Asian Journal of Chemistry; Vol. 27, No. 7 (2015), 2624-2626

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18615

A Green Approach to Synthesize Dihydropyrimidinone Derivatives by Using Anhydrous $ZnCl_2$ Catalyst Under Refluxing Condition in Heptane-Toluene Medium *via* Biginelli Reaction

KAWSARI AKHTER*, KHORSHADA JAHAN, U.K.R. ROMMAN, M. GIASUDDIN AHMED, MD. SHARIFUR RAHMAN and MD. AL-AMIN

Department of Chemistry, University of Dhaka, Dhaka 1000, Bangladesh

*Corresponding author: E-mail: kawsariakhter@yahoo.com

Received: 19 August 2014; *Accepted*: 17 December 2014; *Published online*: 30 March 2015; AJC-17091

Aldehydes, **1a-g** (**1a**, Ar = 4-Cl-C_6H_4, **1b**, Ar = 4-CH_3-C_6H_4, **1c**, Ar = 2-Cl-C_6H_4, **1d**, Ar = 2-CH_3- C_6H_4, **1e**, Ar = -C_6H_5, Ar = 4-Cl- C_6H_4, **1g**, Ar = 2-Cl-C_6H_4) reacted with acetylacetone **2a** and urea/thiourea **3a-b** in the presence of anhydrous zinc chloride under refluxing condition in heptane-toluene medium to give the corresponding 5-aceto-4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine **4a-d** and 5-aceto-4-aryl-6-methyl-2-thio-1,2,3,4-tetrahydropyridimidine **4e-g**. The structure of the compounds **4a-g** were confirmed by their UV, IR, ^{1}H NMR and ^{13}C NMR analysis.

Keywords: Aldehydes, Acetylacetone, Urea/thiourea, Dihydropyrimidinones, Biginelli reaction.

INTRODUCTION

Pyrimidinones or dihydropyrimidinones (DHPMs) and their derivatives has been a subject of considerable interest during the past decades because of their therapeutic and pharmacological properties[1]. Several of them have been found to exhibit a wide spectrum of biological effects[2] including antiviral, antitumor, antibacterial and anti-inflammatory activities. In addition 4-aryl dihydropyrimidinones have emerged as potent calcium channel blockers, antihypertensive, α1a-adrenergic antagonists and neuropeptides antagonists[3]. For example dihydropyrimidines **2**, **3**, **4**, were shown to have antiviral, calcium channel blocking and antihypertensive activity[4], and dihydropyrimidinones (derivatives of 4-(3-hydroxyphe-nyl)-2-thiones) and monastrol, which has excellent anticancer activity[5] as cell permeable lead compounds for the development of new anticancer drugs, that specifically affects cell division (mitosis). Moreover several alkaloids containing the DHPM unit have been isolated from marine natural sources including batzelladine alkaloids, which were found to be potent-HIV gb-120-CD4 inhibitors[6,7]. The classical Biginelli reaction requires long reaction times (20 h) and often suffers from low yields of products in case of substituted aromatic and aliphatic aldehydes[8]. Multi-step synthesis[9] produces somewhat higher yields but lacks the simplicity of original one-pot Biginelli protocol. Hence the Biginelli reaction continues to attract the attention of organic chemists interested in finding milder and more efficient procedures for the synthesis of dihydropyrimidinones. Thus several methods were reported for the synthesis of these compounds[10-16]. Although these methods each have their own merits, they also suffer from the drawbacks with respect to reaction time, cost of reagent and reaction work-ups. Consequently the Biginelli reaction still requires an efficient protocol for the synthesis of pyrimidinone compounds. This prompted us to develop a convenient method for the synthesis of 4-aryl substituted 3,4-dihydropyrimidinones and we report herein the synthesis of 4-aryl substituted 3,4-dihydropyrimidinones *via* Biginelli reaction and cyclocondensation reaction using zinc-chloride as catalyst in *n*-heptane toluene reflux condition (**Scheme-I**). The structures of the compounds were confirmed by their IR and NMR (^{1}H and ^{13}C) data.

EXPERIMENTAL

Thin layer chromatography (TLC) was carried out on plates percolated with silica gel 60 F254 (E. Merck) and spots were detected with iodine vapor. Melting points were determined on an Electro thermal micro melting point apparatus and uncorrected. The UV spectra were recorded using Shimadzu UV-160A spectrophotometer. IR spectra were recorded using Shimadzu IR-470A spectrophotometer. The ^{1}H NMR was taken in DMSO-d_6 and ^{13}C NMR spectra were taken in DMSO with TMS as an internal standard in Bruker 400 MHz spectrophotometer.

