One pot synthesis of Biginelli 3,4-dihydro-1H-pyrimidin-2-ones and 1,2,3,4-tetrahydro pyrimidines

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Abstract

A simple and practical route for the Biginelli cyclocondensation reaction using anhydrous ZnCl2 as a catalyst in n-heptane-toluene medium by reaction of substituted benzaldehydes, 1a-d (1a=2-CIC6H4, 1b=2-BrC6H4, and 1c=4-CIC6H4, 1d=2-HCC6H4) with 1, 3-dicarbonyl compounds, 2a-b (2a= ethyl acetoacetate and 2b= acetylacetone) and urea or thiourea, 3a-b to give the corresponding Biginelli 3,4-dihydro-1H-pyrimidin-2-ones and 1,2,3,4-tetrahydro pyrimidines, 4a-d. The structures of the compounds 4a-d were confirmed by their ultraviolet, infrared, 1H NMR, 13C NMR spectra and elemental analyses.

Keywords: Substituted benzaldehydes; Ethyl acetoacetate; Acetylacetone; Zinc chloride; Biginelli reaction

Introduction

The classical Biginelli condensation (Biginelli 1893) involving the reaction of an aldehyde, β-keto ester and urea or thiourea under strong acidic conditions to give 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) which exhibit widespread biological applications. A large number of catalysts, solvent systems have been developed in accelerating this reaction since then. DHPMs are well known for their wide range of bioactivity and their application as calcium channel blockers, α 1-1-a-agonists, antihypertensive agents, inhibitors of the fatty acid transporter and mitotic kinesin inhibition (Rovnyak et al., 1995; Van Zandt et al., 2005). These compounds have also been found to possess antiviral, antitumor, anti-inflammatory and antibacterial properties (Tsuruo et al., 1983; Kappe 1993, 2000). A huge number of reviews (Mirzaei et al., 2001; Shaaban et al., 2008; Cho et al., 1989; Rajeshwari et al., 2013) on synthesis and chemical properties of dihydropyrimidinones have already been published. Several marine alkaloids with interesting biological activities also contain the dihydropyrimidinone-5-carboxylate core (Snider et al., 1993). Most notably among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors (Snider et al., 1996; Patil et al., 1995). The anti-cancer agent monastrol (Fig. 1) has been shown to specifically affect mitosis via a new mechanism consisting of the specific and reversible inhibition of the motility of the motor protein mitotic kinesin (Dondoni et al. 2002; Laville et al., 2009).

In order to improve the efficiency of Biginelli reaction coupled with the biological study of synthesized compounds many catalysts have been developed such as zirconium(IV) chloride (Reddy et al., 2002), indium(III) bromide (Fu et al., 2002), ceric ammonium nitrate (CAN) (Yadav et al., 2001), indium(III) chloride (Ranu et al., 2000),

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lanthanum chloride (Lu et al., 2000), Boric acid (Tu et al., 2003), lithium bromide (Maiti et al., 2003) silica/sulfuric acid (Salehi et al., 2003), vanadium(III) chloride (Sabitha et al., 2003), FeCl₃·6H₂O (Lu et al., 2000), zinc triflate (Xu et al., 2003), trichloroacetic acid (Jaber et al., 2012), nanosilica-supported tin(II) chloride (Ghomi et al., 2013), Bronsted acid (Anjaneyulu et al., 2015), L-proline nitrate (Bahekar et al., 2017), InBr₃ (Maskrey et al., 2018) and Hf(OTf)₄ (Kong et al., 2019). Some of these catalysts are really very fascinating from a synthetic chemist’s point. Despite their tremendous success, however, some drawbacks still remain. For example, some of the catalysts are expensive, complex or unavailable.

In the past 20 years, several one-pot methodologies for the synthesis of DHPM derivatives have been developed and several modifications have been introduced. Most of them are based on Lewis acid-catalyzed reactions (Paraskar et al., 2003; Sabitha et al., 2005; Azizian et al., 2006; Sadek et al., 2010; Shapiro and Vigalok, 2008; Salim and Akamanchi, 2011; Chitra and Pandiarajan, 2009; Mandhane et al., 2010) which permits the reaction to proceed under milder conditions and with higher yields, than those out-lined by Biginelli in the original procedure. Microwave irradiation has also proved beneficial (Pasunooti et al., 2011). Natural acidic catalysts have been also utilized (Patil et al., 2011).

