Microwave-Assisted Michael Addition of Some Pyrimidine and Purine Nucleobases with α,β-Unsaturated Esters: A Rapid Entry into Carboacyclic Nucleoside Synthesis

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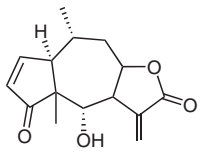
Abstract: An efficient procedure for the synthesis of some carboacyclic nucleosides via microwave-assisted Michael addition of various nucleobases to α,β-unsaturated esters in the presence of tetrabutylammonium bromide (TBAB) and DABCO is described. Using this method, some pyrimidine and purine nucleobases have been alkylated regioselectively in moderate to high yields and short reaction time.

Key words: carboacyclic nucleosides, microwave, Michael addition, nucleobases, α,β-unsaturated esters

Microwave-assisted organic reactions have been used as an effective technique in organic synthesis. Microwave irradiation often leads to large reduction in reaction time, increased yields, easier workup, matches with green chemistry protocols, and can enhance the regio- and stereoselectivity of reactions.[1,2a] Furthermore, its unique capabilities allow its application in reactions which are difficult or impossible to carry out by means of customary conventional methods.[3] In fact, the high usefulness of microwave-assisted synthesis, encouraged us to increase the efficiency of several organic transformations and synthesis.[2]

The reaction of nucleobases with α,β-unsaturated esters is significant as this reaction provide a direct and appealing route into carboacyclic nucleoside synthesis.[4] This class of compounds has found particular interest for a variety of biological studies.[5] Moreover, it is demonstrated that some α,β-unsaturated ketones as well as α,β-methylene lactones could be served as alkylating agent useful in cancer therapy, as their reaction with electron-rich site of nucleobases by conjugated addition (Michael addition) inhibits DNA replication in tumor cells.[6] The naturally occurring sesquiterpene helenalin (Figure 1) is exemplified to have conspicuous antitumor activities.[7] Therefore, the reaction of nucleobases with α,β-unsaturated carbonyl compounds seems to be significant from the standpoint of medicinal chemistry.

Michael addition reactions have been used in the formation of carbon–oxygen,[8a] carbon–sulfur,[8b] and carbon–carbon[8c,d] bonds. However, they normally require strong bases or Lewis acids to activate nucleophiles or Michael acceptors. For example, NaOEt[4a,d] and K_2CO_3[4h] catalyze the Michael reaction of various Michael acceptors with pyrimidine and purine nucleobases. Catalysts, such as basic clay,[9a] transition metal complexes,[9b–f] lanthanides,[9g] proline,[9h] salen-Al complex,[9i] and enzyme[4c] have been used to facilitate Michael additions. The conventional thermal methods for Michael additions of nucleobases to α,β-unsaturated esters are associated with several drawbacks: (i) to dissolve the nucleobases in reaction media the use of solvents such as DMF or DMSO is inevitable, therefore, the workup of reaction is not only cumbersome but also the green aspect of reaction is annihilated by using DMF; (ii) long reaction times; and (iii) low reaction yields and selectivity. To overcome these drawbacks and also in extension of our previous studies on application of microwave technique in synthesis of some acyclic nucleoside analogs published in this journal,[2f] herein we report a clean, facile, and rapid microwave-assisted regioselective Michael addition of some nucleobases to α,β-unsaturated esters, which to the best of our knowledge has not been reported so far.



Helenalin

Figure 1 Structure of helenalin

To obtain optimized reaction conditions, we have selected the reaction of uracil with ethyl acrylate as a model reaction to provide compound **1a** (Scheme 1). For this purpose, the influence of various bases was examined to evaluate their capabilities as well as their selectivity. The results are summarized in Table 1. As Table 1 indicates, higher yields and shorter reaction times were observed when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB). Therefore, DABCO was the base of choice for our reactions. We have also extended this reaction to adenine as a purine nucleobase that provided compound **2a** in high yield (Scheme 2).

