Synthesis and characterization of 3, 4-dihydro-2 (H) -pyrimidinones based organo phosphorous heterocyclic functionalised vinyl polymer

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Abstract — A novel Biginelli- like cyclocondensation reaction is efficiently catalysed by citric fruits under room temperature and solvent free conditions in excellent yields. The Biginelli reaction is a multicomponent one pot reaction. The present investigation aimed towards cyclo condensation of β-keto ester, urea, aliphatic and aromatic aldehyde which leads to the synthesis of functionalized 3,4-dihydro-2 (H) -pyrimidinones (DHPM's). Owing to the increasing of green technology approach, due to its various merits over classical methodology and as the need for sustainable chemistry, this reaction has received renewed interest in preparing DHPM's in an environmentally thoughtful manner with improved yields. The classical reaction has been modified using various catalysts in different solvent to synthesis, large number of Biginelli type compounds. These DHPM's (synthetic and natural) possess a wide range of pharmacological activities. An Organo phosphorous compound has been synthesized using acidic hydrogen of DHPMs followed by functional modification of polyvinyl alcohol. Efforts have been taken towards the bacterial active phosphorous containing polymers. Synthesized compounds were characterized using FTIR and NMR. Thermal stability of synthesized compounds was also studied using TGA.

Keywords: green synthesis, dihydro pymidinones, citrus fruit, functionalised PVA, MIC.

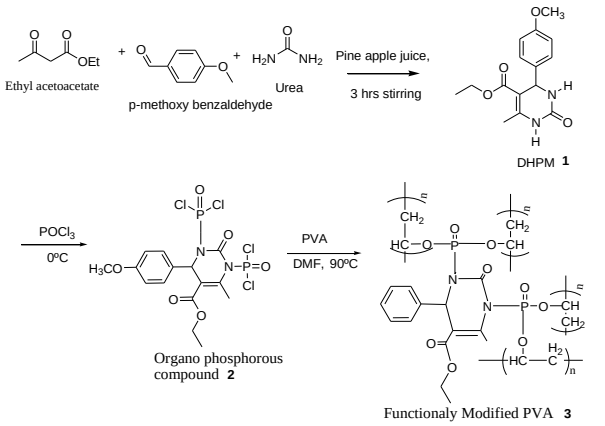
I. INTRODUCTION

Dihydropyrimidinones (DHPMs) occupy a particular position in the field of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties. [1] Dihydropyrimidinones scaffold emerged as an integral backbone of several drugs used as calcium channel blockers, antihypertensive and anticancer agents. DHPMs also elicit antidiabetic activity. Most famous among the isolated marine alkaloids is batzelladine, a potent HIVgp-120- CD4 inhibitor. [2] The most simple and straight forward procedure for the synthesis of DHPMs was reported by Biginelli in 1893. This involves one-pot condensation of ethylacetoacetate, aryl aldehydes and urea under strongly acidic conditions. Ace of the drawbacks of this method is low yield. Synthesis of DHPMs has attracted renewed attention and many improved procedures have been described. Many of these reported methods have employed the effect of various catalyston the synthesis of DHPMs such as H_2SO_4, BF_3OEt_2, polyphosphate esters, montmorillonite KSF, zeolites, etc., [3-7]

The above methods require expensive catalysts, strong acidic conditions, higher temperatures and prolonged response time. Most of the routes require costly reagents, toxic/hazardous organic solvents and tedious work-up. Hence chemists are putting more efforts to modify reaction conditions of the Biginelli protocol by using some green creatures. Multicomponent strategies offer significant advantages over conventional by linear type syntheses. To overcome the setbacks, non-hazardous and simple eco-friendly approaches towards the chemical operations are required for energy conservation or even less hazardous waste generation are desirable in the production of safer chemical products. Due to acidic nature, pineapple juice (pH=3. 7) [8] as a natural catalyst has been found to be a worthy substitute for various homogeneous acid catalysts.