Biginelli reaction has also been conducted under basic conditions. This involves the use of PPh₃, under solvent free conditions (Debache et al., 2008), t-BuOK at 70°C (Shen et al., 2010), chiral primary amines (Ding and Zhao, 2010) and ammonium carbonate in water (Tamaddon et al., 2010). It is worth mentioning that many of these existing methods displayed drawbacks, such as environmental pollution caused by utilizing catalysts in stoichiometric quantities, exotic reaction conditions, unsatisfactory yields and complicated operations while others possess some advantages overcoming these drawbacks. Zinc chloride, a very inexpensive and easily available Lewis acid catalyst, has been widely used in organic reactions, but it hasn’t been carefully studied as a catalyst in Biginelli condensation until now, except for a few mentions in literature (Sun et al., 2004).

In continuation of our interest in the synthesis of fused pyrimidines (Akhter et al., 2015), we report herein a simple and practical route for the Biginelli cyclocondensation reaction using ZnCl₂, as a catalyst in n-heptane-toluene medium. This is a novel, one pot combination that not only preserves the simplicity of Biginelli’s one pot reaction but also consistently produce excellent yields of the di (or tetra) hydropyrimidinones, 4a-d (Scheme 2). The compounds 4a-d do not seem to be available in the literature.

Materials and methods

All chemicals were purchased from E. Merck. Thin layer chromatography (TLC) was carried out on plates percolated with silica gel 60 F254 and spots were detected with iodine vapour. Melting points were determined on an Electro thermal micro melting-point apparatus and uncorrected. The Ultraviolet spectra of the samples were recorded on a Shimadzu UV-160A spectrometer with a scanning range of 800-200 nm using methanol as solvent. IR spectra were recorded with Shimadzu IR 470A spectrophotometer in the range 4000-400 cm⁻¹. The ¹H NMR and ¹³C NMR spectra of
the samples were recorded on a Bruker 400 MHz spectrophotometer using DMSO-d$_6$ as solvent with Tetramethylsilane (TMS) as an internal standard.

**General procedure**

A mixture of a benzaldehyde (10 mmol), a 1,3-dicarbonyl compound (10 mmol), urea or thiourea (15 mmol) and ZnCl$_2$ (273 mg, 2mmol) was refluxed in heptane-toluene (30mL, 1:1) medium under magnetic stirring for 4 hours. Upon completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, poured onto 30 ml of water. The resulting solid was filtered under suction and successively washed with H$_2$O (30 ml) and petroleum ether-EtOAc (5:1, 30 ml). The crude product was then purified by re-crystallization (acetone-ethanol mixture) to give pure product. Compounds obtained according to this procedure were characterized and identified by their melting points, UV, FT-IR, $^1$H-NMR, $^{13}$C-NMR and elemental analyses.

**Scheme 2. Synthesis of the compounds, 4a-d**

Yield 78%; white crystalline solid; mp 164-165°C; $R_f$ value in TLC 0.85 (Ethyl acetate: Chloroform,1:4); UV ({$\lambda_{max}$} in nm): 305 ($\pi$→$\pi^*$/n→$\pi^*$ of C=O); IR (KBr) ({$v_{max}$} cm$^{-1}$): 3180 (N-H stretching), 1708 (C=O), 1654 (C=C in conj. with C=O), 1444 (C=S stretching), 1089 (Aromatic-Cl); $^1$H NMR $\delta$ (in ppm): 8.81 (s, 1H, N-H, 1-H), 7.67 (s, 1H, N-H, 3-H), 7.36 (d, 1H, J=7.8 Hz, 3'-H), 7.24-7.20 (m, 3H, 4', 5' & 6'-H), 5.89 (d, 1H, J=3.0 Hz, 4'-H), 4.01 (q, 2H, J=7.2, CH$_2$CH$_2$COO$^-$), 2.43 (s, 3H, CH$_3$), 1.05 (t, 3H, J=7.2 Hz, CH$_3$), 1.05 (t, 3H, J=4.8 Hz, CH$_2$CH$_2$COO$^-$); $^{13}$C NMR $\delta$ (in ppm): 174.02 (C-2), 164.82 (CH), 153.13 (C-2), 165.64 (CH$_2$COO$^-$), 144.62 (C-6), 138.50 (1'), 132.51(2'), 129.78(3'), 129.57(6'), 128.51(4'), 127.60(5') (6C-aromatic), 100.73 (5-C), 60.26 (CH$_2$CH$_2$COO$^-$), 52.56 (4-C), 17.74 (CH$_3$), 13.79 (CH$_2$CH$_2$COO$^-$). Anal. Found: C, 65.61; H, 6.70; N, 10.11; Calc. for C$_{14}$H$_{15}$ClN$_2$O$_2$: C, 54.10; H, 4.86; N, 9.01%.

