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A Convenient One-Pot Biginelli Reaction Catalyzed by $Y(OAc)_3$: An Improved Protocol for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Their Sulfur Analogues

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Yttrium(III) acetate hydrate-catalyzed novel synthesis of 3,4-dihydropyrimidin-2(1*H*)-(thio)one derivatives was achieved through one-pot three-component condensation of diversified aldehydes, β-ketoesters and urea or *N*-methylurea or thiourea with a molar ratio of 1:1:1.4. In comparison to the classical Biginelli approach, this catalytic method has the advantages of short reaction time and improved product yield.

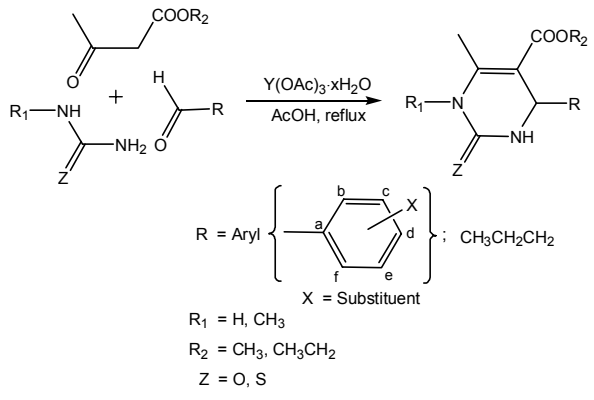
Key Words: Biginelli reaction, 3,4-Dihydropyrimidin-2(1*H*)-one, Yttrium acetate

Introduction

Multicomponent reactions (MCRs)[1-3] are emerged as a well established technique for the facile construction of complex and structurally different target molecules in one-pot fashion from at least three diverse simple building blocks. Owing to the distinctive synthetic features like selectivity, atom-economy and convergence, MCR offers remarkable advantages over conventional linear multi-step synthesis and consequently gains increasing importance in the field of organic and medicinal chemistry. Diversely functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) synthesized by way of the one-pot Biginelli three-component condensation have attracted considerable interest in industry as well as in academia because of their wide scope of promising pharmacological activities, such as calcium channel blockers, antihypertensive, antifungal, antiviral, antibacterial, anti-inflammatory, analgesic and anticancer drugs. Hence, they are classified as one of the most important groups of drug like scaffold.[4-7] A recent emphasis in this perspective has been the identification of the structurally simple DHPM derivative viz., monastrol as a mitotic kinesin Eg5 motor protein inhibitor for the development of anticancer drugs.[8] The great potential of DHPMs in biological and pharmaceutical fields has accordingly triggered growing interest in their synthetic study.

Even though the most simple and straightforward practice to synthesize DHPMs is the century-old Biginelli's reaction[9] involving mineral acid-catalyzed three-component condensation of aldehyde, easily enolizable carbonyl compound and urea, it often provides only low to moderate yields of the desired target molecules when substituted aromatic aldehydes or thioureas are employed and also requires longer reaction time.[4,10-14] Therefore, a plethora of improved synthetic procedures based on the modifications of traditional Biginelli condensation have been developed during the past few years which instead of traditional protic acids, such as HCl,[9] con. H_2SO_4[14,15] and silica H_2SO_4,[16] involves the use of a variety of Lewis acid catalysts, such as BF_3-OEt_2/CuCl/HOAc,[10] $NiCl_2{\cdot}6H_2O$/HCl,[11] $InBr_3$,[17] $Mn(OAc)_3{\cdot}2H_2O$,[18] $Fe(CF_3CO_2)_3$,[19] $Fe(CF_3SO_3)_3$,[19] $SiCl_4$,[20] VCl_3,[21] $Y(NO_3)_3{\cdot}6H_2O$,[21a] Yttria-zirconia[21b] and *p*-TsOH[22] *etc*. Nevertheless, in spite of their potential utility, some of the reported methods involve longer reaction time, unsatisfactory yield, incompatibility with wide range of functional groups, catalyst which needs dry condition and difficult product isolation procedures. Although yttrium nitrate[21a] requires minimum reaction time with reasonable yield, the methodology has not been extended well to the synthesis of biologically important diversified *N*-methyl and thio derivatives of DHPMs.[4,5] Consequently, development of efficient catalyst for the synthesis of this multifunctionalized DHPMs with variations of substituents in all three components besides improvement in yield would be desirable. The literature survey indicates that $Y(OAc)_3$ hydrate has not been reported as Lewis acid catalysts for Biginelli reaction.

