SHORT PAPER

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3,4-Dihydropyrimidin-2(1H)-ones via the Biginelli condensation promoted by triphenylphosphonium perchlorate

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A variety of 3,4-dihydropyrimidinones were synthesised using triphenyl phosphonium perchlorate as a catalyst.

Keywords: dihydropyrimidinone, triphenyl phosphonium perchlorate, Biginelli condensation, multi-component reaction

There is increasing interest in multi-component reactions such as the Biginelli condensation, which leads to 3,4-dihydropyrimidinones (DHPM) in a one-pot reaction.[1-3] Indeed, the interest in DHPM stems from the fact that these compounds act as potential antiviral, antitumor, and cardiovascular agents in addition to being present in naturally occurring nucleic acids.[4] Furthermore, they are potential α-$_{1a}$ calcium channel antagonists[5] and several marine alkaloids with the DHPM nucleus display interesting biological activities.[6]

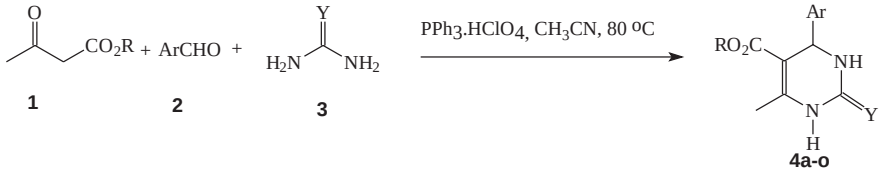
Although the Biginelli synthesis of 3,4-dihydropyrimidinones is normally performed by refluxing an acidified ethanolic solution of urea, a 1,3-dicarbonyl compound and an aldehyde,[7,8] the yields and purity of the products are not good, especially with *ortho* substituted aromatic aldehydes. To overcome these difficulties, a wide range of modified methods and catalysts such as $BF_3.Et_2O$,[9a] $InCl_3$,[9b] $FeCl_3.6H_2O$,[9c] $Ln(OTf)_3$,[9d] $Mn(OAc)_2$,[9e] solid state catalysts,[9f] solid phase reaction,[9g] chemo-enzymatic reaction,[9h] multistep strategies[10] and ionic liquid solvents[11] have been reported. We have recently exploited the mild and efficient catalytic activity of triphenylphosphonium perchlorate (TPP)[12] for hetero Diels–Alder reactions. The present work describes the use of TPP to promote the Biginelli one-pot cyclocondensation. The facile preparation of the TPP, a milder reagent than perchloric acid, which is freely soluble in organic solvents and the small amount of catalyst (2 mol%) used coupled with its facile removal by crystallisation of the DHPMs from 15 % ethyl acetate:petroleum ether are added advantages of the present procedure to prepare DHPMs.

DHPMs are prepared readily by heating 1,3-dicarbonyl compounds (**1**), the urea (**3**) and aromatic aldehydes (**2**) with 2 mol % of TPP in acetonitrile at reflux (80°) in an oil bath. The formation of the products was observed by the separation of a white solid from the reaction mixture after 10 minutes. The reflux was continued for appropriate times till completion of the reaction (Table 1). The reaction was extended to a variety of aldehydes (*ortho*-substituted, electron-deficient and electron-rich types), 1,3-dicarbonyl compounds and thiourea afforded high yields (85–91%) of the products. In contrast, the

Table 1 Synthesis of 3,4-dihydropyrimidin-2(1H)-ones[a] with TPP

Entry	DHPM	Yield/%	Time/h	M.p./°C	Lit. m.p./°C
1	**4a**	91	2	198–199	202–204
2	**4b**	89	2.5	232–234	227–229
3	**4c**	85	1	213–215	214[9e]
4	**4d**	95	1	216–218	213–215[8]
5	**4e**	87	1.5	205–207	206–208[9e]
6	**4f**	85	3	237–238	–[b]
7	**4g**	85	3	199–200	203–204[8]
8	**4h**	94	3	192–193	192–193[9c]
9	**4i**	92	2.5	228–230	226–227[8]
10	**4j**	90	3.5	205–206	205–206[13]
11	**4k**	87	3	196–198	–[b]
12	**4l**	91	3	166–168	–[b]
13	**4m**	86	2	209–211	209–211[9a]
14	**4n**	86	1.5	204–206	204–207[9a]
15	**4o**	91	1.5	236–238	235–237[9a]

[a]Molar ratio of ethyl (methyl) acetoacetate:urea:aldehyde 1.2:1.2:1.
[b]New compound.