Functional modification of PVA or introducing functional groups into the polymer chain has been believed to have basic significance with expanding its application. Many research articles have been reported concerning with the modification of polymer for the purpose of introducing carboxylic, sulfonate, and amino groups.[9-12] The synthesis of PVA that contains phosphorus and heteroaromatics in the main chain attracts the attentions of many researchers due to their peculiar characteristics viz, nonflammability, thermal stability, high melting points, and appreciable biological activities.[13–15] Among the nitrogen-containing compounds, six-membered heterocyclic compounds are used in various applications as herbicides, insecticides, pharmaceuticals, and adhesives. Five membered heterocyclic compounds are used in electrical and pharmaceutical applications. [16] Phosphorus-containing

compounds showed their usefulness in the preparation of water-soluble polymers. Incorporation of P=O unit into PVA showed improved flame retardancy, thermal oxidative stability, and good adhesion.[17] Phosphorus-containing polymers meet the requirements of low toxicity and low smoke during combustion for environmental and health considerations. The synthesis of polymers that contains phosphorus in the main chain or side chain attracts the interest of polymer specialists. Phosphorus-containing polymers are able to increase the char during burning and thus decrease the amount of flammable zone and reduce the heat transfer from the flame to the material [18-22]. While analyzing the literature, considerable attention has been paid for phosphorus-containing polymers perhaps there was not much report on biologically active phosphorus-containing polymers [21]. Hence, the scope of the present investigation is to synthesize phosphorus-containing nitrogen heterocyclic-based polymer by the reaction of PVA with nitrogen heterocyclic phosphonyl dichloride. The properties of the modified polymers such as thermal (TGA), flame retardancy, Spectral (FTIR, and NMR), and biological activities (MIC) have also been investigated. The synthetic route towards organophosphourous N-heterocyclic functionalised polymer has been listed in **Scheme 1.**



Scheme 1. Green synthesis of DHPMs using citric fruits and organophosphorous heterocyclic functionalized vinyl polymer.

1-DHPM **2-** Organophosphorous compound **3-** Functional modified vinyl polymers

II. EXPERIMENTAL

Materials and methods

The ultra pure chemicals viz., p-methoxy benzaldehyde, ethylacetoacetate**,** urea were purchased from Avra chemicals, Hyderabad and were used as such. Silica gel (TLC and Column grade) was purchased from Merck. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Advance III 400 MHz multi nuclei solution NMR. FTIR spectra (KBr pellets) were measured on the Alpha Bruker FTIR instrument with scanning the entire region of 4000 - 400 cm^{-1} with typical resolution of 1.0 cm^{-1}. Melting point was determined using an X-5A melting point measurement instrument.

Thermal Analysis.

Thermogravimetric analysis (TGA) has been carried out using a Netzsch STA 409 simultaneous thermal analyzer. The samples were heated from 35 to 900ºC at a heating rate of 10ºC/min under a nitrogen atmosphere. Flame retardance can also be evaluated from the char residue on pyrolysis. Van Krevelen has established a linear relationship between limiting oxygen index (LOI) and char residue for halogen free polymers. The LOI was calculated by using Van Krevelen's equation [21].

$$LOI = 17.5 + 0.4\ (\sigma)$$

Where σ is the percentage of char yield.

Biological activity

Microorganisms tested

Bacillus cereus, Staphylococcus aureus and Escherichia coli

Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC), which is considered as the least concentration of the sample which inhibits the visible growth of a microbe was determined by the broth dilution method.

Preparation of inocula

Organisms were subcultured on nutrient agar, followed by incubation for 24h at 37°C. Inocula were prepared by transferring several colonies of microorganisms to sterile nutrient broth. The suspensions were mixed for 15sec and incubated for 24h at 37°C. The required volume of suspension culture was diluted to match the turbidity of 0.5 Mc Farland standard (1.5x108 CFU/ml).

