An Efficient Protocol for the Synthesis of Carboacyclic Nucleosides via *Aza*-Conjugate Addition Reaction

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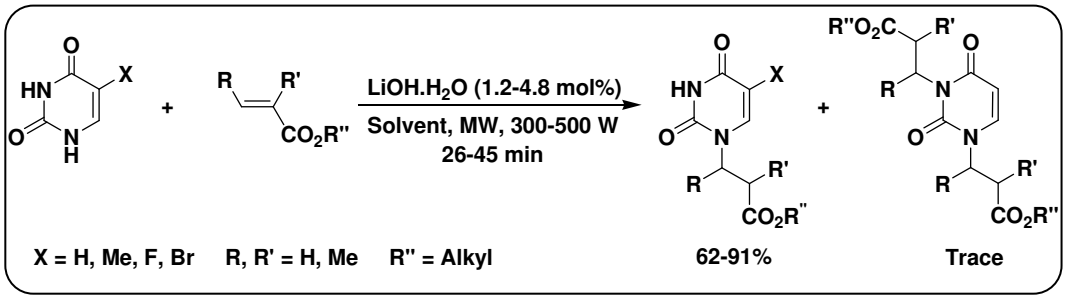
ABSTRACT: *A new efficient method for the synthesis of carboacyclic nucleosides as biologically interesting compounds via aza-conjugate addition of pyrimidine nucleobases to α,β-unsaturated esters in the presence of catalytic amount of LiOH.H_2O (1.2-4.8 mol%) under microwave irradiation is described. This method affords the title compounds in good to excellent yields and in short reaction times.*



KEY WORDS: *Carboacyclic nucleoside, Aza-conjugate addition reaction, Pyrimidine nucleobase, α,β-unsaturated ester, Microwave.*

INTRODUCTION

The *aza*-conjugate addition of nucleobases to electrophilic multiple bonds is of importance as this reaction provides a direct and appealing route toward carboacyclic nucleosides synthesis [1-10]. Several biological activities have been reported for this class of compounds, such as anticancer [11,12], antiviral [13], antipsychotic [14], antibiotic [15], and receptor properties [16]. Catalysts such as KF/Al_2O_3 [1], PBu_3 [2], zinc oxide/tetrabutylammonium bromide [3], *t*-BuOK [4], K_2CO_3 [5], Cs_2CO_3/[bmim]Br [6], NaOEt [7],

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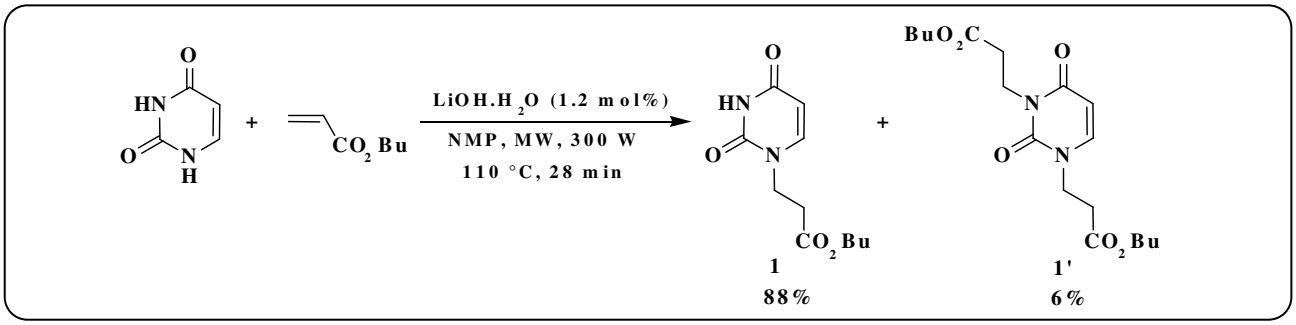
Table 1: Influence of different molar ratios of $LiOH.H_2O$ on the reaction between uracil and n-butyl acrylate.

