Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2014, 5(6):90-95

Pelagia Research Library

ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and characterization of organophosphorous dihydro pyrimidinone derivatives

D. Somasundaran[1] and S. Guhanathan[2*]

[1]*PG and Research Department Chemistry, Voorhees College, Vellore, India*
[2]*PG and Research Department Chemistry, Muthurangam Government Arts College (Autonomous), Vellore, India*

ABSTRACT

Dihydropyrimidinone's (DHPMs) is a nitrogen containing heterocyclic ring which possesses biological and pharmaceutical importance. One-pot multi component syntheses of DHPMs have been achieved from aromatic and aliphatic aldehyde, ethylacetoacetate and urea under solvent free condition. This method is really easy and shorter time duration for the synthesis of DHPMs derivatives. Citric acid acts as a natural catalyst in the present investigation. The DHPMs derivatives were further treated with phosphorous Oxy chloride to obtain organo phosphorous compound. The formations of the compounds were characterized by FTIR, ^{1}HNMR and ^{31}PNMR.The antibacterial activity among aliphatic and aromatic substituted based dihydropyrimidinone have also been prepared and compared.

Keywords: dihydropyrimidinone; green synthesis; citrus fruits; three component one pot synthesis; organo phosphorus; spectral studies.

INTRODUCTION

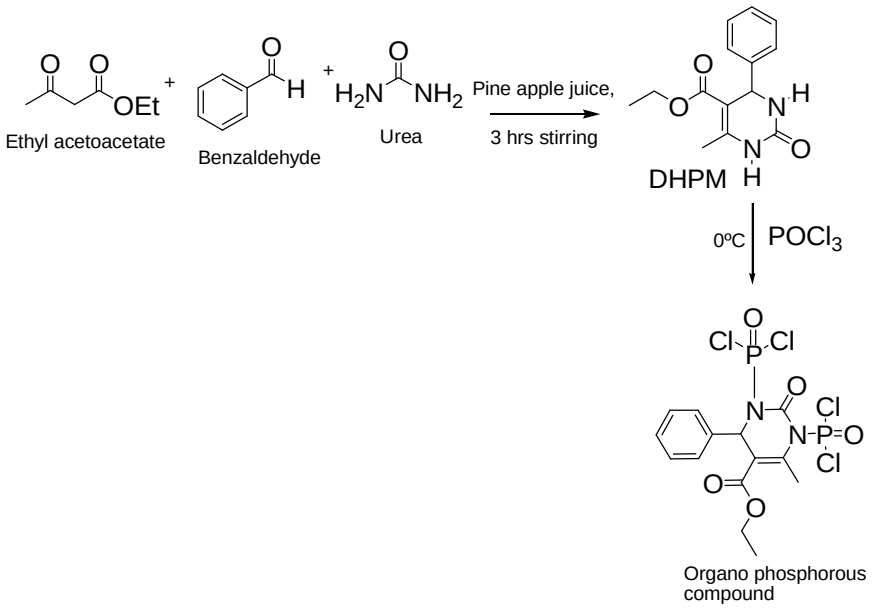
The eco-friendly transformations and environmental concerns in research and industry using heterogeneous catalysts are of considerable importance among the researchers [1]. Multicomponent reactions (MCRs) are having the most important protocols [2] in organic synthesis and medicinal chemistry. The Biginelli reaction [3] is the most significant and useful multicomponent reaction which offers an efficient way to access 3, 4-dihydropyrimidin-2 (1H) -ones. The 3, 4-dihydropyrimidin-2 (1H) -ones and their derivatives [4] are medicinally important [5] as calcium channel blockers, anti-hypertensive and anti-inflammatory agents and α1-an antagonist. These have recently emerged as important target molecules due to their therapeutic and pharmacological properties [6] such as antiviral [7], antimitotic [8], anticarcinogenic [9] etc., More recently Suresh and J. S. Sandhu [10] has reviewed the past, present and future of the Biginelli reactions with respective of its critical perspective. Biginelli in 1893, reported the first one pot- synthesis of 3, 4-dihydropyrimidines by condensation of an aldehyde, β-keto ester and urea or thio-urea under acidic condition [3]. Several procedures [10] have been reported using homogeneous as well as heterogeneous catalysts as promoters. Furthermore, several alkaloids containing the dihydropyrimidine nucleus obtained from marine sources are well known to exhibit biological activities [10]. Owing to the wide synthetic utility and potential applications, the synthesis of this heterocyclic nucleus is of much importance. A number of improved methods [11-13] involving the use of transition-metal-based catalysts/reagents, ionic liquids, polymer immobilized reagents, microwave and ultrasound irradiation have been recently reported for DHPMs synthesis.

