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Bangladesh J. Sci. Ind. Res. **53(4)**, 327-332, 2018

Short Communication

BANGLADESH JOURNAL OF SCIENTIFIC AND INDUSTRIAL RESEARCH

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Synthesis of potential pharmaceutically active dihydropyrimidine-2-oxo and their 2-thio analogues

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Received: 24 September 2017
Revised: 19 February 2018
Accepted: 23 May 2018

DOI: http://dx.doi.org/10.3329/bjsir.v53i4.39198

Abstract

The Biginelli one - pot three-component cyclocondensation was applied to prepare 3, 4 - dihydropyrimidin - 2 (1*H*) – ones from aldehydes, β-dicarbonyl compounds and urea (or thiourea) using $ZnCl_2$ as a catalyst. The method offers several advantages including short reaction times and easy experimental work up procedures.

Keywords: Cyclocondensation; Aldehydes; β - dicarbonyl; Urea and thiourea

Introduction

Multicomponent reactions have drawn significant attention from the pharmaceutical point of view (Clark and Macquarrie 1996). The Biginelli reaction is a three component chemical reaction used to synthesize 3, 4-dihydropyrimidin-2 (1*H*)-ones from an ester, an aryl aldehyde, and urea catalyzed by Brønsted and/or Lewis acids (Hu *et al.,* 1998; Kappe and Stadler, 2004). 3, 4-dihydropyrimidin-2 (1*H*)-ones used as calcium channel modulators and antihypertensive α_{1a}-antagonists (Atwal *et al.,* 1991, Rovnyak *et al.,* 1992). For novel Biginelli-like scaffold syntheses, the use of common open chain β-dicarbonyl compounds has been extended to cyclic β-diketones, β-ketolactones, cyclic β-diesters or β-amides, benzocyclic ketones, and α-ketoacids (Byk *et al.,* 2000; Kappe, 2000; Abelman *et al.,* 2003; Yarim *et al.,* 2003; Shaabani *et al.,* 2004). As these reactions suffer from some limitations, efforts are continuing to minimize the limitations. In order to improve the efficiency of Biginelli reaction, many Lewis acids such as $Yb(OTf)_3$ (Ma *et al.,* 2000), $InCl_3$ (Brindban and Jana, 2000), VCl_3 (Salitha *et al.,* 2003), $CuCl_2.2H_2O$ (Gohain *et al.,* 2004), LiBr (Maiti *et al.,* 2003), $RuCl_3$ (Suryak and Gibbs, 2005), $SnCl_2.2H_2O$ (Russowsky *et al.,* 2004), $BF_3.OEt_2$ (Hu *et al.,* 1998), $ZrCl_4$ (Rodríguez-Domínguez *et al.,* 2007), $Y(NO_3)_3.6H_2O$ (Nandurkar *et al.,* 2007), Cu $(OTf)_2$ (Paraskar *et al.,* 2003), CuI (Kalita and Phukan, 2007), In Br_3 (Fu *et al.,* 2002), B $(OH)_3$ (Tu *et al.,* 2003), In $(OTf)_3$ (Ghosh *et al.,* 2004), PhB $(OH)_2$ (Debache *et al.,* 2006), Fe $(OAc)_3$, $Fe(OTf)_3$ (Adibi *et al.*, 2007), HBF_4 (Chen *et al.,* 2007) and Bronsted acids such as *p*-toluenesulfonic acid (Jin *et al.,* 2002), silica sulfuric acid (Salehi *et al.,* 2003), potassium hydrogen sulphate (Tu *et al.,* 2004), formic acid (Jiang and Qi, 2007), chloroacetic acid (Yu *et al.,* 2007) have been developed as catalysts. Heteropolyacids such as 12-molybdophosphoric acid $H_3PMo_{12}O_{40}$ (Heravi *et al.,* 2006) and 11-molybdo -1-vanadophosphoric acid $H_4PMo_{11}VO_{40}$ (Maradur and Gokavi, 2007), also have been used as catalyst. Even bakers' yeast has been used as efficient catalyst in Biginelli reaction (Kumar and Maurya, 2007). In addition, significant improvements in the reaction rate and yield for the reaction carried out under microwave condition have been reported (Gohain *et al.,* 2004). Moreover, asymmetric syntheses of dihydropyrimidinones using $CeCl_3$ or In Cl_3 or $Yb(OTf)_3$ as catalysts in presence of chiral ligands have been reported (Munoz-Muniz and Juaristi, 2003; Huang *et al.,* 2005). Some of these reactions are really interesting from a synthetic chemist's point of view. Despite their tremendous success, however, some drawbacks still remain including catalysts are expensive, complex or unavailable.

