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Highly efficient synthesis of carboacyclic nucleosides catalyzed by zinc oxide in 1-butyl-3-methylimidazolium bromide (ZnO/[bmim]Br)

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ABSTRACT

Michael addition of pyrimidine and purine nucleobases to substituted as well as unsubstituted α,β-unsaturated esters efficiently proceeds in the presence of catalytic amount of zinc oxide in ionic liquid 1-butyl-3-methylimidazolium bromide (ZnO/[bmim]Br) under microwave irradiation to afford carboacyclic nucleosides, as biologically important compounds, in good to excellent yields and in short reaction times.

Keywords*: Carboacyclic nucleoside, Michael addition, Zinc oxide, Ionic liquid, 1-Butyl-3-methylimidazolium bromide ([bmim]Br), Microwave irradiation.*

1. Introduction

Green chemistry has been defined as a set of principles which reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials. Along this line, room temperature ionic liquids have been emerged as a new class of green solvents because of their unique properties, such as non-volatility, non-flammability, high thermal and chemical stability, reusability, wide liquid-state temperature range and favorable salvation behavior [1-9]. Furthermore, ionic liquids exhibit high polarity due to their ionic nature and a great ability to dissolve polar and non-polar organic compounds [1-4]. Thus, this family of ionic moieties presents several superior properties compared with classical solvents. Moreover, the immiscibility of ionic liquids with some solvents and their very low vapor pressure makes them very good solvents for extraction [1-3]. Up to now, various organic reactions have been carried out and investigated in ionic liquids, including carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-sulfur bonds formation [1-4]. Catalytic activity has been also reported for these green solvents [5-9].

Nucleoside derivatives are known due to possessing various biological activities. Among them, carboacyclic nucleosides have been frequently used as antiviral [10,11], anticancer [12], antibiotic [13], antipsychotic agents [14], receptors [15], and anti-HIV agents [16,17]. Therefore, there is a great deal of interest in the synthesis of this class of compounds. The Michael addition of nucleobases to electrophilic multiple bonds has been used as a useful route towards carboacyclic nucleosides synthesis [18-25]. Several catalysts have been used to achieve this type of Michael reaction, including PBu_3 [18], Cs_2CO_3 in 1-butyl-3-methylimidazolium bromide [19], K_2CO_3 [20], *t*-BuOK/18-crown-6 [21], 1,4-diazabicyclo[2,2,2] octane [22], enzyme [23], 1,8-diazabicyclo[5.4.0] undec-7-ene [24], and lithium hydroxide [25]. However, these reported methods are associated with one or more of the following disadvantages: long reaction times, low yields, low selectivity, the use of stoichiometric amount of catalyst, application of only pyrimidine or only purine nucleobases in the reaction, the use of only unsubstituted electrophilic multiple bonds (inefficiency of the method in the case of substituted electrophilic multiple bonds), and no agreement with the green chemistry protocols. We have previously used zinc oxide-tetrabutylammonium bromide tandem to perform Michael addition of nucleobases to α,β-unsaturated esters for the preparation of carboacyclic nucleosides [26]. The most important drawback of this method is its low

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efficiency when substituted α,β-unsaturated esters such as ethyl metacrylate and ethyl crotonate are applied in the reaction.

In recent years, zinc oxide (ZnO) has attracted the attention of synthetic organic chemists because it is inexpensive, moisture stable, reusable, commercially available and environmentally safe catalyst. Owing to its unique catalytic properties, ZnO has been used in various organic transformations [26-31]. Moreover, the coupling of microwave irradiation with the use of catalysts or mineral-supported reagents provides chemical processes with special attributes, such as enhanced reaction rates, higher yields, better selectivity and improved ease of manipulation [32-35]. Having the above facts in mind, and also in extension of our previous studies on nucleosides chemistry [19,22,25,26,36-39], we report here zinc oxide in ionic liquid 1-butyl-3-methylimidazolium bromide (ZnO/[bmim]Br) as a highly efficient, green and reusable catalytic system for the synthesis of carboacyclic nucleosides *via* Michael addition of pyrimidine and purine nucleobases to α,β-unsaturated esters under microwave irradiation (Schemes 1 and 2). It is noteworthy that this method is highly efficient for both unsubstituted and substituted α,β-unsaturated esters, and has none of the above-mentioned disadvantages at all.