Therefore, in continuation of our recent work on the construction of biologically potent heterocyclic frameworks,[23,24] we describe in this paper a simple and improved approach for the generation of library of 3,4-dihydropyrimidin-2(1*H*)-ones and their sulfur analogues through Biginelli's three component condensation by using yttrium(III) acetate hydrate as a new Lewis acid catalyst preserving the simplicity of the classical one-pot protocol (Scheme 1).



Scheme 1. General synthetic pathway for the synthesis of compounds **1-46**

Experimental Part

Yttrium(III) acetate hydrate (product code no. 326046 - 99.9%) and all other reagents were procured from Sigma Aldrich and used as received. The course of the reactions and purity of the products were assessed by performing TLC. Melting points were read using Electrothermal-9100 (Japan) instrument and are uncorrected. NMR spectra were run on JEOL (Japan) JNM ECP-400 instrument operating at 400 MHz for ^{1}H and 100.6 MHz for completely proton decoupled ^{13}C using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were taken on a JEOL, JMS-700 instrument. Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), dd (double doublet), triplet (t), quartet (q), broad (br), and multiplet (m)], integration, coupling constants [quoted to the nearest 0.1 Hz] and assignment).

General procedure for the synthesis of *N*-unsubstituted and/or *N*-methyl substituted 3,4-dihydropyrimidin-2(1*H*)-(thio)ones (1-46). A solution of aldehyde (5 mmol), β-keto ester (5 mmol) and urea or *N*-methylurea or thiourea (7 mmol) in acetic acid (3 mL) was heated at 115 °C in the presence of yttrium(III) acetate hydrate (0.4 mmol - 8 mol %) for a specified time (as mentioned in Table 1). The reaction mixture (after being cooled to room temperature) was poured onto crushed ice and quenched with 10% $NaHCO_3$ solution. The solid separated after stirring for 15 - 20 min was filtered under suction, washed with ice-cold water (100 mL), ethanol-water mixture (7 + 13 mL) and dried. Pure compound was obtained by recrystallization in excess of hot ethanol or in aqueous ethanol.

All the known products in the literature were identified by comparing their analytical and spectral data while the new compounds (given below) were characterized by their melting point, NMR and mass spectra. The results are summarized in Table 1.

5-Ethoxycarbonyl-1,6-dimethyl-4-(2-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (16): Solid, mp 142 - 143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, 1H, J = 3.29, H-3), 7.58 (d, 1H, J = 8.06, H-c), 7.36-7.29 (m, 2H, H-d and H-f), 7.21-7.17 (m, 1H, H-e), 5.60 (d, 1H, J = 3.66, H-4), 3.97-3.88 (m, 2H, CH_2 of ester), 3.15 (s, 3H, N-CH_3), 2.55 (s, 3H, CH_3 at C-6), 1.01 (t, 3H, J = 7.14, CH_3 of ester); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 152.0, 151.3, 142.5, 132.6, 129.5, 128.5, 128.4, 122.3, 101.3, 59.3, 52.7, 29.6, 15.9, 13.9; MS *m/z*, (%) 354 [$(M+2)^+$, 5.18], 352 (M^+, 4.84), 323 (12.8), 279 (17.23), 273 (43.34), 243 (6.83), 197 (100), 169 (40.06), 151 (31.28), 115 (6.79), 56 (65.16).

5-Ethoxycarbonyl-1,6-dimethyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (17): Solid, mp 150 - 151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, 1H, J = 3.66, H-3), 7.53 (d, 2H, J = 8.42, H-c and H-e), 7.19 (d, 2H, J = 8.06, H-b and H-f), 5.16 (d, 1H, J = 3.66, H-4), 4.04 (q, 2H, J = 6.96, J = 14.28, CH_2 of ester), 3.11 (s, 3H, N-CH_3), 2.50 (s, 3H, CH_3 at C-6), 1.12 (t, 3H, J = 7.14, CH_3 of ester); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 152.8, 150.9, 143.4, 131.3, 128.3, 120.3, 101.9, 59.5, 51.9, 29.7, 15.9, 13.9; MS *m/z*, (%) 354 [$(M+2)^+$, 6.37], 352 (M^+, 7.22), 339 (7.40), 323 (31.27), 279 (18.59), 197 (100), 169 (40.86), 151 (35.20), 115 (6.87), 66 (7.21), 56 (61.29); Anal. Calcd for $C_{15}H_{17}BrN_2O_3$: C, 51.01; H, 4.85; N 7.93. Found: C, 50.81; H, 4.72; N, 7.85.