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Heterocyclic moiety is a vital structure in many bioactive natural products therapeutic compounds. Multicomponent reactions are becoming increasingly prevalent due to their improved efficiency, simple procedure, one-pot character, quantitative yields, and high number of accessible backbones. Oliver Lecnik and his co-workers reported the separation of pharmacologically active dihydropyrimidinones using carboxymethyl-β-cyclodextrin as chiral selector by capillary electrophoresis (Lecnik *et al.,* 2001). Derivatives of 3,4-dihydropyrimidin-2 (1*H*)-ones show a diverse range of therapeutical properties and pharmacological activities such as antimitomic, analgesic, antiviral, anticancer, anti-inflammatory, and antihypertensive agents (Kappe, 1993; 2000). However, in spite of their potential utility, many of these methods generally require strong acidic conditions, stoichiometric amount of the catalysts, expensive reagents, prolonged reaction times and high temperatures. Thus, to avoid these limitations, we describe in this report an effective and rapid method for the preparation of 3, 4-dihydropyrimidin-2 (1*H*)-ones using a new catalytic agent $ZnCl_2$ in refluxed *n*-heptane-toluene.

Experimental

Reagent grade chemicals were purchased from commercial sources and used as received. Ultraviolet-visible spectra of were recorded on a SHIMADZU-UV-160A ultraviolet spectrometer with a scanning range of 800-200 nm. IR spectra were recorded as KBr pellets using a SHIMADZU-IR-470 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 400 MHz NMR spectrophotometer. Mass spectra were obtained with a JEOL JMS-HX-110A spectrophotometer.

General procedure for the synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones (4a-4f)

A mixture of 4-methoxybenzaldehyde/4- methylb enzaldehyde (10 mmol), acetylacetone/ ethylacetoacetate (10 mmol), urea/thiourea (15 mmole), and $ZnCl_2$ (2 mmol) was refluxed in *n*-heptane-toluene (30 mL, 1:1) medium until the consumption of all the starting material (monitored by analytical TLC). Upon completion of the reaction, the solid was filtered and successively washed with H_2O. The crude product was then purified by recrystallization from appropriate solvent system.

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4a)

Yield 15.9%; mp 181-183 °C; UV-Visible (λ_{max}): 295.0 nm; IR (KBr): 3350, 3110, 2900, 1700, 1680, 1618, 1252 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.15 (s, 1H), 7.77 (s, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.20 (s, 1H), 3.70 (s, 3H), 2.27 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: δ 196.5, 158.7, 150.3, 145.0, 135.5, 128.0, 114.1, 106.8, 55.9, 47.7, 27.0, 15.0; EI-MS *m/z* (%): 261 (M^+ + 1, 100), 260 (M^+, 44), 259 (40), 245 (14), 218 (18), 153 (62), 136 (24); Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.27; H, 6.18; N, 10.80.