Preparation of sample

Samples were prepared in dimethylsulphoxide (DMSO) at the concentration of 2 mg/ml.

Broth dilution assay

A series of 15 tubes were filled with 0.5 ml sterilized nutrient broth. Sequentially, test tubes 2–14 received an additional 0.5 ml of the sample serially diluted to create a concentration sequence from 500 – 0.06µg. The first tube served as the control. All the tubes received 0.5ml of innoculum. The tubes were vortexed well and incubated for 24h at 37°C. The resulting turbidity was observed, and after 24 h MIC was determined to be where growth was no longer visible by assessment of turbidity by optical density readings at 600nm.

Synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3, 4-dihydro pyrimidin-2(1H) - one (1)

The equimolar quantities of p-methoxy benzaldehyde (1.36g, 10mmol), ethyl acetoacetate, (1.30g, 10mmol) and urea (0.6g, 10mmol), in 1ml pineapple juice were stirred for 3 hours at room temperature with monitoring by TLC. Then the reaction mixture was filtered, washed with little water. The yellow solid obtained was then

recrystallized with ethanol to get fine yellow crystals of 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydro pyrimidin-2(1H)-one. The formation of the compound was confirmed by IR, NMR and its melting point found to have 202-203°C.

Synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-methoxy phenyl)-3,4-dihydro pyrimidine-2(1H)–one-1,3-diphosphonyl tetra chloride (2)

About 1 mmol (0.290g, 10mmol) of 5-ethoxycarbonyl-6-methyl-4- (4-methoxyphenyl) - phenyl- 3,4-dihydro pyrimidine-2(1H)–one- (**2**) and 1mmol (0.153g) of phosphorus oxychloride were dissolved separately in 20ml of dry THF each and added slowly one over the other using dropping funnel with constant stirring for 30min at 0ºC in the presence of catalytic amount of pyridine. The reaction has been carried out for 3 hrs. Then the reaction mixture was filtered, and the solvent was evaporated to get **(2).** The progress of the reaction was monitored by TLC and separated by column chromatography using solvent system (ethyl acetate: hexane).

Functional modification of PVA using DHPM diphosphonyl tetrachloride moieties (3)

DHPMs diphosphonyl tetrachloride (1 mmol) and PVA (12 mmol) were dissolved in 50 mL of dry dimethylformamide at 90° C for 12 h with constant stirring. Then the solvent was removed under reduced pressure, and the resulting product was dried at 50° C using vacuum oven.

Spectral data for the compounds

5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydro pyrimidin-2(1H) - one (1) Yellow solid, Yield: 90%, melting point : 201-202 ºC; IR (KBr) ν_{max}/cm^{-1}: 3315 (N-H), 1749 (C=O), 1662 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.28 (t, 3H, -OCH_2CH_3), 2.09 (s, 3H, -CH_3), 2.48 (q, 2H, -OCH_2CH_3), 3.35 (s, 3H, -OCH_3), 3.92 (s, 1H, -CH), 5.1(s, 1H, -NH), 6.9-7.9 (m, 5H, Ar-H), 9.87 (s, 1H, -NH); Elemental analysis (CHN): Carbon – 61.54% (62.07%), Hydrogen – 5.82% (6.21%), Nitrogen – 9.25% (9.65%).

5 - ethoxycarbonyl - 4- (4-methoxyphenyl) - 3, 4 - dihydro pyrimidine-2 (1H) - one - 1, 3-diphosphonyl tetra chloride (2)

Brown waxy compound, IR (KBr) ν_{max}/cm^{-1}: 1739 (C=O), 1650 (C=C), 1230 (P=O), 1154 (P-N), 590 (P-Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.21 (t, 3H, -OCH_2CH_3), 1.68 (s, 3H, -CH_3), 2.67 (s, 3H, -OCH_3), 3.52 (q, 2H, -OCH_2CH_3), 3.81 (s, 1H, -CH), 7.9 – 8.1 (m, 5H, Ar-H). ^{31}P NMR (400 MHz, DMSO-d_6) δ ppm: -1.18, -12.89ppm

