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Der Pharma Chemica, 2012, 4 (1):417-427
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Amberlyst ® 15 DRY Resin: A green and recyclable catalyst for facile and efficient one-pot synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones

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ABSTRACT

Ion exchange resin catalyzed multicomponent Biginelli reaction is studied for the synthesis of 3, 4-dihydropyrimidin-2-ones. Among the various solid acid catalysts Amberlyst® 15 DRY was found to be most efficient, recyclable and environmentally benign heterogeneous catalyst regarding reaction time, yield and ease of work up procedure.

Keywords: Biginelli Reaction, 3,4-dihydropyrimidin-2-ones, Ion exchange resin, Heterogeneous Catalyst, Amberlyst® 15 DRY.

INTRODUCTION

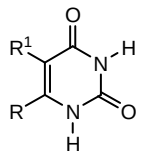
Replacement of conventional, toxic and polluting Bronsted and Lewis acid catalysts with eco-friendly reusable solid acid heterogeneous catalysts like acidic zeolites, clays, sulfated zirconia and ion exchange resins is an area of current interest [1-2]. The use of solid acid catalyst instead of liquids includes many advantages, such as reduced equipment corrosion, ease of product separation, recycling of the catalyst and environmental acceptability. In the recent past ion exchange resins in general and styrene-DVB mattrixed resin sulfonic acid (Amberlyst® 15 DRY) in particular, which are strongly acidic and chemically as well as thermally stable have been found to be excellent catalysts for a variety of the major organic reactions like esterification, alkylation, acetalisation, acylation and condensation [3-6].

The Biginelli reaction is one of the most important multi-component reactions for the synthesis of dihydropyrimidinones. Dihydropyrimi- dinone are known to exhibit a wide range of biological activities such as antiviral, antitumour, antibacterial, and anti-inflammatory properties [7]. In addition, these compounds have emerged [8] as potential calcium channel blockers, antihypertensive, α1a–adrenergic antagonists and neuropeptide antagonists. Furthermore the 2-

oxodihydropyrimidine-5-carboxylate core unit is also found in many marine natural products [9], including the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.

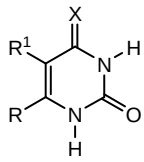
The clinically important antiretroviral like agents like AZT, DDC, DDI possess the pyrimidine **1a** scaffold. Another related framework of the **1b** type is also very easily accessible via Multi Component Reaction involving Urea, active methylene compounds and aldehydes in the presence of a catalyst as originally reported [10] by Biginelli. In recent years type **1b** pyrimidine scaffold has been under intensive investigation [11] as it has a very high pharmalogical profile.

The chemistry of C_5-C_6 double bond has been extensively explored in type **1a** skeleton and careful manipulation of this bond have led to interesting chemistry [12] and many useful new structures. In contrast C_5-C_6 double bond in Biginelli scaffold is relatively less explored and only a few useful transformations are attempted [13] involving very careful manipulations. This less developed chemistry of C_5-C_6 bond in Biginelli compounds appears to be due to difficulties in manipulating the methyl group at C_6 and ester group at C_5 which are traditionally placed in these positions.



