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SHORT COMMUNICATION

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Phenylphosphinic acid-catalyzed synthesis of 6-unsubstituted dihydropyrimidinones under solvent-free conditions

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Abstract

Phenylphosphinic acid is found to catalyze the three-component condensation of an aldehyde, enaminone, and urea or thiourea to afford the corresponding 6-unsubstituted dihydropyrimidinones in high to excellent yields. This methodology is simple and fast synthetic route for the preparation of interesting class of heterocycles.

1 | INTRODUCTION

Dihydropyrimidinones (DHPMs) have been the subject of chemical and biological studies[1] due to their wide spectrum of biological and therapeutic properties including anti-inflammatory,[2] anticancer,[3] and calcium channel blocker.[4] One of the most common procedures for the synthesis of dihydropyrimidinones was reported by Biginelli using three-component reaction of aromatic aldehydes, β-ketoesters, and urea.[5] Recently, several improved protocols for the synthesis of dihydropyrimidinones have been reported by modification of classical Biginelli reaction using new catalysts,[6] ionic liquids,[7] and microwave[8] and ultrasound irradiation[9] and extending its substrate scope.[10] Enaminones are highly reactive building blocks in the synthesis of heterocyclic compounds.[11] In the last decade, Wan[12] and co-workers developed a protocol for the synthesis of 6-unsubstituted DHPMs by employing enaminone as the active methylene donor, aldehyde and urea/thiourea. However, few studies have used enaminones as a substrate,[13–16] which lead to large number of multifunctionalized pyrimidinones. Using organic solvents and excess amount of catalyst, moderate yields and long reaction time have been described in most cases. Organocatalysis is an important area of research in recent years because they are usually robust, inexpensive, readily available, low toxic, and high tolerance to molecular oxygen and traces of water.[17] Reactions which are carried out in solvent-free conditions are often rapid, regio- or chemoselective with high yields, and have environmental and economic advantages.[18]

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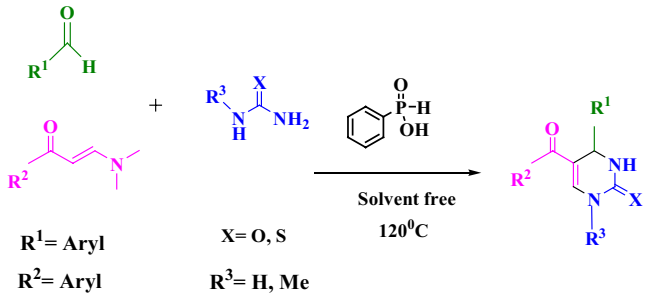
For these reasons, we decided to pursue solvent-less synthesis of 6-unsubstituted dihydropyrimidinones from aldehydes, enaminones, and ureas/thiourea in the presence of phenylphosphinic acid as an organocatalyst. The results obtained in this investigation are reported herein (Scheme 1).

2 | RESULTS AND DISCUSSION

In this study, we initially optimized the reaction conditions using 4-nitrobenzaldehyde (1 mmol), phenyl enaminone (1 mmol), and urea (1.2 mmol) as model substrates under solvent-free conditions (Table 1). As it is clear from this table, the best result was obtained when the reaction was carried out in the presence of 5 mol% of phenylphosphinic acid at 120°C (Table 1, entry 6).

In order to show the generality of this reaction, we synthesized different 6-unsubstituted DHPMs using variety of aldehydes with enaminones and ureas or thiourea under solvent-free conditions (Table 2). As shown in Table 2, various aromatic aldehydes bearing electron-withdrawing groups and electron-donating groups reacted with enaminones and urea in the presence of phenylphosphinic acid under solvent-free conditions at 120°C to give 6-unsubstituted DHPMs in excellent yields (Table 2, entries 2–14). This reaction was also successfully performed with *N*-substituted urea. 4-(4-Nitrophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1*H*) was isolated in high yield when *N*-methyl urea, phenyl enaminone, and 4-nitro benzaldehyde were employed (Table 2, entry 15). However, aliphatic aldehydes, such as isobutyraldehyde, resulted in a very low product yield of 15%



SCHEME 1 Solvent-less synthesis of 6-unsubstituted dihydropyrimidinones

(Table 2, entries 16). The investigation of this method indicated that reaction of thiourea with aromatic aldehydes and various enaminones afforded corresponding thio-derivatives of dihydropyrimidinones under optimum reaction conditions (Table 2, entries 16–22).