Entry	Mol% of $LiOH.H_2O$	Time (min)	Yield[a] (%)	
			Compound 1	Compound 1'
1	1	35	83	4
2	1.2	28	88	6
3	1.5	26	78	11
4	2	22	64	19

[a]*Isolated yield.*



Scheme 1

1,4-diazabicyclo[2,2,2]octane [8], and enzyme [9] have been applied for the *aza*-conjugate addition of nucleobases to electrophilic multiple bonds. However, these reported methods have one or more of the following drawbacks: long reaction time, low yield, low selectivity, the use of large amount of catalyst, application of only unsubstituted electrophilic multiple bonds, and the use of expensive catalysts. Moreover, the *aza*-conjugate addition of pyrimidine nucleobases to electrophilic double bonds has been performed using [bmim]OH [10]. But, this method is not general, and in which among the different pyrimidine nucleobases and alkyl acrylates; uracil, 5-fluorouracil and thymine have been added to only methyl acrylate. Furthermore, in this report, substituted α,β-unsaturated esters such as ethyl methacrylate or ethyl crotonate has not been used. Another disadvantage of this method is application of large amount of the catalyst in the reaction. Thus, search for finding a rapid, efficient, inexpensive and general procedure for the *aza*-conjugate reaction of nucleobases is still of practical importance.

In the last few years, Microwave-induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid synthesis, and many researchers have described accelerated organic reactions, with a large number of papers proving the synthetic utility of MORE chemistry in routine organic synthesis [17-20]. It can be termed "e-chemistry" because it is easy, effective, economical and eco-friendly and is believed to be a step toward green chemistry [19].

Having the above facts in mind, we report here a new efficient method for the preparation of carboacyclic nucleosides via *aza*-conjugate addition of pyrimidine nucleobases to α,β-unsaturated esters using $LiOH.H_2O$ (1.2-4.8 mol%) under microwave irradiation (300-500 W) (scheme 1). Interestingly, our method has none of the above-mentioned disadvantages at all.

RESULTS AND DISCUSSION

At first, *aza*-conjugate addition of uracil (2 mmol) to *n*-butyl acrylate (2.1 mmol) was examined in the presence of different molar ratios of $LiOH.H_2O$ in 1-methylpyrrolidin-2-one (NMP) (5 mL) under microwave irradiation (300 W, 110 °C) to give carboacyclic nucleoside **1**, and *N*1,*N*3-dialkylated uracil **1'** as a side product (Scheme 1). The results are summarized in Table 1. As it can be seen in Table 1, higher yield of compound **1** was obtained when 1.2 mol% of the catalyst was used.

In the next step, the capability and the efficiency of microwave heating compared with conventional heating on the reaction was investigated. For this purpose, compounds **1** and **1'** were also prepared via the

Table 2: The synthesis of carboacyclic nucleosides via aza-conjugate addition of pyrimidine nucleobases to α,β-unsaturated esters using $LiOH.H_2O$ under microwave irradiation.

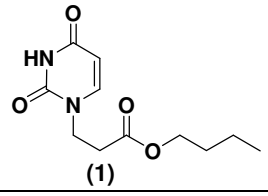
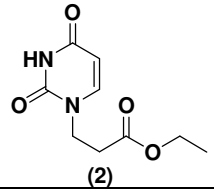
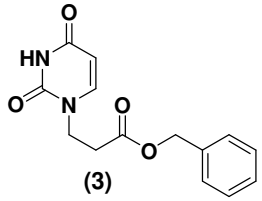
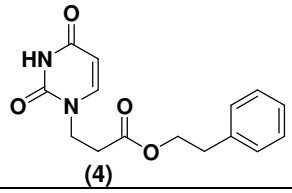
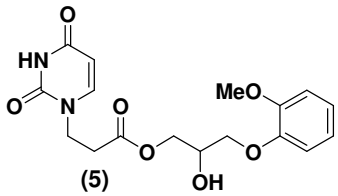
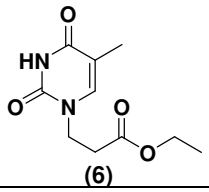
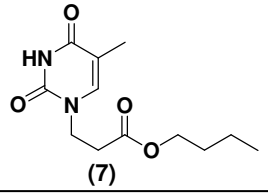
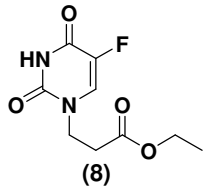
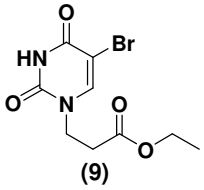
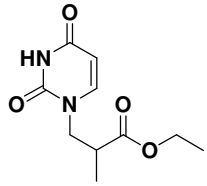
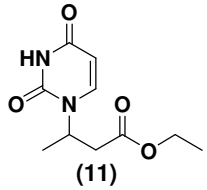
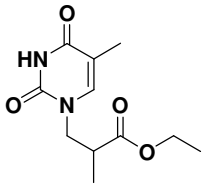
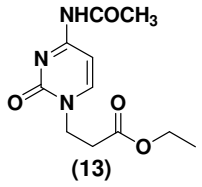
Entry	Product	Solvent	Power (W)	Temperature (°C)	Time (min)	Yield[a] (%)
1	 (1)	NMP	300	110	28	88
2[b]	 (2)	NMP	300	110	28	87
3	 (3)	NMP	300	110	32	86
4	 (4)	NMP	300	110	34	84
5	 (5)	NMP	300	110	38	83
6[b]	 (6)	NMP	300	110	30	87
7	 (7)	NMP	300	110	30	89