1a

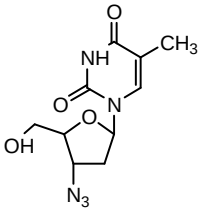
R or R^1 = H, alkyl, aryl



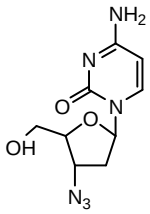
1b

X = alkyl or aryl, R = CH_3

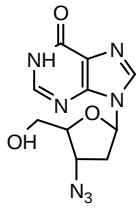
R^1 =COOEt, $COCH_3$ etc



AZT

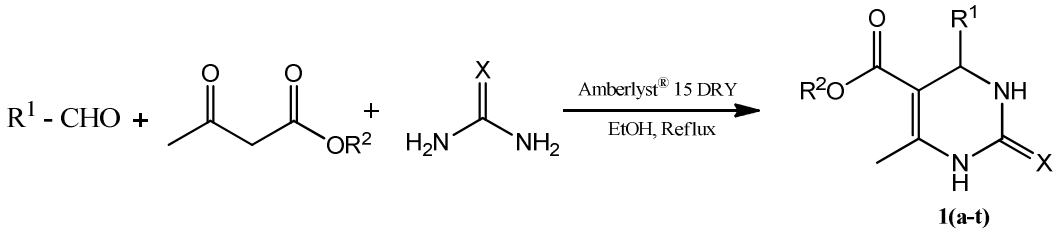


DDC



DDI

A plethora of reagents/methods have been reported for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones such as ceric ammonium nitrate under ultrasonication [14], Lewis acids (such as BF3. Et2O) in combination with transition metal and suitable proton source [15, 16], lanthanide triflates [17], lanthanide chloride [18], indium chloride [19], antimony chloride [20], bismuth nitrate under microwave irradiation [21], copper iodide [22], molecular iodine [23], heteropolyacids [24], ionic liquids [25]. However, inspite of their potential utility many of the existing methods suffer from the drawbacks, such as the use of strong acidic conditions, longer reaction times, tedious workup, environmental disposal problems and lower yields of the products, leaving scope for further development of an efficient and versatile method for Biginelli reaction.



1(a-t)

Scheme-1

Growing concern about environmental damage leads to an urgent requirement for the development of eco-friendly technology and economic processes. It is of great practical importance to synthesize DHPM derivatives by the Biginelli reaction by using a solid acid catalyst, because of the ability to modify the acid strength, ease of handling, recycling of the catalyst and environmental compatibility. In view of the above requirement, and as a part of our program towards green synthesis, we herein report a single-step and ecofriendly protocol for the synthesis of DHPM derivatives by the multicomponent reactions of β-dicarbonyl compound, aldehydes and urea (Scheme **1**) over Amberlyst® 15 DRY with good yields and selectivity.

MATERIALS AND METHODS

General

All solvents and reagents were purchased from Aldrich and Merck with high-grade quality, and used without any purification. The Indion-130 and Indion-190 were purchased from Ion Exchange India Ltd. Nafion-H, Amberlyst-70 and Amberlyst ® 15 DRY were purchased from Aldrich. Melting points were determined on electro thermal apparatus by using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d6 solutions on a Bruker AVANCE 400NMR spectrometer operating at 400 (^{1}H) and 100 (^{13}C) MHz LCMS analysis (EI, 70V) were performed on a Hewlett-Packard HP 5971 instrument.

Physical properties of Amberlyst ® 15 DRY

Physical form	Opaque beads
Ionic form as shipped	Hydrogen
Concentration of acid sites	≥4.7eq/Kg
Water content	≤1.5% (H^+ form)
Shipping weight	610g/L (38lbs/ft)
Fines content	< 0.300mm: 1.0%max
Surface area	45m^2/g
Average pore diameter	250A^0
Swelling	60 to 70 % (dry to water)
	10 to 15% (dry to hexane)
	10 to 15% (dry to toluene)
	15 to 20% (dry to ethylene dichloride)
	30 to 40% (dry to ethyl acetate)
	60 to 70% (dry to ethyl alcohol, 95%)
	15 to 20% (dry to benzene)

General procedure for the synthesis 4-aryl substituted 3, 4 dihydropyrimidinones
A mixture of β-diketone (1.0 mmol), aldehyde (1.0 mmol), urea/thiourea (1.2 mmol), and Amberlyst ® 15 DRY (50 mg) in anhydrous ethanol (10 mL) were refluxed for an appropriate time as indicated by TLC. The catalyst was filtered and washed with ethyl acetate until free from organic material. The solvent was evaporated at reduced pressure and obtained solid was crystallised from ethanol to afford pure 3, 4-dihydropyrimidin-2-one/thione **1** in excellent yields.

General procedure for the synthesis 3, 4-dihydro-4, 6-diphenylpyrimidin-2(1H)-ones
To a solution of acetophenone (1.0mmol) in ethanol (10mL) was added benzaldehyde (1.0mmol), urea (1.5mmol) and Amberlyst ® 15 DRY (50 mg) and was refluxed for an appropriate time as indicated by TLC. The catalyst was filtered and washed with ethyl acetate until free from organic material. The solvent was evaporated at reduced pressure and solid obtained was recrystallised from ethanol to afford pure 3, 4-dihydro-4, 6-diphenylpyrimidine-2(1H)-one **2** in excellent yields.

5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–one (**1a**): Mp 206–208 °C; ^{1}HNMR (DMSO-d_6) δ: 1.09 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.97 (q, 2H, *J* = 7.1 Hz, OCH2), 5.05 (d, 1H, *J* = 2.15 -CH), 7.28 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.11, 17.94, 54.91, 60.05, 100.95, 112.85, 113.05, 125.15, 125.81, 129.05, 131.20, 150.16, 155.47, 163.81; IR (ν_{max}.; KBr, cm^{-1}): 3240, 1722, 1638; ESI-MS 261 (M+H); HRMS calcd.for $C_{14}H_{16}N_2O_3$ 260.1161 found 260.1163.