Interestingly, with our method both pyrimidine and purine nucleobases were regioselectively alkylated. Pyrimidine nucleobases were exclusively alkylated at N-1 position

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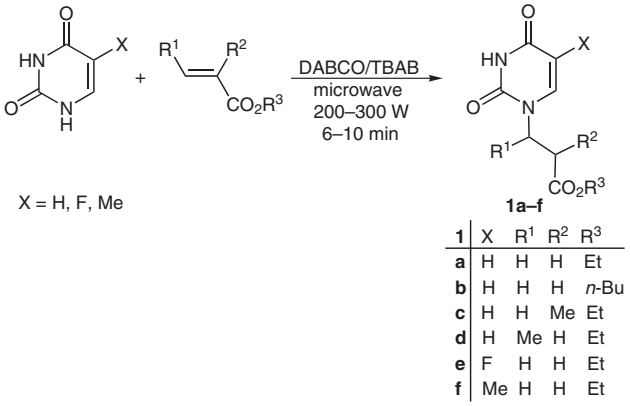
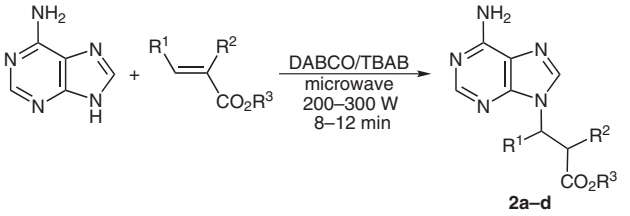


1	X	R^1	R^2	R^3
a	H	H	H	Et
b	H	H	H	*n*-Bu
c	H	H	Me	Et
d	H	Me	H	Et
e	F	H	H	Et
f	Me	H	H	Et

Scheme 1



2	R^1	R^2	R^3
a	H	H	Et
b	H	H	*n*-Bu
c	H	Me	Et
d	Me	H	Et

Scheme 2

Table 1 The Effect of Bases on Results of Michael Addition of Uracil to Ethyl Acrylate

Entry	Base	Microwave power (W)	Reaction time (min)	Yield (%)[a]
1	DABCO	200	6	83
2	DMAP	200	8	70
3	Cs_2CO_3	200	8	65
4	K_2CO_3	200	8	59
5	DBU	200	8	52
6	CaO	300	10	41
7	MgO	300	12	18

[a] Isolated yield.

and adenine was restrictively alkylated at N-9 rather than N-7 position. The site of N-alkylation in both pyrimidine and purine nucleobases were indicated by assigned ^1H and ^{13}C NMR spectra analysis. Several literatures also confirmed this site of N-alkylation.[4c–e]

To realize the capability of our method in comparison to conventional methods, we have examined the synthesis of compounds **1a** and **1b** (Scheme 1) with the method reported by Cai et al.[4c] (Table 2). As Table 2 indicates, the microwave method is more efficient.

Table 2 A Comparative Synthesis of Compounds **1a** and **1b** Using Conventional Thermal Versus Microwave Method

Product	Time (h)[a]	Yield (%)[a]	Time (min)[b]	Yield (%)[b]
1a	12	47	6	83
1b	12	44	6	85

[a] Conventional thermal method.
[b] Microwave method.

To study the structural influence of α,β-unsaturated esters (Michael acceptors) on our reaction, we have also investigated the reaction of uracil as well as adenine with more sterically hindered ethyl methacrylate and ethyl crotonate which afforded products **1c**, **1d** and **2c**, **2d**, respectively. The results are depicted in Table 3. As shown in Table 3, low yields of products were obtained when nucleobases were introduced to sterically hindered α,β-unsaturated esters (Table 3, entries 3,4,10,11). Prolonging the irradiation times or exposing to higher microwave power has no effect on the efficiency of reaction. Interestingly, the length of alkoxy group (OR) in α,β-unsaturated esters has negligible influence on the result of reaction. This can be easily understood by comparing reaction yields of compounds **1a**, **1b** and **2a**, **2b** accordingly (Table 3).

The reactions of uracil and adenine with ethyl cinnamate were not successful (Table 3, entries 5, 12). This can be attributed to the effect of the phenyl moiety, which can not only deactivate α,β-ethylenic bonds owing to their conjugation, but its steric bulk can affect the progress of reaction.

