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Study of catalytic activity of ammonium dihydrogen orthophosphate in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one

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Application of ammonium dihydrogen orthophosphate as a catalyst in the one pot synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one by Biginelli condensation is reported. The effect of temperature and the presence of solvents such as ethanol, acetonitrile, toluene, chloroform, acetic acid, *n*-hexane, *etc*. on the activity of the catalyst are studied.

Keywords: Biginelli condensation, ammonium dihydrogen orthophosphate, 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one, acetic acid, *n*-hexane

Dihydropyrimidinones (DHPM) are important materials due to their biological and therapeutic activities such as protection of wool from moths, antiviral activity, antibacterial activity, antitumor, anti-inflammatory, analgesic, blood platelets aggregation inhibitor, cardiovascular activity, potent calcium channel blockers, *etc*.[1] The presence of several interacting functional groups in these compounds determines their great synthetic potential. Such compounds are synthesized by Biginelli reaction[2]. It is a one-pot acid catalyzed three-component (multicomponent) cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea to form 3,4-dihydropyrimidin-2-(1*H*)-ones.

In recent years, multicomponent reactions such as Biginelli reaction have received considerable attention and emerged as one of the most important protocols in organic and medicinal chemistry[3]. The multi-component strategies have significant advantage over conventional synthesis due to the fact that the synthesis can be performed without the isolation of the intermediates (one step synthesis), without loosing any functional groups and to obtain new products with short reaction time.

However, the disadvantage of such multi-component synthetic route is the low yield of the desired product due to the formation of various side products. It is observed that generally, the experimental procedure involves the use of mineral acids, organic solvents, high temperature, *etc*. From the viewpoint of the potential applications of 3,4-dihydropyrimidin-2-(1*H*)-ones it is necessary to find out a versatile, simple and eco-friendly process. In recent times, Biginelli reactions with modified experimental conditions have been reported. Modifications have been made with respect to catalysts, solvents, temperatures, *etc*.[4,5]

A survey of the literature indicates various inorganic salts such as lanthanidetriflate[6], indium halides[7], indiumtriflate[8], iodine[9], strontium(II) triflate[10], fluorapatite[11], zirconium tetrachloride[12], manganous chloride, cobaltous chloride[13], zinc chloride[14], copper(II) complex[15], stannous chloride[16], ferric chloride[17], natural Zeolite[18], lanthanum chloride[19], cupric oxide[20], lithium bromide[21], 12-tungstophosphoric acid[22], manganese acetate[23], montmorillonite[24], diammonium hydrogen phosphate[25], alumina supported MoO_3[26], *etc*. have been employed as catalysts.

Many of these methodologies are associated with drawbacks such as expensive catalysts, acidic conditions, *etc*. Synthesis of 3,4-dihydropyrimidone under solvent free condition at RT using a very cheap chemical as a catalyst is cost effective and eco-friendly.

Hence, in the present work, a preliminary investigation has been made for one pot synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-

2-(1*H*)-one in the presence of hitherto unused ammonium dihydrogen orthophosphate as a catalyst. Ammonium dihydorgen orthophosphate is a very inexpensive and easily available compound. For comparison, the experiments have been performed at RT, reflux condition in the absence and in the presence of solvents.

Results and Discussion

As mentioned in the Experimental Section, Biginelli reaction between benzaldehyde, ethyl aceto acetate and urea was carried out in the presence of ammonium dihydrogen orthophosphate as a catalyst **(Scheme I)**.

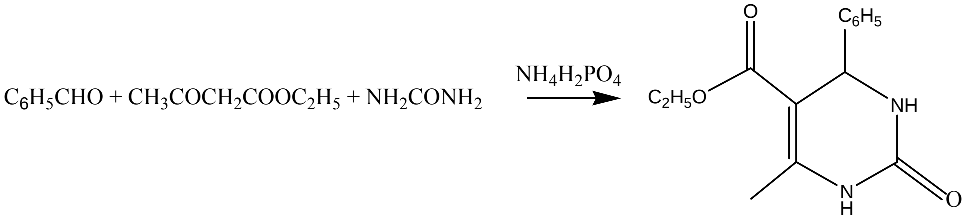
The influence of temperature and various solvents on the formation of the product was studied. The reaction was carried out at RT, under reflux condition, in the absence and in the presence of solvents. The results are compiled in **Table I**. Under solvent free condition 63% yield of the product was isolated. After 30 min stirring, solidification of the reaction-mixture was noticed. On the other hand, heating reduced the yield to 55%. In the presence of solvents, the best results were achieved at RT with *n*-hexane and under reflux condition in the presence of acetic acid. In the presence of solvents, an increase in the percentage yield was noted on heating generally except in the case of *n*-hexane.