5–(Ethoxycarbonyl)–4–(4–methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1b**): Mp 201–202 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.12 Hz, OCH_2CH_3), 2.33 (s, 3H, CH_3), 3.78 (s, 3H, -OCH_3), 4.06 (q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.34 (d, 1H, *J* = 2.28 -CH), 6.82 (d, 2H, *J* = 8.60, Ar-H), 7.22 (d, 2H, *J* = 8.60, Ar-H), 7.76 (s, 1H, NH), 9.26 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ:14.32, 18.80, 55.23, 55.40, 60.17, 101.68, 114.06, 127.97, 136.22, 146.16, 153.59, 159.30, 165.87; IR (ν_{max}.; KBr, cm^{-1}): 3232, 1720, 1638; ESI-MS 291 (M+H); HRMS calcd. for $C_{15}H_{18}N_2O_4$ 290.1267 found 290.1265.

5–(Ethoxycarbonyl)–4–(4-dimethylamino-phenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1c)**: Mp 255–257 °C; ^{1}H-NMR (DMSO-d_6) δ: 0.99 (t, 3H, *J* = 7.12 Hz, OCH_2CH_3), 2.11 (s, 3H, CH_3), 2.84 (s, 6H, N(CH_3)2), 4.09(q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.05 (d, 1H, *J* = 2.21, -CH), 6.42 (d, 2H, *J* = 8.55, Ar-H), 7.12 (d, 2H, *J* = 8.56, Ar-H), 7.15 (s, 1H, NH), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.28, 18.78, 44.47, 55.23, 60.15, 101.60, 112.05, 125.65, 134.25, 141.16, 153.46, 159.02, 165.24; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 304 (M+H); HRMS calcd. for $C_{16}H_{21}N_3O_3$ 303.1583 found 303.1585.

5–(Ethoxycarbonyl)–4–(4-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one(**1d**):
Mp 211-213 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H, *J* = 7.04 Hz, OCH_2CH_3), 2.32 (s, 3H, CH_3), 4.03 (q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.78 (d, 1H, *J* = 2.28, -CH), 7.51 (d, 2H, *J* = 9.18, Ar-H), 7.69 (s, 1H, NH), 8.16 (d, 2H, *J* = 9.16, Ar-H), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.22, 18.71, 55.81, 60.15, 101.60, 118.15, 130.37, 138.34, 152.26, 153.41, 159.15, 165.85; IR (ν_{max}.; KBr, cm^{-1}): 3235, 1740, 1631; ESI-MS 306 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1010.

5–(Ethoxycarbonyl)–4–(4-chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one(1**e**): Mp 215–216 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.12 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.91 (q, 2H, *J* = 7.16 Hz, OCH_2CH_3), 5.70 (d, 1H, *J* = 2.28, -CH), 7.21 (d, 2H, *J* = 9.18, Ar-H), 7.69 (s, 1H, NH), 7.94 (d, 2H, *J* = 9.18, Ar-H), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.18, 18.62, 55.72, 60.21, 101.55, 118.17, 130.32, 142.29, 152.31, 153.39, 159.17, 165.83; IR (ν_{max}.; KBr, cm^{-1}): 3225, 1720, 1615; ESI-MS 295 (M+H); HRMS calcd. for $C_{14}H_{15}ClN_2O_3$ 294.0771 found 294.0773.

5–(Ethoxycarbonyl)–4–(3-chlorophenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–one (**1f**): Mp 192–193 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.28 (s, 3H, CH_3), 3.88 (q, 2H, *J* = 7.16 Hz, OCH_2CH_3), 5.65 (d, 1H, *J* = 2.28, -CH), 7.25-7.41 (m, 4H, Ar-H), 7.61 (s, 1H, NH), 9.11 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.17, 18.60, 55.70, 60.20, 101.52, 126.312, 127.92, 128.42, 130.29, 135.51, 142.21, 153.23, 159.32, 165.75; IR (ν_{max}.; KBr, cm^{-1}): 3234, 1724, 1631; ESI-MS 295 (M+H); HRMS calcd. for $C_{14}H_{15}ClN_2O_3$ 294.0771 found 294.0772.

