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Microwave Synthesis of β-Uramino Crotonic Ester and its Derivatives

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The new and rapid synthesis of β-uramino crotonic ester and its derivatives involves the condensation of ethyl acetoacetate and urea, thiourea and 1,3-dimethyl urea in presence of ethanol. These compounds are important intermediates for the synthesis of 6-methyl pyrimidinedione derivatives, which are biologically active compounds used in medicinal and pharmaceutical chemistry. The structure of the synthesized compounds has been elucidated with spectral analysis: UV, FTIR and GC-MS.

Key Words: Microwave, Condensation, 6-Methyluracil, GC-MS.

INTRODUCTION

The main purpose of using microwave radiations in organic synthesis is to dramatically reduce the reaction time. Microwave radiation is an alternative approach to conventional heating for introducing energy into reactions. The use of microwave radiations gives the introduction of new concepts in chemistry. The microwave technique can be applied to a number of useful processes[1]. The time saved by using focused microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high-speed combinatorial and medicinal chemistry[2,3].

β-Uramino crotonic ester is an important intermediate for the synthesis of 6-methyl-2,4-(1*H*,3*H*)pyrimidinedione. These are biologically active compounds 6-methyluracil serves a variety of purposes. It primary role is in the synthesis and repairing of DNA and RNA. Its means that 6-methyl uracil is an excellent supplement for improving both muscle repair and growth. It can be used in pharmaceutical industry for synthesis of cardiovascular drugs[4]. Synthesis of 6-methyluracil and its derivatives required 5-7 days as it was involved the formation of intermediate β-uramino crotonic ester which was formed by the condensation of urea, ethyl acetoacetate in presence of absolute ethyl alcohol.

Under conventional method 5-7 days required for the complete formation of dry β-uramino crotonic ester. This long period of formation was reduced by using microwave technique which required only few seconds. Domestic microwave oven is most popularly used in synthesis because of its low cost and ready availability[5].

EXPERIMENTAL

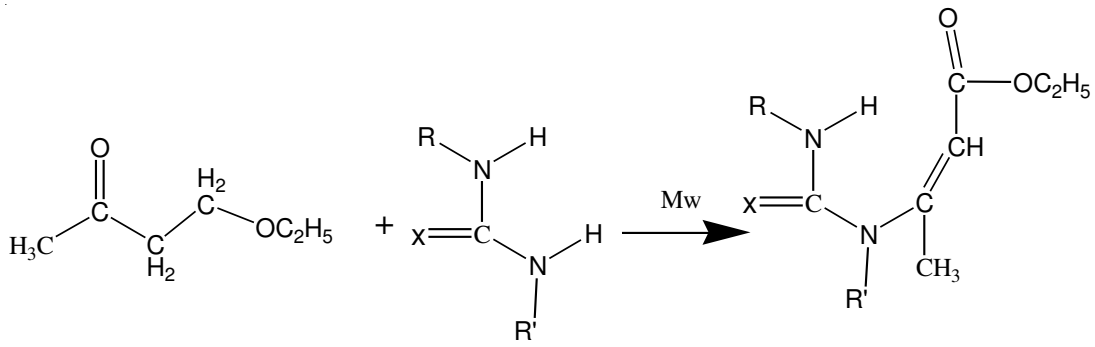
Melting points were determined by using Gallenkamp melting point apparatus. UV spectra were recorded within the range 200-500 nm on Hitachi U-2800 spectrophotometer. FTIR spectra were recorded within the range 4000-400 cm^{-1} as KBr pellets on a Midac M-2000 spectrometer (USA) while mass data were recorded on GC-MS Shimadzu QP-2010 spectrometer (Japan). For the synthesis of compounds, a microwave oven DW-180, 2450 MHz, 950W was used.

The comparable experiments were performed applying conventional conditions The synthesis of β-uramino crotonic ester by using urea and its derivatives is shown by Fig. 1.

Synthesis of β-uramino crotonic ester I-A

Conventional: 10.0 g urea was stirred into a mixture of 20.0 g ethyl acetoacetate, 25.0 mL absolute alcohol and 5 drops of concentrated HCl in a crystallizing dish. The reagents were mixed well and the dish was covered loosely with a watch glass and placed in vacuum desiccators over concentrated H_2SO_4. The desiccator was evacuated continuously with a water pump till the mixture has gone to dryness after 6 days. The crude β-uramino crotonic ester was thoroughly dried yield 80 %, m.p. 160 ºC, soluble in water.

Microwave IA: β-Uramino crotonic ester was prepared by using 1.33 mol of urea, 1.23 mol of ethyl acetoacetate, 25 mL of absolute alcohol and 1-2 drops of conc. HCl. The reagents were mixed well and then irradiated under microwave for 30 s. Yield 95 %, m.p. 160 ºC soluble in water (Tables 1 and 2).



