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Phosphorofluoridic Acid as an Efficient Catalyst for One Pot Synthesis of Dihydropyrimidinones under Solvent Free and Ambient Condition

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Abstract

An efficient and simple protocol has been developed for the synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) from aldehydes, ethyl acetoacetate and urea using phosphorofluridic acid as the catalyst under solvent free conditions. In comparison with the classical Biginelli reaction, with the given conditions and catalysts, 10 mol% of phosphorofluroridic acid showed excellent catalytic activity. This method has the advantage of being eco-friendly, has an easy work up process and produces high yields in short reaction time.

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Keywords: Dihydropyrimidinones, phosphorofluoridic acid, efficient and simple protocol, solvent free reaction.

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advantages including high yields, short reaction time, easy work-up and use of relatively moderate acidic and safe catalyst.

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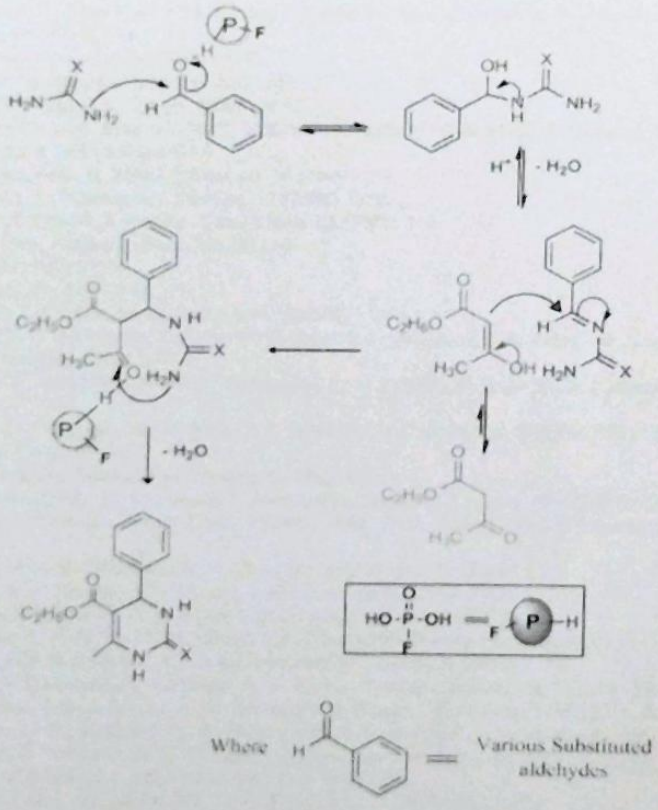
h	4-NO_2 Ph	3	86	223-224	220-225 (Ref. 38)
i	2-NO_2 Ph	5	80	218-220	217-220 (Ref. 40)
j	3-NO_2 Ph	3	94	227-228	226-227 (Ref. 37)
k	3-BrPh	4.5	84	186-188	187-189 (Ref. 38)
l	3-OHPh	5	82	180-181	179-182 (Ref. 38)

[a]Reaction conditions: aromatic aldehyde (2 mmol), EAA (2 mmol), urea (3 mmol) and 10 mol % catalyst under solvent free condition; [b] Monitored by TLC; [c]Isolated yield.

4. Proposed reaction mechanism

In order to understand the in depth reaction mechanism with phosphorofluoridic acid catalyst on the basis of obtained results in this study, a plausible reaction mechanism has been constructed for the development of dihydropyrimidinone derivatives as depicted in **Scheme II**. It is proposed that initially acidic proton of phosphorofluric acid gets interfaced with the oxygen atom of aldehyde functionality, that activates carbonyl group to generate the carbonium ion and it facilitates nucleophilic attack by NH_2 of urea resulting in imine. The resulting imine attack with ethyl acetoacetate bond and consequently the ring closes by the nucleophilic attack by the amine (second NH_2 group of urea) on to the carbonyl group. Finally, DHPMs product form through removal of water.



Scheme II: Probable mechanism for the synthesis of DHPM usingphosphorofluric acid catalyst.

