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An Acid Catalyzed Efficient Synthesis of Dihydropyrimidone Derivatives Using Phosphoric Acid.

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ABSTRACT

The requirement of simple and clean synthesis of the heterocyclic compound has been largely increased due to the hazardous nature of the chemicals, so we developed the acid-catalysed one-pot synthesis of dihydropyrimidone derivatives using aryl aldehyde, keto ester and urea at room temperature results in the desired product. Simple and low-cost methodology, short reaction time, excellent yield, easy and clean work-up process are important features of the synthesis.

KEYWORDS

Cost-effective, methodology, short reaction time, excellent yield.

1. INTRODUCTION

The multicomponent reaction for the synthesis of heterocyclic compounds has major significance in organic as well as in medicinal chemistry [1]. Pyrimidine and its derivatives show distinct biological and pharmaceutical activities like antimicrobial [2], antitumor, antibacterial, anti-inflammatory and antifungal activities [3], and calcium channel blocker [4].

In 1893, Pietro Biginelli reported the synthesis of dihydropyrimidone firstly by a very simple one-pot condensation reaction of aromatic aldehyde, urea and ethyl acetoacetate in the presence of the catalytic amount of conc. HCl in ethanolic solution. This condensation reaction termed as a Biginelli reaction or condensation [5].

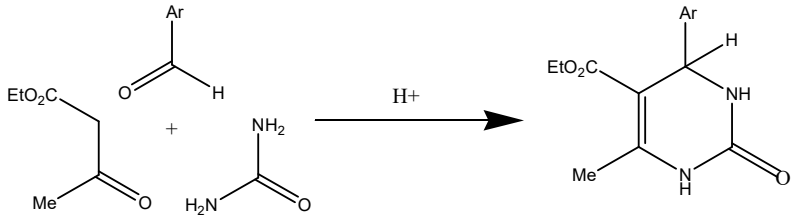


Fig. 1. Biginelli reaction or condensation.

Recently, several methods have been reported for the synthesis of dihydropyrimidone derivatives. Synthesis of dihydropyrimidone and its derivatives was carried out using various catalyst such as TPP [6], CAN [7], heteropoly acids [8], zinc complex [9], phenylboronic acid [10], Mg $(NO_3)_2$[11], lanthanum chloride heptahydrate [12], oxalic acid [13], DDQ [14], $ZnCl_2$ [15], $Cacl_2$ [16], PTSA [17]. Synthesis of dihydropyrimidone can also be synthesized by using ionic liquid [18]. The restriction in the synthesis of dihydropyrimidone and its derivatives is due to harsh reaction conditions, long reaction time, poor yield, high temperature, and costly reagents, use of harmful reaction solvent, toxic and hazardous metals. So there is a need to improve the procedure for synthesis. So we developed simple and general procedures in the one-pot synthesis of dihydropyrimidone and its derivatives using phosphoric acid. Phosphoric acid is weak acid with chemical formula H_3PO_4.

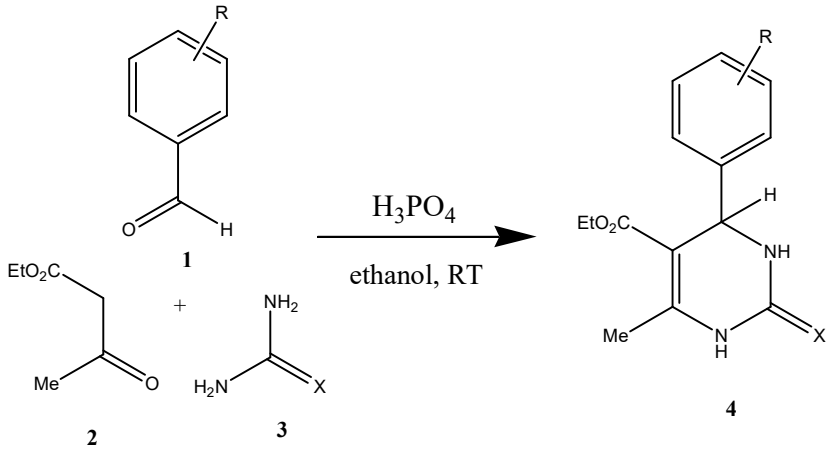
2. MATERIALS AND METHODS

All the chemicals were obtained from commercial suppliers and are used without further purification. All the melting points were determined in an open capillary tube and are found uncorrected and compared with reported literature. ^{1}NMR spectra were recorded for compound 4a ,4b, 4e and 4g on 400MHz instruments using dimethyl sulphoxide (DMSO) as a solvent and TMS as an internal standard. LCMS were taken for compound 4a, 4b, 4e and 4g which shows M^+. Analytical TLC for all reactions was performed on Merck prepared plates using 3:7 ethyl acetate: hexane solvent system and all other compound were confirmed from the TLC. The spot was visualized in the UV chamber. Percentage yield is given for all compounds.

