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A Simple & Efficient Method for One Pot Synthesis of Dihydropyrimidin-2(1H)-ones by using Phosphoric Acid

KEYWORDS: One pot synthesis, Phosphoric Acid, Dihydropyrimidones.

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ABSTRACT *A simple and economic synthesis of 3,4-dihydropyrimidin-2(1H)-ones by using phosphoric acid.Phosphoric acid has been found to be mild and efficient reagent for syntheisis of dihydropyrimidones and its corresponding thio-analoges in refluxing ethanol.*

Introduction:
The synthesis of dihydropyrimidones and their thio-analogous have become popular in the world of synthetic Organic Chemistry due to their activities such as antibacterial, antiviral, anti-inflammatory, antihypertensive & antitumor[1]. Although the mechanism of the Biginelli reaction has been debated for a number of years, most researchers now agree on the following sequence of steps, as proposed by Kappe[2].

It is note worthy that the Biginelli Reaction produces a 3,4-dihydropyrimidinone, an example of class of compounds exhibiting the pharmacological activity. Recently,4-aryl-dihydropyrimidin -ones have been recognized as a new class of calcium channel blockers and several biologically active marine alkaloids with the Biginelli product core have been isolated[3]. Other biological activities have also been noted[4].

The identification of biginelli products as a new class of calcium channel blockers is a subject that is of interest to many students,especially those who are pre-health majors or oriented towards biology. Calcium channel blockers are popular antihypertensive that inhibit the movement and binding of calcium ions, which leads to a relaxation of vascular smooth muscles and reduction of vascular resistance.

Recently, some marine alkaloids possessing dihydropyrimidin-5-carboxylate core have been shown to exhibit interesting biological activities such as potent HIV-gp-120-CD4 inhibitors as well as anti HIV agents[5].

The first synthesis reported Biginelli involves a one-pot condensation of an aldehyde, ethyl acetoacetate and urea in ethanolic medium in the presence of strong mineral acid in 1893. However this method suffered from drawbacks that the lower yields and longer reaction time especially with the aliphatic as well as substituted aromatic aldehyde have been observed. The reaction remained ignored almost for a century but with the confirmation that dihydropyrimidin-ones possess diverse and important biological properties the interest in their syntheisis has been greatly increased from last decades. A different things gave inspiration to organic chemist to find out more suitable protocol and simple methods for the synthesis of dihydropyrimidones.

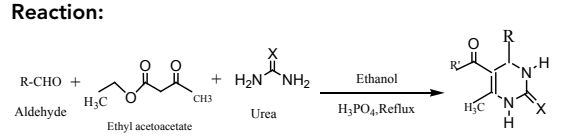
The different protocols like PPA, $AlCl_3$, H_3BO_3, conc. HCl, $BF_3.OEt_2$, NH_4Cl, NBS, Triflates of lanthanides compounds and In, Bi, Cu along with the microwave irradiation etc. have been tried6-10 to improve yields and conditions of Biginelli Reaction. A few methods involve the use of ionic liquids12. However, out of several methos and those involving different catalysis suffer from drawbacks that the use of expensive reagens like triflate of Bi, Cu, lanthanides etc. prolonged reaction times(classical biginelli reaction) and strongly workup procedures(e.g. ferric oxide nanocomposites),. An efficient synthesis of dihyropyrimidin-2(1H)-ones using phosphorous pentaoxide was studied by M.B.Deshmukh and etal.[6] & thus we have requires the development of new protocol for high yield and the use of inexpensive reagent, which requires shorter reaction time and with easier workup procedure.

Result and Discussion :
In the presence of the phosphoric acid the Bigineli areaction satisfactorily fulfilled the entire above requirements. Again the phosphoric acid or the phosphorus pentaoxide is an inexpensive reagent, act as an acid and dehydrating reagent. In the Biginelli reaction water molecules formed during the progress of reaction are absorbed by phosphorus pentaoxide and get converted into the phosphoric acid. This increases in acidic condition of the reaction mixture and due to which the rate of the rate of the reaction is increases, which leads to shorter reaction time. Also phosphorus pentaoxide being soluble in water is easily removed.

In this communication, we report the used of phosphoric acid for the one pot synthesis of 3,4-dihydropyrimidones. As in the trial case, benzaldehyde(1.06g,10mmoles), ethyla cetoacetate(1,30gm,10mmoles), urea(1.80gm,30mm0les) & phosphoric acid (0.5gm,3.54mmoles) urea mixed thoroughly and the reaction mixture refluxed on water bath. After the completion of the reaction, the mixture was poured on the crushed ice(100gm),, after the stirring the desired dihydropyrimidones separated out as a white solid in the quantitative yield(Scheme!). the same reaction then attempted with variable quantities of the phosphorus pentaoxide. However excess addition of phosphoric acid does not increase the yield of the product.

Effect of the amount of the phosphorus pentaoxide on the yield of 3,4-dihydropyrimidin-2(1H)-ones was investigated by using amount of phosphoric acid.

Reaction:



R=Ph,alkyletc. R'=OEt,Me X=O,S

As per our observation 100 mg of phosphoric acid gives 30-40% yield, 200 mg of phosphoric acid gives 55-60% yield, 300mg gives 60-70% yield, 400mg gives 75-80% yield while 500mg of phosphoric acid gives 85-90% yield in refluxing ethanol..