5-Ethoxycarbonyl-1,6-dimethyl-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (18): Solid, mp 145 - 146 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, 1H, J = 3.29, H-3), 7.25-7.21 (m, 1H, J = 8.42, H-d), 7.04 (dd, 1H, J = 1.65, J = 7.51, H-f), 6.96 (d, 1H, J = 8.06, H-e), 6.86 (t, 1H, J = 7.32, H-c), 5.46 (d, 1H, J = 3.29, H-4), 3.99-3.94 (m, 2H, CH_2 of ester), 3.77 (s, 3H, O-CH_3), 3.10 (s, 3H, N-CH_3), 2.49 (s, 3H, CH_3 at C-6), 1.05 (t, 3H, J = 7.14, CH_3 of ester); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 156.6, 153.1, 150.4, 130.8, 128.7, 126.9, 120.1, 111.1, 101.1, 59.3, 55.4, 47.9, 29.6, 15.9, 13.9; MS *m/z*, (%) 304 [M^+, 26.41], 289 (21.72), 275 (100), 257 (15.57), 232 (10.66), 231 (64.70), 216 (15.22), 197 (86.17), 169 (50.09), 151 (45.67), 115 (11.74), 91 (10.26), 77 (16.86), 56 (93.19).

5-Ethoxycarbonyl-6-methyl-4-(2-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (22): Solid, mp 149 - 150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H, H-1), 9.60 (s, 1H, H-3), 7.59 (d, 1H, J = 8.06, H-c), 7.39 (t, 1H, J = 7.39, H-e), 7.29 (d, 1H, J = 6.59, H-d), 7.23-7.19 (m, 1H, H-f), 5.62 (d, 1H, J = 2.93, H-4), 3.92 (q, 2H, J = 6.96, J = 14.28, CH_2 of ester), 2.33 (s, 3H, CH_3 at C-6), 1.01 (t, 3H, J = 7.14, CH_3 of ester); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 164.7, 145.4, 142.3, 132.7, 129.7, 129.3, 128.4, 122.2, 100.1, 59.4, 54.1, 16.9, 13.8; MS *m/z*, (%) 356 [$(M+2)^+$, 36.55], 354 (M^+, 33.63), 327 (23.34), 275 (50.28), 199 (100), 171 (26.57), 153 (13.67), 126 (9.03), 102 (15.53), 67 (10.56), 51(6.12).

5-Ethoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (23): Solid, mp 182 - 183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H, H-1), 9.66 (s, 1H, H-3), 7.56 (d, 2H, J = 8.42, H-c and H-e), 7.17 (d, 2H, J = 8.42, H-b and H-f), 5.15 (d, 1H, J = 3.66, H-4), 4.00 (q, 2H, J = 6.96, J = 13.51, CH_2 of ester), 2.29 (s, 3H, CH_3 at C-6), 1.09 (t, 3H, J = 7.14, CH_3 of ester); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 164.9, 145.3, 142.7, 131.4, 128.6, 120.7, 100.2, 59.6, 53.5, 17.1, 13.9; MS *m/z*, (%) 356 [$(M+2)^+$, 34.91], 354 (M^+, 32.20), 327 (52.12), 281 (34.22), 199 (100), 171 (33.56), 153 (18.49), 126 (14.43), 102 (15.56), 67 (13.54), 51 (7.07); Anal. Calcd for $C_{14}H_{15}BrN_2O_2S$: C, 47.33; H, 4.26; N 7.89. Found: C, 47.56; H, 4.14; N, 7.96.