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (4b)

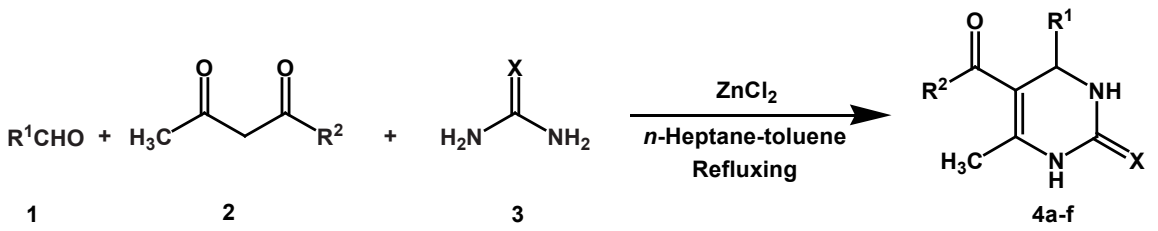
Yield 5.8%; mp 170-172 °C; UV-Visible (λ_{max}): 322.0 nm; IR (KBr): 3360, 3060, 2810, 1705, 1670, 1447, 1020 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.25 (s, 1H), 9.70 (s, 1H), 7.15 (d, *J* = 10.0 Hz, 2H), 6.90 (d, *J* = 10.0 Hz, 2H), 5.25 (s, 1H), 3.74 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H); ^{13}C NMR: δ 196.5, 174.5, 158.7, 158.0, 135.5, 128.0, 114.1, 104.6, 55.9, 52.8 27.0, 15.7; EI-MS *m/z* (%): 277 (M^+ + 1, 100), 276 (M^+, 24), 261 (12), 233 (9), 218 (20), 154 (36), 136 (26); Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 61.17; H, 5.88; N, 10.17.

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4c)

Yield 24.8%; mp 192-194 °C; UV-Visible (λ_{max}): 286.0 nm; IR (KBr): 3200, 3060, 2940, 1727, 1685, 1600, 1485, 1210, 760 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.16 (s, 1H), 7.68 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.10 (s, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.71 (s, 3H), 2.23 (s, 3H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ 167.2, 158.7, 150.3, 147.3, 135.5, 128.0, 114.1, 106.4, 61.7, 55.9, 49.5, 14.9, 14.2; EI-MS *m/z* (%): 291 (M^+ + 1, 100), 290 (M^+, 20), 289 (22), 261 (27), 245 (9), 217 (13), 183 (2), 154 (53), 136 (42); Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 60.63; H, 6.14; N, 10.12.

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (4d)

Yield 22.3%; mp 145-147 °C; UV-Visible (λ_{max}): 305.0 nm; IR (KBr): 3300, 3080, 2940, 1717, 1680, 1438, 1180, 760 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.52 (s, 1H), 7.21 (d, *J* = 11.0 Hz, 2H), 6.98 (s, 1H), 6.86 (d, *J* = 11.0 Hz, 2H), 5.36 (s, 1H), 4.10 (q, J = 6.0 Hz, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 1.19 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR: δ 174.5, 167.2, 160.3, 158.7, 135.5,



Scheme 1. Synthesis of 3, 4 - dihydropyrimidin - 2 - (1*H*) - ones.

Table 1. $ZnCl_2$ mediated synthesis of 3, 4 - dihydropyrimidin - 2 - (1*H*) - ones under n - heptane - toluene refluxing conditions

Entry	Product	R^1	R^2	X	Reaction time (hour)	Recrystallizing solvent system
1	4a	4-MeO-C_6H_4	Me	O	4.0	Acetone-ethanol
2	4b	4-MeO-C_6H_4	Me	S	6.0	Acetone-ethanol
3	4c	4-MeO-C_6H_4	OEt	O	5.0	Ethylacetate
4	4d	4-MeO-C_6H_4	OEt	S	7.5	Ethanol
5	4e	4-Me-C_6H_4	OEt	O	5.0	Ethanol
6	4f	4-Me-C_6H_4	OEt	S	8.0	Ethanol

128.0, 114.1, 104.2, 61.7, 55.9, 54.6, 15.6, 14.2; EI-MS *m/z* (%): 307 (M^+ + 1, 100), 306 (M^+, 8), 305 (10), 277 (8), 275 (9), 261 (7), 161 (8); Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.24; H, 5.89; N, 9.12.