TBAB has an undeniable effect on the progress of our reaction. The absence of TBAB in the reaction media gave low yields even by enhancing the reaction time and microwave power. Thus, the presence of TBAB in our reaction is critically significant. TBAB absorbs the microwave irradiation as well as generates in situ heat and increases the temperature higher than its melting point (100–103 °C). In this conditions, TBAB creates homogeneous media whose resemblance is not far from that of ionic liquids.[2f,10]

In summary, we have developed an efficient, rapid, and operationally simple method for regioselective Michael additions of different nucleobases to various α,β-unsaturated esters under microwave irradiation. This new method affords carboacyclic nucleosides as biologically interesting compounds in short reaction time and reasonable yields.

Table 3 Michael Addition Reactions of Some Nucleobases to α,β-Unsaturated Esters under Microwave Irradiation

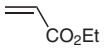
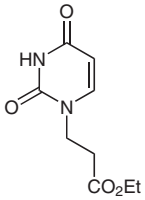
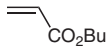
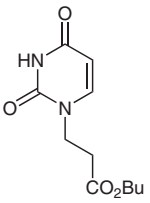
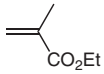
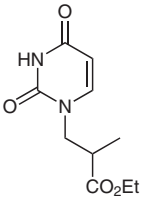
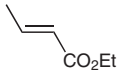
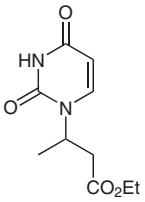
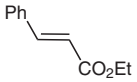
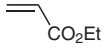
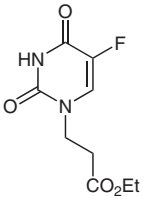
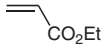
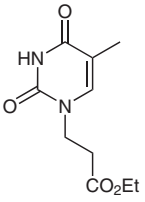
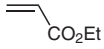
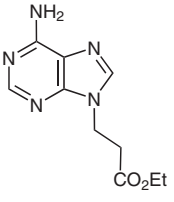
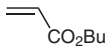
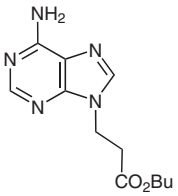
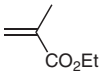
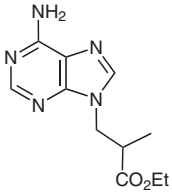
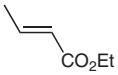
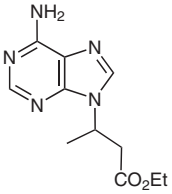
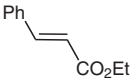
Entry	Ester	Product	Microwave power (W)	Reaction time (min)	Yield (%)[a]
1			200	6	83
2			200	6	85
3			200	10	40
4			300	9	27
5[b]		–	400	10	–
6			200	6	81
7			200	6	78
8			200	8	72

Table 3 Michael Addition Reactions of Some Nucleobases to α,β-Unsaturated Esters under Microwave Irradiation (continued)

Entry	Ester	Product	Microwave power (W)	Reaction time (min)	Yield (%)[a]
9			200	8	73
10			200	12	38
11			300	10	24
12[b]		–	400	10	–

[a] Isolated yield.
[b] No reaction was observed.

All chemicals were obtained from Fluka or Merck. Solvents were purified and dried according to reported methods and stored over molecular sieves.[11] The progress of reaction was followed by TLC analysis using silica gel SILG/UV 254 plates . IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR and ^{13}C NMR were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm, *J* in Hz). Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Melting points were recorded on a Büchi 510 apparatus in open capillary tubes and are uncorrected. Microwave oven: MB 245 domestic microwave oven from Butan Industrial Co.

