International Journal of Universal Print
ISSN: 2454-7263 ID: ACTRA 2018 030 Published Mar. 2018
Volume No. 04, Issue No.03, Copyright © Universal Print
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Title Key: EFFICIENT SYNTHESIS OF 4-(4-HYDROXY-3-METHOXYPHENYL)-…

EFFICIENT SYNTHESIS OF 4-(4-HYDROXY-3-METHOXYPHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE BY USING 4-HYDROXY-3-METHOXYBENZALDEHYDE

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ABSTRACT

The large number of production of vanillin takes place in eastern region of world and its chemical name is 4-Hydroxy-3-methoxybenzaldehyde.Traditionally it was isolated from the bean of vanilla (Vanilla planifolia Andrews). This work gives information about the application of vanillin as starting material for synthesizing a biologically important chemical structure 3,4-dihydropyrimidinone. The reaction was undertaken in one step following multi component reaction. Product identification was undergone using FTIR and UV-Vis spectrophotometry and also liquid chromatography-mass spectrometry (LCMS). After purification under flash column chromatography in ethyl acetate-hexane, it was found a white solid of 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one in very good yield with a very trace amount of an unreacted vanillin.

Keywords - Dihydropyrimidinone, Multi component reaction, *Vanilla planifonia*.

INTRODUCTION

Vanillin is a well-known food and cosmetic additive and has antioxidant and antimutagenic properties. It has also been observed that it is having antifungal activity against major human pathogenic fungi, although it is not very effective. It is found that a structural relationship between the vanillin derivatives and antifungal activity, showing that the hydroxyl or alkoxy group is more advantageous than the halogenated or nitrated group in benzaldehyde. Among the vanillin derivatives with a hydroxyl or alkoxy group, o-vanillin and o-ethyl vanillin showed the highest antifungal activity. Vanillin is an aldehyde compound, also known as 4-hydroxy-3-methoxybenzaldehyde. It was isolated naturally from the beans of vanilla plant (*Vanilla planifonia* A.) [1,2]. The large number of production of vanillin takes place in eastern countries becoming the second largest producer of natural vanillin after Madagascar [3,4]. The total domestic production was mostly sent to abroad mainly to American market. It was also noted about 37 metric ton per month of US vanillin import from Indonesia.

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Thus diversifying the potency and application rather than direct export as raw material of the local natural vanillin to gain more values and economic benefits become an important strategy. The interesting methodology that applies an aldehyde molecule as starting material to afford an important molecular backbone for medicinal and pharmaceuticals application is multicomponent reaction (MCR). It was defined as a reaction that involves more than two reactants to producing a specific single product contained essential part of the reactants in single step process [5]. Biginelli reaction is an example first developed by P. Biginelli (1893), involved three reagents to afford dihydropyrimidinone [6]. Beside an aldehyde, urea or thiourea and □-keto-ester were needed. Generally, reaction requires a acid catalysis in ethyl alcohol under reflux stirring (**Figure 1**) [7]. Some examples of molecules have been prepared including evaluation of their biological activity such as antifungal, antibacterial [11,12,13,14,15,16,17,18], antiinflammation [8], and antitumor [18] have been reported recently. This paper discloses a recent application of vanillin, isolated from Indonesian natural source of *Vanilla planifoli* Andrews as starting material for synthesis dihydropyrimidinone alkaloid.