Table 2: Continued

Entry	Product	Solvent	Power (W)	Temperature (°C)	Time (min)	Yield[a] (%)
8[b]	 (8)	NMP	300	110	26	91
9[b]	 (9)	NMP	300	110	28	86
10	 (10)	[Bmim]Br	450	130	42	77
11[c]	 (11)	[Bmim]Br	500	135	45	62
12	 (12)	[Bmim]Br	450	130	45	74
13[b]	 (13)	NMP	300	110	30	82

a) Isolated yield.

b) In this reaction, the α,β-unsaturated ester/nucleobase (mol/mol) ratio was 1.1/1.

c) This reaction was carried out in the presence of 4.8 mol% of the catalyst.

aza-conjugate reaction between uracil and *n*-butyl acrylate in NMP under thermal conditions (110 °C). However, these conditions were not efficient, and afforded compounds **1** and **1'** in 48 and 21%, respectively, after 150 min. Increasing the temperature or the reaction time didn't improve the yield.

To assess the generality and the scope of the method, different pyrimidine nucleobases were introduced to structurally diverse α,β-unsaturated esters. The results are displayed in Table 2. As Table 2 indicates, all reactions proceeded efficiently and the desired carboacyclic nucleosides were obtained in good to excellent yields and in short reaction times. The results showed that the bulkiness of alkoxy group (-OR) of α,β-unsaturated esters had little effect on the reaction results; the yields slightly decreased, and the reaction times enhanced when nucleobases were added to the esters possessing bulky alkoxy group (Table 2, entries 3-5). The presence of substituents (Me, F and Br) on 5-position of the nucleobases had no significant effect on the reaction times and the yields (Table 2, entries 6-9 and 12). The structural influence of α,β-unsaturated esters on the reaction was also studied. Lower yields of the products were obtained when nucleobases were introduced to the sterically hindered α,β-unsaturated esters, ethyl methacrylate and ethyl crotonate (Table 2, entries 1 0-12). The *aza*-conjugate reaction of *N*-(2-oxo-1,2-dihydropyrimidin-4-yl)acetamide was also successfully performed (Table 2, entry 13). Amazingly, we observed that the reaction of nucleobases with unsubstituted α,β-unsaturated esters (alkyl acrylates) using $LiOH.H_2O$ was efficiently performed in NMP (Table 2, entries 1-9 and 13); however, the best solvent for the substituted esters (ethyl methacrylate and ethyl crotonate) was ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) (Table 2, entries 10-12).

Interestingly, the regioselectivity of our method was high. All nucleobases were alkylated at *N*1 positions, and the yields of *N*1,*N*3-dialkylated products were trace.

In conclusion, we have developed a new method for the *aza*-conjugate addition of nucleobases to α,β-unsaturated esters. This method for the preparation of carboacyclic nucleosides is associated with many advantages, including efficiency, generality, high yield, high selectivity, short reaction time, low cost, and simplicity.