5-Acetyl-4-(2-bromophenyl)-6-methyl-3,4-dihydro-1H-pyrimidine-2-one, 4b:

Yield 78%; Off white crystalline solid; mp 224-226°C; $R_f$ value in TLC 0.44 (Neat Chloroform); UV ({$\lambda_{max}$} in nm): 301 ($\pi$→$\pi^*$ of C=O); IR (KBr) ({$v_{max}$} cm$^{-1}$): 3252 (N-H stretching), 1705 (C=O), 1624 (C=C in conj. with C=O), 1026 (Aromatic-Br); $^1$H NMR $\delta$ (in ppm): 9.27 (s, 1H, N-H, 1-H), 7.67 (s, 1H, N-H, 3-H), 7.59 (d, 1H, J=8.4 Hz, 3'-H), 7.35 (d, 1H, J=7.8 Hz, 5'-H), 7.25 (d, 1H, J=7.2 Hz, 6'-H), 7.19 (d, 1H, J=7.8 Hz, 4'-H), 5.61 (d, 1H, J=3.0 Hz, 4'-H), 2.32 (s, 3H, CH$_3$CO$^-$), 2.03 (s, 3H, CH$_3$), 1.05 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$COO$^-$). $^{13}$C NMR $\delta$ (in ppm): 201.26 (CH$_2$CO$^-$), 160.83 (C-2), 139.56 (C-6), 145.22 (1'), 122.80 (2'), 130.56 (3'), 129.46 (6'), 128.02 (6').
4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, 4c:

Yield 38%; yellowish crystalline solid; mp 168-170°C; Rf value in TLC 0.52 (Neat ethyl acetate); UV (λmax in nm): 285 (π→π*/n→π* of C=O); IR (KBr) (νmax cm⁻¹): 3276 (N-H stretching), 1750 (C=O), 1612 (C=C in conj. with C=O), 1415 (C=S stretching), 1084 (Aromatic-Cl). 1H NMR δ (in ppm): 7.44 (s, 1H, N-H, 1-H), 7.41 (s, 1H, N-H, 3-H), 7.29 (d, 2H, J=7.8 Hz, 3' & 5'-H), 7.22 (d, 2H, J=8.4 Hz, 2' & 6'-H), 5.36 (d, 1H, J=2.49 Hz, 4-H), 4.08 (q, 2H, J=6.6, CH₂CH₂COO⁻), 2.34 (s, 3H, CH₃C₆H₄C=), 1.17 (t, 3H, J=7.2 Hz, CH₂CH₂COO⁻); 13C NMR δ (in ppm): 173.89 (C-2), 165.02 (CH₂CH₂COO⁻), 145.22 (C-6), 139.50 (1'), 128.52(2'), 129.88(3'), 128.58(6'), 130.51(4'), 129.90(5') (6C-aromatic), 101.61 (5-C), 59.96 (CH₂CH₂COO⁻), 52.12 (4-C), 17.77 (CH₂C₆H₄C=), 13.72 (C₆H₅). Anal. Found: C, 54.22; H, 4.82; N, 9.01%.

6-Methyl-2-oxo-4-o-tolyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, 4d:

Yield 70%; white crystalline solid; mp 207-208°C; Rf value in TLC 0.72 (Ethyl acetate; Chloroform, 1:1); UV (λmax in nm): 292 (π→π*/n→π* of C=O); IR (KBr) (νmax cm⁻¹): 3235 (N-H stretching), 1700 (C=O), 1643 (C=C in conj. with C=O); 1H NMR δ (in ppm): 8.43 (s, 1H, N-H, 1-H), 5.81 (s, 1H, N-H, 3-H), 7.24-7.20 (m, 4H, 3', 4', 5' & 6'-H), 5.64 (bs, 1H, 4-H), 3.97 (q, 2H, J=7.2, CH₂CH₂COO⁻), 2.41 (s, 3H, Ar-CH₃), 2.35 (s, 3H, CH₂C₆H₄C=), 1.05 (t, 3H, J=7.2 Hz, CH₂CH₂COO⁻); 13C NMR δ (in ppm): 153.13 (C-2), 165.64 (CH₂CH₂COO⁻), 141.40 (C-6), 146.82 (1'), 132.59 (2'), 130.66 (3'), 127.86 (6'), 127.17 (4'), 126.84 (5') (6C-aromatic), 100.64 (5-C), 59.89 (CH₂CH₂COO⁻), 52.18 (4-C), 18.92 (CH₂C₆H₄C=), 18.45 (Ar-CH₃), 14.04 (CH₂CH₂COO⁻). Anal. Found: C, 65.61; H, 6.70; N, 10.11; Calc. for C₁₅H₁₄N₂O₂: C, 65.68; H, 6.61; N, 10.21%.