Michael Addition of Nucleobases to α,β-Unsaturated Esters Under Microwave Irradiation; General Procedure

In a mortar, a mixture of compounds consisting of nucleobase (0.010 mol), TBAB (0.644 g, 0.002 mol) and DABCO (1.120 g, 0.010 mol) was crushed vigorously to give a homogeneous mass. The mixture was transferred into a test tube, and then the corresponding α,β-unsaturated ester (0.015 mol) was added and mixed carefully with a tiny spatula. The mixture was irradiated in the microwave oven at 200–300 W (Table 3) for several time intervals (1.5 min). After each irradiation time interval, the microwave irradiation was stopped and the progress of the reaction was monitored by TLC analysis. The irradiation was continued until no progress in the reaction was observed, as indicated by TLC. The irradiation was stopped and the reaction mixture was suspended in $CHCl_3$ (300 mL). The $CHCl_3$ was washed with H_2O (2 × 200 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography on silica gel with EtOAc–hexane (3:1).

3-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)propionic Acid Ethyl Ester (1a)

Colorless crystals; yield: 1.76 g (83%); mp 78–80 °C (Lit.[4c] mp 79–81 °C).

3-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)propionic Acid Butyl Ester (1b)

Colorless crystals; yield: 2.03 g (85%); mp 63–65 °C; (Lit.[4c] mp 64–66 °C).

3-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)-2-methylpropionic Acid Ethyl Ester (1c)

Yellow oil; yield: 0.91 g (40%).

IR (neat): 3179, 3060, 2953, 1732s, 1686s, 1641s cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14–1.19 (m, 6 H, CH_2CH_3 and $CHCH_3$), 2.97 (m, 1 H, O=CCH), 3.67 (dd, 1 H, *J* = 9.5, 13.4 Hz, NCH_2), 3.87 (dd, 1 H, *J* = 4.5, 13.4 Hz, NCH_2), 4.10 (q, 2 H, *J* = 6.9 Hz, OCH_2), 5.61 (d, 1 H, *J* = 7.9 Hz, 5-H of uracil), 7.25 (d, 1 H, *J* = 7.9 Hz, 6-H of uracil), 10.23 (s, 1 H, NH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.44, 15.47, 39.01, 51.98, 61.48, 102.23, 145.01, 151.59, 164.81, 174.89.

MS: *m/z* (%) = 227 (M^+ + 1, 8.7), 226 (M^+, 15.6), 181 (20.8), 153 (14.9), 125 (26.1), 112 (13.3), 84 (100), 69 (47.9), 55 (17.8), 41 (38.2).

3-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)butyric Acid Ethyl Ester (1d)

Colorless crystals; yield: 0.61 g (27%); mp 116–118 °C.

IR (KBr): 3149, 3092, 2934, 1730s, 1686s, 1654 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.19 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.43 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$), 2.63 (dd, 1 H, *J* = 5.8, 16.2,

O=CCH$_2$), 2.85 (dd, 1 H, J = 7.9, 16.2, O=CCH$_2$), 4.07 (q, 2 H, J = 7.0 Hz, OCH$_2$), 4.68 (m, 1 H, CH$_3$C*H*), 5.67 (d, 1 H, J = 7.9 Hz, 5-H of uracil), 7.23 (d, 1 H, J = 7.9 Hz, 6-H of uracil), 9.70 (s, 1 H, NH).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 14.47, 19.21, 39.32, 51.66, 61.40, 102.49, 142.77, 151.18, 164.06, 170.64.

MS: *m*/*z* (%) = 227 (M$^+$ + 1, 31.4), 226 (M$^+$, 22.5), 181 (23.3), 153 (18.8), 152 (61.2), 139 (23.7), 112 (14.4), 96 (100), 69 (85.3), 41 (77.1).

3-(5-Fluoro-2,4-dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)propionic Acid Ethyl Ester (1e)
Pale yellow crystals; yield: 1.86 g (81%); mp 122–124 °C (Lit.[4c] mp 124–126 °C).

3-(5-Methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)propionic Acid Ethyl Ester (1f)
Colorless crystals; yield: 1.76 g (78%); mp 148–149 °C (Lit.[4c] mp 149–150 °C).

3-(6-Aminopurine-9-yl)propionic Acid Ethyl Ester (2a)
Colorless crystals; yield: 1.69 g (72%); mp 165–167 °C (Lit.[4a] mp 167–168 °C).