5. Conclusion

In conclusion, we have developed an efficient procedure for the one-pot synthesis of dihydropyrimidinones under solvent-free conditions. Various reaction parameters such as effected catalyst dosage, effect of different csolvnet as well as effect of reaction time were also determined. In addition, using the optimised reaction condition various dihydropyrimidinones derivatives were prepared by using this simple protocol. This protocol offers several

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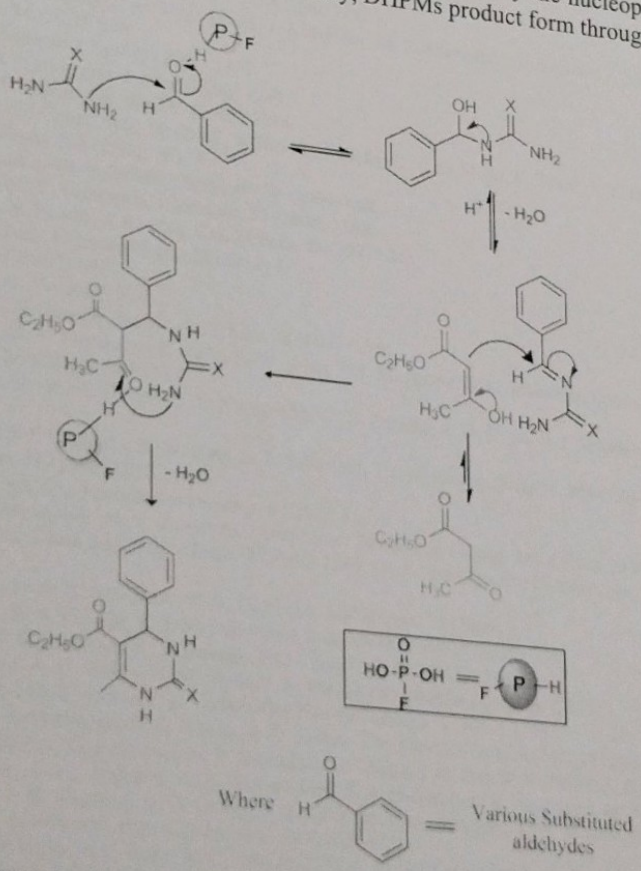

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Based on screening of above experiments, the optimal reaction conditions were identified as, 10 mol% of phosphorofluoridic acid catalyst in solvent free conditions at 60°C gives efficient and rapid transformation of EAA (2 mmol), azosalicyaldehyde (2 mmol) and urea (3 mmol) in to desired product. With the optimized conditions in hand, we have proceeded to investigate the scope and generality of this procedure using a range of various substituted aldehydes providing the corresponding derivative of DHPMs in good to excellent yield, as publicized in Table 3. As marked from Table 3, aromatic aldehydes with electron donating groups (4-CH_3, 4-OCH_3, 4-$N(CH_3)_2$, 4-OH and 4-OH, 3-OCH_3) (Entries b to f) as well as electron withdrawing groups (4-Cl, 4-NO2, 2-NO_2, 3-NO_2, 3-Br) (Entries g to k) showed good to excellent yield of dihydropyrimidinone derivatives. In general, the electronic effect slightly influences the results, whereas the steric effect plays an important role on controlling the yield of product, as demonstrated by that the orthosubstitutedbenzaldehydes afforded lower yield (Table 3, entry i). However, from these results it can be concluded that 10 mol% of phosphorofluoridic acid is a highly suitable catalyst for the synthesis of dihydropyrimidinone with any functional substitution on the aromatic rings. In addition, these substituted functionalities were preserved throughout the course of reaction in presence of reported catalyst and optimized reaction conditions.

Table 1. Comparative effect of various catalyst with respective to Phosphorofluoridic acid catalyst on the reaction of DHP synthesis using benzaldehyde, urea and EAA.[a]

Entry	Catalyst	Solvent	Reaction Temp. (°C)	Reaction Time[b] (h)	Yield (%) [c]
1	Catalyst free	Solvent free	60	6	25
2	Catalyst free	Ethanol	60	6	52
3	Phosphorofluoridic acid	Solvent free	60	3	92
4	PPA	Solvent free	60	5	82
5	DPA	Solvent free	60	3	85
6	Spinal phosphoric Acid	Tolulene	70	38 min.	85 [44]
7	Sulfamic acid	Xylene	50	6 days [d]	47 [45]
8	Chlorosulfonic Acid	Solvent free	50	3 days [d]	90 [45]
		Solvent free	60	3 days	30
		Solvent free	60	5	82
		Ethanol	60	6	80
		Reflux	60	3	86 [46]

[a]Reaction conditions: Benzaldehyde (2 mmol), EAA (2 mmol), urea (3 mmol) and 10 mol % catalyst under various condition; [b] Monitored by TLC;[c]Isolated yield. [d]using thiourea.