Results and discussion

The one-pot synthesis of di (or tetra) hydroxypyrimidines 4a-d were synthesized by the three component condensation of substituted benzaldehydes 1a-d, with corresponding β-dicarbonyl compounds 2a-b and urea or thiourea 3a-b in presence of anhydrous zinc chloride in heptane-toluene under refluxing conditions in an analogous manner reported previously (Akhtar et al., 2015). The structures of the compounds 4a-d were confirmed based on their UV, FT-IR, 1H NMR, 13C NMR and elemental analyses.

The compounds 4a-d agree well to the expected λmax values in their UV spectra. The absorption bands in the range 305-285 nm may be assigned to the π→π* absorption of C=O in these compounds. The weak n→π* absorption bands in the cases of these compounds due to C=O were probably masked within the π→π* absorption range.

The IR data of the compounds 4a-d showed sharp as well as broad bands in the range (νmax) 3276-3180 cm⁻¹ indicating the presence of N-H group. The absorption bands at 1750-1700 cm⁻¹ indicate the presence of non-conjugated C=O stretching including the pyrimidine moieties. The bands at 1654-1612 cm⁻¹ were assigned to C=C of aromatic rings in conjugation with C=O and 1444-1415 cm⁻¹ for C-S stretching of compounds 4a and 4c. Additional bands were observed at 1089-1026 cm⁻¹ due to presence of halogenated aromatics of compounds 4a, 4b and 4c.

In their 1H NMR spectra of compounds 4a-d, the N-H protons were relatively deshielded (δ 9.27-7.44) and appeared as singlet due to anisotropy and presence of electronegative atoms attached to this group. The proton at position 4 appeared as a doublet (or broad singlet) gave signals at δ 5.89-5.36 due to the vicinal coupling with the proton at position 3. The methylene protons (4a, 4c and 4d) appeared as quartet being attached to a methyl in one side and an ester on the other side further deshielded due to direct link with one oxygen of ester group and gave peaks at δ 4.08-3.97 ppm. The methyl protons in these compounds attached to an alkene carbons gave peaks at δ 2.43-2.03 ppm and another methyl protons (4b) attached to carbonyl group gave peaks at δ 2.32 ppm as singlet. The aromatic methyl of compound 4d appeared as singlet and gave signal at δ 2.41 ppm. The methyl protons of ester group (4a, 4c and 4d) appeared as triplets and gave signals at δ 1.17-1.04 ppm. All aromatic protons have shown peaks in their expected positions.

The structures of the compounds 4a-d were further confirmed by their 13C NMR spectra. The chemical shifts of carbonyl carbon at 2-C were found to be deshielded in the range of δ 174.02-153.13. The chemical shifts of CH(CO) of compound 4b was further deshielded (δ 201.26). The chemical shift values for -COOHCH₃ in compounds 4a, 4c and 4d were observed at (δ 165.64-164.82). The chemical shifts of 6-C were similarly deshielded (δ 145.22-139.56). The 5-C of the compounds showed chemical shift values at δ 105.40-100.64. The chemical shift values for 4-C in these compounds were
observed at $\delta$ 52.56-51.92. The chemical shift values for methyl carbon attached to alkene (C$_5$-C$_6$) in these compounds were observed at $\delta$ 18.92-17.74. The chemical shift values for -COOCH$_2$CH$_3$ and -COOCH$_2$CH$_3$ in compounds 4a, 4c and 4d were observed at $\delta$ 60.26-59.89 and 14.04-13.71 respectively. The chemical shift values for CH$_3$CO- in compound 4b and aromatic methyl carbon in compound 4c were observed at $\delta$ 26.22 and 18.45 respectively. The $^{13}$C NMR chemical shifts for the carbons of aromatic rings were found in their expected positions.

Although different mechanistic pathways have been proposed previously (Tamaddon et al 2010), we believe that the reaction may proceed through an initially formed imine intermediate [II] from the reaction of the aldehyde, 1 and urea or thiourea, 3 (Scheme-3). The co-ordination of the lone pair of the nitrogen atom with the Lewis acid could lead to the in situ formation of iminium ion [II] which is sufficient electrophile to react with the enol form of ethyl acetoacetate, 2 affording finally intramolecular cyclization with loss of H$_2$O molecule, producing di (or tetra) hydropyrimidines, 4a-d.

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![Scheme 3. A plausible reaction mechanism for 4a-d](image-url)
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