Mechanistically,[11] the reaction may be done via *N*-acyliminium ion formation by acid-catalyzed condensation of aldehyde and urea. Subsequently, addition of the enaminone to this iminium followed by condensation affords 6-unsubstituted DHPM (Scheme 2).

3 | CONCLUSIONS

In summary, we have developed simple, efficient, and environmentally friendly approach for the preparation of 6-unsubstituted DHPMs by three-component cyclocondensation of various aldehydes, enaminones, and thiourea or substituted- and unsubstituted urea in the presence of phenylphosphinic acid as an organocatalyst. The reactions are solvent less, fast, and the yields of the products are excellent in most cases.

4 | EXPERIMENTAL

Materials were purchased from Fluka and Merck companies. Enaminones were prepared according to the reported procedure.[19] Products were characterized by comparison of their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and MS) and physical properties with those of authentic samples.

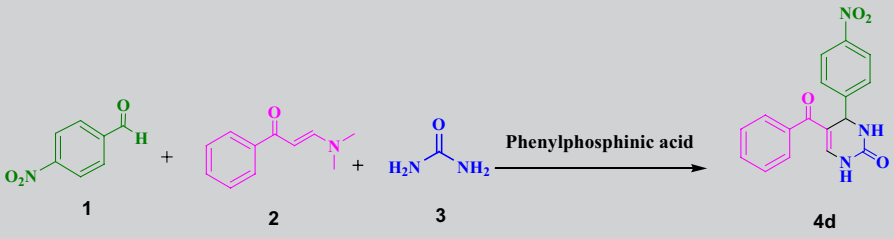
General procedure for the synthesis of DHPMs 4a–v. Aldehyde (1 mmol), enaminone (1 mmol), and urea or thiourea (1.2 mmol) were ground with phenylphosphinic acid (5 mol%) in a pestle mortar at 120°C under solvent-free conditions for 20 min. The reaction mixture was then cooled to room temperature and water (5 mL) was added to the mixture. The catalyst was dissolved in water and filtered for separation of the crude product. The residue was washed twice with 5 mL of water. Then, product was purified by recrystallization procedure in EtOH/H_2O.

4.1 | Spectral data for unknown products are as follows

4-(4-Cyanophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-one **(4f)**. IR ν_{max} 905, 1157, 1214, 1375, 1446, 1611, 1655, 1695, 2229, 3330, 3211. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.50 (d, 1H, J = 2.8 Hz), 7.07 (d, 1H, J = 6 Hz), 7.43–7.55 (m, 7H), 7.84 (d, 2H, J = 8.4 Hz), 7.99 (s, 1H), 9.48 (d, 1H, J = 5.2 Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.7, 110.7, 111.8, 119.1, 128.0, 128.5, 131.5, 133.1, 138.7, 142.9, 149.6, 151.4, 191.9. ESI-MS: *m/z* 303.1 ([M]$^+$).

4-(2-Iodophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-one **(4g)**. IR ν_{max} 1075, 1155, 1214, 1368, 1441, 1620, 1656, 1702, 2929, 3224, 3401. ^{1}H NMR

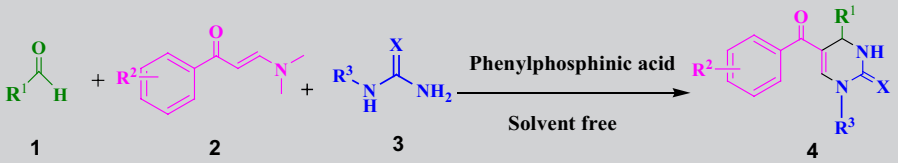
TABLE 1 Optimization reaction conditions for the synthesis of dihydropyrimidinones



Entry	Mol% of catalyst	Temperature (°C)	Time (min)	Yield (%)[a]
1	5	80	20	55
2	5	100	20	80
3	5	120	20	97
4	10	120	20	90
5	3	120	20	88
6	-	120	20	40

[a]Yields refer to isolated products.