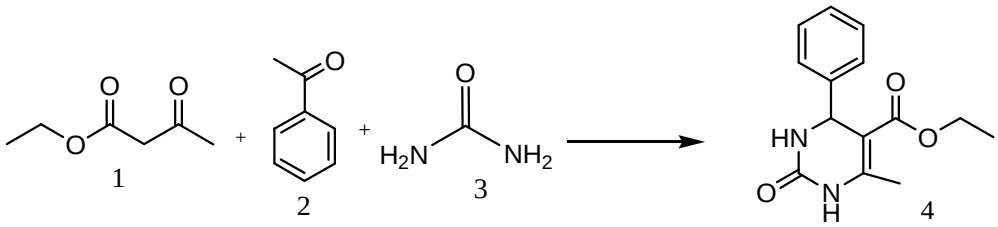

Figure 1. Schematic representation of Biginelli reaction

EXPERIMENT

Chemicals and instrumentation

Chemicals for this research were used as received from the manufacturer.Vanillin gave from local producer (98% purity), acetone, urea, magnesium sulfate anhydrate, ethyl acetate, n-hexane, ethanol, pre-coated of TLC silica gel F_{254} (Merck), silica gel 60 (Merck).

Instrumentation operated for analysis such as gas chromatography-mass spectrometry, infrared spectrophotometer), - Vis UV Spectrophotometry, LCMS/MS

Synthesis procedure

A dried of a 100 mL round-bottom flask was added vanillin (152.14 mg; 1.00 mmol), urea (60.05g, 1.00 mmol), and acetone (1.00 mL, 13.62 mmol). A drop of glacial acetic acid was added. This mixture was stirred at 60^{o}C until reaction complete by monitoring in TLC. The product mixture was extracted with ethyl acetate, and dried under magnesium sulfate anhydrate. Then, the product was concentrated using rotary evaporator in vacuum. The crude product was further purified using flash column chromatography with silica as stationary

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phase and n-hexane/ethyl acetate as solvent. After TLC monitoring, the product fraction was added magnesium sulfate anhydrate and concentrated in vacuum to afford a pure white solid of 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one in 70% yield. Analysis using UV-Vis spectrophotometer found λ_{max} in 214.60, 232.40, 284.20, 308.20, and 350.40 nm (solution in ethanol). FTIR (KBr plate, cm^{-1}) 3435.31, 3358.77, 3218.97, 1670.30, 1623.36; The GCMS analysis using Agilent developed method on Agilent manual for analysis alkaloid (injector temperature 200 ^{o}C, column temperature 210 ^{o}C isoterm for 30 min) did not give both of chromatogram and mass spectra data. LCMS/MS (Low resolution) found a single peak at 4.55 min with molecular weight 235.00 (100% intensity). Yield 67%. ^{1}H-NMR (400 MHz, methanol-*d*) 2.26 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 5.35 (1H, s overlap, OH), 5.36 (1H, d, H5), 5.56 (1H, d, H4), 5.83 (2H, s, broad, 2xNH), 6.80-7.25 (3H, m, ArH). ^{13}C-NMR (125 MHz, methanol-*d*) 17.5; 56.0; 56.1; 101.1; 112.4; 115.4; 118.4; 134.2; 136.9; 146.7; 147.3; 150.2.

RESULT AND DISCUSSION

Synthesis of 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 7

The reaction was started by mixing of vanillin, urea and acetone in equivalent molar ratio (**Figure 2**). This mixture was not completely dissolved, and a few drop of ethanol was added. The reaction was maintained under reflux condition. Monitoring the reaction product was performed using spotting an aliquot sample on TLC aluminum plate. Appearing of new spot was an indication the reaction occur. First experiment was accomplished in 7.5 h. After the reaction was stopped and concentrated in vacuum, direct separation on flash chromatography afforded product in low yield. The un-reacted vanillin was isolated in significant amount as white solid (**Table 1**). Second experiment was performed by increasing of acetone quantity. It replaced the usage of ethanol as in previous reaction. It was not only homogenized the reaction mixture but also accelerate the reaction time to a half. Besides that, the reaction temperature was also much lower.

