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A one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones catalyzed by triphenylphosphine as Lewis base

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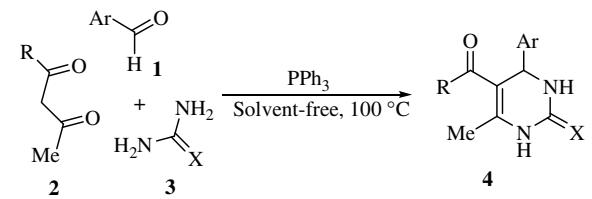
ABSTRACT

We report herein the use of triphenylphosphine (TPP) as a new catalyst for the one-pot Biginelli reaction coupling of β-ketoesters, aldehydes and urea (or thiourea) to afford the corresponding dihydropyrimidinones/thiones.

In 1893, Petro Biginelli reported the first synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) of type **4** by a very simple one-pot condensation reaction of an aromatic aldehyde **1**, β-ketoesters **2** and urea **3** under strongly acidic conditions.[1] However, this protocol often provides only low to moderate yields of the desired target molecules.

In recent years, interest in these compounds has increased rapidly, mainly due to the apparent structural similarity of DHPMs to the well-known dihydropyridine calcium channel modulators of the Hantzsh type.[2] In addition, several alkaloids containing the dihydropyrimidine core unit, exhibiting interesting biological properties, have been isolated from marine source.[3–5] Among these the crambine[3] and batzelladine alkaloids[4] were found to be potent HIVgp-120-CD4 inhibitors. The scope of this pharmacophore has been increased further by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative (±)-**4i** called monastol,[6] as a novel cell-permeable lead molecule for the development of anticancer drugs. Due to the importance of the Biginelli reaction products, much work on improving the yields and reaction conditions has been actively pursued. For example, modification and improvements include using Lewis acids such as $BF_3{\cdot}OEt_2$,[7] $FeCl_3$ and HCl,[8] $LaCl_3{\cdot}7H_2O$,[9] $La(OTf)_3$,[10] $Yb(OTf)_3$,[11] $ZrCl_4$,[12] $BiCl_3$,[13] $Mn(OAc)_3$,[14] $LiClO_4$,[15] H_3BO_3[16] and polyphosphorate ester.[17] Many other synthetic methods for preparing these compounds have been reported including classical conditions with microwave[18] and ultrasound irradiation.[19,20] Also, two asymmetric syntheses utilizing $CeCl_3/InCl_3$ or $Yb(OTF)_3$ in the presence of chiral ligands have been investigated recently.[21,22] Further, aluminium hydrogen sulfate $Al(HSO_4)_3$ and potassium hydrogen sulfate $KHSO_4$ were applied with success as a source of both protic and metallic Lewis acids.[23,24] Many combinatorial approaches towards DHPMs have been advanced using solid phase[25] or fluorous phase[26] reaction conditions. Several improved procedures have been reported using heteropoly acids[27] such as $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $H_3PMo_{11}VO_{40}$ and propane phosphoric acid.[28] On the other hand, this condensation was found to be equally effective when Lewis acids were replaced by a strong Brönsted base (KOH), but in this case the reaction involves two steps.[29]

As part of our continued interest in the Biginelli reaction,[30] we report here our preliminary investigation dealing with the use of triphenylphosphine as a Lewis base catalyst under neutral conditions preserving the simplicity of Biginelli's one-pot reaction (Scheme 1).



Scheme 1.

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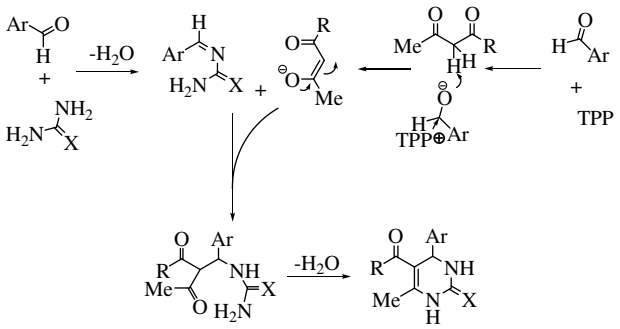
Table 1
TPP-catalyzed synthesis of DHPM **4** in different solvents[a] and under solvent-free conditions at 100 °C[b]

Entry	Solvent	Amount of TPP (mol %)	Time (h)	Yield (%)
1	Ethanol	10	18	Trace
2	Dioxane	10	18	Trace
3	Toluene	10	18	25
4	MeCN	10	18	16
5	Solvent-free	10	10	35, 54[c]
6	Solvent-free	15	10	31
7	Solvent-free	20	10	28
8	Solvent-free	5	10	10

[a] Reflux temperature.
[b] 2-Thiophenecarboxaldehyde/ethyl acetoacetate/urea, 1:1:1.5.
[c] 2-Thiophenecarboxaldehyde/ethyl acetoacetate/urea, 1:1.25:1.25.



Scheme 2.

We started our study of the three-component Biginelli condensation using TPP as the catalyst (Scheme 1), by examining the conditions for the reaction using 2-thiophenecarboxaldehyde, ethyl acetoacetate and urea to afford the corresponding DHPM product (Table 1).