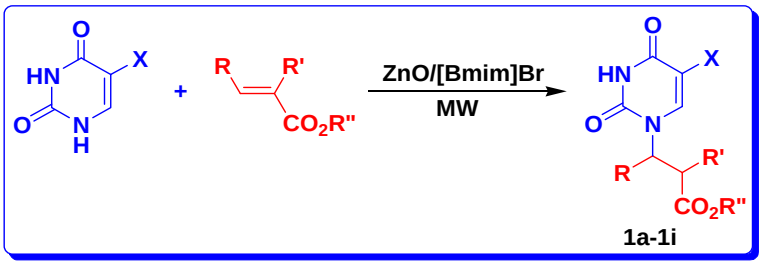
2. Experimental

2.1. General

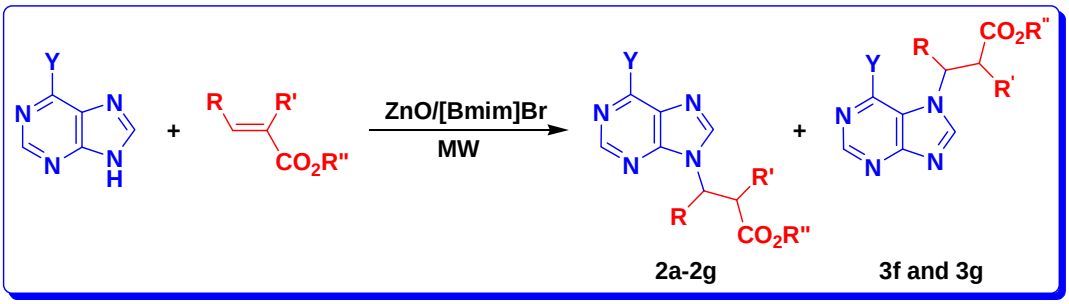
All chemicals were purchased from Merck or Fluka Chemical Companies. All reactions were carried out using domestic microwave oven: MB 245 from Butan Industrial Company. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (250 MHz) and ^{13}CNMR (62.5 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.2. General procedure for the synthesis of carboacyclic nucleosides via Michael reaction

To a well-ground mixture of nucleobase (2 mmol) and ZnO (0.033 g, 0.4 mmol) in a test tube was added [bmim]Br (0.5 g) and α,β-unsaturated ester (2.1 mmol), and mixed carefully with a small rod. The resulting mixture was irradiated in a microwave oven at 200-500 W for several one-minute time intervals. After completion of the reaction (as monitored with TLC), the reaction mixture was cooled to room temperature, Et_2O (50 mL) was added to it, stirred for 1 min, and after standing for 1 min, the mixture was decanted to separate the product from ZnO/[bmim]Br system (in fact, the product is soluble in large amount of Et_2O; however, ZnO/[bmim]Br isn't soluble in this solvent; thus, the catalytic system remained in the vessel after separation of the product). The extraction of the product by Et_2O (as mentioned above) was repeated for three other times. Afterward, the Et_2O extracts were combined, and the solvent (Et_2O) was evaporated to afford the crude product, which was purified by column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/1 to 3/1). After extraction of the product for four times as mentioned above, the remaining ZnO/[bmim]Br in the vessel was warmed at 70 °C for 10 min, and then used for the next run under similar reaction conditions. The catalytic system was recycled and reused for three times without significant decrease in the reaction yields.



Scheme 1. The synthesis of pyrimidine-based carboacyclic nucleosides.



Scheme 2. The synthesis of purine-based carboacyclic nucleosides.

Selected spectral data

*Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) propanoate (**1a**)*:

Colorless solid. m.p.= 77-79 °C (lit. [22] 78-80 °C). ^{1}HNMR ($CDCl_3$): δ= 1.25 (t, 3H, *J*= 7.0 Hz, CH_3), 2.74 (t, 2H, *J* = 6.0 Hz, O=CCH_2), 3.85 (t, 2H, *J* = 6.0 Hz, NCH_2), 4.11 (q, 2H, *J* = 7.0 Hz, OCH_2), 5.64 (d, 1H, *J*= 7.9 Hz, H (5) of the nucleobase), 7.26 (d, 1H, *J*= 7.9 Hz, H (6) of the nucleobase), 10.19 (s, 1H, NH) ppm.

*Butyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) propanoate (**1b**)*:

Colorless solid. m.p.= 62-64 °C (lit. [22] 63-65 °C). ^{1}HNMR ($CDCl_3$): δ= 0.92 (t, 3H, *J* = 6.8 Hz, CH_3), 1.35 (m, 2H, CH_3CH_2), 1.56 (m, 2H, $CH_3CH_2CH_2$), 2.72 (t, 2H, *J* = 5.9 Hz, O=CCH_2), 3.80 (t, 2H, *J*= 5.9 Hz, NCH_2), 4.09 (t, 2H, *J*= 6.9 Hz, OCH_2), 5.66 (d, 1H, *J*= 7.9 Hz, H (5) of the nucleobase), 7.25 (d, 1H, *J*= 7.9 Hz, H (6) of the nucleobase), 10.22 (s, 1H, NH) ppm.

*Benzyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) propanoate (**1c**)*:

Yellow buff (lit. [26] buff). ^{1}HNMR ($CDCl_3$): δ= 2.73 (t, 2H, *J* = 5.9 Hz, O=CCH_2), 3.77 (t, 2H, *J*= 5.9 Hz, NCH_2), 4.89 (s, 2H, OCH_2), 5.56 (d, 1H, *J*= 7.9 Hz, H (5) of the nucleobase), 7.09-7.23 (m, 6H, H (1)-H (5) of the phenyl group and H (6) of the nucleobase), 10.32 (s, 1H, NH) ppm.

*Phenethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) propanoate (**1d**)*:

Yellow buff (lit. [26] buff). ^{1}HNMR ($CDCl_3$): δ= 2.71 (t, 2H, *J*= 5.8 Hz, O=CCH_2), 2.86 (t, 2H, *J*= 7.0 Hz, $PhCH_2$), 3.81 (t, 2H, *J* = 5.8 Hz, NCH_2), 4.32 (t, 2H, *J*= 7.0 Hz, OCH_2), 5.60 (d, 1H, *J* = 7.9 Hz, H (5) of the nucleobase), 7.11-7.25 (m, 6H, H (1)-H (5) of the phenyl group and H (6) of the nucleobase), 10.26 (s, 1H, NH) ppm.

*Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methylpropanoate (**1e**)*:

Pale yellow oil (lit. [22] oil). ^{1}HNMR ($CDCl_3$): δ= 1.14-1.19 (m, 6H, CH_2CH_3 and $CHCH_3$), 2.97 (m, 1H, O=CCH), 3.67 (m, 1H, one hydrogen of NCH_2), 3.87 (m, 1H, one hydrogen of NCH_2), 4.10 (q, 2H, *J*= 6.9 Hz, OCH_2), 5.61 (d, 1H, *J*= 7.9 Hz, H (5) of the nucleobase), 7.25 (d, 1H, *J*= 7.9 Hz, H (6) of the nucleobase), 10.23 (s, 1H, NH) ppm.

*Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) butanoate (**1f**)*:

Pale yellow solid. m.p.= 115-117 °C (lit. [22] 116-118 °C). ^{1}HNMR ($CDCl_3$): δ= 1.22 (t, 3H, *J*= 7.0 Hz, CH_2CH_3), 1.39 (d, 3H, *J*= 6.9 Hz, $CHCH_3$), 2.65 (m, 1H, one H of O=CCH_2), 2.86 (m, 1H, one H of O=CCH_2), 4.11 (q, 2H, *J*= 7.0 Hz, OCH_2), 4.65 (m, 1H, CH_3CH), 5.65 (d, 1H, *J*= 7.9 Hz, H (5) of the nucleobase), 7.25 (d, 1H, *J*= 7.9 Hz, H (6) of the nucleobase), 10.24 (s, 1H, NH) ppm.

*Ethyl 3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (**1g**)*:

Colorless solid. m.p.= 146-148 °C (lit. [23] 149-150 °C). ^{1}HNMR ($CDCl_3$): δ= 1.24 (t, 3H, *J*= 7.1 Hz, CH_2CH_3), 1.88 (s, 3H, CH_3), 2.75 (t, 2H, *J*= 6.0 Hz, O=CCH_2), 3.83 (t, 2H, *J* = 6.0 Hz, NCH_2), 4.12 (q, 2H, *J*= 7.1 Hz, OCH_2), 7.25 (s, 1H, H (6) of the nucleobase), 10.19 (s, 1H, NH) ppm.

