ORIGINAL ARTICLE

An efficient one-pot multicomponent synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones/ imines via a Lewis base catalyzed Biginelli-type reaction under solvent-free conditions

S. Sheik Mansoor [a],*, S. Syed Shafi [b], S. Zaheer Ahmed [a]

[a] Research Department of Chemistry, C. Abdul Hakeem College, Melvisharam 632 509, Tamil Nadu, India
[b] Research Department of Chemistry, Thiruvalluvar University, Vellore 632 106, Tamil Nadu, India

Abstract 3,4-Dihydropyrimidin-2(1*H*)-one, 3,4-dihydropyrimidin-2(1*H*)-thione, and 3,4-dihydro-pyrimidin-2(1*H*)-imine derivatives were synthesized by modified Biginelli cyclocondensation reaction catalyzed by triphenylphosphine as Lewis base. The structures of the synthesized compounds have been elucidated by IR, ^{1}H NMR and elemental analysis.

1. Introduction

The Biginelli reaction (Kappe, 1993) is a well-known, simple and straightforward procedure for the synthesis of 3,4-dihydropyrimidinones (3,4-DHPMs) by the three-component condensation of an aliphatic or aromatic aldehyde, β-ketoester and an urea. The original reaction was first reported by Biginelli (1893) and was catalyzed by mineral acids. This simple procedure has been successful in a number of Biginelli reactions involving substrates lacking sterically demanded groups. By the three-component Biginelli condensation many 3,4-DHPMs have been synthesized. These non-planar DHPMs represent a heterocyclic system of remarkable pharmacological efficiency, including antiviral, antibacterial and anti-inflammatory activities (Kappe, 1993). More recently DHPMs have emerged as the integral backbones of several calcium channel modulators, anti-hypertensive agents and α-1a-antagonists (Atwal et al., 1989, 1991; Rovnyak et al., 1992; Kappe et al., 1997). Apart from synthetic DHPMs derivatives, some alkaloids are isolated from marine sources with interesting biological activities containing the dihydropyrimidine-5-carboxylate core (Snider and Shi, 1993). 3,4-DHPMs are also used as starting material for the synthesis of so called 'superstatin' rosuvastatin selective and competitive inhibitor of HMG-CoA reductase (Carswell et al., 2002), the enzyme responsible for the biosynthesis of cholesterol. Moreover, the 3,4-DHPM motif is present in many products isolated from natural material such as several species of sponges.

* Corresponding author. Tel.: + 91 9944093020; fax: + 91 4172 266487.
E-mail addresses: smansoors2000@yahoo.co.in (S. Sheik Mansoor), suban_shafi@yahoo.com (S. Syed Shafi).

More recently, advances in the involvement of newer catalytic systems involvement in solid phase, parallel and other combinatorial synthetic approaches contributed toward the expansion of Biginelli cyclocondensation applications. The three-component cyclocondensation reaction constituting aldehyde, β-ketoester, and urea in an acidic medium was refluxed using ethanolic/methanolic HCl in the classical synthesis while other solvent-cum-acidic catalytic systems such as THF–HCl and dioxane–HCl were also employed with H_2SO_4 as a replaceable acidic source in later developments. The major drawbacks associated with acid-catalyzed reactions were lower yields (Kappe, 1993) (from 26% to 60%), particularly for tri- and tetra-substituted aldehydes of aromatic and aliphatic origins as well as extended reaction times from 24 to 36 h. The increasing interest in this class of compounds led to the development of other synthetic strategies with alternate catalysts.