Table 2: Influence of concentration of phosphorofluoridic acid and other parameter in reaction mixture on yield of DHPMs derivatives.[a]

Entry	Catalyst used	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield (%) [b]
a	5 mol %	Solvent free	60	5	80
b	10 mol %	Solvent free	60	3	92
c	15 mol %	Solvent free	60	4	90
d	10 mol %	Solvent free	Room temp.	10	36
e	10 mol %	Solvent free	80	6	84
f	10 mol %	EtOH	60	6	86
g	10 mol %	MeOH	60	6	82
h	10 mol %	CH_3CN	60	10	62
i	10 mol %	Toluene	60	10	54
j	10 mol %	H_2O	60	18	20

[a]Reaction conditions: Benzaldehyde (2 mmol), EAA (2 mmol), urea (3 mmol) and Phosphorofluoridic acid catalyst under various condition; [b] Monitored by TLC;[c]Isolated yield.

Table 3: Analytical data of synthesized dihydropyrimidinone derivatives 4 (a-l)

Entry	Aldehyde	Reaction time in hr. [b]	Yield[c] in %	M.P. in °C	
				Observed	Reported
a	Ph	3	92	204-205	202-204 (Ref. 37)
b	4-CH_3 Ph	3.5	93	206-207	206-208 (Ref. 38)
c	4- OCH_3 Ph	2.5	94	202-203	201-202 (Ref. 37)
d	4- $N(CH_3)_2$Ph	3	84	253-254	252-255 (Ref. 39)
e	4- OHPh	4	80	231-232	232-234 (Ref. 38)
f	4-OH, 3-OCH_3 Ph	3	84	147-148	146-148 (Ref. 38)
g	4-ClPh	4	86	214-215	213-215 (Ref. 37)

3. Result and Discussion

With the phosphorofluoridic acid in hand, we have synthesized dihydropyrimidinone derivatives with superior yield. The current protocol comes with eco-friendly, easier with simple work up process, use of inexpensive and readily available catalyst. During preliminary studies, the condensation of benzaldehyde (2 mmol), EAA (2 mmol) and urea (3 mmol) was utilized as the model for finding the optimization conditions. Effect of various phosphoric and sulfuric acid derivative on current transformation studied and results were summarized in **Table 1**.

3.1 Influence of catalyst on synthesis of Dihydropyrimidinone

Initially, the reaction was performed in the absence of catalyst and stirred at 60ºC. However, negative results were obtained with 25% & 52% yield under solvent free conditions and using ethanol solvent respectively (Table 1, Entry a & b). Again, the same reaction was carried out using phosphoric acid derivatives such as PPA (poly phosphoric acid) and DPA (dodecyl phosphonic acid) catalysts. 10 mol% of these catalysts was more than sufficient for 100% conversion of reactants into desired product with 82% and 85% yield respectively (Table 1, Entry d & e). By increasing thereaction temperature from 60 to 70°C, DPA catalyst gave better performance. Notably, it reports same yield in very short reaction time [40]. However, in the next step we have used spinal phosphoric acid as catalyst for the same reaction but it comes with very disappointing results which gave just 30% of product. The reaction vessel was stirred at 60ºC under solvent free conditions and it consumed 3 days (Table 1, Entry f). Surprisingly,the same catalyst reported for given transformation while changing urea to thiourea in toluene as well as xylene solvent at 50ºC temperature, after 3 to 6 days reaction gave us 47% and 90% yield of desired product [41]. It can hence be concluded that spinal phosphoric acid is a unique catalyst but it is very expensive and requires long reaction time period. Similarly, we have carried out the same reaction with sulfur containing acids under solvent free condition at 60ºC. Sulfamic acid catalyst reported 82% yield after 5 h, whereas chlorosulfonic acid gave 80% yield in 6 h (Table 1, Entry g & h). Additionally, same chlorosulfonic acid catalyst gave satisfactory results of 86 % yield in ethanol solvent at reflux temperature [42].