Functional modification of PVA using DHPM diphosphonyl tetrachloride moieties (3)

Pale yellow crystals, IR (KBr) ν_{max}/cm^{-1}: 1727 (C=O), 1656 (C=C), 1239 (P=O), 1137 (P-N), 1085 (P-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.39 (d, -CH_2 vinyl), 1.33 (t, 3H, -OCH_2CH_3), 2.52 (s, 3H, -CH_3), 2.75 (t, -CH vinyl), 3.88 (q, 2H, -OCH_2CH_3), 5.56 (s, 1H, -CH), 7.9 – 8.3 (m, 5H, Ar-H).; ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: δ14.6 (-OCH_2CH_3), 35.4(CH_3),30.8 (-CH_2, vinyl), 63.9(-OCH_3), 66.3 (-OCH_2CH_3), 68.2 (-CH, vinyl), 105.1& 142.0 (C=C), 134.0-141.0 (Ar-C), 162.2 & 181.5(-C=O).

III. RESULTS AND DISCUSSION

Spectral studies

The formation of the DHPM **1** was identified by the FTIR information through the showing peaks at 3315, 1749, 1662cm^{-1} for N-H, C=O and C=C respectively. The elemental analysis (CHN) have also been supported the formation of compound **1**. FTIR information for the formation of the N-heterocyclic diphosphonyl tetrachloride **2** were confirmed by the appearance of P-N and P=O stretching at 1230 and 1154 cm^{-1} respectively in. P-Cl stretching for the synthesized compound have shown around 590 cm^{-1}. Phosphorus-containing DHPM modified PVA were presented in **Scheme 1.** Disappearance of P-Cl stretching and formation of P-O-C stretching at 1085 cm^{-1} have confirmed the formation of the compound **3** as shown.

The compound **1** showed the ^{1}H NMR signals at 5.1 and 9.87 for two N-H groups in **Fig 1** and the peaks were disappeared in compound **2** in **Fig 2a.** ^{31}P NMR showed a peak at 4.59 ppm further supported the formation of N-P bonds in compound **2** have shown in **Fig 2b.** ^{1}H NMR signals at δ ppm 1.33, 2.52, 3.88, 5.56 for DHPM and 7.9-8.3 for aromatic ring and 1.39, 2.75 corresponds to CH_2 and CH of PVA in **3** have shown in **Fig 3a.** ^{13}C NMR signals at δ ppm 14.6, 35.4, 63.9, 66.3, 105.1, 142.0 have been related to DHPM carbons. There have been a multiplet at 134.0-141.0 corresponds to aromatic carbon and single peaks at 162.2 and 181.5 ppm for carbonyl groups in **3**. A Singlet of 30.8 and 68.2 ppm attributed to CH_2 and CH of PVA respectively have hown in **Fig 3b.**

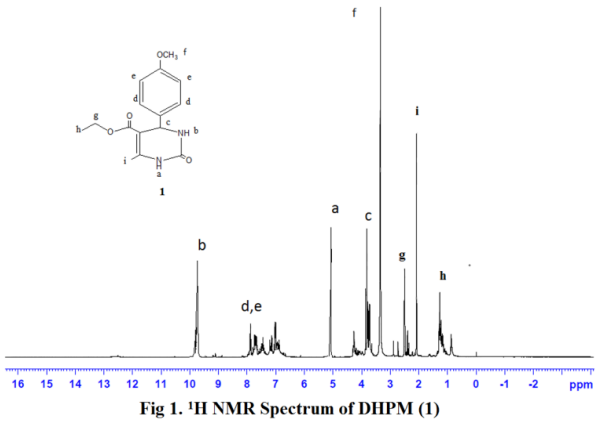


Fig 1. ^{1}H NMR Spectrum of DHPM (1)