3. RESULTS AND DISCUSSION

3.1. General procedure for the synthesis of Dihydropyrimidone Derivatives

In a 50 ml round bottom flask a mixture of aromatic aldehyde (1mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken in solvent ethanol (5 ml) in presence of a catalytic amount (10mol%) of phosphoric acid. The reaction mixture was stirred for 15 min at room temperature. After 15 min. the reaction is completed this is monitored by TLC. Then the reaction mixture was poured in crushed ice and the solid product was obtained is filtered and dried through the Buchner funnel. The crude product was recrystallized in ethanol solvent. The amount of catalysts can be optimized by varying its concentration. For 0.1 mmol concentration of phosphoric acid gives a better yield in short reaction time. All other derivatives of dihydropyrimidone were synthesized by the same above procedure.



Scheme 1. Biginelli reaction or condensation.

3.2. Optimization of reaction condition

3.2.1. Comparison with different catalyst for the synthesis of 4a.

To check efficiency of the catalyst phosphoric acid, we compare it with different reported catalyst such as methane sulfonic acid, P_2O_5, chlorosulfonic acid, P_2O_5/SiO_2, $ZnCl_2$, I_2. From this it was observed that phosphoric acid catalyst work very well and required 12 min. and room temperature condition for synthesis of 4a using benzaldehyde, ethyl acetoacetate and urea in presence of ethanol as a solvent which is indicated in table-1 entry 7.

Table 1. Comparison of reaction condition and time with reported method versus present method.

Entry	Catalyst	Solvent	Condition	Time in min	Reference
1	Methane sulfonic acid	ethanol	reflux	60	19
2	P_2O_5	ethanol	reflux	240	20
3	Chlorosulfonic acid	solvent free	60^0c	30	21

4	P_2O_5/SiO_2	solvent free	85^0c	120	22
5	$ZnCl_2$	solvent free	80^0c	20	23
6	I_2	solvent free	90^0c	15	24
7[a]	Phosphoric acid 10 mol%	ethanol	RT	12	-

[a]reaction condition: benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken in presence of a 10mol% phosphoric acid.

3.2.2. Optimization of amount of catalyst for reaction

To optimized amount of catalyst, we performed some reactions with varying percentage of catalyst phosphoric acid for synthesis of 4a from benzaldehyde, ethyl acetoacetate and urea in presence of ethanol as a solvent. from this we examined that 10 mol% of phosphoric acid was the most suitable amount of catalyst showing maximum yield (85%) in minimum possible time (12 min.) which is indicated in table-2 entry 2. with increase in percentage of catalyst 15 mol%, 20 mol% we observed that there is no increase in yield of product which is indicated in entry 3 and 4. From above observations we, synthesized all other derivatives with 10 mol% amount of catalyst phosphoric acid.

Table-2: optimization of amount of catalyst[a]:

Entry	Catalyst in mol %	Time in min	Yield %
1	5	40	70
2	**10**	**12**	**85**
3	15	12	85
4	20	12	85

[a]Reaction condition: benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken solvent ethanol (5ml) in presence of phosphoric acid

3.2.3. Optimization of best solvent for reaction

To obtain best solvent for synthesis of 4a, some trial reactions were conducted with combination of benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) in presence of different solvents (5 ml) with catalytic amount (10mol%) of phosphoric acid which is summarized in table 3. we examined some organic solvents such as toluene, 1-4 dioxane, THF and ethanol. we have noted that ethanol was the most suitable solvent showing better yield (85%) in 12 min. of time which is indicated in table -3 entry 4 among all other solvents. So all other derivatives were synthesized in ethanol.

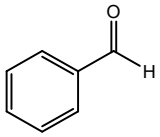
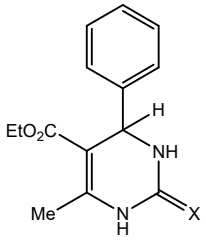
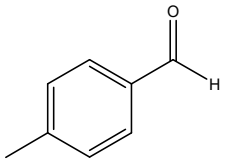
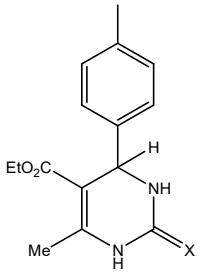
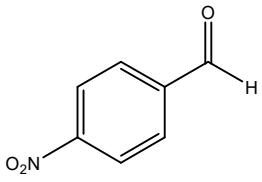
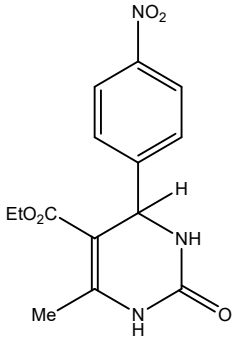
Table 3. Optimization of best solvent for reaction[a]