5-Methoxycarbonyl-6-methyl-4-(2-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (28): Solid, mp 240 - 242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H, H-1), 7.71 (s, 1H, H-3), 7.57 (d, 1H, J = 7.69, H-c), 7.37 (t, 1H, J = 7.14, H-e), 7.31 (dd, 1H, J = 1.83, J = 7.69, H-d), 7.21-7.17 (m, 1H, H-f), 5.59 (d, 1H, J = 2.93, H-4), 3.45 (s, 3H, CH_3 of ester), 2.29 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 151.2, 149.3, 143.2, 132.6, 129.3, 128.6, 128.4, 122.1, 98.1, 53.9, 50.6, 17.7; MS *m/z*, (%) 326 [$(M+2)^+$, 2.79], 324 (M^+, 2.81), 265 (18.44), 245 (75.29), 169 (100), 137 (49.63), 115 (14.88), 102 (15.37), 89 (8.14), 75 (17.37), 50 (9.47).

5-Methoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (29): Solid, mp 218 - 220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H, H-1), 7.79 (s, 1H, H-3), 7.53 (d, 2H, J = 8.42, H-c and H-e), 7.18 (d, 2H, J = 8.42, H-b and H-f), 5.12 (d, 1H, J = 3.29, H-4), 3.53 (s, 3H, CH_3 of ester), 2.25 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 151.9, 148.9, 143.9, 131.3, 128.4, 120.3, 98.5, 53.3, 50.8, 17.8; MS *m/z*, (%) 326 [$(M+2)^+$, 6.00], 324 (M^+, 7.09), 309 (17.79), 265 (18.04), 245 (11.99), 169 (100), 137 (49.46), 110 (11.90),

102 (8.52), 75 (13.13), 50 (7.81); Anal. Calcd for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N 8.62. Found: C, 48.21; H, 4.12; N, 7.50.

5-Methoxycarbonyl-6-methyl-4-(propyl)-3,4-dihydropyrimidin-2(1*H*)-one (34): Solid, mp 151 - 152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H, H-1), 7.35 (s, 1H, H-3), 4.06-4.02 (m, 1H, H-4), 3.59 (s, 3H, CH_3 of ester), 2.15 (s, 3H, CH_3 at C-6), 1.37-1.15 [m, 4H, $(CH_2)_2$ of propyl], 0.83 (t, 3H, J = 6.77, CH_3 of propyl); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.0, 152.9, 148.6, 99.3, 50.8, 49.9, 17.8, 17.1, 13.9; MS *m/z*, (%) 212 [$(M)^+$, 0.47], 181 (4.88), 169 (100), 137 (63), 125 (9.26), 110 (7.93), 96 (8.04), 67 (6.49).

5-Methoxycarbonyl-1,6-dimethyl-4-(2-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (36): Solid, mp 164 - 165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, 1H, J = 3.66, H-3), 7.58 (d, 1H, J = 8.06, H-c), 7.36-7.29 (m, 2H, H-f and H-e), 7.21-7.17 (m, 1H, H-d), 5.58 (d, 1H, J = 3.66, H-4), 3.48 (s, 3H, CH_3 of ester), 3.15 (s, 3H, N-CH_3), 2.55 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 152.1, 151.5, 142.4, 132.7, 129.5, 128.5, 128.4, 122.2, 101.1, 52.5, 50.9, 29.6, 16.0; MS *m/z*, (%) 340 [$(M+2)^+$, 7.80], 338 (M^+, 8.12), 323 (22.38), 279 (14.84), 183 (100), 151 (50.71), 94 (7.14), 66 (5.85), 56 (40.35).

5-Methoxycarbonyl-1,6-dimethyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (37): Solid, mp 161 - 162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, 1H, J = 4.03, H-1), 7.52 (d, 2H, J = 8.42, H-c and H-e), 7.18 (d, 2H, J = 8.42, H-b and H-f), 5.15 (d, 1H, J = 3.66, H-4), 3.58 (s, 3H, CH_3 of ester), 3.09 (s, 3H, N-CH_3), 2.50 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 152.9, 151.2, 143.2, 131.4, 128.3, 120.4, 101.6, 51.7, 51.1, 29.7, 16.1; MS *m/z*, (%) 340 [$(M+2)^+$, 6.60], 338 (M^+, 6.86), 323 (20.72), 279 (14.04), 183 (100), 151 (47.33), 115 (5.01), 94 (7.94), 75 (6.34), 56 (44.42).