Thermal studies

The thermo gravimetric analysis is one of the commonly used techniques for rapid evaluation of thermal stability of different materials. It also indicates the decomposition of polymers at various temperatures. **Fig 4a and Fig 4b** showed the TGA/DTA scanned report on PVA and modified PVA (compound **3**) respectively contents from 0 to 800ºC at the heating rate of 10ºC/min under nitrogen atmosphere. The sample weight was taken around 5.8–7.2 mg. The slope of the curve indicates the rate of weight loss of the material, and the rate of weight loss decreases with decreasing value of the slope of the curve.

The thermal stability of 5% initial weight loss of PVA (MW = 78,000) was observed at 260ºC, which might be higher than the modified PVA when the thermal degradation have just started [24-25]. PVA has two stage disintegration, but modified polymer has three stage disintegration. Around 15% weight loss was identified at 275ºC in **3**. This might be due to the less strength of the phosphorus bonds (P-O, P-N, and P-O-C) in polymers at relatively low temperature region than the ordinary polymer chain [26]. 45-60% weight loss was noticed at 440ºC. This can be related to the cleavage of four modified vinyl linkages attached to **3**. 61-75% weight loss was observed at 470ºC due to deformation of N-heterocyclic ring in the moieties. Based on the observation clearly pointed out that compound **3** found to be thermally stable than that of PVA.

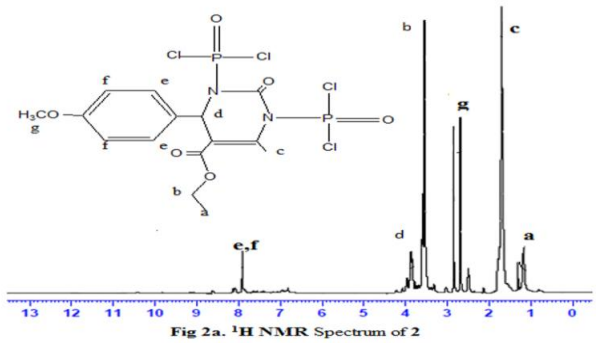


Fig 2a. ^{1}H NMR Spectrum of 2

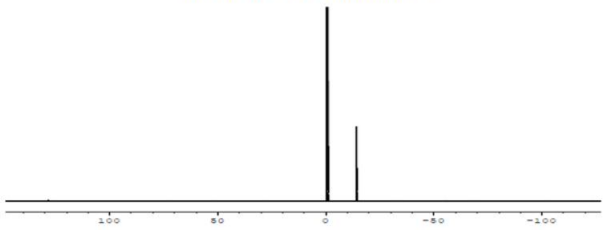


Fig 2b. ^{31}P NMR Spectrum of 2

The limiting oxygen index (LOI) value of modified and unmodified PVA has been listed in **Table 1.**

Table 1: Limiting oxygen index (LOI) Values of pure PVA and Functionalised PVA **3**

Polymer Code	**LOI**			
	400ºC	500ºC	600ºC	700ºC
PVA	29.00	21.00	17.28	---
Compound **3**	35.57	23.88	21.56	18.40

According to this, N-heterocyclic modified PVA **3** was observed at 35.57, 23.88, 21.56 and 18.40 at 400ºC, 500ºC, 600ºC and 700 ºC respectively, whereas unmodified PVA was 29, 21 and 17.28 at 400ºC, 500ºC and 600ºC, also no LOI value at 700 ºC, which implies that heterocyclic modified PVA has good flame retardants than unmodified PVA. This behavior was mainly due to the presence of P-N, P-C bonds, and heterocyclic compounds in the modified polymers. These structures act as weak links and they were highly susceptible to chain scission during thermal degradation [26]. However, polymer **3** has excellent flame retardance character. The increased property of **3** may be due to the presence of two N-P bonds (increases the overall flame retardancy) than other polymers.