*Ethyl 3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (**1h**)*:

Pale yellow solid. m.p.= 121-123 °C (lit. [23] 124-126 °C); ^{1}HNMR ($CDCl_3$): δ= 1.22 (t, 3H, *J*= 7.1 Hz, CH_3), 2.79 (t, 2H, *J*= 5.7 Hz, O=CCH_2), 3.80 (t, 2H, *J*= 5.7 Hz, NCH_2), 4.10 (q, 2H, *J*= 7.1 Hz, OCH_2), 7.28 (s, 1H, *J*= 6.7 Hz, H (6) of the nucleobase), 10.25 (s, 1H, NH) ppm.

*Ethyl 3-(5-bromo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (**1i**)*:

Pale yellow solid. m.p.= 140-145 °C (dec.) (lit. [23] 143-150 °C (dec.)). ^{1}HNMR ($CDCl_3$): δ= 1.25 (t, 3H, *J*= 7.0 Hz, CH_3), 2.79 (t, 2H, *J*= 5.8 Hz, O=CCH_2), 3.82 (t, 2H, *J*= 5.8 Hz, NCH_2), 4.12 (q, 2H, *J*= 7.0 Hz, OCH_2), 7.61 (s, 1H, H (6) of the nucleobase), 10.27 (s, 1H, NH) ppm.

*Ethyl 3-(6-amino-9H-purin-9-yl)propanoate (**2a**)*:

Colorless solid. m.p.= 165-167 °C (lit. [22] 165-167 °C). ^{1}HNMR ($CDCl_3$): δ= 1.19 (t, 3H, *J*= 6.9 Hz, CH_3), 2.95 (t, 2H, *J*= 5.9 Hz, O=CCH_2), 4.12 (t, 2H, *J*= 6.9 Hz, OCH_2), 4.49 (t, 2H, *J*= 5.9 Hz, NCH_2), 6.41 (s, 2H, NH_2), 7.96 (s, 1H, H (2) of the nucleobase), 8.45 (s, 1H, H (8) of the nucleobase) ppm.

*Butyl 3-(6-amino-9H-purin-9-yl)propanoate (**2b**)*:

Colorless solid. m.p.= 135-137 °C (lit. [22] 134-136 °C). ^{1}HNMR ($CDCl_3$): δ= 0.93 (t, 3H, *J* = 6.7 Hz, CH_3), 1.36 (m, 2H, CH_3CH_2), 1.58 (m, 2H, $CH_3CH_2CH_2$), 2.93 (t, 2H, *J*= 5.8 Hz, O=CCH_2), 4.11 (t, 2H, *J*= 6.8 Hz, OCH_2), 4.53 (t, 2H, *J*= 5.8 Hz, NCH_2), 6.38 (s, 2H, NH_2), 7.99 (s, 1H, H (2) of the nucleobase), 8.40 (s, 1H, H (8) of the nucleobase) ppm.

*Ethyl 3-(6-amino-9H-purin-9-yl)-2-methylpropanoate (**2c**)*:

Colorless solid. m.p.= 134-136 °C (lit. [22] m.p. 134-137 °C). ^{1}HNMR ($CDCl_3$): δ= 1.12-1.21 (m, 6H, CH_2CH_3 and $CHCH_3$), 3.13 (m, 1H, O=CCH), 4.09 (q, 2H, *J*= 6.9 Hz, OCH_2), 4.22 (m, 1H, one hydrogene of NCH_2), 4.43 (m, 1H, one hydrogene of NCH_2), 6.24 (s, 2H, NH_2), 7.83 (s, 1H, H (2) of the nucleobase), 8.35 (s, 1H, H (8) of the nucleobase) ppm.