TABLE 2 Synthesis of 6-unsubstituted dihydropyrimidinones in the presence of phenylphosphinic acid[a]



1 2 3 4

Entry	R^1	R^2	X/R^3	Product	Yield (%)[b]	M.p. °C[ref]
1	C_6H_5	H	O/H	**4a**	93	282–284[13]
2	4-MeC_6H_4	H	O/H	**4b**	91	232–234[12]
3	4-MeOC_6H_4	H	O/H	**4c**	90	229–231[12]
4	4-$O_2NC_6H_4$	H	O/H	**4d**	97	251–253[12]
5	3-O_2N C_6H_4	H	O/H	**4e**	94	286–288[12]
6	4-NCC_6H_4	H	O/H	**4f**	97	264–265
7	2-IC_6H_4	H	O/H	**4g**	91	202–205
8	4-BrC_6H_4	H	O/H	**4h**	92	255–257
9	3-MeOC_6H_4	H	O/H	**4i**	90	175–177
10	4-ClC_6H_4	H	O/H	**4j**	95	257–260
11	2-Cl, 5-$O_2NC_6H_3$	H	O/H	**4k**	92	201–202
12	4-NC_6H_4	4-NO_2	O/H	**4l**	95	166–168
13	3-MeOC_6H_4	4-NO_2	O/H	**4m**	93	238–240
14	4-$O_2NC_6H_4$	4-NO_2	O/H	**4n**	94	195–198
15	4-$O_2NC_6H_4$	H	O/Me	**4o**	83	223–225[12]
15[c]	$(CH_3)_2CHCH_2$	H	O/H	**4p**	15	232–234[12]
16	C_6H_5	H	S/H	**4q**	91	278–280[12]
17	4-MeC_6H_4	H	S/H	**4r**	89	279–281[12]
18	4-MeOC_6H_4	H	S/H	**4s**	87	266–268[12]
19	4-ClC_6H_4	H	S/H	**4t**	92	269–271[12]
20	4-BrC_6H_4	H	S/H	**4u**	90	283–285[12]
21	2-Cl, 5-$NO_2C_6H_3$	H	S/H	**4v**	93	235–238
22	4-Me C_6H_4	NO_2	S/H	**4x**	90	235–237[12]

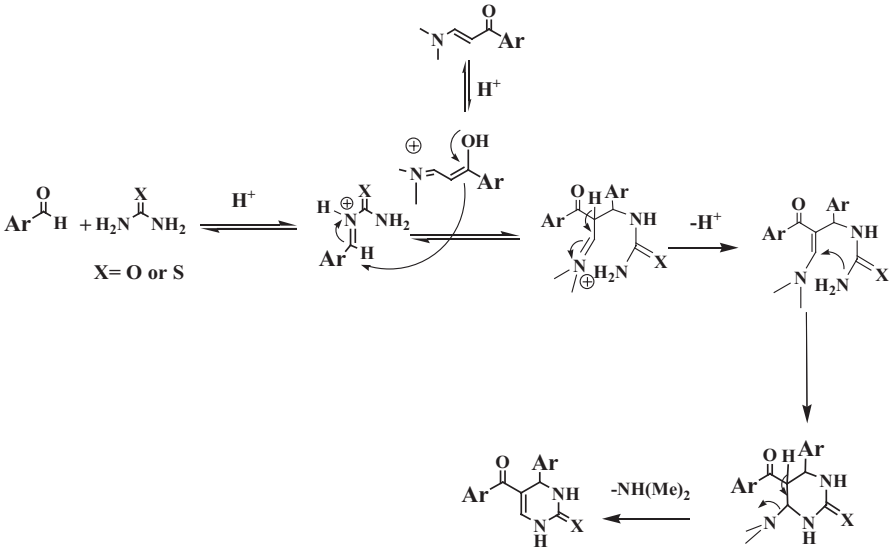
[a]Reactions were performed using benzaldehydes (1 mmol), enaminones (1 mmol), ureas/thiourea (1.2 mmol), and phenylphosphinic acid (5 mol%) at 120°C for 20 min without solvent.
[b]Yields refer to isolated products.
[c]Reaction was performed for 120 min.