Biological studies

The biological activity of the investigated system **3** have been tested against a representative number of pathogenic organisms like E. coli, S. aureus, and Basillus using minimum inhibition concentration (MIC), [26] the smallest amount of the agent that inhibits the multiplication of the pathogen. Therefore, it is found that the MIC for the system having certain activity have presented in **Table 2.**

Table 2: Minimum Inhibition Concentration (MIC) values of Functionalised PVA **3**

Sample	Minimum Inhibitory Concentration (µg/ml)		
	Escherichia coli	Staphylococcus aureus	Bacillus cereus
Compound **3**	62.5	250	62.5

Compound **3** was considered to be good for Bacillus cereus, Staphylococcus aureus and Escherichia coli. The improved bacterial activity due to the incorporation of phosphorus heterocyclic moieties into the PVA.

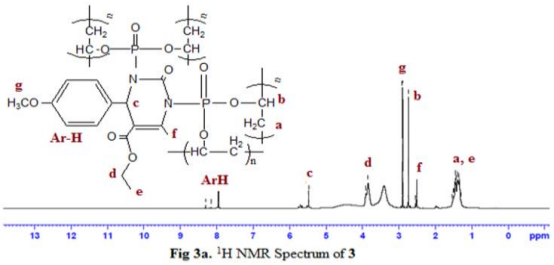


Fig 3a. ^{1}H NMR Spectrum of 3

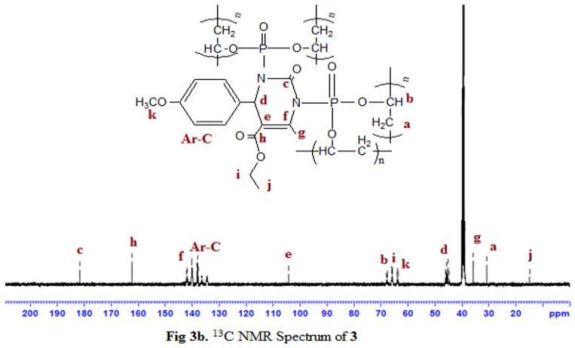


Fig 3b. ^{13}C NMR Spectrum of 3

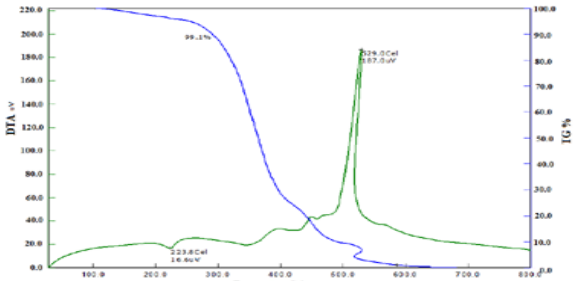


Fig 4a. TGA for pure PVA

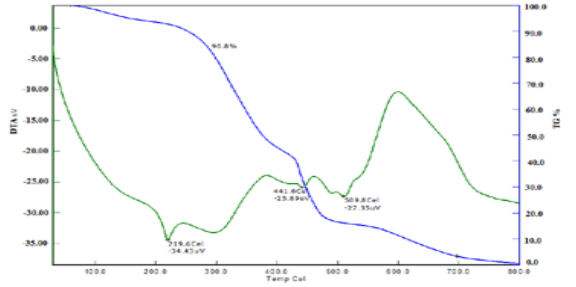


Fig 4b. TGA for Functionalised PVA

IV. CONCLUSIONS

Based on the careful analyses of the present investigation, biologically active phosphorus-containing N-heterocyclic functionally modified PVA was synthesized. Formation of compounds was confirmed by using FTIR, and NMR studies, respectively. TGA scans explain phosphorus-containing fused heterocyclic-based modified PVA was thermally stable and more flame retardancy than PVA. Compound **3** was considered to be good for Bacillus cereus, Staphylococcus aureus and Escherichia coli.

V. ACKNOWLEDGEMENT

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