5–(Ethoxycarbonyl)–4–(3-bromophenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–one (**1g**): Mp 185–186 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.02 (t, 3H, *J* = 7.05 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.75 (q, 2H, *J* = 7.05 Hz, OCH_2CH_3), 5.41 (d, 1H, J = 2.25, -CH), 7.05-7.34 (m, 4H, Ar-H), 7.51 (s, 1H, NH), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.16, 18.59, 55.74, 60.18, 101.57, 126.35, 127.82, 128.48, 130.32, 135.59, 143.94, 153.21, 159.30, 165.74; IR (ν_{max}.; KBr, cm^{-1}): 3212, 1731, 1620; ESI-MS 339 (M+H); HRMS calcd. for $C_{14}H_{15}BrN_2O_3$ 338.0266 found 338.0268.

5–(Ethoxycarbonyl)–4–(2,4-dichlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1h**): Mp 249–250 °C; ^{1}HNMR (DMSO-d_6) δ: 1.18 (t, 3H, *J* = 7.23 Hz, OCH_2CH_3), 2.64 (s, 3H, CH_3), 4.07 (q, 2H, *J* = 7.24 Hz, OCH_2CH_3), 5.92 (d, 1H, *J* = 2.30, -CH), 7.21-7.51 (m, 3H, Ar-H), 7.69 (s, 1H, NH), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.20, 18.60, 55.75, 60.24, 101.56, 127.82, 128.91, 129.52, 131.29, 142.52, 143.25, 153.23, 159.32, 165.75; IR (ν_{max}.; KBr, cm^{-1}): 3255, 1731, 1651; ESI-MS 329 (M+H); HRMS calcd. for $C_{14}H_{14}C_{l2}N_2O_3$ 328.0381 found 328.0379.

5–(Methoxycarbonyl)–4–(4-chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1i**): Mp 204–205 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 3.92 (s, 3H, $COOCH_3$), 5.44 (d, 1H, *J* = 2.15, -CH), 7.14 (d, 2H, *J* = 9.05, Ar-H), 7.51 (s, 1H, NH), 7.87 (d, 2H, *J* = 9.06, Ar-H), 9.02 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.65, 52.05, 54.36, 109.59, 113.19, 128.23, 136.25, 148.25, 153.39, 159.17, 167.75; IR (ν_{max}.; KBr, cm^{-1}): 3240, 1711, 1647; ESI-MS 281 (M+H); HRMS calcd. for $C_{13}H_{13}ClN_2O_3$ 280.0615 found 280.0617.

5–(Methoxycarbonyl)–4–(4-nitrophenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–one (**1j**): Mp 236–238 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.90 (s, 3H, -$COOCH_3$), 5.51 (d, 1H, *J* = 2.15, -CH), 7.42 (d, 2H, *J* = 9.11, Ar-H), 7.44 (s, 1H, NH), 8.05 (d, 2H, *J* = 9.10, Ar-H), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.64, 52.40, 55.40, 109.60, 113.23, 128.31, 137.20, 149.65, 155.45, 160.36, 166.20; IR (ν_{max}.; KBr, cm^{-1}): 3232, 1724, 1631; ESI-MS 292 (M+H); HRMS calcd. for $C_{13}H_{13}N_3O_5$ 291.0855 found 291.0853.

5–(Methoxycarbonyl)–4–(4-methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1k**): Mp 192–194 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 3.92 (s, 3H, -$COOCH_3$), 3.75 (s, 3H, -OCH_3), 5.22 (d, 1H, *J* = 2.21 -CH), 6.76 (d, 2H, *J* = 8.58, Ar-H), 7.18 (d, 2H, *J* = 8.58, Ar-H), 7.62 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.61, 53.36, 55.05, 55.87, 108.54, 113.21, 128.47, 137.64, 148.54, 154.16, 160.81, 165.94; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 277 (M+H); HRMS calcd. for $C_{14}H_{16}N_2O_4$ 276.1110 found 276.1108.

5–(Methoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–one (**1l**): Mp 209–211 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 3.87 (s, 3H, -$COOCH_3$), 5.02 (d, 1H, *J* = 2.07 -CH), 7.25 (m, 5H, Ar-H), 7.64 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.65, 52.32, 54.70, 108.47, 113.36, 122.41, 131.17, 130.51, 154.11, 160.20, 164.42; IR (ν_{max}.; KBr, cm^{-1}): 3246, 1732, 1664; ESI-MS 247 (M+H); HRMS calcd. for $C_{13}H_{14}N_2O_3$ 246.1004 found 246.1004.

