

A RAPID MICROWAVE-ASSISTED ONE POT SYNTHESIS OF 3, 4-DIHYDROPYRIMIDIN-2-(1H)-ONES

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ABSTRACT: An environmentally benign approach for one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones derivative (DHPMs) using ethyl acetoacetate, urea and benzyl alcohol instead of aldehyde under microwave cavity is described. This one-pot oxidation-cyclocondensation protocol based on the Swern oxidation was performed in presence of $\text{Bi}(\text{NO}_3)_2$ without isolation of any intermediate (aldehyde) and thus reducing time, energy and raw materials with good yield of product. This study gave a new strategy of synthesis i.e by employing microwave as a tool in order to diminish reaction time and to avoid side products with increased yield and simplicity of the course of reaction. All the reported reactions were also pursued via conventional methods for a comparative study. The results obtained confirmed the superiority of the microwave irradiation method over the classical reflux heating. The compound was characterized by spectral analysis using UV, FTIR and GC-MS techniques.

Keywords: Biginelli compound, Microwave, Swern oxidation, $\text{Bi}(\text{NO}_3)_2$, One-pot reaction.

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INTRODUCTION

The need of today is to develop technologies which are cheaper and environmental friendly. Microwave-assisted synthetic techniques are one of these. Microwave-assisted organic synthesis has been known since 1986(Giguere,1986).This non-conventional synthetic method has shown broad applications as a very efficient way to accelerate the course of many organic reactions giving better yield, high selectivity, lower quantities of side products , consequently easier work-up and purification of the products (Mingos and Whittaker,1997).Therefore the growing interest in academic research and industrial laboratories is not surprising and is reflected in an exponential increase in the production of scientific papers, books and reviews related to the use of this technology. (Loupy, 2002; Kappe, 2004 and Hayes, 2004).

The importance of DHPM (dihydropyrimidine) ring as pharmacophore is well known by the pharmacological properties of their derivatives, like calcium channel antagonists, α -adrenergic neuropeptide γ antagonists, antihypertensive, antitumor, antibacterial and anti-inflammatory agents (Ronyar and Kinball, 1995, Grover and Dzwonczyk, 1995 and Kappe, 1993). Thus the developments of microwave-assisted synthetic methods towards dihydropyrimidinones constitutes an active area of investigation in organic synthesis. A Swern type oxidation-cyclocondensation method has been described in different research reports during traditional method of heating (Ireland and Norbeck,

1985). A one-pot conversion of alcohol to the corresponding dihydropyrimidinones in presence of $\text{Bi}(\text{NO}_3)_3$ using conventional method has been reported by (Khosropour *et al*,2005). This study gave new strategy of synthesis i.e employing microwave as a tool to reduce reaction time and to avoid side products with increased yield.

MATERIALS AND METHODS

Chemicals: Analytical grade chemicals were used in these syntheses

Instrumentation Gallenkamp melting apparatus was used for melting point determination. UV spectra were recorded on Hitachi U-2800 spectrophotometer within the range of 200-500 nm. FTIR spectra using KBr pellets were recorded on a Midac M-2000 Spectrometer (USA) within the range of 400-4000 cm^{-1} while Mass spectrum was recorded on GC-MS Shimadzo QP- 2010 (Japan). A microwave oven DW-180, 2450 MHz, 950W was used for synthesis.

Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones (DHPM) by Conventional method:- $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (0.63 g) was added to the solution of benzyl alcohol (0.1 g, 0.97 mmol) in acetonitrile (2.0 ml) and mixture was refluxed for 6 hrs with stirring. When heating was completed, ethyl acetoacetate (0.3 ml) and urea (0.09 g, 1.5 mmol) were added and mixture was again refluxed. The progress of reaction was checked by TLC. Hot ethanol (10 ml) was added to this heated mixture. The

mixture was filtered. After cooling the product crystallized out as white solid. The product was washed, recrystallized with a mixture of H₂O /ethanol 1:1 and dried by using the method of (Khodaei and Beygzadeh, 2004).