General procedure: A mixture of aldehyde **1a-g** (10 mmol), β-dicarbonyl compound **2a** (10 mmol), urea/thiourea **3a-b** (15 mmol) and $ZnCl_2$ (273 mg, 2 mmol) were refluxed

in heptane-toluene medium (30 mL, 1:1) under magnetic stirring for 5 h. Upon completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, poured onto 30 mL water. The resulting solid was filtered under suction and successively washed with H_2O (30 mL) and petroleum ether- EtOAc (5:1,30 mL). The crude product was then purified by recrystallization (acetone-EtOH) to give pure product.

RESULTS AND DISCUSSION

The one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones (**Scheme-I**) was achieved by the three-component condensation of aromatic aldehydes **1a-g**, β-dicarbonyl compounds **2a** and urea, **3a**/thiourea, **3b** in the presence of anhydrous zinc chloride. All of the reactions were performed under refluxing condition in heptane-toluene medium. The structures of **4a-g** were confirmed with the help of their UV, IR, ^{1}H NMR and ^{13}C NMR analysis.

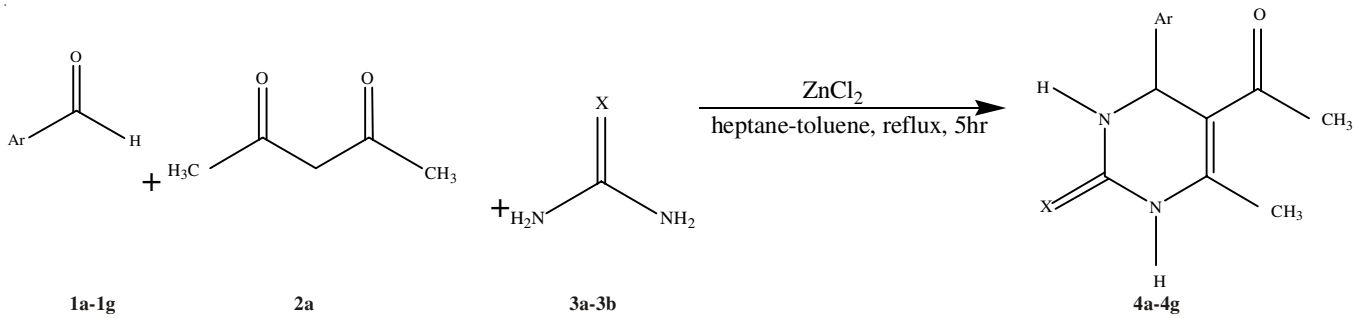
5-Aceto-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine (4a): Yield 84 %; white crystalline solid; m.p. 227-229 °C; R_f value: 0.33 ($CHCl_3$: EtOAc = 1:1); IR (KBr, ν_{max}, cm^{-1}): 3260 (N-H), 3090 (aromatic C-H stretching), 2910 (aliphatic C-H stretching), 1690 (-C=O), 1610, 1455 (C=C stretching of phenyl), 1385 (aliphatic C-H bending), 1010 (C-Cl stretching), 785, 740, 675 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 9.20 (s, 1H, NH, H-1), 7.83 (s, 1H, NH, H-3), 7.27 (d, 2H, *J* = 8.4 Hz, ArH), 7.37 (d, 2H, *J* = 8.4 Hz, ArH), 5.26 (d, 1H, *J* = 3.34, H-4), 2.29 (s, 3H, C<u>H</u>$_3$-CO), 2.12 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 194.11 (CH$_3$-<u>C</u>O), 152.02 (C-2), 148.39, 143.17, 128.28 (C × 2), 128.44 (C × 2) (6C-aromatic), 131.83 (C-5), 109.52 (C-6), 53.09 (C-4), 30.544 (<u>C</u>H$_3$-CO), 18.364 (<u>C</u>H$_3$-C=C).