Due to the importance of the Biginelli reaction products, much work on improving the yields and reaction conditions has been actively pursued. For example, Lewis acid catalysts like $Mn(OAc)_3 \cdot 2H_2O$ (Kumar et al., 2001), $Cu(OTf)_2$ (Paraskar et al., 2003), VCl_3 (Sabitha et al., 2003), $Yb(OTf)_3$ (Ma et al., 2000) and $LaCl_3 \cdot 7H_2O$ (Lu et al., 2004) have significantly improved the reaction output with reduced reaction times. The polymer-supported, resin-bound isothiourea (Kappe, 2001), poly(4-vinylpyridine-co-divinyl benzene–Cu-II) complex (Yarapathi et al., 2004), ceria/vinyl-pyrimidine polymer nanocomposite (Sabitha et al., 2005), N-butyl-N,N-dimethyl-a-phenyl-ethyl ammonium bromide (Reddy et al., 2003), and various other catalysts have been successfully used for the synthesis of Biginelli products. Further, aluminum 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 (Tu et al., 2004; Khodaei et al., 2004). Several improved procedures have been reported using heteropoly acids (Amini et al., 2006; Heravi et al., 2006; Maradur and Gokavi, 2007) such as $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $H_3PMo_{11}VO_{40}$ and propane phosphoric acid (Zumpe et al., 2007). 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 (Anatoly et al., 1998). Therefore synthesis of this type of heterocyclic compounds has been the focus of much interest from organic and medicinal chemistry. Many synthetic methods have been developed and Biginelli reaction has gained an active ongoing research.

2. Experimental

Melting points are uncorrected. IR spectra were taken on a Perkin–Elmer Joel 983 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM300 (300 MHz) spectrometer using TMS as the internal standard. Column chromatography employed silica gel of 100–200 mesh. Elemental analyses were measured by means of Perkin–Elmer 2400 CHN elemental analyzer flowchart. Chemicals were purchased from Lancaster or Fluka Ltd.

2.1. General procedure for the preparation of 3,4-dihydropyrimidinones / thiones / imines

A mixture of aldehyde (2 mmol), ethyl acetoacetate (2.5 mmol), urea/thiourea/guanidine (2.5 mmol) and triphenylphosphine (0.2 mmol) was heated with stirring at 100 °C for 8 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 (1–18) (80–90%). All compounds were fully characterized by elemental analysis, mp, IR and ^{1}H NMR spectroscopy. The structures of all synthesized compounds (1–18) have been depicted in Fig. 1.

2.1.1. 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (1)

IR (KBr): 3420, 3217, 2885, 1711, 1641 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.08 (t, J = 7.1 Hz, 3H, CH$_3$-10), 2.33 (s, 3H, CH$_3$-7), 3.92 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.22 (s, 1H, CH-4), 7.30–7.23 (m, 5H, Ar-H), 8.48 (s, 1H, NH-3), 9.48 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_3$: C, 64.62; H, 6.15; N, 10.72. Found: C, 64.58; H, 6.13; N, 10.72.

2.1.2. 5-ethoxycarbonyl-6-methyl-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (2)

IR (KBr): 3411, 3224, 2876, 1701, 1633 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.05 (t, J = 7.1 Hz , 3H, CH$_3$-10), 2.24 (s, 3H, CH$_3$-7), 3.94 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.20 (s, 1H, CH-4), 4.10 (d, 1H, Ar-OH), 7.40–6.8 (m, 4H, Ar-H), 8.40 (s,1H, NH-3), 9.20 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_4$: C, 60.86; H, 5.80; N, 10.14. Found: C, 60.88; H, 5.78; N, 10.18.

2.1.3. 5-ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (3)

IR (KBr): 3404, 3236, 2866, 1718, 1628 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.08 (t, J = 7.1 Hz , 3H, CH$_3$-10), 2.22 (s, 3H, CH$_3$-7), 3.92 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.22 (s, 1H, CH-4), 7.30–6.9 (m, 4H, Ar-H), 8.10 (s, 1H, NH-3), 9.12 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$ClN$_2$O$_3$: C, 57.14; H, 5.10; N, 9.52. Found: C, 57.10; H, 5.06; N, 9.56.