Compared to the results obtained by Heravi, *et al.*[27] using 12-molybdophosphoric acid as a catalyst, the current reaction with acetic acid as a solvent under reflux condition yielded more of the product with shorter reaction time. On the other hand, the results are comparable with the observation made by Tu, *et al.* in the presence of H_3BO_3 as a catalyst at 100°C[28]. This could be due to the influence of the nature of catalyst on product formation.

To examine the reusuability of the catalyst, ammonium dihydrogen phosphate was recovered by filtration after the first run, washed with ethanol and dried. The resusability was checked under reflux condition using acetic acid as solvent. The yields of the product obtained after 2nd and 3rd runs are given in **Table I**.

Experimental Section

Melting points were determined by using open capillaries on Sunbim melting point apparatus and are uncorrected. The products obtained by the above method were characterized by ^1H NMR and FTIR spectroscopic techniques. FTIR spectra were recorded in the range of 4000-400 cm^{-1} on Thermo Nicolet Avatar 330 FTIR spectrometer by KBr pellet



Scheme I

Table I — Biginelli reaction using $NH_4H_2PO_4$

Solvent	Stirring at RT			Heating at reflux temperature		
	Yield (%)	m.p. (°C)	Time (hr)	Yield (%)	m.p. (°C)	Time (hr)
None	63	198	0.5	55[a]	204	0.25
Ethanol	33	202	4	81	202	2
Acetonitrile	77	200-02	4	74	200-02	4
Toluene	46	205-07	2	70	196-98	2
Chloroform	38	198-00	5	78	200-02	2
Acetic acid	65.3	206-08	2	91,88[b],84[b]	202-04	2
n-Hexane	83	200-02	2	61.5	200-02	2

[a] reaction was carried out at 80°C
[b] yield after 2nd and 3rd run.

technique. ^{1}H NMR spectra were recorded (200 MHz) using TMS as internal standard.

Experiments at room temperature

A mixture of benzaldehyde (20 mmoles), ethyl acetoacetate (20 mmoles), urea (20 mmoles) and ammonium dihydrogen orthophosphate (20 mmoles) was stirred without solvent for 30 min at RT. After the completion of the reaction (monitored by TLC), the reaction-mixture was washed with water and the residue was dried and purified by recrystallization from ethanol.

Similarly, the reaction-mixture was stirred with 20 mL of each of a solvent at RT. The solvents studied are: ethanol, acetonitrile, toluene, chloroform, acetic acid and *n*-hexane. The progress of the reaction was monitored by TLC. The ingredients were filtered and the catalyst was removed. The filtrate was poured into cold water. The precipitate obtained was separated, dried and purified by recrystallization from ethanol to afford the pure product.

Experiments under reflux condition

The experiments have been performed under reflux condition in the absence of solvent as well as in the presence of the solvents mentioned above. In the absence of solvent the reaction was carried out at 80°C. The progress of the reaction was monitored by TLC. The pure product was obtained by recrystallization from hot ethanol.

FTIR and ^{1}H NMR data are given below:

FTIR (KBr): 3246, 1725, 1701, 1649 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.163 (1H, s, NH), 7.711 (1H, s, NH), 7.233 (5H, m, Ar-H), 5.126 (1H, s, CH), 3.961 (2H, q, CH_2), 2.234 (3H, s, CH_3), 1.063 (3H, t, CH_3).

Conclusion

The use of inexpensive ammonium dihydrogen phosphate as a catalyst in Biginelli condensation was investigated for the first time under various experimental conditions. Reaction between benzaldehyde, ethyl acetoacetate and urea was taken as a model reaction. Best yield was obtained with acetic acid as a solvent under reflux condition.

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