5-Aceto-4-(4-methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine (4b): Yield 82 %; white solid; m.p. 229-230 °C; R_f value: 0.49 (Neat $CHCl_3$); IR (KBr, ν_{max}, cm^{-1}): 3260 (N-H), 3100 (aromatic C-H stretching), 2980 (aliphatic C-H stretching), 1700 (C=O), 1610, 1455 (C=C stretching of phenyl), 1380 (aliphatic C-H bending), 960, 810, 760 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 9.09 (s, 1H, NH, H-1), 7.72 (s, 1H, NH, H-3), 7.11 (d, 2H, *J* = 8.0 Hz, ArH), 6.99 (d, 2H, *J* = 8.0 Hz, ArH), 5.21 (d, 1H, *J* = 3.34, H-4), 2.26 (s, 3H, C<u>H</u>$_3$-CO), 2.25 (s, 3H, C<u>H</u>$_3$-Ar), 2.07 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 194.57 (CH$_3$-<u>C</u>O), 152.22 (C-2), 148.01, 141.32 , 129.14 (C × 2), 126.43 (C × 2) (6C-aromatic), 136.65 (C-5), 109.72 (C-6), 53.67 (C-4), 30.26 (<u>C</u>H$_3$-CO), 20.70 (<u>C</u>H$_3$-Ar), 18.92 (<u>C</u>H$_3$-C=C).

5-Aceto-4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine (4c): Yield 91 %; white crystalline solid; m.p. 235-237 °C; R_f value: 0.52 (EtOAc); IR (KBr, ν_{max}, cm^{-1}): 3244 (N-H), 3093 (aromatic C-H stretching), 2935 (aliphatic C-H stretching), 1705 (-C=O), 1624, 1462 (C=C stretching of phenyl), 1380 (aliphatic C-H bending), 1047 (C-Cl stretching), 780, 675 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 9.25 (s, 1H, NH, H-1), 7.68 (s, 1H, NH, H-3), 7.40 (d, 1H, *J* = 7.8 Hz, ArH), 7.30-7.20 (m, 3H, ArH), 5.65 (d, 1H, *J* = 2.41, H-4), 2.32 (s, 3H, C<u>H</u>$_3$-CO), 2.02 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 193.79 (C<u>H</u>$_3$-CO), 152.02 (C-2), 148.39, 143.17, 128.40 (C × 2), 127.68 (C × 2) (6C-aromatic), 129.48 (C-5), 108.48 (C-6), 53.09 (C-4), 29.90 (<u>C</u>H$_3$-CO), 18.75 (<u>C</u>H$_3$-C=C).

5-Aceto-4-(2-methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine (4d): Yield 82 %; white solid; m.p. 225-226 °C; R_f value: 0.85 ($CHCl_3$: EtOAc = 4:1); IR (KBr, ν_{max}, cm^{-1}): 3241 (N-H), 3096 (aromatic C-H stretching), 2919 (aliphatic C-H stretching), 1704 (C=O), 1624,1432 (C=C stretching of phenyl), 1332 (aliphatic C-H bending), 1110, 750 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 9.09 (s, 1H, NH, H-1), 7.72 (s, 1H, NH, H-3), 7.11 (d, 2H, *J* = 8.0 Hz, ArH), 6.99 (d, 2H, *J* = 8.0 Hz, ArH), 5.21 (d, 1H, *J* = 3.34, H-4), 2.26 (s, 3H, C<u>H</u>$_3$-CO), 2.25(s, 3H, C<u>H</u>$_3$-Ar), 2.07 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 194.88 (CH$_3$-<u>C</u>O), 145.54 (C-2), 139.94, 131.26, 128.43, 127.20 ,127.04 (C × 2) (6C-aromatic), 134.51 (C-5), 109.90 (C-6), 52.96 (C-4), 29.79 (<u>C</u>H$_3$-CO), 19.76 (<u>C</u>H$_3$-Ar),18.95 (<u>C</u>H$_3$-C=C).