2.1.4. 5-ethoxycarbonyl-6-methyl-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4)

IR (KBr): 3422, 3222, 2866, 1704, 1628 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.06 (t, J = 7.1 Hz , 3H, CH$_3$-10), 2.16 (s, 3H, CH$_3$-7), 3.90 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.30 (s, 1H, CH-4), 7.40–6.8 (m, 4H, Ar-H), 8.08 (s, 1H, NH-3), 9.30 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$ClN$_2$O$_3$: C, 57.14; H, 5.10; N, 9.52. Found: C, 57.12; H, 5.08; N, 9.50.
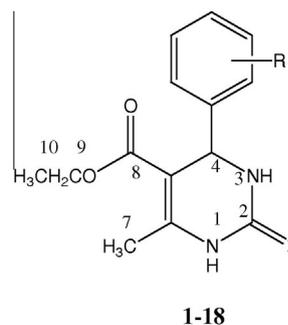

1-18

Figure 1 General structures of compounds 1–18.

2.1.5. 5-ethoxycarbonyl-6-methyl-4-(3-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (5)

IR (KBr): 3411, 3230, 2878, 1718, 1622 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.08 (t, J = 7.1 Hz , 3H, CH$_3$-10), 2.18 (s, 3H, CH$_3$-7), 3.94 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.28 (s, 1H, CH-4), 7.30–6.80 (m, 4H, Ar-H), 7.92 (s, 1H, NH-3), 9.04 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$FN$_2$O$_3$: C, 60.43; H, 5.39; N, 10.07. Found: C, 60.39; H, 5.36; N, 10.08.

2.1.6. 5-ethoxycarbonyl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (6)

IR (KBr): 3418, 3220, 2866, 1700, 1628 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.08 (t, J = 7.1 Hz , 3H, CH$_3$-10), 2.22 (s, 3H, CH$_3$-7), 3.92 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.24 (s, 1H, CH-4), 7.40–6.85 (m, 4H, Ar-H), 8.18 (s, 1H, NH-3), 9.12 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$FN$_2$O$_3$: C, 60.43; H, 5.39; N, 10.07. Found: C, 60.40; H, 5.35; N, 10.10.

2.1.7. 5-ethoxycarbonyl-6-methyl-4-(2-chloroyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (7)

IR (KBr): 3422, 3344, 1712, 1668, 1366, 1288 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.04 (t, J = 7.2 Hz, 3H, CH$_3$-10), 2.15 (s, 3H,CH$_3$-7), 4.22 (q, J = 7.2, 4.3 Hz , 2H, CH$_2$O-9), 4.22 (s, 1H, CH-4), 7.21–6.81 (m, 4H, Ar-H), 8.46 (s, 1H, NH-3), 9.57 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$ClN$_2$O$_2$S: C, 54.19; H, 4.84; N, 9.03; S, 10.32. Found: C, 54.15; H, 4.80; N, 9.05; S, 10.30.

2.1.8. 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (8)

IR (KBr): 3426, 3134, 2982, 1698, 1633, 1325, 1287 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.20 (t, J = 7.9 Hz, 3H, CH$_3$-10), 2.34 (s, 3H, CH$_3$-7), 3.88 (s, 3H, Ar-OCH$_3$-4′), 4.12 (q, J = 7.9, 4.6 Hz, 2H, CH$_2$O-9), 5.26 (s, 1H, CH-4), 6.9 (s, 1H, NH-3), 7.81–6.84 (m, 4H, Ar-H), 9.56 (s, 1H, NH-1). Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_3$S: C, 58.82; H, 5.88; N, 9.15; S, 10.45. Found: C, 58.78; H, 5.86; N, 9.16; S, 10.43.

2.1.9. 5-ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)thione (9)

IR (KBr): 3322, 3266, 2980, 1690, 1622, 1366, 1320 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.18 (t, J = 7.2 Hz, 3H, CH$_3$-10), 2.0 (s, 3 H, CH$_3$-7), 4.12 (q, J = 7.2, 4.3 Hz, 2H, CH$_2$O-9), 5.11 (s, 1H, CH-4), 7.4–6.8 (m, 4H, Ar-H): 7.43 (s, 1H, NH-3), 9.26 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$N$_3$O$_4$S: C, 52.33; H, 4.67; N, 13.08; S, 9.97. Found: C, 52.30; H, 4.66; N, 13.10; S, 9.99.