*Ethyl 3-(6-amino-9H-purin-9-yl)butanoate (**2d**)*:

Colorless solid. m.p.= 101-103 °C (lit. [22] 100-101 °C); ^{1}HNMR ($CDCl_3$): δ= 1.15 (t, 3H, *J*= 6.8 Hz, CH_2CH_3), 1.67 (d, 3H, *J*= 4.7 Hz, $CHCH_3$), 2.86 (m, 1H, one hydrogen of $O=CCH_2$), 3.15 (m, 1H, one hydrogen of $O=CCH_2$), 4.06 (q, 2H, *J*= 6.8 Hz, OCH_2), 4.97 (m, 1H, NCH), 6.31 (s, 2H, NH_2), 7.80 (s, 1H, H (2) of the nucleobase), 8.27 (s, 1H, H (8) of the nucleobase) ppm.

*Butyl 3-(6-(benzylamino)-9H-purin-9-yl)propanoate (**2e**)*:

Dark yellow oil (lit. [26] oil). ^{1}HNMR ($CDCl_3$): δ= 0.89 (t, 3H, *J*= 6.8 Hz, CH_3), 1.37 (m, 2H, CH_3CH_2), 1.55 (m, 2H, $CH_3CH_2CH_2$), 2.96 (t, 2H, *J*= 5.7 Hz, $O=CCH_2$), 4.09 (t, 2H, *J* = 6.9 Hz, OCH_2), 4.45 (t, 2H, *J*= 5.7 Hz, NCH_2), 4.78 (s, 2H, $PhCH_2$), 7.14-7.25 (m, 6H, H (1)-H (5) of the phenyl group and NH), 7.94 (s, 1H, H (2) of the nucleobase), 8.45 (s, 1H, H (8) of the nucleobase) ppm.

*Butyl 3-(6-chloro-9H-purin-9-yl)propanoate (**2f**)*:

Colorless oil (lit. [26] oil). ^{1}HNMR ($CDCl_3$): δ= 0.90 (t, 3H, *J* = 6.7 Hz, CH_3), 1.33 (m, 2H, CH_3CH_2), 1.56 (m, 2H, $CH_3CH_2CH_2$), 2.95 (t, 2H, *J*= 5.8 Hz, $O=CCH_2$), 4.09 (t, 2H, *J*= 6.9 Hz, OCH_2), 4.61 (t, 2H, *J*= 5.8 Hz, NCH_2), 8.52 (s, 1H, H (8) of the nucleobase), 8.99 (s, 1H, H (2) of the nucleobase) ppm.

*Butyl 3-(6-chloro-9H-purin-7-yl)propanoate (**3f**)*:

Pale yellow solid. m.p.= 59-61 °C (lit. [26] 60-62 °C). ^{1}HNMR ($CDCl_3$): δ= 0.93 (t, 3H, *J* = 6.8 Hz, CH_3), 1.35 (m, 2H, CH_3CH_2), 1.60 (m, 2H, $CH_3CH_2CH_2$), 2.99 (t, 2H, *J* = 5.8 Hz, $O=CCH_2$), 4.11 (t, 2H, *J* = 6.7 Hz, OCH_2), 4.87 (t, 2H, *J* = 5.8 Hz, NCH_2), 8.61 (s, 1H, H (8) of the nucleobase), 9.09 (s, 1H, H (2) of the nucleobase) ppm.

*Butyl 3-(6-oxo-1,6-dihydropurin-9-yl)propanoate (**2g**)*:

Colorless solid. m.p.= 83-85 °C (Lit. [26] 83-85 °C). ^{1}HNMR ($CDCl_3$): δ= 0.92 (t, 3H, *J* = 6.8 Hz, CH_3), 1.35 (m, 2H, CH_3CH_2), 1.58 (m, 2H, $CH_3CH_2CH_2$), 2.87 (t, 2H, *J*= 5.8 Hz, $O=CCH_2$), 4.12 (t, 2H, *J*= 6.9 Hz, OCH_2), 4.52 (t, 2H, *J*= 5.8 Hz, NCH_2), 7.99 (s, 1H, H (8) of hypoxanthine), 8.56 (s, 1H, H (2) of hypoxanthine), 10.43 (s, 1H, NH) ppm.

