1}H NMR (CDCl$_3$): δ 1.22 (3H, t, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 1.39 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 2.65 (1H, m, one H of O=CCH$_2$), 2.86 (1H, m, one H of O=CCH$_2$), 4.11 (2H, q, *J* = 7.0 Hz, OCH$_2$), 4.65 (1H, m , CH$_3$C*H*), 5.65 (1H, d, *J* = 7.9 Hz, H$_5$ of uracil), 7.25 (1H, d, *J* = 7.9 Hz, H$_6$ of uracil), 10.24 (1H, s, NH).

Ethyl 3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1g). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a colorless solid; mp 145-147 °C (Lit.[11] mp 149-150 °C); ^{1}H NMR (CDCl$_3$): δ 1.24 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 1.88 (3H, s, CH$_3$), 2.75 (2H, t, *J* = 6.0 Hz, O=CCH$_2$), 3.83 (2H, t, *J* = 6.0 Hz, NCH$_2$), 4.12 (2H, q, *J* = 7.1 Hz, OCH$_2$), 7.25 (1H, s, H$_6$ of thymine), 10.19 (1H, s, NH).

Ethyl 3-(5-bromo-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1h). Column chromathography on silica gel and eluting with EtOAc/*n*-hexane (2/1) gave a pale yellow solid; mp 139-145 °C (dec.) [(Lit.[11] 143-150 °C (dec.)]; ^{1}H NMR (CDCl$_3$): δ 1.25 (3H, t, *J* = 7.0 Hz,

CH_3), 2.79 (2H, t, J = 5.8 Hz, O=CCH_2), 3.82 (2H, t, J = 5.8 Hz, NCH_2), 4.12 (2H, q, J = 7.0 Hz, OCH_2), 7.61 (1H, s, H_6 of 5-bromouracil), 10.27 (1H, s, NH).

Ethyl 3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (1i). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (2/1) gave a colorless solid; mp 122-124 °C (Lit.[11] mp 124-126 °C); ^{1}H NMR ($CDCl_3$): δ 1.22 (3H, t, J = 7.1 Hz, CH_3), 2.79 (2H, t, J = 5.7 Hz, O=CCH_2), 3.80 (2H, t, J = 5.7 Hz, NCH_2), 4.10 (2H, q, J = 7.1 Hz, OCH_2), 7.28 (1H, s, J = 6.7 Hz, H_6 of 5-fluorouracil), 10.25 (1H, s, NH).

Ethyl 3-(6-amino-9*H*-purin-9-yl)propanoate (2a). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a colorless solid; mp 164-166 °C (Lit.[9] mp 167-168 °C); ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, t, J = 6.9 Hz, CH_3), 2.95 (2H, t, J = 5.9 Hz, O=CCH_2), 4.12 (2H, t, J = 6.9 Hz, OCH_2), 4.49 (2H, t, J = 5.9 Hz, NCH_2), 6.41 (s, 2H, NH_2), 7.96 (1H, s, H_2 of adenine), 8.45 (1H, s, H_8 of adenine).

Butyl 3-(6-amino-9*H*-purin-9-yl)propanoate (2b). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a colorless solid; mp 135-137 °C (Lit.[7] 134-136 °C); ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, J = 6.7 Hz, CH_3), 1.36 (2H, m, CH_3CH_2), 1.58 (2H, m, $CH_3CH_2CH_2$), 2.93 (2H, t, J = 5.8 Hz, O=CCH_2), 4.11 (2H, t, J = 6.8 Hz, OCH_2), 4.53 (2H, t, J = 5.8 Hz, NCH_2), 6.38 (2H, s, NH_2), 7.99 (1H, s, H_2 of adenine), 8.40 (1H, s, H_8 of adenine).

2-Hydroxy-3-(2-methoxyphenoxy)propyl 3-(6-amino-9*H*-purin-9-yl)propanoate (2c). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a pale yellow oil; IR (neat): 3452, 3291, 3115, 3069, 2941, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.96 (2H, t, J = 5.8 Hz, O=CCH_2), 3.72 (3H, s, CH_3); 3.92-4.03 (3H, m), 4.19-4.29 (3H, m), 4.46 (2H, t, J = 5.8 Hz, NCH_2), 6.47 (2H, s, NH_2), 6.68-6.77 (4H, m), 7.94 (1H, s, H_2 of adenine), 8.46 (1H, s, H_8 of adenine); ^{13}C NMR ($CDCl_3$): δ 39.4, 46.9, 56.3, 64.9, 68.6, 71.0, 113.1, 114.8, 120.2, 121.9, 122.7, 140.6, 146.3, 149.4, 150.3, 153.0, 155.8, 171.4; MS (*m/z*): 387 (M^+); Anal. calcd. for $C_{18}H_{21}N_5O_5$: C, 55.81; H, 5.46; N, 18.08. Found: C, 55.98; H, 5.22; N, 18.21.