2.1.10. 5-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione (10)

IR (KBr): 3426, 3278, 2966, 1718, 1628, 1344, 1278 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.18 (t, J = 7.5 Hz, 3H, CH$_3$-10), 2.23 (s, 3H,CH$_3$-7), 4.12 (q, J = 7.4, 4.4 Hz, 2H, CH$_2$O-9), 4.12 (s, 1H, CH-4), 7.29–6.23 (m, 4H, Ar-H), 7.40 (s, 1H, NH-3), 9.32 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{15}$N$_3$O$_4$S: C, 52.33; H, 4.67; N, 13.08; S, 9.97. Found: C, 52.30; H, 4.66; N, 13.09; S, 9.98.

2.1.11. 5-ethoxycarbonyl-6-methyl-4-(3-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (11)

IR (KBr): 3418, 3146, 2958, 1700, 1622, 1318, 1278 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.20 (t, J = 7.9 Hz, 3H, CH$_3$-10), 2.34 (s, 3H, CH$_3$-7), 3.88 (s, 3H, Ar-OCH$_3$-4′), 4.12 (q, J = 7.9, 4.6 Hz, 2H, CH$_2$O-9), 5.26 (s, 1H, CH-4), 6.8 (s, 1H, NH-3), 7.81–6.84 (m, 4H, Ar-H), 9.5 (s, 1H, NH-1). Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_3$S: C, 58.82; H, 5.88; N, 9.15; S, 10.45. Found: C, 58.78; H, 5.86; N, 9.16; S, 10.44.

2.1.12. 5-ethoxycarbonyl-6-methyl-4-(4-N,N-dimethylaminophenyl)-3,4-dihydropyrimidin-2(1H)-thione (12)

IR (KBr): 3330, 3124, 2944, 1690, 1618, 1320, 1282 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.16 (t, J = 7.9 Hz , 3H, CH$_3$-10), 2.40 (s, 3H, CH3-7), 5.47 (s, 1H, CH-4), 2.71 (s, 6H, N(CH$_3$)$_2$), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH$_2$O-9), 8.21 (s, 1H, NH-3), 9.48 (s, 1H, NH-1), 7.30–7.23 (m, 4H, Ar-H): Anal. Calcd for C$_{16}$H$_{21}$N$_3$O$_2$S: C, 60.19; H, 6.58; N, 13.16; S, 10.03. Found C, 60.16; H, 6.56; N, 13.14; S, 10.06

2.1.13. 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-imine (13)

IR (KBr): 3340, 3287, 2875, 1700, 1641,1330 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.09 (t, J = 7.1 Hz , 3H, CH$_3$-10), 2.33 (s, 3H, CH$_3$-7), 3.34 (s, 1H, =NH-2), 4.08 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.30 (s, 1H, CH-4), 7.30–7.23 (m, 5H, Ar-H), 8.4 (s, 1H, NH-3), 9.4 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{17}$N$_3$O$_2$: C, 64.86; H, 6.56; N, 16.21. Found: C, 64.84; H, 6.54; N, 16.20.

2.1.14. 5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-imine (14)

IR (KBr): 3222, 3120, 2978, 1692, 1650, 1344 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.09 (t, J = 7.9 Hz, 3H, CH$_3$-10), 2.40 (s, 3H, CH$_3$-7), 5.47 (s, 1H, CH-4), 1.64 (s, 3H, Ar-CH$_3$-4′), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH$_2$O-9), 7.30–6.94 (m, 4H, Ar-H), 7.22 (s, 1H, NH-3), 9.22 (s, 1H, NH-1). Anal. Calcd for C$_{15}$H$_{19}$N$_3$O$_2$: C, 65.59; H, 6.96; N, 15.38. Found: C, 65.58; H, 6.96; N, 15.40.

### 2.1.15. 5-ethoxycarbonyl-6-methyl-4-(2,3,4-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-imine (15)

IR (KBr): 3257, 3104, 2976, 1711, 1641, 1330 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.09 (t, J = 7.9 Hz, 3H, CH$_3$-10), 2.40 (s, 3H, CH$_3$-7), 5.47 (s, 1H, CH-4), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH$_2$O-9), 3.80 (s, 3H, Ar-OCH$_3$-2′), 3.84 (s, 3H, Ar-OCH$_3$-3′), 3.70 (s, 3H, Ar-OCH$_3$-4′), 7.44 (s, 1H, NH-3), 7.30–7.06 (m, 2H, Ar-H), 8.88 (s, 1H, NH-1). Anal. Calcd for C$_{17}$H$_{23}$N$_3$O$_5$: C, 58.45; H, 6.59; N, 12.03. Found: C, 58.44; H, 6.58; N, 12.02.