5-Aceto-6-methyl-4-phenyl-2-thio-1,2,3,4-tetrahydropyridimidine (4e): Yield 80 %; white solid; m.p. 230-231 °C; R_f value: 0.49 neat $CHCl_3$; IR (KBr, ν_{max}, cm^{-1}): 3260 (N-H), 3170 (aromatic C-H stretching), 2995 (aliphatic C-H stretching), 1735 (C=O), 1600,1455 (C=C stretching of phenyl), 1370 (aliphatic C-H bending), 1250 (C=S stretching), 935,



1a-1g **2a** **3a-3b** **4a-4g**

Here,

1a, Ar = 4-Cl- C_6H_4
1b, Ar = 4-CH_3- C_6H
1c, Ar = 2-Cl- C_6H_4
1d, Ar = 2-CH_3- C_6H_4
1e, Ar = C_6H_5
1f, Ar = 4-Cl- C_6H_4
1g, Ar = 2-Cl- C_6H_4

3a, X= O
3b, X= S

4a, Ar = 4-Cl- C_6H_4, X = O
4b, Ar = 4-CH_3- C_6H_4, X = O
4c, Ar = 2-Cl- C_6H_4 X = O
4d, Ar = 2-CH_3- C_6H_4 X = O
4e, Ar = -C_6H_5, X = S
4f, Ar = 4-Cl- C_6H_4 X = S
4g, Ar = 2-Cl- C_6H_4 X = S

Scheme-1: Synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones **4a-4d** and 3,4-dihydropyrimidin-2 (1*H*)-thiones **4e-4g**

840, 770 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 10.28 (s, 1H, NH, H-1), 9.75 (s, 1H, NH, H-3), 7.28 (m, 5H, *J* = 8.0 Hz, ArH), 5.31 (d, 1H, *J* = 3.8, H-4), 2.33 (s, 3H, C<u>H</u>$_3$-CO), 2.15 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 194.84 (CH$_3$-<u>C</u>O), 174.12 (C-2), 144.59, 142.93, 128.67 (C × 2), 127.75 (C × 2) (6C-aromatic), 126.59 (C-5), 110.52 (C-6), 53.85 (C-4), 30.45 (<u>C</u>H$_3$-CO), 18.31 (<u>C</u>H$_3$-C=C).

5-Aceto-4-(4-chlorophenyl)-6-methyl-2-thio-1,2,3,4-tetrahydropyridimidine (4f): Yield 86 %; white crystalline solid; m.p. 227-229 °C; R_f value: 0.33 ($CHCl_3$: EtOAc = 1:1); IR (KBr, ν_{max}, cm^{-1}): 3250 (N-H), 3150 (aromatic C-H stretching), 2995 (aliphatic C-H stretching), 1750 (C=O), 1620, 1450 (C=C stretching of phenyl), 1385 (aliphatic C-H bending), 1345 (C=S stretching), 1010 (C-Cl stretching), 820, 765, 640 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 10.33 (s, 1H, NH, H-1), 7.83 (s, 1H, NH, H-3), 7.41 (d, 2H, *J* = 8.2Hz, ArH), 7.25 (d, 2H, *J* = 8.2 Hz, ArH), 5.29 (d, 1H, *J* = 3.34, H-4), 2.33 (s, 3H, C<u>H</u>$_3$-CO), 2.17 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 194.69 (CH$_3$-<u>C</u>O), 174.24 (C-2), 144.95, 141.82, 128.64 (C × 2), 128.45 (C × 2) (6C-aromatic), 132.32 (C-5), 110.38 (C-6), 53.09 (C-4), 30.54 (<u>C</u>H$_3$-CO), 18.36 (<u>C</u>H$_3$-C=C).

5-Aceto-4-(2-chlorophenyl)-6-methyl-2-thio-1,2,3,4-tetrahydropyridimidine (4g): Yield 80 %; white crystalline solid; m.p. 174-175 °C; R_f value: 0.33 ($CHCl_3$: EtOAc = 1:1); IR (KBr, ν_{max}, cm^{-1}): 3399 (N-H), 3173 (aromatic C-H stretching), 3102 (aliphatic C-H stretching), 1745 (-C=O), 1629, 1474 (C=C stretching of phenyl), 1371 (aliphatic C-H bending), 1331 (C=S stretching), 1033 (C-Cl stretching), 781, 759, 612 (C-H bending of aromatic ring); ^{1}H NMR δ (in ppm): 8.39 (s, 1H, NH, H-1), 7.49 (s, 1H, NH, H-3), 7.40 (d, 1H, *J* = 9 Hz, ArH), 7.25 (t, 2H, *J* = 4.2 Hz, ArH), 7.17 (d, 1H, *J* = 7.2Hz, ArH), 5.87 (d, 1H, *J* = 2.4, H-4), 2.40 (s, 3H, C<u>H</u>$_3$-CO), 2.02 (s, 3H, C<u>H</u>$_3$-C=C); ^{13}C NMR δ (in ppm): 195.20 (CH$_3$-<u>C</u>O), 174.32 (C-2), 143.69, 137.31, 128.28 (C × 2), 128.44 (C × 2) (6C-aromatic), 132.59 (C-5), 108.78 (C-6), 53.10 (C-4), 29.50 (<u>C</u>H$_3$-CO), 18.98 (<u>C</u>H$_3$-C=C).