(DMSO–d_6, 400 MHz): δ 5.71 (d, 1H, $J = 1.6$ Hz), 7.01–7.08 (m, 2H), 7.40–7.53 (m, 7H), 7.79 (s, 1H), 7.83 (d, 1H, $J = 7.6$ Hz), 9.42 (d, 1H, $J = 4.4$). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 59.3, 99.7, 112.4, 128.5, 128.8, 129.2, 129.5, 130.0, 131.4, 138.9, 139.8, 142.6, 145.8, 150.8, 191.7. ESI-MS: *m/z* 403.0 ($[M-1]^+$).

4-(4-Bromophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-one (**4h**). IR ν_{max} 905, 1153, 1202, 1370, 1485, 1574, 1613, 1654, 1700, 2924, 3280. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.41 (d, 1H, $J = 2.4$ Hz), 7.03 (d, 1H, $J = 6$ Hz), 7.29 (d, 2H, $J = 8.4$ Hz), 7.43–7.53 (m, 5H), 7.54 (d, 2H, $J = 8.4$ Hz), 7.92 (s, 1H), 9.41 (d, 1H, $J = 4.8$ Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.3, 112.4, 120.9, 128.4, 128.8, 129.2, 131.4, 131.8, 138.8, 142.3, 142.4, 143.8, 151.4, 191.9. ESI-MS: *m/z* 356.1 ($[M]^+$).

4-(3-Methoxyphenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-one (**4i**). IR ν_{max} 899, 1153, 1201, 1254, 1371, 1452, 1489, 1608, 1651, 1702, 2927, 3275. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 3.74 (s, 3H), 5.41 (d, 1H, $J = 2.4$ Hz), 6.84 (d, 1H, $J = 8.0$ Hz), 6.88 (s, 1H), 6.91 (d, 1H, $J = 7.6$ Hz), 7.03 (t, 1H, $J = 2.8$ Hz), 7.28 (t, 1H, $J = 7.6$ Hz), 7.44–7.55 (m, 5H), 7.88 (s, 1H), 9.34 (d, 1H, $J = 5.2$ Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.5, 55.4, 112.7, 112.8, 112.9, 118.8, 128.4, 128.8, 130.1, 131.4, 138.9, 142.2, 145.9, 151.7, 159.7, 192.0. ESI-MS: *m/z* 308.2 ($[M]^+$).

4-(4-Chlorophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-one (**4j**). IR ν_{max} 906, 1204, 1247, 1325, 1370, 1446, 1488, 1616, 1654, 1698, 2925, 3127, 3274. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.43 (s, 1H), 7.03 (t, 1H, $J = 2.8$ Hz), 7.35–7.53 (m, 9H), 7.91 (s, 1H), 9.40 (d, 1H, $J = 4.8$ Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.3, 112.4,



SCHEME 2 Plausible mechanism for the synthesis of 6-unsubstituted dihydropyrimidinone derivatives

128.4, 128.8, 128.9, 131.4, 132.4, 138.9, 142.2, 142.4, 143.4, 151.4, 151.5, 191.9. ESI-MS: *m/z* 312.0 ($[M]^+$).

4-(2-Chloro-5-nitrophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-one **(4k)**. IR ν_{max} 742, 833, 910, 1049, 1132, 1156, 1219, 1251, 1346, 1445, 1525, 1616, 1657, 1701, 2925, 3308, 3411. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.93 (d, 1H, J = 2.4 Hz), 7.16 (s, 1H), 7.46–7.56 (m, 5H), 7.76 (d, 1H, J = 8.8 Hz), 8.12 (d, 1H, J = 2.8 Hz), 8.15 (d, 1H, J = 2.8 Hz), 8.21 (d, 1H, J = 2.8 Hz), 9.51 (s, 1H). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 52.9, 110.4, 124.4, 128.5, 128.8, 131.5, 138.6, 139.5, 142.7, 143.5, 147.0, 150.7, 191.7. ESI-MS: *m/z* 359.1 ($[M + 2]^+$).