*Butyl 3-(6-oxo-1,6-dihydropurin-7-yl)propanoate (**3g**)*:

Colorless solid. m.p.= 99-102 °C (lit. [26] 99-102 °C). ^{1}HNMR ($CDCl_3$): δ= 0.90 (t, 3H, *J*= 6.8 Hz, CH_3), 1.38 (m, 2H, CH_3CH_2), 1.59 (m, 2H, $CH_3CH_2CH_2$), 2.90 (t, 2H, *J*= 5.9 Hz, $O=CCH_2$), 4.08 (t, 2H, *J*= 6.8 Hz, OCH_2), 4.74 (t, 2H, *J*= 5.9 Hz, NCH_2), 8.10 (s, 1H, H (8) of hypoxanthine), 8.64 (s, 1H, H (2) of hypoxanthine), 10.48 (s, 1H, *NH*) ppm.

3. Results and Discussion

Firstly, as a model reaction, we examined Michael addition of uracil (2 mmol) to *n*-butyl acrylate (2.1 mmol) in [bmim]Br (0.5 g) in the presence of different amount of ZnO under microwave irradiation (200 W) (Scheme 1). The results are summarized in Table 1. As it can be seen, the best results were obtained when 20 mol% of ZnO was applied. This reaction was also tested with ethyl crotonate (as a substituted α,β-unsaturated ester) in which the desired Michael adduct was obtained in 84% yield after 11 min at 400 W of microwave power. Considering these excellent results, ZnO/[bmim]Br (20 mol%/0.5 g) catalytic system was used for all other reactions.

To determine whether ionic liquid is an essential factor to promote the reaction, Michael reaction between uracil (2 mmol) and *n*-butyl acrylate (2.1 mmol) was also carried out in some classical solvents (2 mL) using ZnO (20 mol%) at 200 W of microwave power. The results are displayed in Table 2.

As Table 2 indicates, longer reaction times were required in these classical solvents compared with [bmim]Br. Furthermore, the yields in the classical solvents were low. Therefore, it is clear that ionic liquid efficiently accelerates the reaction rate. Ionic liquids have ionic and polar structure; thus, absorbs

Table 1. The influence of different molar ratios of ZnO on the Michael addition of uracil to n-butyl acrylate in [bmim]Br under microwave irradiation (200 W).

Entry	Mol% of ZnO	Time (min)	Yield (%)[a]
1	10	16	78
2	15	14	85
3	20	10	94
4	30	8	86
5	40	5	71

[a]Isolated yield.

Table 2. Comparison of the reaction of uracil with *n*-butyl acrylate using ZnO in different solvents versus [bmim]Br, under microwave irradiation.

Entry	Solvent	Time (min)	Yield (%)[a]
1	-	25	19
2	DMSO	18	46
3	DMF	15	57
4	HMPTA	15	39
5	[Bmim]Br	10	94

[a]Isolated yield.

microwave irradiation and increase the reaction temperature rapidly [22,26]. Moreover, these solvents create a homogeneous reaction media in which starting materials can easily react [22,26].

In another study, the capability and efficiency of microwave heating with respect to conventional heating on the Michael reaction was investigated. For this purpose, compounds **1b** and **2b** were also prepared via Michael addition of uracil as well as adenine to *n*-butyl acrylate in the presence of ZnO in [bmim]Br under thermal conditions (110 °C) (Table 3). In thermal conditions, increasing the temperature more than 110 °C, and the reaction time more than 180 min, did not improve the yields. As Table 3 demonstrates, the microwave method is more efficient.

To assess the scope and generality of the catalyst, the Michael reaction was examined with various pyrimidine and purine nucleobases and structurally diverse α,β-unsaturated esters under the optimized conditions (Tables 4 and 5).