Thirty percent yield of white solid was obtained with mp 187-190 °C. It was soluble in water and showed UV-VIS λ_{max} . (ethanol) at 260,310 nm, FTIR (KBr disc) spectrum gave vibrational frequencies at ν =3421.57, 3243.82, 2461.10, 1724.08, 1702.0, 1489, 1123 cm⁻¹, MS, m/z (%) were 18(90), 28(50), 44(70), 60(62), 77(20), 91(10), 110(10), 137(38), 55(42), 183(100), 214(18), 213(42) and 260(22)

Microwave:- Benzyl alcohol (0.1g, 0.97mmol) was added to a mixture of acetonitrile (2.0 mL), Bi(NO₃)₃.5H₂O(0.63 g), urea (0.09g,1.5 mmol) and ethyl acetoacetate (0.3 ml) and was subjected to microwave radiation for 40 seconds. The mixture was filtered after adding hot ethanol (10 ml). Product was washed, recrystallized and dried (Yadav *et al*, 2000).

Seventy percent yield was obtained (mp 187°C) which was soluble in water. UV-VIS. spectrum showed λ_{max} . (ethanol) at 260, 310 nm. and FTIR spectrum using KBr disc gave vibrational frequencies at ν 3410.21, 3175.13, 2450.30, 1665.24, 1620.62, 1453.68, 1224.27 cm⁻¹, MS, m/z (%) were 18(90), 28(50), 44(70), 60(62), 77(20), 91(10), 110(10), 137(38), 55(42), 183(100), 214(18), 213(42) and 260(22)

RESULTS AND DISCUSSION

The melting points of synthesized compounds were determined and it seemed to be comparable to those compounds which synthesized under microwave. The compound synthesized by both methods i.e conventional and microwave-assisted showed the remarkable reduction in heating time along with better yield as is shown in Table-1

The structure was confirmed by spectral analysis using UV, FTIR and Mass spectrometry. The UV and FTIR spectra of the compound synthesized by both methods are shown in Table-2

The Mass spectral analysis of synthesized compound was done by using GC-MS and result is depicted in Table- 3 and shown by Figure.1

Several procedures have been reported for classic synthesis of Biginelli compounds by condensing urea, aldehydes and beta dicarbonyl compounds (Hue and Sidler, 1998). Many modifications of this method have also been reported (Qu *et al*,2013 and Maneepom *et al* ,2015). By taking the notice of oxidative and catalytic behaviors of Bi(NO₃)₃.5H₂O in organic transformations, this conventional synthesis was conducted by using

benzyl alcohol instead of aldehyde which undergoes cyclocondensation with urea and ethyl acetoacetate in presence of acetonitrile(Khodaei and Nikoofar,2003 ; Khodaei and Beygzadeh,2004 and Khosropour and Khodaei , 2005).The same synthesis i.e one pot oxidation-cyclocondensation was reported by utilizing microwaves energy which gave dihydropyrimidinones in higher yields with reduce reaction time than those obtained in the traditional method(Qingjian,*et al*,2013). The compound synthesized by both methods i.e conventional and microwave-assisted showed the remarkable reduction in heating time along with better yield as shown in Table-1 .The progress of reaction was determined by TLC. The structure elucidation was done by spectral analysis. The UV spectra of the compound synthesized by both methods exhibited the maximum absorption at λ_{max} 260,310 nm as shown in Table-2.The FTIR spectra of the compound was studied and compared to those synthesized by microwave-assisted method. The important band frequencies are listed in Table-2. The presence of carbonyl group was indicated by stretching vibration frequency near 1665-1730 cm⁻¹. The absorption band of (N-H)str. appeared at 3218-2690 cm⁻¹, the C₄-C₆H₅ showed the peak at 1620 cm⁻¹ the (C =C) str. vibrational region (aromatic) appeared at 1453 cm⁻¹, the bending vibration frequency of (C₅-COOC₂H₅) lied within range of 1225-950 cm⁻¹.The presence of methyl substituents at C-6 gave peak at 2450 cm⁻¹. The Mass spectral analysis of synthesized compound was done by using GC-MS and result is depicted in Table- 3 and shown by Figure-1. The spectrum showed the molecular ion peak at m/z =260, corresponding to molecular formula of the compound i.e C₁₄H₁₆N₂O₃ (which is the molecular mass of the compound).