Conclusion

As per literature survey, there are no earlier reports for the synthesis of dihydropyrimidinones using acetylacetone in the presence of zinc chloride catalyst under heptane-toluene reflux condition. This prompted us to develop a method which neither involves the use of any high boiling solvent nor involves the use of costly and environmentally toxic catalyst. As well as the reaction time is very short. Except production of water vapour, the reaction is hundred percent atoms economic and therefore, green in nature.

REFERENCES

1. C.O. Kappe, *Tetrahedron*, **49**, 6937 (1993).
2. C.O. Kappe, D. Kumar and R.S. Varma, *Synthesis*, 1799 (1999).
3. (a) K.S. Atwal, G.C. Rovnyak, B.C. O'Reilly and J. Schwartz, *J. Org. Chem.*, **54**, 5898 (1989); (b) K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg and B.C. O'Reilly, *J. Med. Chem.*, **34**, 806 (1991); (c) G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwartz and M.F. Malley, *J. Med. Chem.*, **35**, 3254 (1992); (d) C.O. Kappe, W.M.F. Fabian and M.A. Semones, *Tetrahedron*, **53**, 2803 (1997); (e) K.S. Atwal, G.C. Rovnyak, S.D. Kimball, D.M. Floyd, S. Moreland, B.N. Swanson, J.Z. Gougoutas, J. Schwartz, K.M. Smillie and M.F. Malley, *J. Med. Chem.*, **33**, 2629 (1990).
4. (a) E.W. Hurst and R. Hull, *J. Med. Pharm. Chem.*, **3**, 215 (1961); (b) H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi and K. Aisaka, *J. Med. Chem.*, **32**, 2399 (1989); (c) G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwartz and M.F. Malley, *J. Med. Chem.*, **35**, 3254 (1992).
5. T.U. Mayer, T.M. Kapoor, S.J. Haggarty, R.W. King, S.L. Schreiber and T.J. Mitchison, *Science*, **286**, 971 (1999).
6. (a) A.D. Patil, N.V. Kumar, W.C. Kokke, M.F. Bean, A.J. Freyer, C.D. Brosse, S. Mai, A. Truneh and B. Carte, *J. Org. Chem.*, **60**, 1182 (1995). (b) B.B. Snider, J. Chen, A.D. Patil and A. Freyer, *Tetrahedron Lett.*, **37**, 6977 (1996).
7. L.E. Overman, M.H. Rabinowitz and P.A. Renhowe, *J. Am. Chem. Soc.*, **117**, 2657 (1995).
8. (a) K. Folkers and T.B. Johnson, *J. Am. Chem. Soc.*, **56**, 1180 (1934). (b) K. Folkers, H.J. Harwood and T.B. Johnson, *J. Am. Chem. Soc.*, **54**, 3751 (1932). (c) P. Wipf and A. Cunningham, *Tetrahedron Lett.*, **36**, 7819 (1995).
9. A.D. Shutalev, E.A. Kishko, N. Sivova and A.Y. Kuznetsov, *Molecules*, **3**, 100 (1998).
10. F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, *Tetrahedron Lett.*, **40**, 3465 (1999).
11. J. Peng and Y. Deng, *Tetrahedron Lett.*, **42**, 5917 (2001).
12. J.S. Yadav, B.V.S. Reddy, K. Bhaskar Reddy, K. Sarita Raj and A.R. Prasad, *J. Chem. Soc., Perkin Trans. 1*, 1939 (2001).
13. (a) E.H. Hu, D.R. Sidler and U.H. Dolling, *J. Org. Chem.*, **63**, 3454 (1998); (b) C. Liu, J. Wang and Y.J. Li, *Mol. Catal. A*, **258**, 367 (2006).
14. Y. Ma, C. Qian, L. Wang and M. Yang, *J. Org. Chem.*, **65**, 3864 (2000).
15. J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.*, **41**, 9075 (2000).
16. B.C. Ranu, A. Hajra and U. Jana, *J. Org. Chem.*, **65**, 6270 (2000).