The limitations of the catalysts were found in the literature viz., long reaction time, elevated reaction temperature, harsh reaction conditions, use of expensive reagents, moderate yields of the products, use of harmful organic solvents and hazardous transition metals. To overcome the setbacks, non-hazardous and simple eco-friendly approaches towards the chemical processes are needed for energy conservation or even less hazardous waste

generation are desirable in the production of safer chemical products. Therefore, to address the depletion of natural resources and preservation of the ecosystem, it is just urgent to implement, so called "greener technologies" to make chemical agents for the wellbeing of human health. Due to acidic nature, pineapple juice (pH=3.7) as a natural catalyst [14] has been found to be a suitable replacement for various homogeneous acid catalysts.

The present investigation focused on the use of an infusion of pineapple as a natural catalyst for synthesis of dihydropyrimidinone. The formations of DHPMs were confirmed using various spectral techniques viz., FTIR and ^{1}HNMR.

Organophosphorus compounds have found a broad range of application in the areas of industrial, farming and medicinal chemistry owing to their biological and physical properties, as well as their utility as synthetic intermediates [15, 16]. The synthesis of phosphate esters is an important chemical reaction in organic synthesis since they have found use in the preparation of biologically active molecules [17] and also versatile intermediate in the synthesis of amides and esters [18]. Among the phosphate esters, phosphonate derivatives are of interest as effective fungicides [19]. The Michaelis – Arbuzov reaction is a very versatile way of forming a Phosphorus – Carbon bond from the reaction between trialkylphosphite and alkyl/aryl halide [20]. Michaelis – Arbuzov reaction could be carried out with highly activated benzene as a solvent, by heating under reflux a mixture of trialkylphosphite and alkyl/aryl halide [21]. An unstable trialkoxyphosphonium intermediate formed is subsequently attacked by a halide anion to give a phosphonate. Phosphonates are also synthesized by modified Mannich's procedure using a reaction between phosphorus acid, amine and formaldehyde [22]. The reaction proceeds effectively under acidic condition only. A further limitation of this response is that only formaldehyde could be applied at the carbonyl source at low pH. Alternatively way of synthesizing phosphonates is through Michaelis-Becker reaction which involves the reaction between alkyl halide and potassium or sodium dialkylphosphonates [23-25].



Scheme 1. Green synthesis of DHPMs using citric fruits and organophosphorous compound

MATERIALS AND METHODS

The chemicals benzaldehyde, p-methoxybenzaldehyde**,** acetaldehyde, ethylacetoacetate**,** urea were commercially available from Avra chemicals, Hyderabad and were used as such. Silica gel (TLC and Column grade) was purchased from Merck. The solvents were purified as per the standard procedure reported elsewhere. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Advance III 300 MHz multi nuclei solution NMR. FTIR spectra (KBr pellets) were measured on the Alpha Bruker FTIR instrument 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.

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

The equimolar quantities of benzaldehyde (1.30g, 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 water. The yellow solid obtained was then crystallized with ethanol to get fine yellow crystals of 5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydro pyrimidine-2 (1H) -one. The formations of

the compound have been confirmed using various spectral techniques viz., FTIR, NMR. The melting point of compound **1a** found to have 207-209°C.

Synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2 (1H)–one-1,3-diphosphoryl tetra chloride (1b)

About 1 mmol (0.260g) of 5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydro pyrimidine-2 (1H) – one- **(1a)** 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 **(1b).** The progress of the reaction was monitored by TLC and separated by column chromatography.

Spectral data for the compounds

5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidine-2(1H)-one (1a)

FTIR (KBr pellet, cm^{-1}):	3236 (N-H), 1705 (C=O), 1454 (C=C)
^{1}H NMR (DMSO):	δ 1.19 (t, 3H, $-OCH_2CH_3$), 2.3 (s, 3H, $-CH_3$),
	3.43 (q, 2H, $-OCH_2CH_3$), 3.97 (s, 1H, -CH), 5.2(s, 1H, -NH),
CHN (Elemental Analysis)	7.2-7.7 (m, 5H, Ar-H), 9.2 (s, 1H, -NH)
	Observed: C-63.85%, H-5.92%, N-10.35
	Calculated: C-64.61%, H-6.15%, N-10.77%.

5-ethoxycarbonyl-6-methyl–4–phenyl-3,4-dihydropyrimidine–2(1H)–one-1,3-diphosphoryl tetra chloride (1b)

FTIR (KBr pellet, cm^{-1}):	1738 (C=O), 1453 (C=C), 1301 (P=O), 1129 (P-N)
^{1}HNMR (DMSO):	δ1.74 (t, 3H, $-OCH_2CH_3$), 3.31 (s, 3H, $-CH_3$),
	3.6 (q, 2H, $-OCH_2CH_3$), 3.85 (s, 1H, -CH),
	7.1 – 7.5 (m, 5H, Ar-H).
^{31}P (DMSO):	4.59 ppm

RESULTS AND DISCUSSION

The solubility of the compound **1a** soluble in THF, Ethanol and DMSO and compound 1b have been soluble in THF and DMSO. The N-H peak seems at 3236 cm^{-1} in the FTIR spectrum of compound **1a (Fig 1)**. CHN (Elemental Analysis for **1a**): Observed: C-63.85%, H-5.92%, N-10.35 %, Calculated: C-64.61%, H-6.15%, N-10.77%.

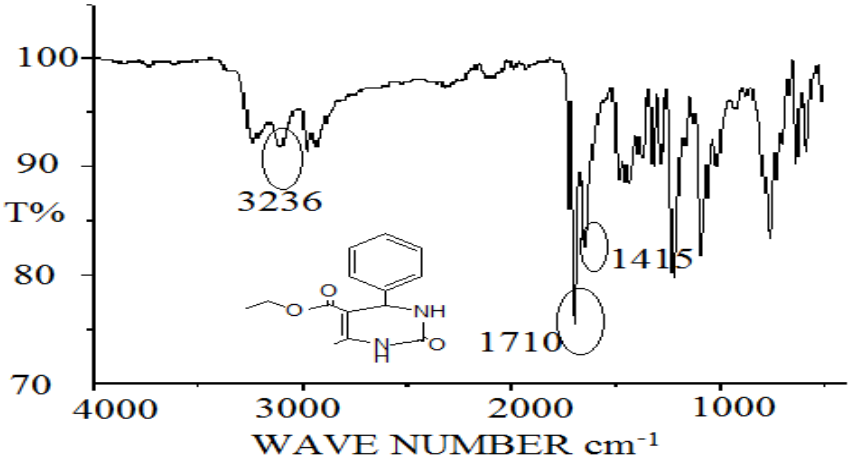


Fig 1. FTIR spectrum of compound **1a**

FTIR information about the formation of the N-heterocyclic diphosphonyltetra chloride **1b** was confirmed by the disappearance of N-H stretching and appearance of N-P and P=O stretching at 1301 cm^{-1} and 1124 cm^{-1} respectively. P-Cl stretching for the all-synthesized compounds were shown around 585cm^{-1} **(Fig 2)**.