X = O, S; R = H, CH_3 and R' = H, CH_3

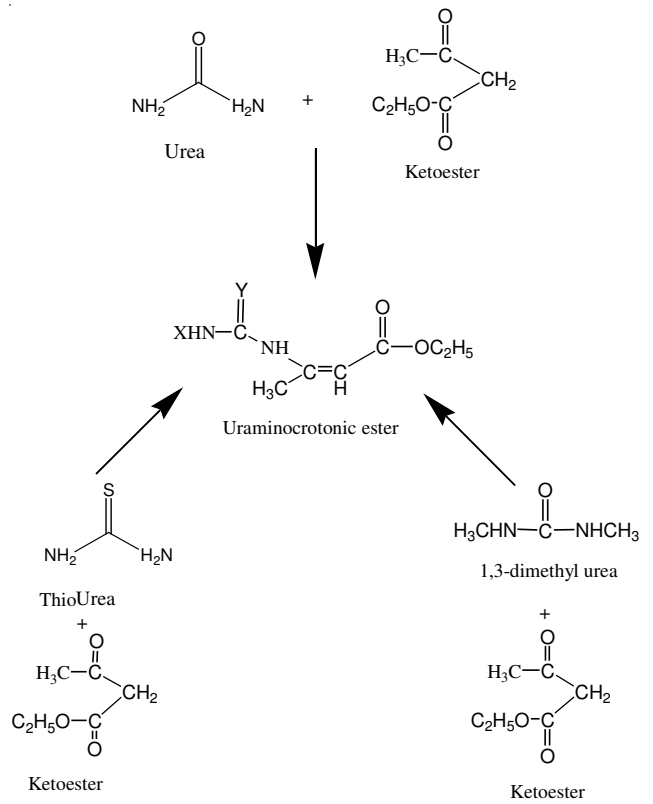


Fig. 1. Synthesis of β-uramino crotonic ester (intermediate of 6-methyluracil); where X = H, CH_3, Y = O, S

TABLE-1
COMPARISON BETWEEN CONVENTIONAL AND MICROWAVE-ASSISTED METHOD IN TERMS OF YIELD AND TIME

Sample number	Conventional		Microwave	
	Time (min)	Yield (%)	Time (s)	Yield (%)
I-A	7200	80	30	95
II-A	7200	85	20	95
III-A	7200	20	25	25

TABLE-2
PHYSICAL DATA OF β-URAMINOCROTONIC ESTER AND ITS DERIVATIVES

Compound No.	Solubility	m.p. (ºC)
I-A Conventional microwave	Water and alcohol Cold water	165 160
II-A Conventional microwave	Water, alcohol Water	180 190
III-A conventional microwave	Water Water	110 106

Spectral analysis was done by using UV, FTIR and GC-MS technique. The results are tabulated in Tables 3-5, respectively.

TABLE-3
UV ABSORPTION SPECTRAL ANALYSIS

Compounds number	λ_{max} (nm) conventional	λ_{max} (nm) microwave
I-A	209, 223, 234, 255, 273, 295	206, 222, 234, 256, 268, 297
II-A	210, 224, 245, 256, 291	213, 230, 248, 260, 296
III-A	201, 248, 379	206, 229, 241, 255, 294

TABLE-4
FTIR ANALYSIS VIBRATION FREQUENCIES (cm^{-1})

Compounds numbers	Methods used	Bands (cm^{-1}) and intensity
I-A	Conventional	3498 s, 3364s, 1689b, 1498 w, 1005b, s, 830s, 702 s, 661 s
	Microwave	3498 w, 3400 w, 1642b, s, 1406b, s, 1002 s, 832 s, 702 s
II-A	Conventional	3896 s, 3561 s, 3220 s, 3095 s, 1670 w, 1601 s, 1350 w, 1105 s, 1001 s, 1001 w, 832 s, 702 s
	Microwave	4062 w, 3620 s, 3167b, 1637 s, 1406 s, 1094 w, 1002 s, 832 s, 702 s
III-A	Conventional	3788 w, 3578 w, 3384 s, 2983b, 2943 s, 1741 s, 1639 w, 1567 w, 1156 s, 1039 s, 937 s, 850 s
	Microwave	3874 s, 3572 w, 3497 s, 1630b, 1405b, 1000 s, 832 s, 702 s, 660 w

TABLE-5
GC-MS INTERMEDIATE OF 6-SUBSTITUTED 2,4-(1*H*,3*H*)PYRIMIDINEDIONE

Compounds No.	Formula	Base peak	Molecular ion peak M^+
I-A	$C_7N_2H_{12}O_3$ β-Uraminocrotonic ester	40	169
II-A	$C_7N_2H_{12}SO_2$	28	167
III-A	$C_9N_2H_{16}O_2$	28	167

Synthesis of II-A

Conventional: 10.0 g thiourea, 3.9 mL ethyl acetoacetate, 15.0 mL absolute alcohol and three drops of concentrated HCl were placed in crystallizing dish. All the reagents were mixed well. The dish was covered and placed in vacuum desiccator. β-Uramino crotonic ester was formed which required five to seven days for complete drying. Yield 90 %, m.p. 180 ºC, soluble in cold water and alcohol.

Microwave of IIA: β-Uramino crotonic ester was prepared by using 1.33 mol of thiourea, 1.23 mol of ethyl aceto acetate, 25 cm^3 of absolute alcohol and 1-2 drops of conc. HCl. The reagent were mixed well and then irradiated under microwave for 20 s. Yield 85 %, mp. 190 ºC, soluble in water.