5–(Ethoxycarbonyl)–4–(4-flurophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1m**): Mp 182–184 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.16 Hz, OCH_2CH_3), 2.41 (s, 3H, CH_3), 4.12 (q, 2H, *J* = 7.17 Hz, OCH_2CH_3), 5.88 (d, 1H, *J* = 2.25, -CH), 7.69 (s, 1H, NH), 7.81 (d, 2H, *J* = 8.5, Ar-H), 7.94 (d, 2H, *J* = 9.18, Ar-H), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.18, 18.62, 55.72, 60.21, 101.55, 121.19, 132.42, 144.20, 153.39, 157.25, 159.17, 165.83; IR (ν_{max}.; KBr, cm^{-1}): 3250, 1741, 1654; ESIMS 279 (M+H); HRMS calcd. for $C_{14}H_{15}FN_2O_3$ 278.1067 found 278.1069.

5–(Ethoxycarbonyl)–4–(3-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**1n**): Mp 227–229 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.12 (t, 3H, *J* = 7.10 Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.65 (q, 2H, *J* = 7.14 Hz, OCH_2CH_3), 5.71 (d, 1H, *J* = 2.20, -CH), 7.21-7.54 (m, 4H, Ar-H), 7.74 (s, 1H, NH), 9.26 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.16, 18.59, 55.74, 60.18, 101.57, 126.25, 127.45, 128.74, 130.56, 135.46, 144.81, 153.64, 159.45, 165.30; IR (ν_{max}.; KBr, cm^{-1}): 3229, 1724, 1630; ESI-MS 306 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1013.

5–(Ethoxycarbonyl)–4–(2-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (1o): Mp 208–210 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.14 (t, 3H, *J* = 7.15 Hz, OCH_2CH_3), 2.27 (s, 3H, CH_3), 3.72 (q, 2H, *J* = 7.17 Hz, OCH_2CH_3), 5.81 (d, 1H, *J* = 2.05, -CH), 7.31-7.64 (m, 4H, Ar-H), 7.81 (s, 1H, NH), 9.24 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.16, 18.59, 55.74, 60.18, 101.57, 127.32, 128.46, 129.64, 131.43, 134.31, 145.01, 153.62, 159.32, 165.16; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1722, 1627; ESI-MS 306 (M+H); HRMS calcd. For $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1011.

5–(Ethoxycarbonyl)–6–methyl-4-styryl–3,4–dihydropyrimidin–2(1H)–one (**1p**): Mp 230–232 °C; ^{1}HNMR (DMSO-d_6) δ: 1.20 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 2.21 (s, 3H, CH_3), 4.09 (q, 2H, *J* = 7.05 Hz, OCH_2CH_3), 4.74 (d, 1H, *J* = 4.80, -CH), 6.20 (dd, *J* = 15.8, 6.0 Hz, 1H, CH=C–H), 6.37 (d, *J* = 15.9 Hz, 1H, H–C=CH) 7.21-7.46 (m, 5H, Ar-H), 7.53 (s, 1H, NH), 9.14 (s, 1H, NH); ^{13}C-NMR (DMSOd_6) δ: 14.21, 17.31, 51.84, 59.45, 98.54, 127.34, 128.54, 129.54, 130.59, 131.24, 135.24, 145.34, 153.62, 165.23; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1704, 1652; ESI-MS 287 (M+H); HRMS calcd. For $C_{16}H_{18}N_2O_3$ 286.1317 found 286.1316.

5–(Methoxycarbonyl)–4–(2,4-dichlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (1q): Mp 252–253 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.61 (s, 3H, CH_3), 3.84 (s, 3H, -$COOCH_3$), 5.79 (d, 1H, *J* = 2.05, -CH), 7.05-7.31 (m, 3H, Ar-H), 7.69 (s, 1H, NH), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.60, 52.45, 55.25, 102.32, 113.21, 128.47, 137.64, 139.24, 142.65, 148.54, 154.16, 160.81, 164.94; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 315 (M+H); HRMS calcd. for $C_{13}H_{12}C_{l2}N_2O_3$ 314.0225 found 314.0227.

5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–thione (**1r**): Mp 208–210 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H, *J* = 7.21 Hz, OCH_2CH_3), 2.29 (s, 3H, CH_3), 4.12 (q, 2H, *J* = 7.24 Hz, OCH_2), 5.16 (d, 1H, *J* = 2.05 -CH), 7.51 (m, 5H, Ar-H), 7.81 (s, 1H, NH), 9.41 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.23, 17.91, 54.85, 60.15, 100.90, 112.84, 115.12, 125.15, 126.85, 129.64, 131.45, 150.27, 162.63, 180.25; IR (ν_{max}.; KBr, cm^{-1}): 3240, 1720, 1640, 1595, 1530; ESI-MS 277 (M+H); HRMS calcd. for $C_{14}H_{16}N_2O_2S$ 276.0932 found 276.0932.