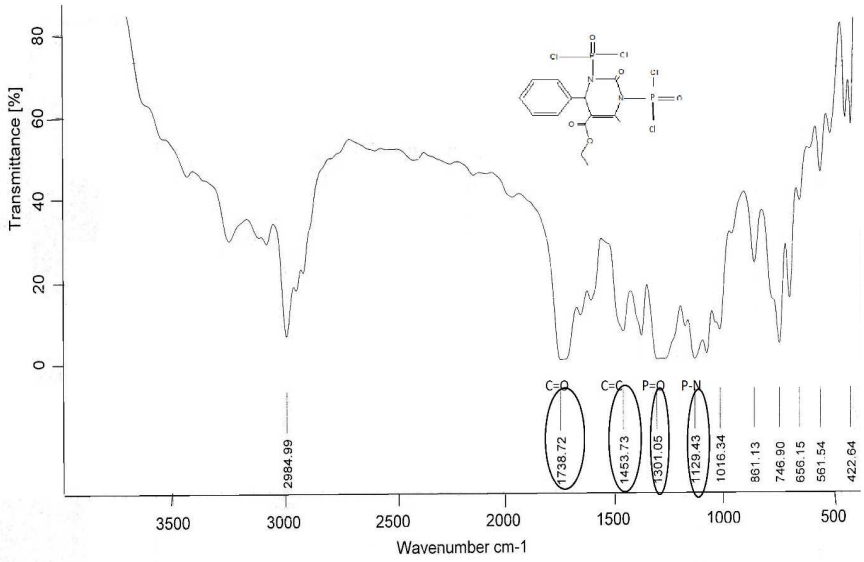


Fig 2. FTIR spectrum of compound 1b

^{1}H NMR information about the formation of the DHPMs and confirms the two N-H groups present in the compound **1a** at 5.2 and 9.2 ppm **(Fig 3).** The absence of N-H peaks was noticed in the DHPM diphosphoryl tetra chloride compound **1b (Fig 4).**

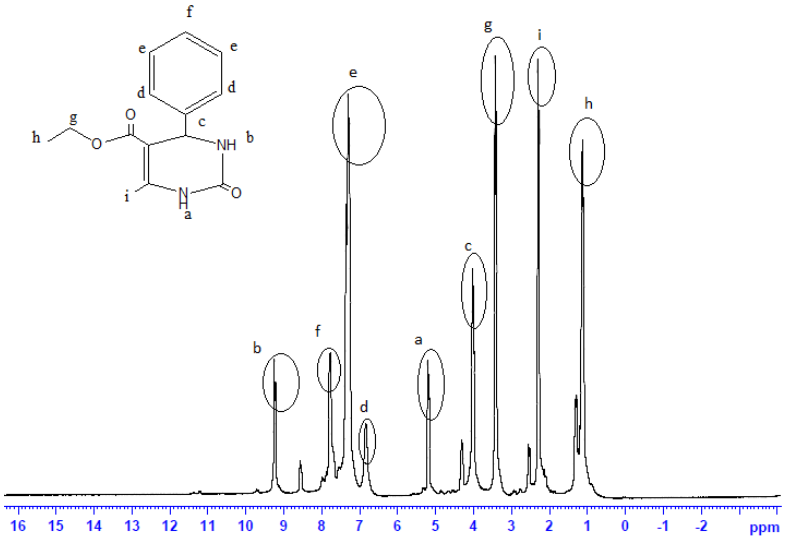


Fig 3. ^{1}H NMR of compound 1a

The ^{31}P NMR information about DHPM diphosphoryl tetra chloride compound **1b** which has been confirmed the presence of P in (N-P) DHPM diphosphoryl tetra chloride at +4.59ppm **(Fig 5).**

Biological Studies:
Antibacterial activity:
Source of microorganism
Klebsiella pneumonia, Staphylococcus aureus (S. Areas), and *Escherichia coli* was used as micro-organism for the present investigation.