The novelty of this synthesis was the conversion of multi-pots reaction to one- pot with dramatic reduction of time from 6 hrs to 40 seconds with enhanced yield. The present work extended the synthesis of Biginelli compound 3,4-dihydropyrimidin-2-(1H)-one derivatived using microwave-assisted method. The structure of the synthesized compound was characterized with GC-MS which gave the molecular ion peak at m/z =260, corresponding to molecular formula of the compound C₁₄H₁₆N₂O₃, as recorded in Table-3

From the data of present investigation it was concluded that microwave assisted method gave the quick and rapid synthesis. The time required for conventional heating was greatly reduced from six hours to only forty seconds. It was concluded that by selecting such novel synthetic method, a large number of medicinally important, bioactive compound can be synthesized under safe, clean and environment-friendly conditions with increased yield, saving both the time and energy.

Table-1. Analysis of Conventional heating versus Microwave irradiation for the synthesis of DHPM

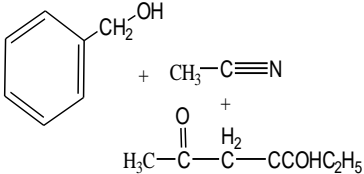
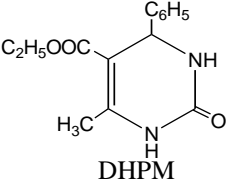
Substrate	Product	Conv. Time (minutes)	Yield %	MW Time (seconds)	Yield %
 <p>Benzyl Alcohol + Acetonitrile Ethylacetoacetate + urea</p>	 <p>DHPM</p>	360	30	40	70

Table-2. Ultraviolet and FTIR analysis of 3,4-Dihydropyrimidin-2-(1H)-one(DHPM)

UV Amax.(nm)	FTIR V(cm ⁻¹)	N ₁ -H	N ₃ -H	C ₆ -CH ₃	C ₂ =O	C ₄ -Ph	C ₅ =C ₆	C ₅ -COOR
260,310	Microwave	3410.21	3175.13	2450.30	1665.24	1620.62	1453.68	1224.27
	Conventional	3421.57	3243.82	2461.10	1724.08	1702	1489	1123

Table-3. GC-MS analysis of 3,4-Dihydropyrimidin-2-(1H)-one(DHPM).

S. No.	Compound.	Formula	Base peak	Molecular ion M ⁺ peak
1.	DHPM	C ₁₄ H ₁₆ N ₂ O ₃	183	260

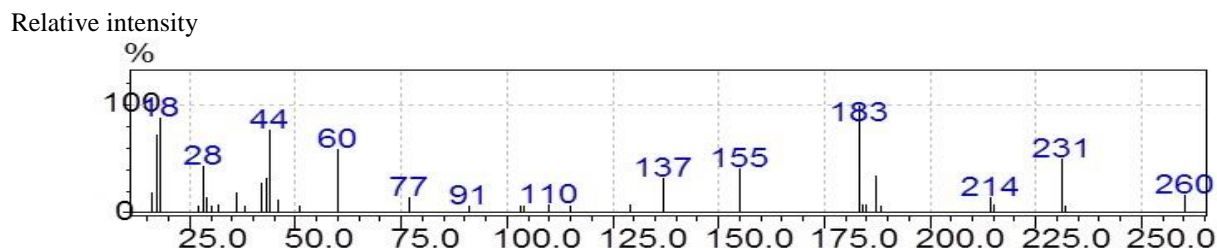


Fig.1 Mass spectrum of DHPM m/z

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