5-Methoxycarbonyl-1,6-dimethyl-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (38): Solid, mp 170 - 172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, 1H, J = 3.66, H-3), 7.24 (t, 1H, J = 7.14, H-d), 7.02 (d, 1H, J = 6.59, H-f), 6.99 (d, 1H, J = 8.42, H-e), 6.86 (t, 1H, J = 7.32, H-c), 5.45 (d, 1H, J = 3.66, H-4), 3.78 (s, 3H, O-CH_3), 3.51 (s, 3H, CH_3 of ester), 3.09 (s, 3H, N-CH_3), 2.50 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 156.6, 153.2, 150.7, 130.4, 128.7, 126.5, 120.1, 111.2, 100.6, 55.4, 50.9, 47.8, 29.6, 15.9; MS *m/z*, (%) 290 (M^+, 26.08), 275 (69.92), 259 (14.27), 231 (57.78), 216 (19.54), 199 (17.66), 183 (100), 151 (66.84), 115 (12.15), 94 (15.63), 91 (10.64), 77 (18.85), 56 (96.55).

5-Methoxycarbonyl-1,6-dimethyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (40): Solid, mp 176 - 178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, 2H, J = 8.79, H-c and H-e), 8.17 (d, 1H, J = 4.03, H-1), 7.49 (d, 2H, J = 8.79, H-b and H-f), 5.28 (d, 1H, J = 3.66, H-4), 3.58 (s, 3H, CH_3 of ester), 3.10 (s, 3H, N-CH_3), 2.5 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 152.7, 151.9, 151.0, 146.7, 127.4, 123.7, 101.0, 51.9, 51.1, 29.8, 16.1; MS *m/z*, (%) 305 (M^+, 8.98), 290 (28.99), 246 (11.85), 200 (17.50), 183 (100), 151 (69.90), 115 (9.12), 94 (12.76), 66 (10.92), 56 (59.63).

5-Methoxycarbonyl-6-methyl-4-(2-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (42): Solid, mp 172 - 173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H, H-1), 9.61 (s, 1H, H-3), 7.59 (d, 1H, J = 7.69, H-c), 7.39 (t, 1H, J = 7.49, H-e), 7.29 (dd, 1H, J = 1.47, J = 7.69, H-d), 7.23-7.19 (m, 1H, H-f), 5.61 (d, 1H, J = 3.29, H-4), 3.48 (s, 3H, CH_3 of ester), 2.32 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 165.2, 145.5, 142.3, 132.8, 129.7, 129.2, 128.5, 122.1, 99.9, 53.9, 50.9, 16.9; MS *m/z*, (%) 342 [$(M+2)^+$, 26.37], 340 (M^+, 26.54), 327 (7.53), 281 (16.14), 261 (37), 185 (100), 153 (25.70), 143 (8.68), 126 (13.88), 102 (12.93), 75 (9.25), 59 (7.05).

5-Methoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (43): Solid, mp 153 - 154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H, H-1), 9.68 (d, 1H, J = 2.93, H-3), 7.55 (d, 2H, J = 8.42, H-c and H-e), 7.16 (d, 2H, J = 8.42, H-b and H-f), 5.15 (d, 1H, J = 3.66, H-4), 3.55 (s, 3H, CH_3 of ester), 2.29 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.3, 165.5, 145.5, 142.5, 131.5, 128.6, 120.8, 99.9, 53.3, 51.1, 17.2; MS *m/z*, (%) 342 [$(M+2)^+$, 27.17], 340 (M^+, 28.46), 327 (20.59), 281 (19.29), 261 (6.06), 185 (100), 153 (23.61), 143 (8.44), 126 (14.13), 102 (10.92), 67 (9.80), 59 (5.82).

5-Methoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (46): Solid, mp 245 - 246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H, H-1), 9.56 (d, 1H, J = 1.83, H-3), 9.45 (bs, 1H, Ph-OH), 7.01 (d, 2H, J = 8.79, H-b and H-f), 6.71 (d, 2H, J = 8.42, H-c and H-e), 5.06 (d, 1H, J = 3.66, H-4), 3.54 (s, 3H, CH_3 of ester), 2.28 (s, 3H, CH_3 at C-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 165.7, 156.9, 144.7, 133.9, 127.5, 115.2, 100.9, 53.4, 50.9, 17.1; MS *m/z*, (%) 278 (M^+, 78.83), 263 (57.89), 245 (11.76), 219 (94.52), 217 (9.97), 185 (100), 153 (29.83), 145 (22.54), 126 (27.64), 115 (24.53), 94 (11.67), 89 (30.18), 65 (34.37), 59 (23.94).