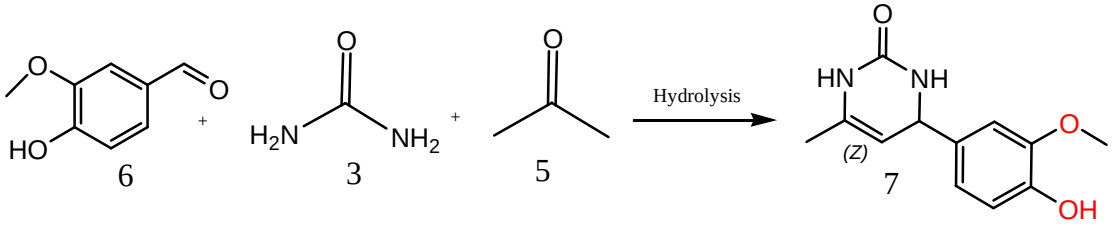

Figure 2. Schematic reaction to yield **7**

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Table 1. Reaction condition to result product **7**

Experiment	Reagent	Solvent	Temperature	Time
1	Vanillin (1.0 mmol), urea (0.5 equiv.), acetone (0.5 equiv.), acetic acid	Ethyl Alcohol	75 ^{o}C	7.5 h
2	Vanillin (1.0 mmol), urea (0.5 equiv.), acetone (6.8 equiv.), acetic acid	Without Solvent	50 ^{o}C	3.5 h

Note: *Heating in water batch

The schematic reaction is displayed as in **Figure 2** (left). An equivalent amount of vanillin **6** and urea **3** reacts with acetone **5**. The resulted product is dihydropyrimidinone structure **7**, and was identified as 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one. A class of heterocyclic alkaloid contains diamine (2xNH) in both side of carbonyl (C=O) group and aromatic substituent.

Figure 3. LCMS chromatogram and molecular weight of **7** (left), and its UV spectra (right)

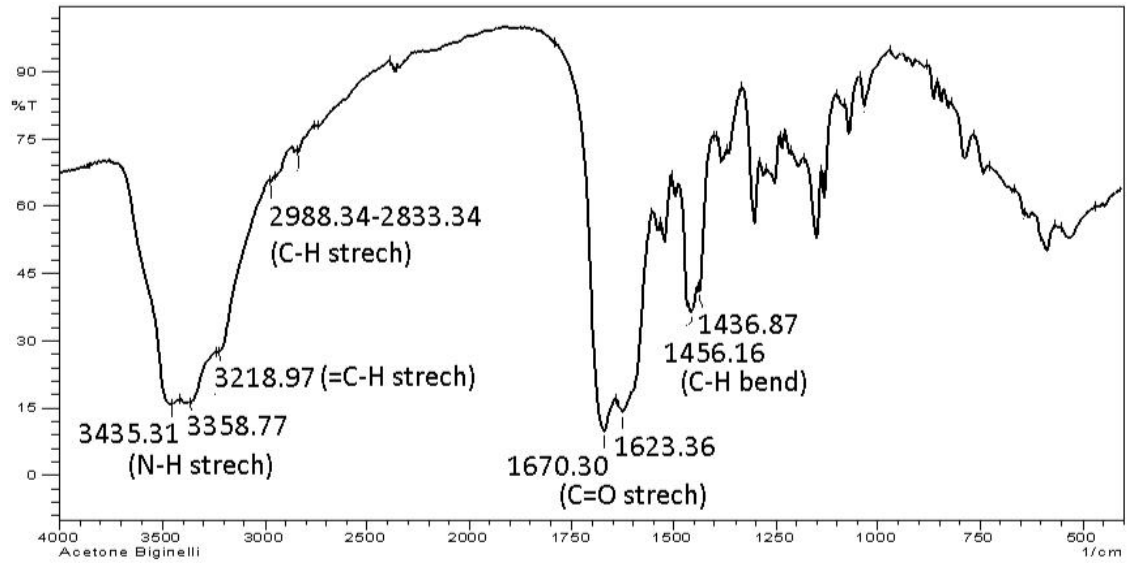

Figure 4. FTIR spectra of product **7**

Analysis the molecular structure of **7** was performed using several spectroscopy techniques. Analysis using ultra violet spectrophotometer gave UV absorption spectra with five a maximum wavelength (**Figure 3**). These spectra