We first examined the reaction in different solvents including acetonitrile, ethanol, dioxane, toluene and solvent-free at 100 °C. The best results were obtained under solvent-free conditions (entry 5).

Next, we optimized the amount of TPP required (entries 5-8) and the optimum amount was found to be 10 mol %.

Finally, in order to improve the yields, we performed the reactions using different quantities of reagents. The best results were obtained with a 1:1.25:1.25:0.1 ratio of 2-thiophenecarboxaldehyde, urea, β-ketoester and TPP, respectively.

In order to investigate the scope of these conditions, several examples were studied and are summarized in Table 2. In all cases, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones in moderate to good yields (entries 1–12). The reaction with both aromatic aldehydes carrying electron-donating substituents (entries 1–6) and heteroaromatic aldehyde (entry 8) gave the corresponding DHMP products in good yields and in high purity (purity was determined by ^{1}H NMR analysis). However, the yield decreased significantly in the reaction involving cinnamaldehyde (entry 7). In a similar manner, thiourea and 2,4-pentandione were also used to provide the corresponding Biginelli products in moderate yields (entries 9–12).

Unlike most of the reported methods, under the present reaction conditions, aromatic aldehydes carrying either electron-withdrawing substituents such as Cl and Br afforded a mixture of bisureide and DHPM products, while nitrobenzaldehyde gave only the corresponding bisureide product. The reaction may proceed through acylimine formation between an aldehyde and urea. Subsequent addition of the enolate of the β-keto-ester to the acylimine followed by cyclodehydration would afford dihydropyrimidinone-(1*H*)-one **4**. The β-ketoester enolate[31] can be formed by coordinating the aldehyde with TPP which promotes deprotonation of the β-ketoester (Scheme 2).

In summary, we have described a novel method for the preparation of substituted dihydropyrimidinones catalyzed by triphenylphosphine (TPP) as Lewis base under neutral and solvent-free conditions. Moderate to good yields of the corresponding DHPM were obtained from readily available starting materials. Further studies to confirm our mechanistic hypothesis and to extend these results to others Lewis bases and chiral trialkylphosphines derivatives are underway.

General procedure for the preparation of 3,4-dihydropyrimidinones/thiones **4**: A mixture of aldehyde **1** (2 mmol), ethyl acetoacetate **2** (2.5 mmol), urea/thiourea **3** (2.5 mmol) and triphenylphosphine (0.2 mmol) was heated with stirring at 100 °C for 10 h. After cooling, the reaction mixture was poured into crushed ice with stirring. The crude product was filtered, washed with cold water, dried and recrystallized from 95% ethanol or ethyl acetate to give pure products **4** (42–70%). All compounds were fully characterized by mp, IR, ^{1}H and ^{13}C NMR spectroscopy.

5-Ethoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4c**: Mp: 255–257 °C. IR (KBr) ν_{max}: 3240, 3117, 2960, 1693, 1643, 1514, 1462 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H 9.14 (1H, br s, NH), 7.31 (1H, br s, NH), 7.24 (1H, m, CH), 7.05 (1H, d, ^3J = 6.2 Hz, CH), 6.99 (1H, d, ^3J = 8.2 Hz, CH), 6.88 (1H, m, CH), 5.49 (1H, d, ^3J = 2.9 Hz, CH), 3.92 (2H, q, ^3J = 7.1 Hz, OCH_2) , 3.94 (3H, s, OCH_3), 2.28 (3H, s, CH_3), 1.03 (3H, t, ^3J = 7.1 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ_C 165.8, 156.9, 152.6, 149.3, 132.0, 129.1, 127.5, 120.6, 111.5, 98.0, 59.4, 55.7, 49.3, 18.1, 14.4. HRMS (EI) calcd for $C_{15}H_{18}N_2O_4$ $[M]^{+\cdot}$: 290.12666, found: 290.1276.

Table 2
TPP-catalyzed synthesis of dihydropyrimidinones/thiones **4**

Entry	Product	Ar	R	X	Yield[a] (%)	Mp (°C)	
						Found	Lit.
1	**4a**	C_6H_5	OEt	O	70	200–202	202–204[32]
2	**4b**	4-(MeO)–C_6H_4	OEt	O	58	202–203	202–204[32]
3	**4c**	2-(MeO)–C_6H_4	OEt	O	51	255–257	–
4	**4d**	4-(Me) –C_6H_4	OEt	O	62	216–217	215–216[32]
5	**4e**	3-(Me)–C_6H_4	OEt	O	66	208–209	207–208[33]
6	**4f**	4-(HO)–C_6H_4	OEt	O	55	225–226	227–228[34]
7	**4g**	C_6H_5CH=CH	OEt	O	38	223–225	225–227[32]
8	**4h**	2-Thienyl	OEt	O	54	213–214	215–217[32]
9	**4i**	C_6H_5	Me	O	62	234–235	233–236[11]
10	**4j**	4-(MeO)–C_6H_4	Me	O	58	168–170	166–168[36]
11	**4k**	C_6H_5	OEt	S	50	202–204	206–207[35]
12	**4l**	4-(Me)–C_6H_4	OEt	S	42	191–193	192–194[32]

[a] Isolated yields.

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