Results and Discussion

In order to assess the catalytic activity of yttrium(III) acetate hydrate in Biginelli's one pot condensation, we have carried out a model reaction using benzaldehyde (5 mmol), ethyl acetoacetate (5 mmol), urea (7.5 mmol) and yttrium acetate hydrate (10 mol %) in refluxing ethanol. Since we got poor yield (28%) in this model reaction, we have tried the same reaction with different solvents (acetonitrile, THF, DCM, DMSO and DMF) at reflux condition. However, there were no appreciable improvements in these trials also. Then, we tried using 1:1 ratio of each of the said solvents in combination with acetic acid and acetic acid alone as a unique solvent. To our delight, acetic acid alone emerged as an efficient solvent instead of the mixture of solvents in enhancing the yield and also reducing the reaction time (from 18 to 4 h) appreciably. For improving the reaction yields, the efficacy of catalyst loading in this reaction was investigated and the optimum amount was found to be 8 mol % whereas further increase of the catalyst amount did not increase the yield appreciably. Similarly to optimize the molar ratio of the building blocks, attention was made to carry out reactions with varying amount of the three components. Finally, the cleanest conversions and highest product yields were ideally obtained by using 1:1:1.4 molar ratios of benzaldehyde, ethyl acetoacetate and urea respectively with 8 mol % of yttrium acetate hydrate as catalyst.

Having an optimized general protocol for this one pot assembly in hand, we next proceeded with ethyl acetoacetate, urea and a broad range of structurally diverse aromatic aldehydes bearing

Table 1. Yttrium acetate hydrate-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-(thio)ones in one-pot