Spectral analysis was done by using UV, FTIR and GC-MS technique which are recorded in Tables 3-5, respectively.

Synthesis of III-A

Conventional: 10.0 g 1,3-dimethyl urea was stirred into a mixture of 20.0 g ethyl acetoacetate, 5.0 mL absolute alcohol and three drops concentrated HCl in crystallizing dish. The reagents were mixed well and dish was covered loosely with watch glass and placed in vacuum desiccators over concentrated H_2SO_4. The desiccator was evacuated continuously with water pump. The dry β-uramino crotonic ester was collected on filter paper, washed and dried. Yield 20 %. m.p. 110 ºC, soluble in water.

Microwave of IIIA: β-Uramino crotonic ester was prepared by using 1.33 mol of 1,3-dimethyl urea, 1.23 mol of ethyl acetoacetate, 25 cm^3 of absolute alcohol and 1-2 drops of conc. HCl. The reagents were mixed well and then irradiated under microwave for 25 s. White crystals were formed slowly on cooling. Yield 25 %, m.p. 106 ºC, soluble in water and alcohol.

Spectral analysis was done by using UV, FTIR and GC-MS spectroscopy. The results are tabulated in Tables 3, 4 and 5, respectively.

RESULTS AND DISCUSSION

An intermediate of 6-methyl uracil and its derivatives were synthesized by using two methods, conventional and microwave assisted techniques. It was observed that the reaction time and yield manifested by the microwave technique were much better compared to the conventional way as shown in Table-1. The time required for conventional synthesis was reduced from days to seconds when microwaves irradiations were used. The compounds synthesized by both methods shows the similar melting points and solubility (Table-2).

Spectral data of UV, FTIR and GC-MS supported the structure assigned. UV absorption spectra are similar in both techniques. The λ_{max} is given in Table-3. FTIR data further confirmed the structure of synthesized compounds. Infrared data of 6-methyl-2,4-(1*H*,3*H*)pyrimidinedione intermediate are given in Table-4. The N-H stretching vibration at 3218-2690 cm^{-1} was observed in compounds **I-A**, **II-A**, **III-A** synthesized by conventionally and microwave technique.

GC-MS: The mass fragmentation data of the compounds **I-A**, **II-A**, **III-A** are given in Table-4 (Figs. 2-4), respectively. In case of **I-A**, mass spectrum showed the base peak at m/z = 40 showing the removal of acetyl group. Other molecular ions peaks appear at m/z = 44, 69, 86, 101 and 169 showing the

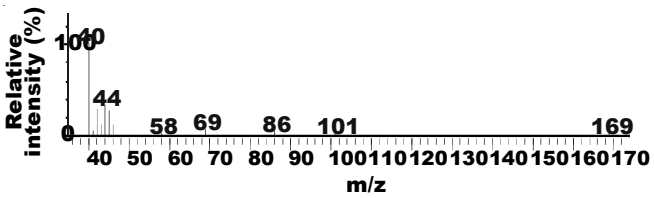


Fig. 2. Mass spectrum of β-uramino crotonic ester (intermediat of 6-methyl substituted uracil)

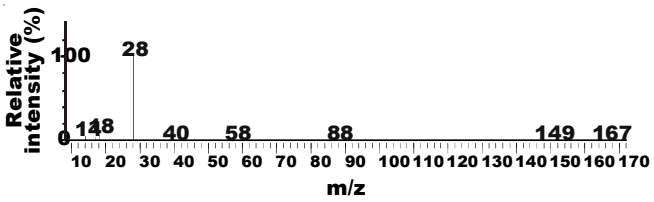


Fig. 3. Mass spectrum of β-uramino crotonic ester-2

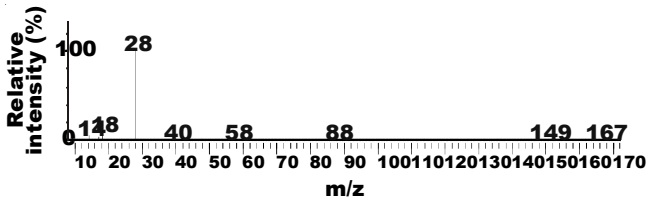


Fig. 4. Mass spectrum of β-uraminocrotonic ester-3

fragmentation of molecule at different points. Molecular ion peak at 136 attributed due to protonation of oxygen and nitrogen atoms. Since oxygen and nitrogen containing compounds from fairly stable oxonium and ammonium ions. Ion molecular collisions take place at pressure higher than 0.5 mm and peaks in the mass spectrum that appear higher than the mass of the molecular ion.

Conclusion

The comparison of the microwave and conventional conditions shows that the slightly higher final yield of the products in microwave conditions but the reaction time for such kind of energy transfer were up to ten times shorter.

In conclusion microwave-assisted method provides an excellent approach for the safe, rapid, inexpensive and simple environment-friendly synthesis of medicinally important 6-methyl substituted 2,4-(1*H*,3*H*)pyrimidinedione.

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