2.1.16. 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-imine (16)

IR (KBr): 3371, 3134, 2975, 1698, 1641, 1322 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.09 (t, J = 7.9 Hz, 3H, CH$_3$-10), 2.40 (s, 3 H, CH$_3$-7), 5.47(s, 1H, CH-4), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH$_2$O-9), 3.78 (s, 3H, Ar-OCH$_3$-4′), 7.33–6.98 (m, 4H, Ar-H), 7.31 (s, 1H, NH-3), 9.97 (s, 1H, NH-1). Anal. Calcd for C$_{15}$H$_{19}$N$_3$O$_3$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.21; H, 6.65; N, 13.14.

2.1.17. 5-ethoxycarbonyl-6-methyl-4-(4-N,N-dimethylaminophenyl)-3,4-dihydropyrimidin-2(1H)-imine (17)

IR (KBr): 3319, 3114, 2965, 1690, 1650, 1318 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 1.09 (t, J = 7.9 Hz, 3H, CH$_3$-10), 2.40 (s, 3H, CH$_3$-7), 5.47 (s, 1H, CH-4), 3.27 (s, 1H, =NH-
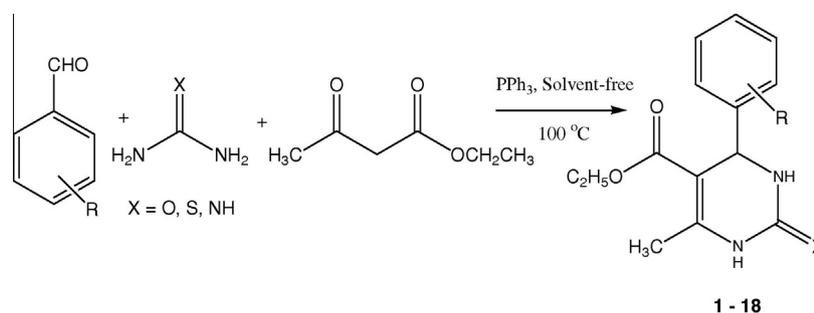
Scheme 1 General synthetic scheme of compounds 1–18.

Table 1 Triphenylphosphine catalyzed synthesis of dihydropyrimidines in different solvents[a] and under solvent-free conditions at 100 °C[b].

Entry	Solvent	Amount of PPh₃ (mol%)	Time (h)	Yield (%)
1	Ethanol	10	16	10
2	Acetonitrile	10	16	10
3	Toluene	10	16	30
4	Dichloromethane	10	16	25
5	Cyclohexane	10	16	25
6	Solvent free	10	8	62
7	Solvent free	15	8	54
8	Solvent free	20	8	50
9	Solvent free	5	8	52
10	Solvent free	10	8	80[c]

[a] Reflux temperature.
[b] Benzaldehyde/ethyl acetoacetate/urea 1:1:1.
[c] Benzaldehyde/ethyl acetoacetate/urea 1:1.25:1.25.

Table 2 Triphenylphosphine catalyzed synthesis of 3,4-dihydropyrimidinones/thione and imine derivatives.