EXPERIMENTAL SECTION

All chemicals were purchased from Merck or Fluka Chemical Companies. All reactions were carried out using laboratory microwave oven (MicroSYNTH, MILESTONE Company, Italy). The ^1H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General Procedure for the Synthesis of Carboacyclic Nucleosides in NMP

To a mixture of nucleobase (2 mmol), α,β-unsaturated ester (2.5 mmol) and $LiOH.H_2O$ (0.002 g, 0.048 mmol, 2.4 mol%) in a microwave vessel was added [bmim]Br (1 g) and the vessel was sealed. The resulting mixture was irradiated and stirred in a microwave oven for suitable time, power and temperature (Table 2). Afterward, the reaction mixture was cooled to room temperature and was extracted with Et_2O (3×50 mL). The organic extracts were then combined, the solvent was evaporated, and the crude product was purified by column chromatography on silica gel eluted with EtOAc/n-hexane (2/1).

Selected Spectral Data of the Products

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

Colorless solid, m.p. 62-64 °C (Lit. [1] m.p. 62-64 °C).

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

Colorless solid, m.p. 77-79 °C (Lit. [1] m.p. 77-79 °C).

Benzyl 3-(2,4- Dioxo -3,4- dihydropyrimidin -1(2H)-yl) propanoate (3)

Pale yellow buff (Lit. [3] buff). ^1H NMR ($CDCl_3$) 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 uracil), 7.09-7.23 (complex, 6H, H-1 to H-5 of the phenyl group and H-6 of uracil), 10.32 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 37.6, 45.3, 66.5, 101.4, 127.9, 128.8, 129.7, 132.0, 144.8, 151.3, 163.3, 171.5.

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

Pale yellow buff (Lit. [3] buff). ^1H NMR ($CDCl_3$) 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 uracil), 7.11-7.25 (6H, complex, H-1 to H-5 of the phenyl group and H-6 of uracil), 10.26 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 34.7, 36.2, 46.4, 65.0, 102.1, 126.3, 128.1, 128.8, 131.9, 145.3, 151.0, 164.1, 170.3.

2-Hydroxy-3-(2-methoxyphenoxy)propyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (5)

Pale yellow oil (Lit. [6] oil). ^{1}H NMR ($CDCl_3$) δ: 2.75 (t, 2H, J = 5.9 Hz, O=CCH_2), 3.66 (s, 3H, CH_3), 3.81-3.92 (m, 5H), 4.15-4.26 (m, 3H), 5.63 (d, 1H, J = 8.0 Hz, H-5 of uracil), 6.71-6.79 (m, 4H), 7.20 (d, 1H, J = 8.0 Hz, H-6 of uracil), 10.25 (s, 1H, 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.

Ethyl 3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (6)

Colorless solid, m.p. 146-148 °C (Lit. [1] m.p. 146-148 °C).

Butyl 3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (7)

Colorless solid, m.p. 82-84 °C (Lit. [9] m.p. 85-86 °C).

Ethyl 3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (8)

Colorless solid, m.p. 121-123 °C (Lit. [1] m.p. 122-124 °C).

Ethyl 3-(5-bromo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoate (9)

Pale yellow solid, m.p. 139-144 °C (dec.) [(Lit. [9] m.p. 143-150 °C (dec.)].

Ethyl 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methylpropanoate (10)

Pale yellow oil (Lit. [8] oil). ^{1}H NMR ($CDCl_3$) δ: 1.16-1.21 (m, 6H, CH_2CH_3 and $CHCH_3$), 2.95 (m, 1H, O=CCH), 3.64 (m, 1H, one H of NCH_2), 3.82 (m, 1H, one H of NCH_2), 4.12 (q, 2H, J = 7.0 Hz, OCH_2), 5.63 (d, 1H, J = 7.9 Hz, H-5 of uracil), 7.22 (d, 1H, J = 7.9 Hz, H-6 of uracil), 10.22 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 14.4, 15.5, 39.0, 52.0, 61.5, 102.2, 145.0, 151.6, 164.8, 174.9.

Ethyl 3-(2,4- dioxo -3,4- dihydropyrimidin -1(2H)-yl) butanoate (11)

Pale yellow solid, m.p. 115-117 °C (Lit. [1] m.p. 116-118 °C).

Ethyl 2- Methyl -3- (5- methyl -2,4- dioxo -3,4-dihydropyrimidin -1(2H)-yl)propanoate (12)

Pale yellow solid, m.p. 40-42 °C (Lit. [1] m.p. 41-43 °C).

Ethyl 3-(4- Acetamido -2- oxopyrimidin -1(2H)-yl) propanoate (13)

Colorless solid, m.p. 127-129 °C (Lit. [3] m.p. 127-129 °C).

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