Ethyl 3-(6-amino-9*H*-purin-9-yl)-2-methylpropanoate (2d). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a colorless solid; mp 133-135 °C (Lit.[7] mp 134-137 °C); ^{1}H NMR ($CDCl_3$): δ 1.12-1.21 (6H, m, CH_2CH_3 and $CHCH_3$), 3.13 (1H, m, O=CCH), 4.09 (2H, q, J = 6.9 Hz, OCH_2), 4.22 (1H, m, one H of NCH_2), 4.43 (1H, m, one H of NCH_2), 6.24 (2H, s, NH_2), 7.83 (1H, s, H_2 of adenine), 8.35 (1H, s, H_8 of adenine).

Ethyl 3-(6-amino-9*H*-purin-9-yl)butanoate (2e). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a colorless solid; mp 101-103 °C (Lit.[7] mp 100-101 °C); ^{1}H NMR ($CDCl_3$): δ 1.14 (3H, t, J = 6.8 Hz, CH_2CH_3), 1.66 (3H, d, J = 4.7 Hz, $CHCH_3$), 2.89 (1H, m, one H of O=CCH_2), 3.15 (1H, m, one H of O=CCH_2), 4.06 (2H, q, J = 6.8 Hz, OCH_2), 4.97 (1H, m, NCH), 6.31 (2H, s, NH_2), 7.80 (1H, s, H_2 of adenine), 8.27 (1H, s, H_8 of adenine).

Butyl 3-(6-chloro-9*H*-purin-9-yl)propanoate (2f). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (1/1) gave a colorless oil (Lit.[6] oil); ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, J = 6.7 Hz, CH_3), 1.33 (2H, m, CH_3CH_2), 1.56 (2H, m, $CH_3CH_2CH_2$), 2.95 (2H, t, J = 5.8 Hz, O=CCH_2), 4.09 (2H, t, J = 6.9 Hz, OCH_2), 4.61 (2H, t, J = 5.8 Hz, NCH_2), 8.52 (1H, s, H_8 of 6-chloropurine), 8.99 (1H, s, H_2 of 6-chloropurine).

Butyl 3-(6-chloro-9*H*-purin-7-yl)propanoate (3f). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (1/1) gave a pale yellow solid; mp 59-61 °C (Lit.[6] mp 60-62 °C); ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, *J* = 6.8 Hz, CH_3), 1.35 (2H, m, CH_3CH_2), 1.60 (2H, m, $CH_3CH_2CH_2$), 2.99 (2H, t, *J* = 5.8 Hz, O=CCH_2), 4.11 (2H, t, *J* = 6.7 Hz, OCH_2), 4.87 (2H, t, *J* = 5.8 Hz, NCH_2), 8.61 (1H, s, H_8 of 6-chloropurine), 9.09 (1H, s, H_2 of 6-chloropurine).
Butyl 3-(6-oxo-1,6-dihydropurin-9-yl)propanoate (2g). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a colorless solid; mp 83-85 °C (Lit.[6] mp 83-85 °C); ^{1}H NMR ($CDCl_3$): δ 0.92 (3H, t, *J* = 6.8 Hz, CH_3), 1.35 (2H, m, CH_3CH_2), 1.58 (2H, m, $CH_3CH_2CH_2$), 2.87 (2H, t, *J* = 5.8 Hz, O=CCH_2), 4.12 (2H, t, *J* = 6.9 Hz, OCH_2), 4.52 (2H, t, *J* = 5.8 Hz, NCH_2), 7.99 (1H, s, H_8 of hypoxanthine), 8.56 (1H, s, H_2 of hypoxanthine), 10.43 (1H, s, NH).
Butyl 3-(6-oxo-1,6-dihydropurin-7-yl)propanoate (3g). Column chromathography on silica gel eluted with EtOAc/*n*-hexane (3/1) gave a colorless solid; mp 100-103 °C (Lit.[6] mp 99-102 °C); ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, *J* = 6.8 Hz, CH_3), 1.38 (2H, m, CH_3CH_2), 1.59 (2H, m, $CH_3CH_2CH_2$), 2.90 (2H, t, *J* = 5.9 Hz, O=CCH_2), 4.08 (2H, t, *J* = 6.8 Hz, OCH_2), 4.74 (2H, t, *J* = 5.9 Hz, NCH_2), 8.10 (1H, s, H_8 of hypoxanthine), 8.64 (1H, s, H_2 of hypoxanthine), 10.48 (1H, s, NH).

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