| Code R	Substitution	X	Molecular formula	M.pt. (°C)	Yield (%)
1	H	O	$C_{14}H_{16}N_2O_3$	204–206	80
2	2-Hydroxy	O	$C_{14}H_{16}N_2O_4$	210–212	88
3	2-Chloro	O	$C_{14}H_{15}ClN_2O_3$	206–208	90
4	3-Chloro	O	$C_{14}H_{15}ClN_2O_3$	198–200	90
5	3-Fluoro	O	$C_{14}H_{15}FN_2O_3$	180–182	86
6	4-Fluoro	O	$C_{14}H_{15}FN_2O_3$	186–188	90
7	2-Chloro	S	$C_{14}H_{15}ClN_2O_2S$	218–220	84
8	4-Methoxy	S	$C_{15}H_{18}N_2O_3S$	140–142	82
9	2-Nitro	S	$C_{14}H_{15}N_3O_4S$	190–192	90
10	3-Nitro	S	$C_{14}H_{15}ClN_2O_3S$	214–216	90
11	3-Methoxy	S	$C_{14}H_{15}N_3O_4S$	160–162	86
12	4-N,N-dimethyl amino	S	$C_{16}H_{21}N_3O_2S$	208–210	90
13	H	NH	$C_{14}H_{17}N_3O_2$	175–177	84
14	4-Methyl	NH	$C_{14}H_{19}N_3O_2$	122–124	90
15	2,3,4-Trimethoxy	NH	$C_{17}H_{23}N_3O_3$	124–126	84
16	4-Methoxy	NH	$C_{15}H_{19}N_3O_3$	108–110	82
17	4-N,N-dimethyl amino	NH	$C_{16}H_{22}N_4O_2$	162–164	80
18	3-Chloro	NH	$C_{14}H_{16}ClN_3O_2$	144–146	80

2), 2.64 (s, 6H, N(CH₃)₂), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH₂O-9), 8.21 (s, 1H, NH-3), 9.48 (s, 1H, NH-1), 7.20–6.90 (m, 4H, Ar-H). Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 62.28; H, 6.57; N, 14.53. Found: C, 62.26; H, 6.54; N, 14.56.

*2.1.18. 5-ethoxycarbonyl-6-methyl-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-imine (**18**)*
IR (KBr): 3338, 3280, 2870, 1700, 1646, 1326 cm⁻¹: ¹H NMR (300 MHz, DMSO-d₆): δ 1.16 (t, J = 7.1 Hz , 3H, CH₃-10),

**Step 1**   Formation of Acylimine intermediate:
This intermediate is formed by the reaction between an aldehyde
and urea
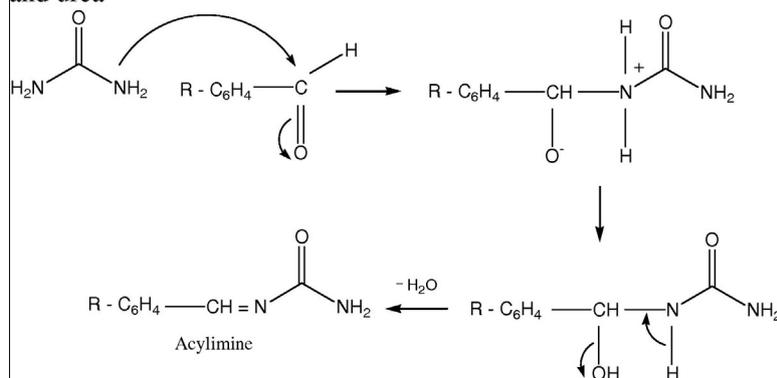
Step 2   Enolisation of ethyl acetoacetate : Triphenylphosphine plays the
role of a Lewis base by interaction with electrophilic carbon of aldehyde.
The β–ketoester enolate can be formed by coordinating the aldehyde
with PPh$_3$, which promotes deprotonation of the β–ketoester.
(Yadav et al., 2004; Debache et al., 2008)
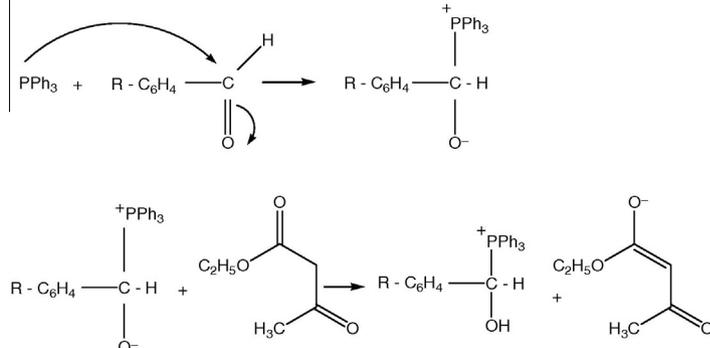
Step 3 Condensation of Enol with the Acylimine to give an intermediate
which undergoes cyclization followed by dehydration to afford the
corresponding dihydropyrimidines.
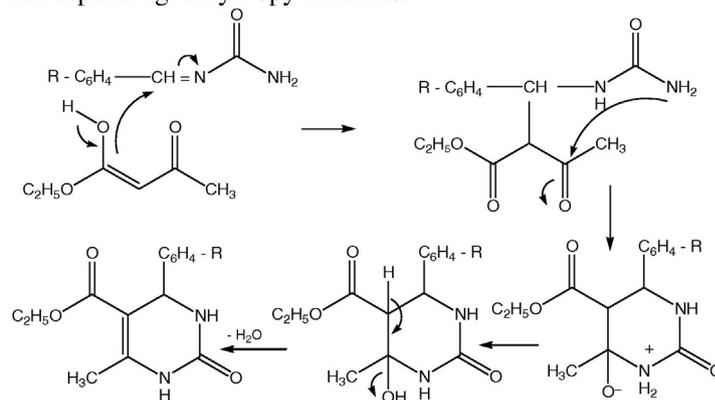
Scheme 2   Suggested mechanism for the Biginelli reaction catalyzed by triphenylphosphine under solvent-free conditions. (See above-mentioned references for further information.)