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characteristic for 3,4-dihydropyrimidinone structure with two N-H amines adjacent to carbonyl groups and an aromatics ring. In addition, infrared spectra recorded significant signal for all the functional groups comprises in the product (**Figure 4**). Stretching vibration for amine groups appear as double band in 3435.31 and 3358.77 cm^{-1}. Next to it is absorption band for =C-H aromatic or double bond and detected at 3218.97 cm^{-1}. The absorption band for stretching vibration of carbonyl amide group was recorded in 1670.30 and 1623.36 cm^{-1}, and also peak 1456.16 cm^{-1} for methyl group vibration. Furthermore, analysis of the mass spectra using LCMS/MS instrumentation gave a single and clear chromatogram peak at 4.55 min. This peak has molecular weight 235.00 that correspond to molecular mass of the ion from protonated molecule, $[M+H]^+$. Molecular formula of product **7** is $C_{12}H_{14}N_2O_3$ and has theoretical mass 234.10 atomic unit. This result proved the presence of the isolated product **7** as 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one.

PROPOSED REACTION MECHANISM

The general mechanism of Biginelli reaction was proposed by C. Oliver Kappe in 1997 [19]. It was initiated by interaction of N-urea with an aldehyde formed an iminium ion. This was promoted by acid catalyst protonate the oxygen of the carbonyl group from the aldehyde. This iminium ion further reacts with ethyl-acetoacetate involving its carbon-α by enolate formation. In the mean time, the other side of N-urea attaches to carbonyl group from ethyl-acetoacetate and provides an intermediate structure, called as ureide, which is then constructs a cyclic form and further displace a hydrate producing a dihydropyrimidinone [19]. Recently, Alvim et al. also reported solvent less mechanism of the Biginelli reaction [20]. Mechanism was favored following iminium formation as key important step. This adduct is clearly also discovered on MS kinetic study. For this course, iminium intermediate could be afforded by two possible pathways (Figure 5).

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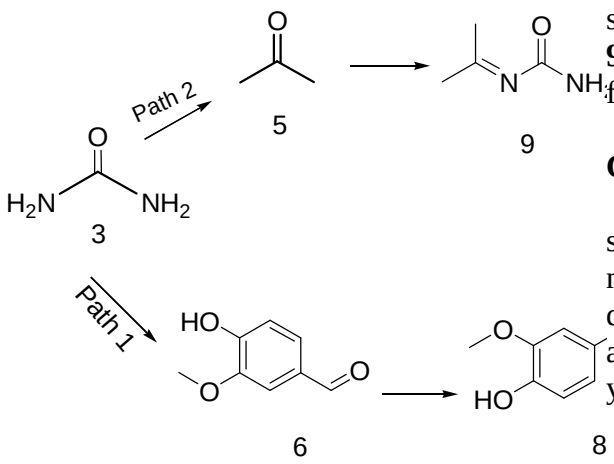

Figure 5. Proposed two possible reaction pathways

First pathway provides the iminium from urea **3** with vanillin **6**, and intermediate iminium **8** was afforded. This intermediate theoretically is stabilized by aromatic ring as well as carbamate groups on urea. And the product **7** was easily be formed. On the other side, route 2 was initiated with smaller substrate but less reactive than vanillin. The adjacents α-hydrogen on iminium intermediate **9** stabilizes its structure by enamine formation. This route ends up provides dihydropyrimidinone **7**. However, stabilization of aromatic ring on iminium **9** was predicted more intent to be favored.

CONCLUSION

An pyrimidinone alkaloid has been synthesized as 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one using naturally abundant vanillin as a yellowish solid in 67% yield.

ACKNOWLEDGMENT

Authors thanks to NCL for giving LCMS/MS analysis. Both the authors have contributed equally during this work. Authors are also thankful to the Head, Department of Chemistry, Department of Chemistry Kohinoor Arts, Commerce and Science College Khultabad. Dist. Aurangabad Dr. Babasaheb Ambedkar Marathwada University, for providing laboratory facility.

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