3-(6-Aminopurine-9-yl)propionic Acid Butyl Ester (2b)
Colorless crystals; yield: 1.92 g (73%); mp 134–136 °C.

IR (KBr): 3265, 3110, 2932, 1728s cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.92 (t, 3 H, J = 6.7 Hz, CH$_3$), 1.34 (m, 2 H, CH$_3$C*H*$_2$), 1.55 (m, 2 H, CH$_3$CH$_2$C*H*$_2$), 2.96 (t, 2 H, J = 5.8 Hz, O=CCH$_2$), 4.09 (t, 2 H, J = 6.7 Hz, OCH$_2$), 4.53 (t, 2 H, J = 5.8 Hz, NCH$_2$), 6.37 (s, 2 H, NH$_2$), 7.99 (s, 1 H, 2-H of adenine), 8.42 (s, 1 H, 8-H of adenine).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 14.32, 19.38, 30.96, 39.85, 46.44, 65.41, 121.67, 138.47, 150.24, 152.78, 156.11, 171.41.

MS: *m*/*z* (%) = 264 (M$^+$ + 1, 20.4), 263 (M$^+$, 22), 234 (4.1), 221 (8.2), 206 (2.1), 190 (14.3), 162 (77.6), 148 (32.7), 135 (100), 108 (24.5), 93 (5.1), 73 (4.1), 57 (9.2), 41 (36.7).

3-(6-Aminopurine-9-yl)-2-methylpropionic Acid Ethyl Ester (2c)
Colorless crystals; yield: 0.95 g (38%); mp 134–137 °C.

IR (KBr): 3511, 3296, 3139, 2930, 1728s cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.09–1.20 (m, 6 H, CH$_2$C*H*$_3$ and CHC*H*$_3$), 3.10 (m, 1 H, O=CCH), 4.04 (q, 2 H, J = 6.6 Hz, OCH$_2$), 4.20 (dd, 1 H, J = 8.3, 13.9 Hz, NCH$_2$), 4.38 (dd, 1 H, J = 8.6, 13.9 Hz, NCH$_2$), 6.19 (s, 2 H, NH$_2$), 7.77 (s, 1 H, 2-H of adenine), 8.28 (s, 1 H, 8-H of adenine).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 14.37, 15.49, 39.05, 46.35, 61.42, 119.76, 141.45, 150.34, 153.22, 156.17, 174.45.

MS: *m*/*z* (%) = 250 (M$^+$ + 1, 12.3), 249 (M$^+$, 18.1), 204 (17.3), 176 (40.8), 149 (85.7), 148 (58.2), 135 (100), 108 (38.8), 93 (6.3), 77 (5.5), 70 (38.7), 55 (46.9), 41 (85.7).

3-(6-Aminopurine-9-yl)butyric Acid Ethyl Ester (2d)
Colorless crystals; yield: 0.59 g (24%); mp 100–101 °C.

IR (KBr): 3335, 3142, 2928, 1729s cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.09 (t, 3 H, J = 6.3 Hz, CH$_2$C*H*$_3$), 1.66 (d, 3 H, J = 4.7 Hz, NCHC*H*$_3$), 2.87 (dd, 1 H, J = 4.7, 16.8 Hz, O=CCH$_2$), 3.14 (dd, 1 H, J = 7.9, 16.8 Hz, O=CCH$_2$), 4.02 (q, 2 H, J = 6.3 Hz, OCH$_2$), 4.95 (m, 1 H, NC*H*CH$_3$), 6.26 (s, 2 H, NH$_2$), 7.78 (s, 1 H, 2-H of adenine), 8.21 (s, 1 H, 8-H of adenine).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 14.29, 20.44, 40.43, 49.18, 61.15, 120.38, 139.71, 149.88, 152.85, 156.40, 170.53.

MS: *m*/*z* (%) = 250 (M$^+$ + 1, 85.8), 249 (M$^+$, 36.7), 204 (12.7), 176 (16.9), 162 (30.6), 135 (100), 108 (34.7), 93 (3.2), 69 (16.4), 55 (8.6), 41 (30.1).

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