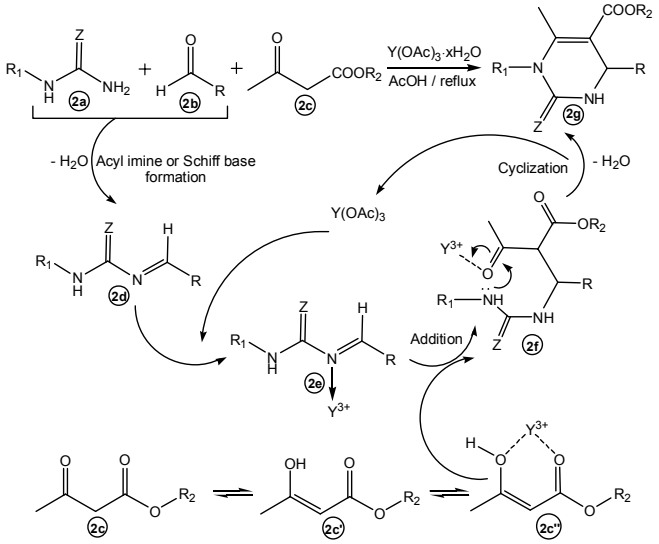
DHPM	R	R_1	R_2	Z	Yield[a] (%)	Time (h)	Mp (°C)[b]
1	C_6H_5	H	C_2H_5	O	92	4.0	201 - 202[10]
2	4-F-C_6H_4	H	C_2H_5	O	89	3.5	179 - 180[25]
3	2-Cl-C_6H_4	H	C_2H_5	O	98	3	218 - 220[18]
4	4-Cl-C_6H_4	H	C_2H_5	O	91	4.5	215 - 216[10]
5	2-Br-C_6H_4	H	C_2H_5	O	90	4	207 - 208[26]
6	3-Br-C_6H_4	H	C_2H_5	O	89	5.5	190 - 192[26]
7	4-Br-C_6H_4	H	C_2H_5	O	87	5	220 - 222[27]
8	4-HO-C_6H_4	H	C_2H_5	O	92	3.5	236 - 237[17]
9	4-NO_2-C_6H_4	H	C_2H_5	O	92	4.5	205 - 207[10]
10	2-CH_3O-C_6H_4	H	C_2H_5	O	97	0.75	260 - 261[20]
11	3-CH_3O-C_6H_4	H	C_2H_5	O	92	5	214 - 215[28]
12	4-CH_3O-C_6H_4	H	C_2H_5	O	89	4.5	200 - 201[10]
13	4-CH_3-C_6H_4	H	C_2H_5	O	89	3	216 - 217[17]
14	$(CH_2)_2CH_3$	H	C_2H_5	O	61	6.5	156 - 158[25]
15	C_6H_5	CH_3	C_2H_5	O	84	3	177[29]
16	2-Br-C_6H_4	CH_3	C_2H_5	O	94	4.5	142 - 143
17	4-Br-C_6H_4	CH_3	C_2H_5	O	93	5	150 - 151
18	2-CH_3O-C_6H_4	CH_3	C_2H_5	O	89	3.5	145 - 146
19	4-CH_3O-C_6H_4	CH_3	C_2H_5	O	82	4	134 - 135[30]
20	4-NO_2-C_6H_4	CH_3	C_2H_5	O	90	4	107 - 109[31]
21	C_6H_5	H	C_2H_5	S	79	4	208 - 209[27]
22	2-Br-C_6H_4	H	C_2H_5	S	82	4	149 - 150
23	4-Br-C_6H_4	H	C_2H_5	S	82	4.5	182 - 183
24	2-CH_3O-C_6H_4	H	C_2H_5	S	93	3.5	188 - 189[20]
25	4-CH_3O-C_6H_4	H	C_2H_5	S	81	4.5	152 - 154[17]
26	4-HO-C_6H_4	H	C_2H_5	S	76	3.5	199 - 200[32]
27	C_6H_5	H	CH_3	O	91	4	212 - 214[10]
28	2-Br-C_6H_4	H	CH_3	O	95	3.5	240 - 242
29	4-Br-C_6H_4	H	CH_3	O	87	3.5	218 - 220
30	2-CH_3O-C_6H_4	H	CH_3	O	90	0.75	287 - 288[20]
31	4-CH_3O-C_6H_4	H	CH_3	O	95	4.5	190 - 191[10]
32	4-HO-C_6H_4	H	CH_3	O	93	3.5	236 - 238[21]
33	4-NO_2-C_6H_4	H	CH_3	O	78	4.5	231 - 232[10]
34	$(CH_2)_2CH_3$	H	CH_3	O	46	6.5	151 - 152
35	C_6H_5	CH_3	CH_3	O	86	4.5	189 - 190[29]
36	2-Br-C_6H_4	CH_3	CH_3	O	96	4.5	164 - 165
37	4-Br-C_6H_4	CH_3	CH_3	O	94	4.5	161 - 162
38	2-CH_3O-C_6H_4	CH_3	CH_3	O	78	4.5	170 - 172
39	4-CH_3O-C_6H_4	CH_3	CH_3	O	76	4.5	135 - 137[29]
40	4-NO_2-C_6H_4	CH_3	CH_3	O	80	4.5	176 - 178
41	C_6H_5	H	CH_3	S	80	4.5	232 - 234[20]
42	2-Br-C_6H_4	H	CH_3	S	75	4.5	172 - 173
43	4-Br-C_6H_4	H	CH_3	S	80	4.5	153 - 154
44	2-CH_3O-C_6H_4	H	CH_3	S	96	1.0	255 - 256[20]
45	4-CH_3O-C_6H_4	H	CH_3	S	80	4.5	179 - 180[20]
46	4-HO-C_6H_4	H	CH_3	S	75	4.5	245 - 246

[a]Isolated yield based on aldehyde while using 8 mol % of catalyst. [b]Compounds are known in the literature and were characterized by their physical and spectral data

Table 2. Comparison of the yield of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (1) synthesized by different catalysts

Entry	Catalyst	Solvent (mL)[a]	Time (h)	Yield (%)	Reference
1	HTMA (Heulandite)	AcOH (25)	4-5	75	25
2	12-Tungstophosphoric acid	AcOH (15)	6-7	75	27
3	$Sr(NO_3)_2$	AcOH (37)	6	78	32
4	12-Molybdophosphoric acid	AcOH (4)	5	80	33
5	Con. H_2SO_4	EtOH (7)	16	71	10,12,13
6	$Y(NO_3)_3 \cdot 6H_2O$	Solvent free	20 min	97	21b
7	**$Y(OAc)_3 \cdot xH_2O$**	**AcOH (3)**	**4**	**92**	**Present work**