Preparation of innoculum
The innoculums was prepared by inoculating a loop of each test organism for 24-h culture into a sterile nutrient broth and incubated at 37^{0}C for 3 h, until an optical density value of 0.3 was reached in polarimeter.

Disc-diffusion method
The medium was sterilized by autoclaving a 121°C for 15 min, cooled to 45°C, and then poured in 20-mL quantity of the Petri dish. A loop of overnight broth culture was spread evenly over the whole plate with a sterile cotton wool swab. The culture plates were dried in an incubator with the lid until its surface was free from visible moisture.

Subsequently, 5-mm diameter sterile disc (made whatmann filter paper sterilized in UV lamp) are dipped in solutions of substituted DHPM's; standard (ciprofloxacin hydrochloride) and control (DMSO) was placed on the surface of agar plates.

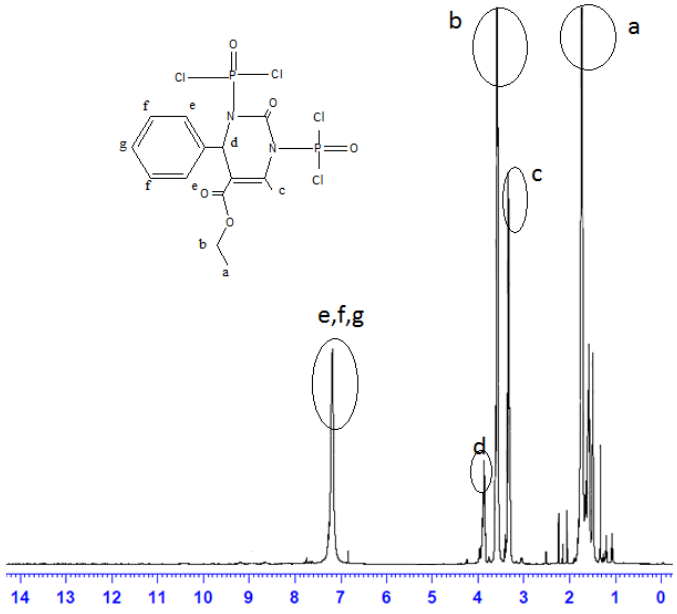


Fig 4 . ^{1}HNMR Spectrum of compound 1b

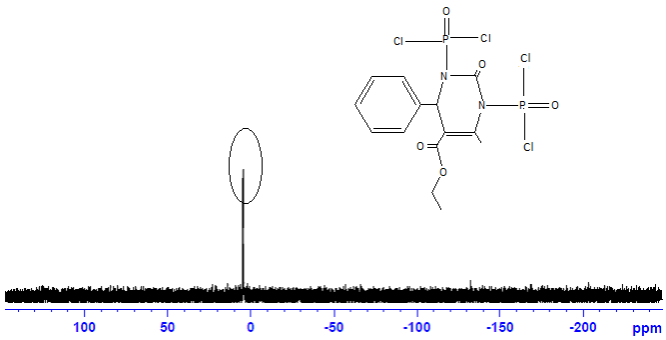


Fig 5 . ^{31}PNMR of compound 1b

The plates were left for 1 h at room temperature as a period of pre-incubation diffusion to minimize the effects of variation in time between the applications of different solutions of substituted DHPM's (s). The plates were incubated at 37°C for 24 h and observed for antibacterial activity. The diameter of the zones of inhibition was measured for the plates in which the zone of inhibition was observed. The average area of the zone of inhibition was compared with that of the standard.

Table 1. Zone of inhibition of selected bacterias

S. No	Microorganisms	1a	Ciprofloxacin
1	*Klebsiellab pneumonia*	4 mm	19 mm
2	*Staphylococcus aureus*	4 mm	20 mm
3	*Escherichia coli*	5 mm	24 mm

Table 1 summarized Compound **1a** showed mild zone of inhibition against ***Klebsiella pneumonia***, ***Staphylococcus aureus*** and ***Escherichia coli*** in comparison with the model drug ciprofloxacin.