5–(Ethoxycarbonyl)–4–(3-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**1s**): Mp 205–207 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.27 (s, 3H, CH_3), 4.02 (q, 2H, *J* = 7.11 Hz, OCH_2CH_3), 5.81 (d, 1H, *J* = 2.06, -CH), 7.23-7.37 (m, 4H, Ar-H), 7.78 (s, 1H, NH), 9.34 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.14, 18.60, 55.64, 60.21, 101.34, 126.25, 128.02, 129.32, 130.75, 135.65, 144.34, 160.40, 165.64, 182.65; IR (ν_{max}.; KBr, cm^{-1}): 3245, 1725, 1632, 1575, 1545; ESI-MS 322 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_4S$ 321.0783 found 321.0781.

5–(Ethoxycarbonyl)–4–(4–methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**1t**): Mp 153–155 °C; ^{1}H-NMR (DMSO-d6) δ: 1.17 (t, 3H, *J* = 7.11 Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 4.12 (s, 3H, -OCH_3), 4.15 (q, 2H, *J* = 7.10 Hz, OCH_2CH_3), 5.44 (d, 1H, *J* = 2.15 -CH), 7.11 (d, 2H, *J* = 8.15, Ar-H), 7.37 (d, 2H, *J* = 8.11, Ar-H), 7.84 (s, 1H, NH), 9.43 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.32, 18.05, 55.24, 55.49, 60.45, 101.84, 114.32, 127.74, 137.25, 147.15, 159.45, 165.62, 182.48; IR (ν_{max}.; KBr, cm^{-1}): 3240, 1725, 1635, 1574, 1540; ESI-MS 307 (M+H); HRMS calcd. for $C_{15}H_{18}N_2O_3S$ 306.1038 found 306.1040.

4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one *(2a):*
Mp.233-236^{o}C; IR (KBr): 3312, 1685, 1598, 1449 cm^{-1} ^{1}H-NMR (DMSO-d_6): δ 9.51(s, 1H, NH), 9.21 (s, 1H, NH), 7.21-7.62 (m, 10H, Ar-H), 5.20 (d, 1H, *J* = 4.1 Hz, C=CH), 5.12 (d, 1H, *J* = 4.1 Hz, CH).

4-(4-chlorophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (2b):
Mp: 267-269^{0}C; IR (KBr): 3319, 1683, 1569, 1463 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.42 (s, 1H, NH), 9.12 (s, 1H, NH), 7.19-7.78 (m, 9H, Ar-H), 5.60 (d, 1H, *J* = 4.3 Hz, C=CH), 5.01 (d, 1H, *J* = 4.3 Hz, CH).

4-(4-methoxyphenyl)-6-phenyl-3, 4-dihydropyrimidin-2(1H)-one *(2d):*
Mp: 259-261^{o}C; IR (KBr): 3345, 1645, 1536, 1422 cm^{-1} ; ^{1}H NMR (DMSO-d_6): δ 9.23 (s, 1H, NH), 8.87 (s, 1H, NH), 7.18 – 7.56 (m, 9H, Ar-H), 5.85 (d, 1H, J = 5.6 Hz, C=CH), 5.26 (d, 1H, *J* = 5.6 Hz, CH), 3.69 (s, 3H, OCH_3).

RESULTS AND DISCUSSION

To evaluate the catalytic effect of various ion exchange resins we started with the model reaction of ethylacetoacetate (1.0 mmol) with benzaldehyde (1.0 mmol) and urea (1.2 mmol) in refluxing ethanol without and with use of various acidic ion exchange resins as catalysts to afford dihydropyrimidine 1a in various yields (Table 1). It can be seen from Table 1 that Amberlyst® 15 DRY was the most efficient (Table 1, entries 3) among the five solid acidic ion exchange resins studied. It was found that 50 mg of Amberlyst® 15 DRY is sufficient to carry out the Biginelli reaction successfully. An increase in the amount of Amberlyst® 15 DRY to more than 50 mg showed no substantial improvement in the yield, whereas the yield is reduced by decreasing the amount of Amberlyst® 15 DRY.