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydro pyrimidin-2(1*H*)-one (4e)

Yield 39.4%, mp 205-207 °C; UV-Visible (λ_{max}): 288.0 nm; IR (KBr): 3200, 3080, 2950, 1700, 1675, 1620, 1590, 1450, 770 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.21 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 2H), 5.39 (s, 2H), 5.28 (s, 1H), 4.08 (q, J = 7.0 Hz, 2H), 2.36 (s, 3H), 2.32 (s, 3H) 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ 167.2, 150.3, 147.3, 140.2, 136.4, 128.9, 126.9, 106.4, 61.7, 49.5, 24.3, 14.9, 14.2; EI-MS *m/z* (%): 275 (M^+ + 1, 100), 274 (M^+, 9), 183 (14), 145 (6); Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 64.63; H, 6.54; N, 10.35.

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydro pyrimidin-2(1*H*)-one (4f)

Yield 10.3%; mp 178-181 °C. UV-Visible (λ_{max}): 301.0 nm; ^1H NMR (DMSO-d_6): δ 10.32 (s, 1H), 9.62 (s, 1H),7.15 (d, *J* = 7.0 Hz, 2H), 7.10 (d, *J* = 7.0 Hz, 2H), 5.12 (s, 1H), 4.00 (q, J = 5.0 Hz, 2H), 2.50 (s, 3H), 2.27 (s, 3H) 1.10 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR: δ 174.5, 167.2, 160.3, 140.2, 136.4, 128.9, 126.9, 104.2, 61.7, 54.6, 24.3, 15.6, 14.2; EI-MS *m/z* (%): 291 (M^+ + 1, 100), 290 (M^+, 12), 261 (7), 245 (5), 154 (11), 136 (9); Anal. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.75; H, 6.22; N, 9.74.

Results and discussion

The one pot synthesis of 3, 4 - dihydropyrimidin-2 (1*H*) - ones and – thiones was achieved by the three-component condensation of aldehydes, *β* - dicarbonyl compounds and urea (or thiourea) in the presence of anhydrous zinc chloride. On heating, a yellow solid precipitate was appeared when approximately 5 mg of crystalline solid product was dissolved in $CHCl_3$ and 2, 4 - dinitrophenylhydrazine was added to it drop wise. This indicates that the compounds contain a keto (>C= O) group. The UV spectra of the compounds displayed characteristic absorption bands ranges from 280 to 290 nm for n→π* transition of >C=O group or very close to 280 to 290 nm due to the bathochromic shift of a conjugated double bond.

The IR spectra of compounds 4a and 4b showed peaks due to C=O groups close to the lower frequency of keto (>C=O) group, indicating the conjugation of keto group to a >C=C< double bond. On the other hand, compounds 4c, 4d, 4e, and 4f exhibited peaks of C=O of ester groups close to the lower frequency value of ester (C=O) group indicating the conjugation of carbonyl group to a >C=C< double bond.

In the ^{1}H NMR spectra, three 3H singlets for compounds 4a and 4b and two 3H singlets for compounds 4c, 4d, 4e, and 4f represent three and two distinct CH_3- groups, respectively. Of these, the resonances due to the CH_3-O- of 4a, 4b, 4c, and 4d are most deshielded and the allylic hydrogens are less deshielded. On the contrary, allylic hydrogens of 4e and 4f are most deshielded and CH_3- attached to the aromatic ring is less deshielded. There are also two resonances for the N-H protons of the amide groups. The N-H conjugated with a C=C bond has a large δ value compared to the other.

In the ^{13}C NMR spectra, the signals at approximately 114 and 128 ppm were very intense due to the presence of aromatic double bond. Signal appears at approximately 196 ppm for the keto group and at 167 ppm due to the presence of C=O of ester group. Based on these results, the most probable structures of the compounds are depicted in Scheme1 and Table I.

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