CONCLUSION

An eco-friendly and economic process for the synthesis of DHPM by pineapple juice as catalysts have been synthesized with good yields. Formations of the compounds were confirmed using various spectral techniques. The compound has certain influence against the microorganism. The solvent free approach is totally offered nonpolluting environment and avoiding the use of toxic materials. The prepared N-heterocyclic compounds (DHPMs) and

phosphorous containing compounds found to have a greater opening for the synthesis of water soluble polymers which is the further scope of the present investigation.

Acknowledgement
One of the authors, Dr. S. Guhanathan, gratefully acknowledge the University Grants Commission, Government of India, New Delhi for financial support [Major Research Project: F. No. 40-50 / 2011 (SR)].

REFERENCES

[1] Xie W, Jin Y, and Wang PG, *Chemtech*, **1999**, 2, 23.
[2] Weber L, *Drug Disc Today*, **2002**, 7, 143.
[3] Biginelli P, *Gazz Chim Ital*, **1893**, 23, 360.
[4] Kidwai M, Venkatramanan R, Garg RK, Bhushan KR, *J Chem Res*, **2000**, 586.
[5] Tabern DL, Volwiler EH, *J Am Chem Soc*, **1935**, 57, 1961.
[6] Kappe CO, *Eur J Med Chem*, **2000**, 35, 1043.
[7] Hurst EW, Hull R, *J Med Pharm Chem*, **1961**, 3, 215.
[8] Mayer TU, Kapoor TM, Haggarty SJ, King RW, Schreiber SI, Mitchison TJ, *Science*,**1999**, 286, 971.
[9] Kato T, *Jpn Kokay Tokkyo Koho*, **1984**, 59, 190, 974, (CA 102 : 32067).
[10] Suresh, Sandhu JS, *ARKIVOV*, **2012**, pp. 66.
[11] Ranu BC, Hajra A, Jana U, *J Org Chem*, **2000,** 65, 6270.
[12] Sagar AD, Pulle JS, Reddy SM, Yadav MV, *J Chem Pharm Res*, **2011**, 3, 1103.
[13] Manjusha V, Yadav etal, *J Chem Pharm Res*, **2013**, 5, 266.
[14] Somasundaran D, Elumalai S, and Guhanathan S, *Int J Frontier science and tech*, **2014**, 2, 82.
[15] Srivastava MK, Raizada RB, *Food and Chemical Toxicology*, **1999**, 37, 649.
[16] Kamil K, Jan P, Jiri C, Frantisek L, *J Applied Biomedicine*, **2004**, 2, 51.
[17] Buchel KH, *Chemistry of Pesticides*, John Wiley and Sons Ltd., **1983**, pp 259.
[18] Vyle JS, Williams NH, Grasby JA, *Tetrahedron Letters*, **1998**, 39, 7975.
[19] Kaboudin B, Farjadian F, *Beilstein Journal of Organic Chemistry*, **2006**, 2, 4.
[20] Hassall KA, The Chemistry of Pesticides: *The Macmillan Press Ltd. London*, **1983**, pp 236.
[21] Timperley CM, Bird M, Holden I, and Black RM, *J Chem Soc, Perkin Trans*, **2001**, 1, 26.
[22] Gandavaram SP, Manubolu M, Kachi RK, Obulam VSR, Cirandur SR, *ARKIVOC* (XVI), **2006**, pp 128.
[23] Murugavel R, Kuppuswamy S, *J Chem Sci*, **2008**, 120, 131.
[24] Meisters A, Swan JM, *Aust. J. Chem.*, **1965**, 18, 163.
[26] Campbell DA, Jacobs JW, Methods for the synthesis of phosphonate esters: *U.S. Patent No.***1994**, no. 943805.