[a]The amount of solvent corresponding to 5 mmol of aldehyde



Scheme 2. Plausible mechanism for the formation of DHPM/DHPM-thione

either electron-withdrawing or electron-donating substituents and achieved the corresponding DHPMs **1-13** (Table 1) in good to excellent yields (87 - 98%). Besides urea, *N*-methylurea (DHPMs **15-20**) and thiourea (DHPMs **21-26**) were also employed successfully as substrate here without causing any significant decrease in yield (76 - 94%). The derived DHPMs by the above said variants are of much interest with regard to their biological activity.[4,5] Encouraged by the results obtained with ethyl acetoacetate, we examined the tolerance of another β-keto ester viz. methyl acetoacetate (DHPMs **27-33**; **35-46**) in this Biginelli reaction with varied aromatic aldehydes and urea or *N*-methylurea or thiourea and also accomplished better results (75 - 96%). Meanwhile, even for aliphatic aldehyde, viz. butyraldehyde, which normally shows extremely poor yield in the Biginelli reaction with β-dicarbonyl compounds and urea, the corresponding dihydropyrimidin-2(1*H*)-ones **14** and **34** could be obtained in moderate yields (Table 1). Majority of the existing synthetic strategies have shown a great deal of variability in yield depending on the aromatic aldehyde and *N*-methylurea or thiourea used. However, our three-component reaction proceeded smoothly to furnish uniformly high yields, irrespective of the type of aromatic aldehyde carrying electron-rich or electron-poor substituents in either *ortho* or *meta* or *para* position, β-dicarbonyl compound and urea derivatives used. Therefore, this protocol tolerates many of the substitution patterns on all the three components to provide an array of dihydropyrimidinones as evidenced from Table 1.

Generally, all the reactions were very clean without any side products. Indeed, the crude products obtained are of high purity (> 95% ascertained by ^{1}H NMR) and did not require any chromatographic separation (However, mild non-polar impurity encountered in few cases was easily removed by simple digestion in hexane for 15 min). Table 2 describes the comparison of the present work towards the synthesis of DHPM **1** with other catalytic methods in literature[25,27,32,33,10-13,21b] which employ acetic acid or ethanol as medium or without any solvent. A close inspection of the Table 2 justifies the superiority of our method in terms of yield and relatively less solvent. Furthermore, the advantage of using acetic acid as medium is that it offers a homogeneous medium wherein the acetate function of yttrium acetate could create more positive charge over yttrium and thus allows the reactive species (**2d** & **2c'** - Scheme 2) to be attracted towards the active sites[34] which in turn reflects in formation of desired products in good yield. An interesting feature of this optimized protocol is that it enhances the yield compared to the classical Biginelli method and markedly decreases the reaction time from 18 h to 45 min - 6.5 h.

Mechanistically, the reaction proceeds through acid catalyzed formation of acylimine or Schiff's base (**2d**) from urea (**2a**) [or *N*-methylurea or thiourea] and aldehyde (**2b**) (Scheme 2). Due to the presence of vacant *4d* orbital in the yttrium(III) ion, it stabilizes the then formed acylimine intermediate *via* coordination with yttrium(III) acetate (**2e**). This was followed by the addition to 1,3-dicarbonyl compound (**2c**), most likely through its yttrium (III) stabilized enolate form (**2c″**), and produces an open chain ureide (**2f**) which upon subsequent cyclization and acid catalyzed dehydration furnished the desired target DHPM/DHPM-thione (**2g**).[14,35]

Conclusion

In conclusion, we have developed a simple and high-yielding protocol for synthesizing a library of 3,4-dihydropyrimidin-2(1*H*)-(thio)ones by using yttrium(III) acetate hydrate as catalyst in a homogeneous medium. In addition to its simplicity and easy work up, the reaction condition is mild enough for the survival of a variety of sensitive functionalities such as F, Cl, Br,

NO_2, OH, OMe and Me, which is lacking in some of the existing procedures. Purities and yields were not affected if *N*-methylurea or thiourea were used instead of urea. Therefore, we deem our protocol will find its way to furnish the needs of academia as well as pharmaceutical industries towards the synthesis of broad range of dihydropyrimidones.

Supporting Information. NMR spectra for all the compounds are furnished.

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