As Tables 4 and 5 shows, the presented method is efficient for both pyrimidine and purine nucleobases as well as unsubstituted and substituted α,β -unsaturated esters. The pyrimidine nucleobases, including uracil, thymine, 5-fluorouracil and 5-bromouracil, were reacted efficiently with unsubstituted α,β-unsaturated esters (ethyl acrylate, *n*-butyl acrylate, benzyl acrylate and phenethyl acryalate) and substituted esters (ethyl methacrylate and ethyl crotonate) to afford the corresponding carboacyclic nucleosides in high yields and short reaction times (Table 4). Nevertheless, the Michael reactions of pyrimidine nucleobases with substituted esters were performed at higher power of microwave in comparison with the unsubstituted ones. Furthermore, the Michael reactions were progressed with high regioselectivity. Michael reaction of pyrimidine nucleobases afforded *N*1-alkylated pyrimidines in high to excellent yields (Table 4). In these cases, *N*1,*N*3-dialkylated products were also produced in trace yields. The purine nucleobases, including adenine, *N*-benzyl-9*H*-purin-6-amine, 6-chloropurine and hypoxanthine, were also effectively added to unsubstituted α,β -unsaturated esters (ethyl acrylate and *n*-butyl acrylate) and substituted ones (ethyl methacrylate and ethyl crotonate) to give the desired products in high yields and short reaction times (Table 5). The reactions of purine nucleobases with substituted esters were also carried out at higher power of microwave with respect to the unsubstituted esters. Among the purine nucleobases, adenine and *N*-benzyl-9*H*-purin-6-amine were alkylated dominantly at the *N*9 positions (Table 5, entries 1-5); however, Michael reaction of 6-chloropurine and hypoxanthine afforded mainly *N*9-alkylated products with the *N*7 products in low yields (Table 5, entries 6 and 7).

The efficiency and capacity of our method was also compared with the reported methods for the Michael reaction of nucleobases (Table 6). For this purpose, we have tabulated the results of the reported methods for the preparation of compounds **1b**, **1e**, **1f**, **2c** and **2d**. As Table 6 indicates, our method significantly improved this type of Michael reaction, and afforded the products in higher yields with respect to the reported ones. The reaction times were also shorter than various methods. Moreover, our protocol was efficient in the case of both pyrimidine and purine nucleobases, and also both substituted and unsubstituted α,β-unsaturated esters (i.e. our method was general). The other advantages of the procedure include high selectivity, low cost, ease of product isolation, potential for recycling of the catalytic system and good compliance with the green chemistry protocols.

There are also some methods for Michael addition of nucleobases to electron-deficient unsaturated bonds in which compounds **1b**, **1e**, **1f**, **2c** and **2d** have not been synthesized. We have displayed the range of yields and reaction times of those protocols in Table 7. The data in Table 7 show that our catalyst afforded the products in higher yields and shorter reaction times. Furthermore, Michael addition of nucleobases to substituted electron-deficient unsaturated bonds has not been achieved using the reported catalysts displayed in Table 7. Thus, ZnO/[bmim]Br was more efficient than the reported catalysts.

4. Conclusions

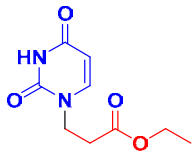
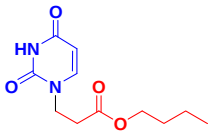
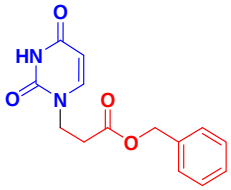
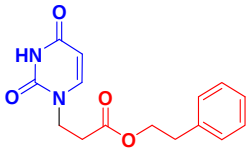
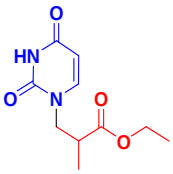
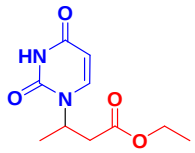
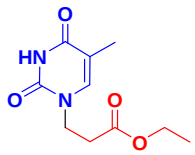
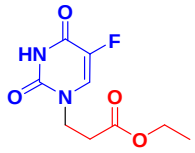
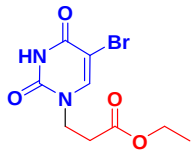
In conclusion, we have demonstrated that the Michael reaction between nucleobases and unsubstituted as well as substituted α,β-unsaturated esters could be effectively performed in ionic liquids using ZnO under microwave conditions. In this reaction, carboacyclic nucleosides, as biologically important compounds, were obtained in good to high yields and in short reaction times.

Table 3. The synthesis of compounds **1b** and **2b** using conventional heating (110 °C) and microwave method.