These obtained results demonstrate that, above reported catalysts comes with certain downsides such as long reaction time, expensive materials, need of solvent and tedious work up process. The present solvent free method showed marvelous production of dihydropyrimidinone from appropriate amounts of reactants in presence 10 mol% phosphorofluoridic acid catalyst showed 100% conversion with excellent 92% yield in just 3 h. (Table 1, Entry c). This is one of the most superior protocols for the synthesis of dihydropyrimidinone derivatives.

3.2 Influence of reaction parameters on the catalytic activity of phosphorofluric acid

To find out appropriate reaction conditions with phosphorofluoridic acid catalyst, reactions were performed by varying amount of catalyst, reaction temperature and solvent for which obtained results summarized in **Table 2**. Further, in order to study more details with the amount of catalyst to attain higher yields for the dihydropyrimidinone formation, we have performed the experiments by using higher amount of phosphorofluoridic acid to 15 mol% at 60ºC under solvent free atmosphere which after 4 h showed 90% yield (Table 2, Entry c). Thereafter, the same reaction was performed by loading lower amount viz. 5 mol% of catalyst which gave 80% yield in 5 h (Table 2, Entry a). These results awarded us the permission to use 10 mol% phosphorofluoridic acid under solvent free conditions for the better outcomes (Table 2, Entry b). To know the effect of temperature on catalytic activity, given reaction took place at room temperature with fixed catalytic amount but it failed to give efficient yield even after 10 h reaction time (Entry d). On further increasing of the reaction temperature to 80ºC also yielded unsatisfactory results. However, the results obtained at 60ºC gave 84% yield of respective product (Table 2, Entry e). Moreover, to determine the effect of solvent on catalytic performance it was also necessary to report clear and proper reaction conditions. Therefore, we have tested many solvents for this protocol wherein the reaction mixture was stirred at 60ºC with 10 mol% phosphorofluoridic acid catalyst. Initially, the reactions were carried out in ethanol and methanol solvents which gave 100 % conversion of reactants with 86% and 82% yield of product respectively after 6 h (Table 2, Entry f & g). In addition, CH_3CN and toluene as solvents also failed to give efficient yields. Results showed that, these solvents acquired 100 % conversion but showed only 62 and 54 % yield of respective dihydropyrimidinone derivative (Table 3, Entry h & i). As per green chemistry concerns, we have followed the given reaction in water as solvent and results showed just 20% yield of target molecule even after long time of 18 h at 60ºC (Table 3, Entry j).

NMR (200 MHz; DMSO in δ ppm): 9.2 (1H, s), 8.8 (1H, s), 7.6 (1H, s), 7.1 (2H, d, J = 8 Hz), 6.8 (2H, d, J = 8 Hz), 5.0 (1H, s), 4.0 (2H, q), 2.3 (3H, s), 1.3 (3H, t); ^{13}C NMR (DMSO in ppm); 166.2, 155.8, 151.9, 148.5, 134.8, 128.1, 115.5, 102.8, 60.0, 54.1, 18.8 and 14.6; MS (m/z): 277 (M+1).

2.2.6. Ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4f*****:** White solid; Yield 84%; m.p. 147-148°C; IR (KBr, in cm^{-1}): 3580, 3477, 3452, 2998, 2862, 1730, 1682, 1562, 1280, 780, 680, 587; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.1 (1H, s,), 8.8 (1H, s), 7.6 (1H, d, J = 2 Hz), 6.8 (1H, d, J = 8 Hz), 6.6-6.5 (2H, m), 5.1 (1H, s), 4.3 (2H, q), 3.8 (3H, s), 2.3 (3H, s), 1.4 (3H, t); ^{13}C NMR (DMSO in ppm); 168.1, 155.4, 149.7, 147.9, 146.4, 136.6, 119.8, 115.8, 12, 105.6, 60.3, 57.2, 53.8, 19.1 and 16.5; MS (m/z): 307 (M+1).

2.2.7. Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4g:*** White solid; Yield 86%; m.p. 214-215°C; IR (KBr, in cm^{-1}): 3462, 3409, 2940, 2795, 1760, 1674, 1548, 1284, 780, 660, 545; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.1 (1H, s), 8.2 (1H, s), 7.4 (2H, d, J = 8 Hz), 7.2 (2H, d, J = 8 Hz), 5.2 (1H, s), 4.0 (2H, q), 2.2 (3H, s), 1.3 (3H, t); ^{13}C NMR (DMSO in ppm); 166.0, 152.6, 148.9, 144.2, 132.5, 128.8, 127.2, 102.9, 59.2, 54.1, 18.5 and 14.3; MS (m/z): 295 (M+1).