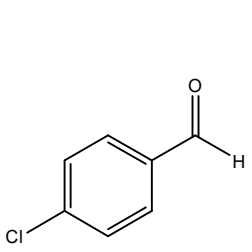
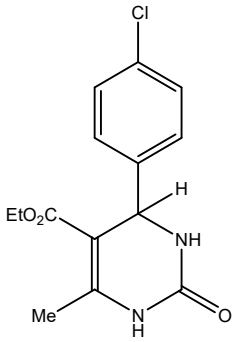
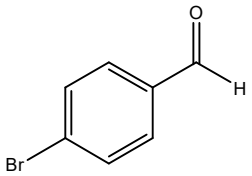
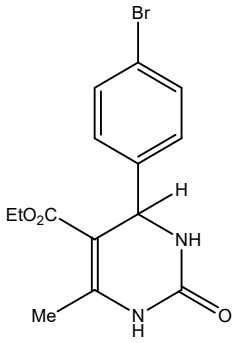
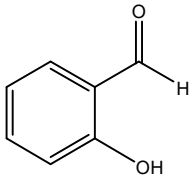
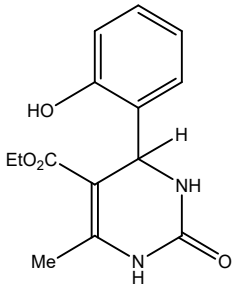
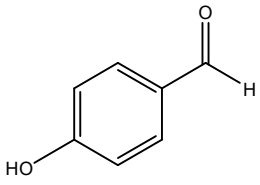
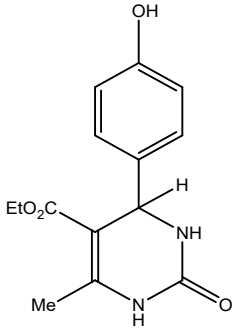
Entry	Catalyst mol%	Solvent	Time in min	Yield %
1	10	toluene	60	60
2	10	1-4 dioxane	40	65
3	10	THF	30	70

4	10	ethanol	12	85

[a]reaction condition: benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken in presence of a catalytic amount of phosphoric acid.

Table 4. Synthesis of dihydropyrimidone using aryl aldehyde, ethyl acetoacetate, and urea using phosphoric acid[a].

Sr. No.	Reactant - 1	Product	Yield[b] %	Time in min	M.P. ^{o}C
1		 4a	85	12	209-210
2		 4b	82	15	205-206
3		 4c	85	12	204-206

4		 4d	80	12	212-214
5		 4e	80	12	216-218
6		 4f	82	15	201-203
7		 4g	80	15	235-236

[a]reaction condition: aromatic aldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken in solvent ethanol (5 ml) in presence of a catalytic amount (10mol%) of phosphoric acid. [b]yield refer to isolated product.

3.3. Spectral Characterization

4a:5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

1H NMR (400 MHz, DMSO-d6): δH 9.18 (s, 1H,NH), 7.73 (s, 1H, NH), 7.21–7.34 (m, 5H, ArH), 5.13 (d,1H, J = 3.3 Hz, CH), 3.97 (q, 2H, J = 7.15 Hz, OCH2), 2.24(s, 3H, CH3), 1.08 (t, 3H, J = 7.15 Hz, CH3); MS (m/z): 260 (M+)

4b: 5-Ethoxycarbonyl-4-(4-methylyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one.

1H NMR (400 MHz, DMSO-*d*6): *δ*H10.28 (s, 1H, NH), 9.60 (s, 1H, NH), 7.12 (d, 2H, *J* =8.1 Hz, ArH), 7.06 (d, 2H, *J* = 8.1 Hz, ArH), 5.10 (d, 1H, *J* =2.8 Hz, CH), 3.97 (q, 2H, *J* = 6.95 Hz, OCH2), 2.25 (s, 3H,CH3), 2.24 (s, 3H, ArCH3), 1.08 (t, 3H, *J* = 7.15 Hz, CH3);
MS (*m/z*): 307 (M+).

4e: 5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

1H NMR (400 MHz, DMSO-d6):δH 9.20 (s, 1H, NH), 7.73 (s, 1H, NH), 7.48 (d, 2H, J =8.1 Hz, ArH), 7.14 (d, 2H, J = 8.1 Hz, ArH), 5.07 (d, 1H, J =2.8 Hz, CH), 3.93 (q, 2H, J = 6.9 Hz, OCH2), 2.20 (s, 3H,CH3), 1.04 (t, 3H, J = 7.15 Hz, CH3); MS (m/z): 339 (M++).

4g: 5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

1H NMR (400 MHz, DMSO-d6):δH 9.06 (s, 1H, NH), 7.57 (s, 1H, NH), 7.02 (d, 2H,ArH), 6.67 (d, 2H, ArH), 5.03 (d, 1H,J = 2.9 Hz, CH), 3.97(q, 2H, J = 7.15 Hz, OCH2), 2.22 (s, 3H, CH3), 1.09 (t, 3H, J= 7.15 Hz, CH3); MS (m/z): 277 (M+H).

4. CONCLUSION

We have developed a simple, general, efficient, clean, economically favorable procedure for the synthesis of dihydropyrimidone derivatives using phosphoric acid in short reaction time. Simple and low-cost methodology, short reaction time, excellent yield, easy and clean work-up process are important features of the synthesis.

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