Table-1: Catalytic Activity of Different Ion Exchange Resins in Biginelli Condensation

Entry	Ion Exchange Resin	Reaction Time (h)	Yield [b] (%)
1	-	10	Trace
2	Amberlyst-70	3	81
3	Amberlyst ® 15 DRY[a]	5.5	94
4	Indion-130	3	92.5
5	Indion-190	3.5	92
6	Nafion-H	4.5	85

[a] *Reaction condotins: ethyl acetoacetate (1.0 mmol), Benzaldehyde (1.0mmol) and Urea (1.2mmol) in dry ethanol (10ml), Ion exchange resin (50 mg) at refluxing temperature*

The effect of solvent on the reaction was studied (Table **2**, entries 1-6) and ethanol was found to be the best solvent when considering the reaction yields and environmental damage.

Table-2: Optimization of the Reaction Conditions for the Synthesis of 1a[a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Amberlyst ® 15 DRY	Water	4	90
2	Amberlyst ® 15 DRY	EtOH	5.5	94
3	Amberlyst ® 15 DRY	CH_3CN	6.5	85
4	Amberlyst ® 15 DRY	THF	6	87
5	Amberlyst ® 15 DRY	Benzene	10	Trace
6	Amberlyst ® 15 DRY	Toluene	10	Trace

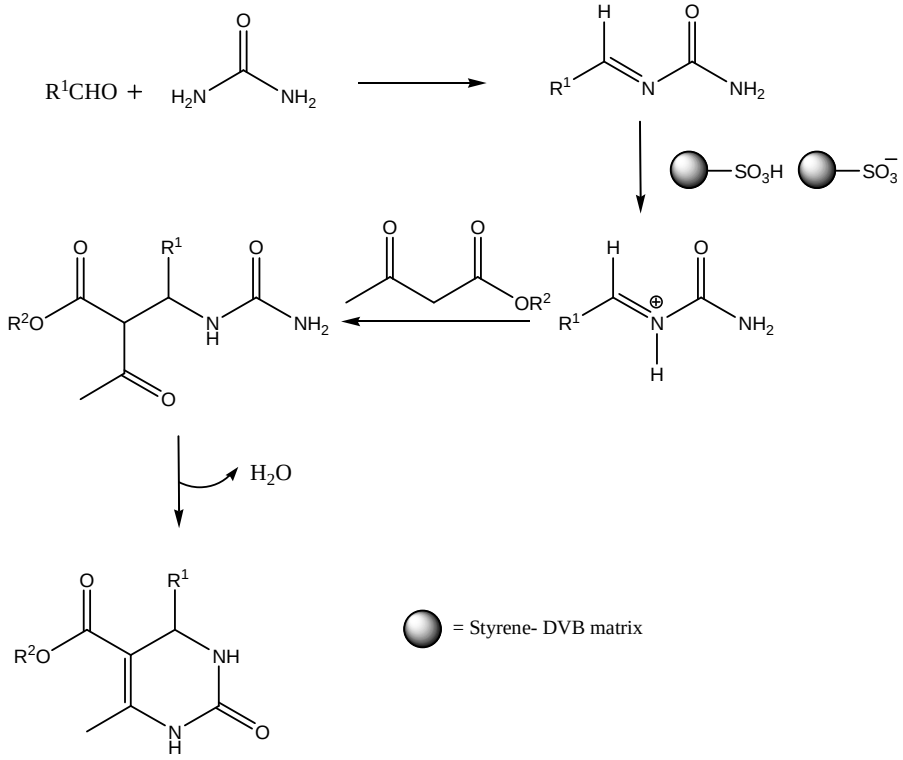
[a] *All Reactions were conducted at reflux temperature of the solvent used.*

All aforementioned reactions proceeded expeditiously and delivered good yields with range of aromatic aldehydes containing electron donating and electron withdrawing groups. This three-component reaction also proceeds efficiently with a broad range of structurally diverse 1, 3-dicarbonyl compounds, aldehydes and urea under this protocol to produce the corresponding DHPMs (Table **3**). A variety of dicarbonyl compounds could be used successfully. Thiourea was also used with similar success. The results are presented in Table - **3**. All the substrates were smoothly converted to their corresponding DHPMs in excellent yields.