2.2.8. Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4h****:* Creamish solid; Yield 86%; m.p. 223-224°C; IR (KBr, in cm^{-1}): 3562, 3450, 2885, 2820, 1768, 1660, 1540, 1380, 1290, 784, 665, 540; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.3 (1H, s), 8.8 (1H, s), 8.2 (2H, d, J = 8 Hz), 7.7 (2H, d, J = 8 Hz), 5.3 (1H, s), 4.1 (2H, q), 2.3 (3H, s), 1.3 (3H, t); ^{13}C NMR (DMSO in ppm): 166.4, 153.2, 150.7, 149.1, 148.4, 133.8, 130.8, 123.6, 122.4, 103.5, 60.2, 54.5, 18.6 and 14.5; MS (m/z): 306 (M+1).

2.2.9. Ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4i****:* Pale brown solid; Yield: 80%; Mp 209–210 °C; IR (KBr, in cm^{-1}): 3545, 3440, 3245, 2801, 1730, 1640, 1504, 1324, 1064, 978, 740, 640; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.3 (1H, s), 8.2 (1H, s), 8.0 (1H,d), 7.7-7.5 (3H, m), 5.5 (1H, s), 3.9 (2H, q), 2.3 (3H, s), 1.2 (3H, s); ^{13}C NMR (DMSO in ppm): 165.6, 160.2, 153.8, 145.0, 135.2, 131.6, 130.2, 128.4, 127.5, 104.8, 59.8, 54.7, 18.4, 14.3; MS (m/z): 306 (M+1).

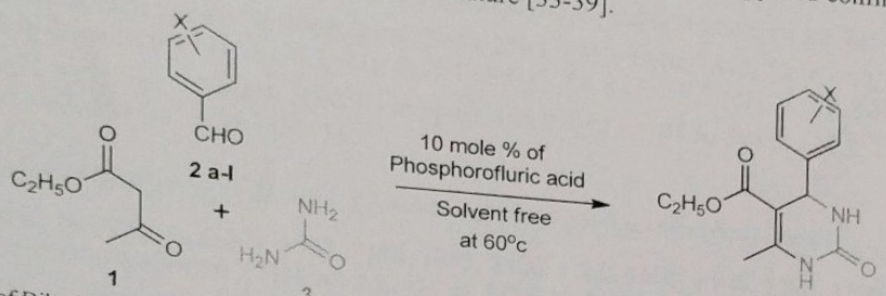
2.2.10. Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4j***: Yellow solid; Yield: 92; Mp 227–228 °C; IR (KBr, in cm^{-1}): 3584, 3465, 2805, 1768, 1670, 1544, 1310, 1265, 1054, 980, 764, 618, 540; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.2 (1H, s), 8.4 (1H, s), 8.2 (1H, s), 7.3-7.5 (3H, m), 5.4 (1H, s), 3.8 (2H, q), 2.3 (3H, s), 1.2 (3H, t); ^{13}C NMR (DMSO in ppm): 165.4, 158.8, 153.7, 145.0, 135.8, 131.4, 128.7, 127.5, 126.2, 104.2, 59.8, 54.9, 18.6, 14.2; MS (m/z): 306 (M+1).

2.2.11. Ethyl 4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4k***: White solid; Yield 90%; m.p. 187-188°C; IR (KBr, in cm^{-1}): 3520, 3462, 2905, 2822, 1775, 1655, 1560, 1292, 778, 660; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.2 (1H, s), 8.0 (1H, s), 7.4-7.3 (2H, m), 7.1-7.0 (2H, m), 5.1 (1H, s), 3.9 (2H, q), 2.2 (3H, s), 1.3 (3H, t); ^{13}C NMR (DMSO in ppm); 166.5, 154.2, 150.6, 148.2, 132.5, 131.1, 130.3, 126.8, 122.9, 104.0, 60.4, 54.4, 18.4 and 14.7; MS (m/z): 340 (M+1).