4-(4-Cyanophenyl)-5-(4-nitrophenyl)-methanone-yl-3,4-dihydropyrimidin-2(1H)-one **(4l)**. IR ν_{max} 852, 913, 1216, 1318, 1349, 1434, 1522, 1559, 1601, 1630, 1700, 2230, 2925, 3368. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.51 (d, 1H, J = 2.8 Hz), 7.54 (d, 2H, J = 6.4 Hz), 7.71 (d, 2H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.4 Hz), 8.07 (s, 1H), 8.25 (d 2H, (d, 1H, J = 8.8 Hz), 9.74 (d, 1H, J = 5.2 Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.6, 110.8, 119.1, 124.05, 128.05, 129.7, 133.1, 144.50, 144.55, 149.0, 149.4, 151.2, 190.3. ESI-MS: *m/z* 348.1 ($[M]^+$).

4-(3-Methoxyphenyl)-5-(4-nitrophenyl)-methanone-yl-3,4-dihydropyrimidin-2(1H)-one **(4m)**. IR ν_{max} 851, 926, 1155, 1253, 1321, 1349, 1489, 1523, 1615, 1670, 1701, 2936, 3105, 3282. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 3.38 (s, 3H), 5.40 (d, 1H, J = 2.8 Hz), 6.84–6.89 (m, 2H), 6.92 (d, 1H, J = 7.6 Hz), 7.07 (d, 1H, J = 5.6 Hz), 7.28 (t, 1H), 7.71 (d, 2H, J = 8.4 Hz), 7.96 (s, 1H), 8.27 (d, 2H, J = 8.8 Hz), 9.60 (d, 1H, J = 5.2 Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.4, 55.4, 112.5, 112.9, 118.8, 124.0, 129.71, 129.75, 130.2, 143.9, 144.7, 145.7, 148.9, 151.5, 159.8, 190.3. ESI-MS: *m/z* 353.2 ($[M]^+$).

4-(4-Nitrophenyl)-5-(4-nitrophenyl)-methanone-yl-3,4-dihydropyrimidin-2(1H)-one **(4n)**. IR ν_{max} 421, 743, 854, 1110, 1217, 1348, 1422, 1521, 1599, 1631, 1700, 1796, 1868, 2923, 3394, 3568. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.56 (d, 1H, J = 3.2 Hz), 7.13 (d, 1H, J = 6.4 Hz), 7.62 (d, 2H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.8 Hz), 8.12 (s, 1H), 8.23–8.29 (m, 4H), 9.77 (d, 1H, J = 4.8 Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.4, 111.6, 124.0, 124.3, 124.6, 128.3, 129.6, 129.7, 144.5, 147.4, 151.1, 151.3, 190.3. ESI-MS: *m/z* 368.0 ($[M]^+$).

4-(2-Chloro-5-nitrophenyl)-5-phenylmethanone-yl-3,4-dihydropyrimidin-2(1H)-thione **(4v)**. IR ν_{max} 736, 827, 932, 1050, 1135, 1203, 1256, 1345, 1472, 1525, 1560, 1634, 1664, 3088, 3169, 3351. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.96 (s, 1H), 6.96 (d, 1H, J = 5.2 Hz), 7.45–7.55 (m, 5H), 7.79 (d, 1H, J = 8.8 Hz), 8.17 (d, 1H, J = 8.8 Hz), 8.21 (s, 1H), 9.82 (s, 1H), 10.67 (d, 1H, J = 4.4 Hz). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 53.0, 111.6, 124.7, 125.3, 128.6, 128.9, 131.8, 131.9, 138.1, 138.9, 139.7, 141.7, 147.0, 174.2, 191.9. ESI-MS: *m/z* 373.0 ($[M]^+$).

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