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Using the optimized quantity of phosphoric acid the reaction was extended to a variety of aldehydes including aromatic ,aliphatic as well as heterocyclic aldehydes to afford corresponding dihydropyrimidones in excellent yields. The versatility of the method was then checked by using thiourea instead of urea to prepare dihydrothiopyrimidones and by replacing ethyl acetoacetate with acetyl acetone, which gave the corresponding DHPMs. Both these variations did not affect appreciably the yield as well as ease of workup procedure. And these results are summarized in Table-I.

Table I : Data for the Synthesis of dihydropyrimidinones in the presence of Phosphuric acid.

Entry	R	R'	X	Time (hrs)	Yield* (%)	m.p.obs.(lit)^{0}C.
1.	C_6H_5	OEt	O	1.0	95	203-204(204)^{0}C
2.	4(C_2H_5))-C_6H_4	OEt	O	1.45	90	196-197(195)^{0}C
3.	4(Cl)-C_6H_4	OEt	O	0.5	95	217-218(210)^{o}C
4.	4(OCH_3)-C_6H_4	OEt	O	1.5	90	203-205(201) ^{o}C
5.	4(NO_2)-C_6H_4	OEt	O	1.0	95	207-208(210) ^{o}C
6.	4(Br)-C_6H_4	OEt	O	2.0	92	216-218(215) ^{o}C
7.	4(OH)-C_6H_4	OEt	O	2.10	85	227-228(228) ^{o}C
8.	2(Cl)-C_6H_4	OEt	O	1.20	88	218-220(218) ^{o}C
9.	4(F)-C_6H_4	OEt	O	1.40	86	207-209 ^{o}C
10.	3(NO_2)-C_6H_4	OEt	O	1.45	88	227-228(227) ^{o}C

Experimental Section:
All the compounds are reported one and their melting points are matched with reported value. All the above products have been characterized by proton NMR. The 1H-NMR spetra were recorded by using DMSO solvent on a Brucker 300MHz spectrometer with tetra methyl silane as an internal standard and the reaction was monitored by TLC using Silica gel 60-F 254 plates.

General Procedure :
The mixture of an aldehyde (10 mmoles), urea /thiourea (30mmoles), ethylaecetoacetate / acetyl acetone (10mmoles) and the phosphoric acid (0.5gm, 3.54 mmoles) in 250 ml round bottom flask refluxed on water bath, cooled and the reaction mixture was poured on crushed ice. The separated solid was then filtered, washed with pet ether, dried and recrystalized using ethanol.

Spectroscopic data of Representative DHPMs:
1) 5-Ethylcarbonyl-4(2-chlorophenyl)-6-methyl,3,4dihydropyrimidin-2(1H)-one(entry-2): m.p 217-218^{0}C (Lit.m.p.210^{0}C) PMR (DMSO):5.6(1H,bs,NH),7.3(5H, m,ArH),9.2(1H,bs,NH), 2.29(3H,s,CH_3),1.01(3H,t,$COCH_2CH_3$). (See Spectra A_1)

2) 5- Ethoxycarbonyl - 4 - (4-ethoxyphenyl) - 6 - methyl - 3,4 dohydropyrimidin- 2(1H) - one (entry-3) : m.p.196-197^{0}C (Lit.m.p. 195^{0}C) PMR (DMSO) : 5.1(1H,bs,NH), 7.1(5H,m,ArH),

9.1(1H,bs,NH), 2.5(3H,s,CH_3), 1.12(3H, t, $COCH_2CH_3$). (See Spectra B_1)

In the conclusion, we have developed a simple quick and efficient method or the synthesis of Biginelli dihydropyrimidones using Phosphoric acid. Apart from its Simplicity, the important advantage of the present protocol is the ability to tolerate variations in all the three components of the reaction. To the best of our knowledge, this is one of the quickest, economical and simple alternatives towards the synthesis of the 3,4 dihydropyrimidones. This introduces another important use of the Phosphoric acid in the synthetic Organic Chemistry.

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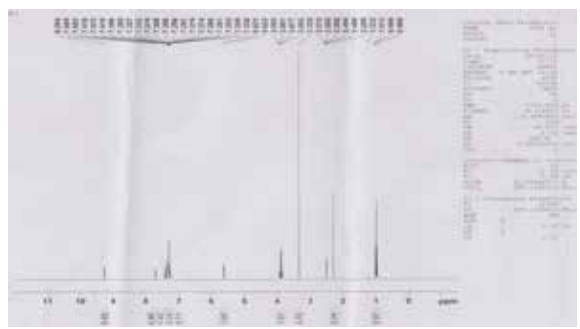
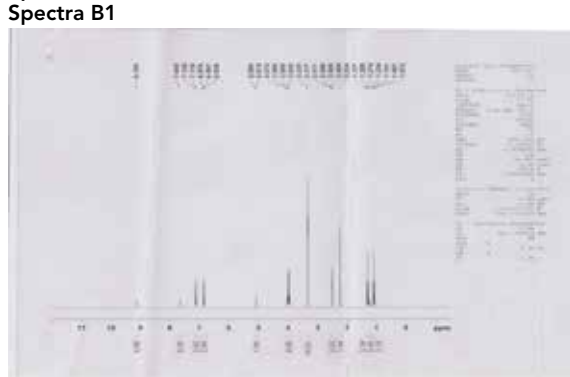


Spectra –A1
Spectra B1



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