2.33 (s, 3H, CH$_3$-7), 3.34 (s, 1H, =NH-2), 3.90 (q, J = 7.1, 4.8 Hz, 2H, CH$_2$O-9), 5.30 (s, 1H, CH-4), 7.32–6.98 (m, 4H, Ar-H), 8.4 (s, 1H, NH-3), 9.4 (s, 1H, NH-1). Anal. Calcd for C$_{14}$H$_{16}$ClN$_3$O$_2$: C, 57.34; H, 5.46; N, 14.33. Found: C, 57.30; H, 5.44; N, 14.36.

3. Results and discussion

Dihydropyrimidines show a diverse range of biological activities. We are interested in studying Biginelli reaction with the aim to develop an operationally simple method for the

synthesis of a large range of DHPMs. We started our study of the one-pot three-component Biginelli condensation using triphenylphosphine as the catalyst (Scheme 1), by examining the conditions for the reaction using benzaldehyde, ethylacetoacetate and urea to afford the corresponding DHPM product. We studied the reaction in different solvents including ethanol, acetonitrile, toluene, dichloromethane, cyclohexane and under solvent-free conditions at 100 °C (Table 1). The best results were obtained under solvent-free conditions (entry 6). The reaction is optimized for the amount of triphenylphosphine required (entries 7–10) and the optimum amount was found to be 10 mol%. In order to improve the yields, the reaction is performed using different quantities of reagents. The best results were obtained with a 1:1.25:1.25:0.1 ratio of benzaldehyde, ethylacetoacetate, urea, and triphenylphosphine, respectively.

In order to investigate the scope of these conditions, we have undertaken the synthesis of different derivatives of 3,4-dihydropyrimidin-2(1H)-one (**1**–**6**), 3,4-dihydropyrimidin-2(1H)-thione (**7**–**12**), and 3,4-dihydropyrimidin-2(1H)-imine (**13**–**18**) from a variety of substrates from aromatic aldehydes, ethylacetoacetate (Kappe, 2001) and either urea/thiourea or guanidine in the presence of triphenylphosphine (PPh$_3$) as catalyst. The benzaldehyde derivatives with substitutions in the aromatic ring with 4-methyl, n-halogens (n = varying ring substitution positions), 2-hydroxy, n-methoxy, varying nitro positions and N,N-dimethylamino groups were reacted with urea, thiourea, and guanidine to furnish a series of products **1**–**18** (Scheme 1, Table 2).

The mechanism of the Biginelli reaction established by Kappe (1997) proposed that the key step in this cyclocondensation process should involve the formation of N-acyliminium ion intermediate. The suggested mechanism for the Biginelli reaction catalyzed by triphenylphosphine under solvent-free conditions is outlined in Scheme 2.