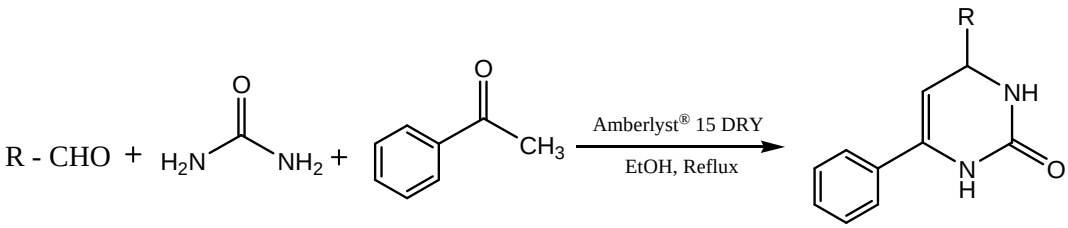
Table-3: Amberlyst ® 15 DRY catalyzed Synthesis of Dihydropyrimidine-2-(1H)- Ones/Thiones

Entry	R^1	R^2	X	Products[a]	Yield [b] (%)	M.P (^oC)
1	C_6H_5	Et	O	**1a**	88	206-208
2	4-(CH_3O)-C_6H_4	Et	O	**1b**	90	201-202
3	4-(NMe_2)-C_6H_4	Et	O	**1c**	80	255-257
4	4-NO_2-C_6H_4	Et	O	**1d**	94	211-213
5	4-(Cl)-C_6H_4	Et	O	**1e**	90	215-216
6	3-(Cl)-C_6H_4	Et	O	**1f**	88	192-193
7	3-(Br)-C_6H_4	Et	O	**1g**	81	185-186
8	2,4-(Cl)-C_6H_3	Et	O	**1h**	92	249-250
9	4-Cl-C_6H_4	Me	O	**1i**	89	204-205
10	4-(NO_2)C_6H_4	Me	O	**1j**	95	236-238
11	4-(CH_3O)-C_6H_4	Me	O	**1k**	85	192-194
12	C_6H_5	Me	O	**1l**	86	209-211
13	4-F-C_6H_4	Et	O	**1m**	92	182-184
14	3-NO_2-C_6H_4	Et	O	**1n**	91	227-229
15	2-NO_2-C_6H_4	Et	O	**1o**	96	208-210
16	C_6H_5-CH=CH	Et	O	**1p**	90	230-232
17	2-4-($Cl)_2$-C_6H_5	Me	O	**1q**	93	252-253
18	C_6H_5	Et	S	**1r**	89	208-210
19	2-NO_2-C_6H_4	Et	S	**1s**	92	205-207
20	4-(CH_3O)-C_6H_4	Et	S	**1t**	89	153-155

[a] *All compounds thus obtained were characterized by comparison of physical and spectral data with authentic samples.* [b] *Isolated Yields*



Scheme-2: The proposed mechanism for the formation of pyrimidine derivative



Scheme-3 **2 (a-f)**

Table-4: Amberlyst ® 15 DRY catalyzed Synthesis of 5- Unsubstitued 3.4-Dihydropyrimidin-2(1H)-ones

Entry	R	Products	Yield [b] (%)	M.P (^{o}C)
1	C_6H_5	**2a**	90	233-236
2	4-(Cl)-C_6H_4	**2b**	92	267-69
3	4-(CH_3)-C_6H_4	**2c**	86	248-250
4	4-(CH_3O)-C_6H_4	**2d**	84	259-261
5	2-(Cl)-C_6H_4	**2e**	91	260-263
6	3-(CH_3O)-C_6H_4	**2f**	88	256-258

[b] *Isolated Yields*

The probable mechanism (Scheme-3) of the reaction appears to involve the activation of the carbonyl function by Amberlyst® 15 DRY, thereby making the methyl group readily enolisable, which in turn reacts with aldehyde and urea derived imine in a Michael type step to produce product 2 as represented in (Table-4).

CONCLUSION

In conclusion, we have developed a simple, efficient, environmentally benign and improved protocol for the synthesis of 3, 4-dihydropyrimidin-2-ones/thiones over Amberlyst ® 15 DRY as the catalyst with excellent yields. The simplicity of the system, ease of separation/reuse of the catalyst due to its heterogeneous nature, excellent yields of the products and ease of work-up fulfill the triple bottom line philosophy of green chemistry and make the present methodology environmentally benign.

Acknowledgements
One of the authors (Srinivasa Rao. Jetti) is grateful to Madhya Pradesh Council of Science and Technology (MPCST), Bhopal for award of fellowship. Authors are also thankful to Deputy Director and Head, SAIF, Central Drug Research Institute (CDRI), Lucknow for providing elemental analysis and spectral data and the Department of Chemistry, Vikram University, Ujjain for extending laboratory facilities and IR data.

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