Entry	Compound	Time (min)	Yield (%)[a]
		Thermal[b]/MW	Thermal[b]/MW
1	**1b**	180/10	49/94 (200 W)
2	**2b**	180/11	36/87 (300 W)

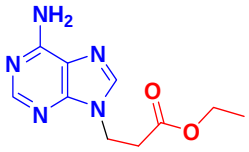
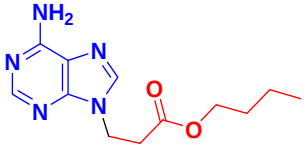
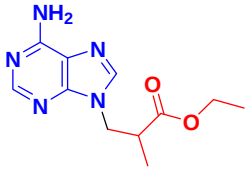
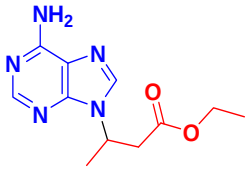
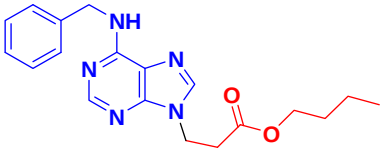
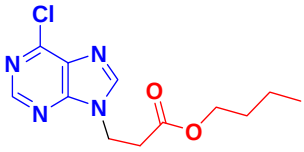
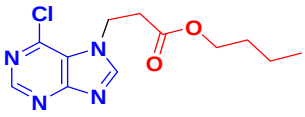
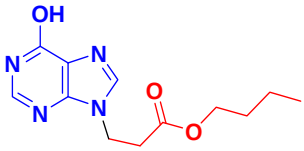
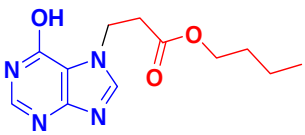
[a]Isolated yield.

Table 4. The Synthesis of carboacyclic nucleosides *via* the Michael addition of pyrimidine nucleobases to α,β-unsaturated .esters using ZnO/[bmim]Br promoted by microwave irradiation

Product number	Product	MW Power (W)	Time (min)	Yield (%)[a]
1a[b]		200	10	91
1b		200	10	94
1c		200	12	92
1d		200	12	91
1e[b]		300	12	88
1f[b]		400	11	84
1g[b]		200	12	89
1h[b]		200	10	92
1i[b]		200	10	90

[a]Isolated yield.
[b]The ester/nucleobase ratio (mol/mol) was 1.25/1.

Table 5. The synthesis of carboacyclic nucleosides *via* the Michael addition of purine nucleobases to α,β-unsaturated esters using ZnO/[bmim]Br under microwave irradiation.

Entry	Product	Product number	MW Power (W)	Time (min)	Yield (%)[a]
1[b]		**2a**	300	11	85
2		**2b**	300	11	87
3[b]		**2c**	400	12	71
4[b]		**2d**	500	10	60
5		**2e**	300	10	92
6[c]		**2f**	300	9	73
		**3f**			22
7[c]		**2g**	300	13	75
		**3g**			19

[a]Isolated yield.

[b]The ester/nucleobase ratio (mol/mol) was 1.25/1.

[c]*N*7-Alkylated product was also produced beside *N*9 isomer.

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

1b	**1e**	**1f**	**2c**	**2d**	Ref.
Time[a]/Yield[b]	Time[a]/Yield[b]	Time[a]/Yield[b]	Time[a]/Yield[b]	Time[a]/Yield[b]	
10/94	12/88	11/84	12/71	10/60	-[c]
5/93	5/67	6/54	10/59	12/46	[19]
6/85	10/40	9/27	12/38	10/24	[22]
28/88	42/77	45/62	-[d]	-[d]	[25]
25/93	20/48	15/41	15/37	20/29	[26]

[a]Reaction time in min.
[b]Yield in %.
[c]Our method.
[d]In this work, the michael reaction of purine nucleobases has not been reported.

Table 7. The results of Michael addition of nucleobases to electron-deficient unsaturated bonds using the reported catalysts and our catalyst.

Catalyst	Range of reaction times	Range of yields (%)	Ref.
ZnO/[bmim]Br	9-13 min	60-94	-[a]
K_2CO_3	4-24 h	64-92	[20]
t-BuOK/18-crown-6	2-40 h	10-41	[21]
1,8-Diazabicyclo[5.4.0]undec-7-ene[b]	2 h	7-91	[24]
1-Butyl-3-methylimidazoliumhydroxide[b]	1-2 h	89-94	[40]
D-aminoacylase amino(an enzyme)[c]	48-72 h	39-92	[41]

[a]Our method.
[b]In this work, only pyrimidine-based carboacyclic nucleosides have been prepared.
[c]In this work, only Michael addition of *N*-benzyl-9*H*-purin-6-amine to α,β-unsaturated esters have been achieved.

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