4. Conclusions

In summary, we have described a novel method for the preparation of substituted dihydropyrimidinones/thiones/imines catalyzed by triphenylphosphine (PPh$_3$) as Lewis base under neutral and solvent-free conditions. Moderate to good yields of the corresponding DHPMs were obtained from readily available starting materials.

References

Amini, M.M., Shaabani, A., Bazgir, A., 2006. Catal. Commun. 7, 843.

Anatoly, D.S., Ekaterina, A.K., Natali, V.S., Aleksei, Y.K., 1998. Molecules 3, 100.

Atwal, K.S., Rovnyak, G.C., O'Reilly, B.C., Schwartz, J., 1989. J. Org. Chem. 54, 5898.

Atwal, K.S., Swanson, B.N., Unger, S.E., Floyd, D.M., Moreland, S., Hedberg, A., O'Reilly, B.C., 1991. J. Med. Chem. 34, 806.

Biginelli, P., 1893. Gazz. Chim. Ital. 23, 360–416.

Carswell, C.I., Plosker, G.L., Jarvis, B., 2002. Drugs 62, 2075–2085.

Debache, A., Amimour, M., Belfaitah, A., Rhouati, S., Carboni, B., 2008. Tetrahedron Lett. 49, 6119–6121.

Heravi, M.M., Bakhtiari, K., Bamaharram, F.F., 2006. Catal. Commun. 7, 373.

Kappe, C.O., 1993. Tetrahedron 49, 6938–6963.

Kappe, C.O., 1997. J. Org. Chem. 62, 7201.

Kappe, C.O., 2001. Bioorg. Med. Chem. Lett. 10, 49.

Kappe, C.O., Fabian, W.M.F., Semones, M.A., 1997. Tetrahedron 53, 2803–2816.

Khodaei, M.M., Salehi, P., Zolfigol, M.A., Sirouszadeh, S., 2004. Pol. J. Chem. 78, 385.

Kumar, K.A., Kasthuraiah, M., Reddy, C.S., Reddy, C.D., 2001. Tetrahedron Lett. 42, 7873.

Lu, J., Bai, Y., Wang, Z., Yang, B., Ma, H., 2004. Tetrahedron Lett. 41, 9075.

Ma, Y., Qian, C., Wang, L., Yang, M., 2000. J. Org. Chem. 65, 3864.

Maradur, S.P., Gokavi, G.S., 2007. Catal. Commun. 8, 279.

Paraskar, A.S., Dewkar, G.K., Sudalai, A., 2003. Tetrahedron Lett. 44, 3305.

Reddy, K.R., Reddy, C.V., Mahesh, M., Raju, P.V.K., 2003. Tetrahedron Lett. 44, 8173.

Rovnyak, G.C., Atwal, K.S., Hedberg, A., Kimball, S.D., Moreland, S., Gougoutas, J.Z., O'Reilly, B.C., Schwartz, J., Malley, M.F., 1992. J. Med. Chem. 35, 3254.

Sabitha, G., Reddy, G.S.K.K., Reddy, K.B., Yadav, J.S., 2003. Tetrahedron Lett. 44, 6497.

Sabitha, G., Reddy, K.B., Yadav, J.S., Shailaja, D., Sivudu, K., 2005. Tetrahedron Lett. 46, 8221.

Snider, B.B., Shi, Z., 1993. J. Org. Chem. 58, 3828.

Tu, S., Fang, F., Zhu, C., Li, T., Zhang, X., Zhang, Q., 2004. Synlett, 537.

Yadav, J.S., Reddy, B.V.S., Basak, A.K., Visali, B., Nasraiah, A.V., Nagaiah, K., 2004. Eur. J. Org. Chem., 546.

Yarapathi, R.V., Kurva, S., Tammishetti, S., 2004. Catal. Commun. 5, 511.

Zumpe, F.L., Flub, M., Schmitz, K., Lender, A., 2007. Tetrahedron Lett. 48, 1421.