2.2.12. Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4l***: White solid; Yield 82%; m.p. 180-181°C; IR (KBr, in cm^{-1}): 3580, 3470, 3440, 2951, 2809, 1762, 1682, 1508, 1260, 782, 675, 504; ^{1}H NMR (200 MHz; DMSO in δ ppm): 8.8 (1H, s), 8.4 (1H, s), 7.1 (1H, t), 6.8 (1H, s), 6.6 (2H, m), 4.9 (1H, s), 3.8 (2H, q), 2.2 (3H, s), 1.1 (3H, t); ^{13}C NMR (DMSO in ppm); 167.6, 160, 155.3, 149.5, 147.6, 132.1, 118.2, 114.8, 114, 103.4, 60.5, 54.4, 18.4 and 15; MS (m/z): 277 (M+1).

2.2. General experimental procedure for synthesis of dihydropyrimidinone derivatives

To a mixture of various substituted aromatic aldehydes (2 mmol), EAA (2 mmol) and urea (3 mmol) was added in 100 mL RB flask. A known catalytic amount of phosphorofluoridic acid was also added in the reaction mixture. There was no addition of solvent or co-catalysts. Then, the obtained mixture was magnetically stirred under open atmosphere at 60°C temperature for appropriate time. After the completion of the reaction (checked by TLC;hexane/ethyl acetate 8:2), reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was collected and evaporated under vacuum on rotary evaporator. The crude solid product was purified by passing it through a short column of silica gel to afford pure product of DHPMs derivatives (Scheme 1). Synthesized compounds were further characterized by ^{1}H and ^{13}C NMR spectroscopy and confirmed by comparing obtained data to analytic and spectral data available in literature [33-39].



Scheme 1. Synthesis of Dihydropyrimidinone derivatives from Ethyl acetoacetate (2 mmol), Urea (3mmol) and various substituted aldehydes (2 mmol) in presence of 10 mole % phosphorofluoridic acid.

2.2.1. Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4a:*** White solid; Yield 94%; m.p.204-205°C; IR (KBr, in cm^{-1}): 3415, 3214, 2865, 1705, 1660, 1490 1280; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.5 (1H, s), 8.2 (1H, s), 7.3-7.2 (5H, m), 5.2 (1H, s), 3.9 (2H, q), 2.4 (3H, s), 1.2 (3H, t); ^{13}C NMR (DMSO in ppm): 166.7, 152.2, 150, 144.1, 129.2, 127.8, 126.8, 106.5, 60.7, 53.7, 18.2 and 15.0; MS(m/z): 261 $(M+1)^{+}$.

2.2.2. Ethyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4b***: White solid; Yield 87%; m.p. 206-207°C;IR (KBr, in cm^{-1}): 3505, 3430, 2815, 1760, 1665, 1503, 1274, 1021, 978, 760, 610; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.3 (1H, s), 8.4 (1H, s), 7.2 (4H, s), 5.1 (1H, s), 3.8 (2H, q), 2.2 (6H, s), 1.2 (3H, t); ^{13}C NMR (DMSO in ppm): 166.8, 154.2, 149.1, 142.6, 138.2, 130.0, 127.4, 105.8, 60.8, 54.3, 21.5, 18.9 and 15.1; MS (m/z): 275 (M+1).

2.2.3. Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4c***: White solid; Yield 90%; m.p. 202-203°C; IR (KBr, in cm^{-1}): 3450, 3340, 3108, 2860, 1720, 1670, 1502, 1285, 670, 590; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.4 (1H, s), 8.2 (1H, s), 7.2 (2H, d, $J = 8$ Hz), 6.7 (2H, d, $J = 8$ Hz), 5.1 (1H, s), 4.2 (2H, q), 3.8 (3H, s), 2.2 (3H, s), 1.2 (3H, t); ^{13}C NMR (DMSO in ppm); 166.4, 158.4, 152.8, 149.1, 138.6, 128.8, 115.2, 108.2, 60.3, 56.2, 52.7, 18.0 and 15.3; MS (m/z): 291 (M+1).

2.2.4. Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4d:*** Creamish solid; Yield 84%; m.p. 253-254°C; IR (KBr, in cm^{-1}): 3560, 3447, 2877, 1765, 1668, 1557, 1308, 1028, 965, 780, 558; ^{1}H NMR (200 MHz; DMSO in δ ppm): 9.0 (1H, s,), 8.6 (1H, s), 7.2 (2H, d, $J = 8$ Hz), 6.8 (2H, d, $J = 8$ Hz), 5.1 (1H, s), 4.0 (2H, q), 2.8 (6H, s), 2.3 (3H, s), 1.1 (3H, t); ^{13}C NMR (DMSO in ppm): 165.2, 152.4, 150.1, 147.5, 132.3, 127.2, 112.5, 102.8, 59.2, 53.7, 18.1 and 13.9; MS (m/z): 304 (M+1).