1 **2** **3** **4a-o**

a) R=Et, Y=O, Ar=C_6H_5 **b)** R=Et, Y=O, Ar=4-HOC_6H_4
c) R=Et, Y=O, Ar=2-ClC_6H_4 **d)** R=Et, Y=O, Ar=4-ClC_6H_4
e) R=Et, Y=O, Ar=2-$NO_2C_6H_4$ **f)** R=Et, Y=O, Ar=4-Me-C_6H_4
g) R=Et, Y=O, Ar=4-$MeOC_6H_4$ **h)** R=Et, Y=O, Ar=3-Cl-C_6H_4
i) R=Et, Y=O, Ar=3-$NO_2C_6H_4$ **j)** R=Et, Y=S, Ar=C_6H_5
k) R=Et, Y=S, Ar=2-ClC_6H_4 **l)** R=Et, Y=S, Ar=4-ClC_6H_4
m) R=Me, Y=O, Ar=C_6H_5 **n)** R=Me, Y=O, Ar=2-ClC_6H_4
o) R=Me, Y=O, Ar=4-$NO_2C_6H_4$

Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

same reactions conducted using acids such as acetic acid, HCl, $HClO_4$, etc. required prolonged heating (4–18 h).[7-9]

The formation of **4** was confirmed by ^{1}H NMR spectra, which displays the C4 CH peaks at δ 5.0–6.0. The IR spectra confirm the presence of the carbonyl absorption of amide and ester at 1650 and 1690 cm^{-1} respectively and intense NH absorptions at 3400–3200 cm^{-1}. Mass spectra show the base peak corresponding to (M^+–Ar) at 183 (for ethyl acetoacetate series), and elemental analysis additionally corroborated the results. The reaction most likely proceeds *via* benzylidene urea intermediate (ArCH=NC(=X)NH_2) which then reacts with 1,3-dicarbonyl compounds to afford **4**. [9a, 14]

In conclusion, we have reported an improved protocol to synthesise DHPMs accelerated by TPP in high yields.

Experimental

Preparation of TP: To a solution of triphenylphosphine 1.00g (3.82 mmol) in 10 ml ether, was added dropwise (3 minutes) 2ml of 70% perchloric acid (density 1.67) until the pH reaches 5. The white solid obtained was collected, washed with ether followed by little ethanol and dried under vacuum to yield 1.25g (90 %), m.p. 148°C.

Ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate **(4a):** To a solution of benzaldehyde (1.00g, 9.43 mmol), ethyl acetoacetate (1.47g, 11.32 mmol) and urea (0.68g, 11.32 mmol) in 30 ml of acetonitrile, was added 0.068g (2 mol%) of TPP in one portion. The mixture was refluxed for 2 h and then poured in ice-cold water and stirred for 1h at room temperature. The solid obtained was collected and recrystallised from 15% ethyl acetate:petroleum ether to yield 2.23 g (91%) of colourless crystals. Characterisation of the compounds by IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, elemental analyses and melting points confirms the formation of products[8,9a,9e,9h] However, the characterisations of new compounds are reported below. **(4k):** pale yellow crystals (30% ethyl acetate:petroleum ether); m.p. 196–198°C; IR (KBr): 3265, 3080, 1690, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 0.96 (t, 3H, *J* = 7.5 Hz, -$OCH_2\underline{CH_3}$), 2.35 (s, 3H, 6-Me), 4.05 (q, 2H, *J* = 7.5 Hz, -$\underline{OCH_2}CH_3$), 5.34 (d, 1H, *J* = 2.4 Hz, 4 - CH), 6.83 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.2 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.35 (s, 1H, NH(3)), 8.00 (s, 1H, NH(1)). Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01. Found C, 54.30; H 4.81; N, 9.17. **(4l):** yellow crystals (30% ethyl acetate:petroleum ether), m.p. 166–168°C; IR (KBr): 3235, 3050, 1674, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.02 (t, 3H, *J* = 7.6 Hz, -$OCH_2\underline{CH_3}$), 2.45 (s, 3H, 6-Me), 3.98 (q, 2H, *J* = 7.6 Hz, -$\underline{OCH_2}CH_3$), 5.90 (d, 1H, *J* = 2.7 Hz, 4 - CH), 7.34 (s, 1H, NH(3)), 7.36–7.41 (m, 4H, Ar-H), 8.25 (s, 1H, NH(1)). Anal. Cald. for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N 9.01; found C, 54.18; H, 4.88; N, 8.99.

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