2.2.5. Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***4e:*** White solid; Yield 80%; m.p. 231-232°C; IR (KBr, in cm^{-1}): 3608, 3487, 3455, 2905, 2857, 1742, 1674, 1560, 1278, 780, 680; ^{1}H

Sr. No.	
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1. Introduction

From the last decade, organic chemists have been focusing on reactions using acid-sensitive substrates mediated by non-metal Brönsted acid catalysts. Acid catalysts such as ammonium [1] and phosphonium [2] salts of sulfonic acids have seeked more attention and are predominantly being developed to achieve such reactions. In contrast, there has been very few reports with phosphorofluoridic acid catalyst in organic transformations due to its lower acidic nature compared to those with phosphoric acid moieties. Acidic potential of phosphoric acid is enhanced by introducing electron-withdrawing groups at the phosphorus atom. Also, phosphorus compounds with fluorine atom add unique catalytic applications in organic transformation [3-5].

Recently, fluorine-containing catalytic applications have undergone rapid growth [6-8]. Fluorinated phosphoric acids are expected to be more acidic than the non-fluorinated corresponding acids. Subsequently, these are less basic and less nucleophilic than the corresponding phosphorates. Additionally, the stability of fluorinated phosphorates is higher than that of other halogen-substituted phosphorates. Therefore, phosphoric acid derivatives bearing a P-F bond have been used as key intermediates leading to biologically interesting molecules [9]. It is evident from the previous literature that phosphorofluoridic acid has invoked enormous interest as a potential green and acid catalyst to construct carbon–carbon and carbon–heteroatom bonds in various organic transformations [10-13]. Furthermore, the introduction of hydrophobic sites to the oxygen atoms of phosphoric acids makes it possible to remove water from the reactive centers while maintaining high catalytic activities. We have focused on the investigation of the catalytic applications of phosphorofluoridic acid in the synthesis of dihydropyrimidinone derivatives under solvent free conditions. Dihydropyrimidinone moiety take more attention due to its broad pharmaceuticals spectrum such as anti-viral, anti-tumor, anti-bacterial, and anti-flammatory properties as well as calcium channel modulating activity [14-20]. Frequent conventional methods [21, 22] and catalyst free [23] synthesis of dihydropyrimidinones have been reported in literature and these came with certain downsides such as long reaction time, poor yield, tedious work-up procedure, etc. Thus, in the last decade, many improved methods, including enantioselective versions, have been exploited and till near about 400 papers have been correspondingly published [24]. In these advanced methods, Lewis or Brønsted acids have been mainly used as catalyst under milder conditions with much better results compared to the results obtained by employing traditional conditions.

Herein, we continued our previous work on synthesis of dihydropyrimidinones [25-27] and developing green protocols [28-32] for organic transformations. We decided to investigate the efficiency of phosphorofluoridic acid catalyst for the synthesis of pyrimidinones derivative in solvent free condition. Presently, we report phosphorofluoridic acid catalysed one pot synthesis of dihydropyrimidinones derivatives from ethyl acetoacetate, urea and various substituted aromatic aldehydes under solvent free and ambient conditions. However, there is not a single report on the use of phosphorofluoridic acid as a catalyst for the synthesis of pyrimidinone moiety. This methodology uses phosphorofluoridic acid as a simple, novel, and highly efficient catalyst with cleaner conversion, solvent-free conditions and higher yields in very short duration.

2. Experimental

2.1 Materials and methods

All the chemicals were obtained from commercial chemical suppliers. and used with further purification. Phosphorofluoridic acid (95%) was purchased from Sigma Aldrich Chemicals Ltd. and necessary purification was done before using. All crucial preliminary materials for pyrimidone derivatives and necessary reagents were acquired from Sigma Aldrich and used without additional distillation. All solvents were purified and dried by typical methods earlier used. All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra (in cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer in KBr pellets. ^{1}HMR spectra were recorded on Varian Gemini (200 MHz) spectrometer using DMSO as solvent and TMS as an internal standard. ^{13}C-NMR spectra were recorded on 50 MHz in DMSO solvent, in δ ppm. All chemical shifts values are reported in δ scale downfield from TMS. Homogeneity of the compound was checked by TLC on silica gel plates.