Indian Journal of Chemistry
Vol. 47B, March 2008, pp. 434-438

An efficient, inexpensive 'Green Chemistry' route to multicomponent Biginelli condensation catalyzed by $CuCl_2.2H_2O$-HCl

Vijai Nath Pathak*[1], Ragini Gupta[2] & Bindu Varshney[1]

[1]Centre for Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur 302 004, India

[2]Department of Chemistry, Malaviya National Institute of Technology, Jaipur 302 017, India

E-mail: pathakvijain@yahoo.com

Received 29 May 2007; accepted (revised) 22 November 2007

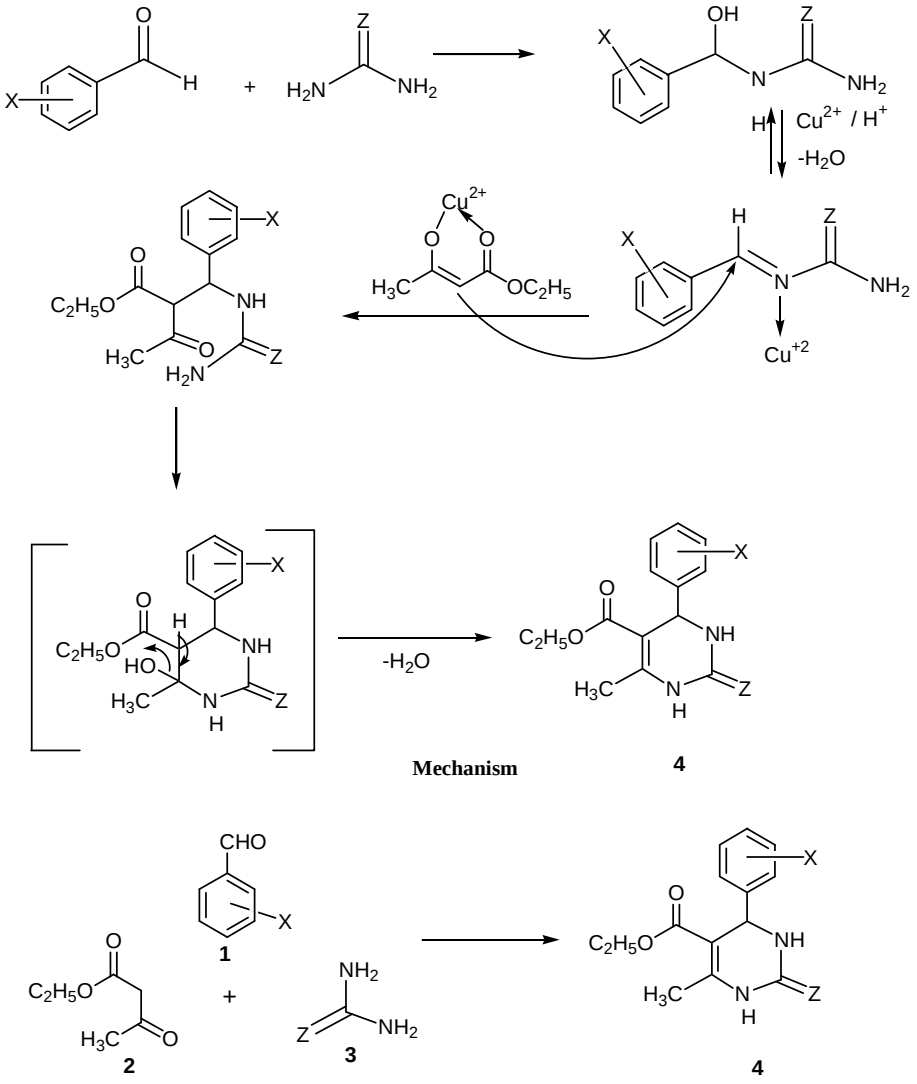
Several Biginelli compounds (dihydropyrimidinones) have been synthesized efficiently and in high yields under mild, solvent-free and eco-friendly conditions by using 'Grindstone Chemistry Technique' catalyzed by $CuCl_2.2H_2O$ and Conc. HCl. The obtained products have been identified by comparison with authentic samples (synthesized by conventional process) and by spectral (^{1}H NMR and IR) data and their melting points.

Keywords: Dihydropyrimidinones, Biginelli condensation, solvent free, Grindstone chemistry, $CuCl_2.2H_2O$-Conc. HCl, Green chemistry

The development of new strategies for the preparation of complex molecules in neat conditions is a challenging area of organic synthesis. For instance, a large number of organic reactions are typically carried out under anhydrous conditions, using volatile organic solvents like benzene, which are the cause of environmental problems and are also potentially carcinogenic. Hence, it is required to develop safe, practical and environment friendly processes. The pioneering work of Toda *et al*.[1] has shown that many exothermic reactions can be accomplished in high yield by just grinding solids together using mortar and pestle, a technique known as 'Grindstone Chemistry' which is one of the 'Green Chemistry Techniques'. Reactions are initiated by grinding, with the transfer of very small amounts of energy through friction[2]. In addition to being energy efficient Grindstone Chemistry also results in high reactivity and less waste products.

This work focuses on the synthesis of Biginelli compounds, or (DHPM's) using the 'Grindstone Technique'. DHPM's have always remained in the forefront due to their therapeutic and pharmacological properties[3]. As early as in 1930 simple derivatives were patented as agents for the protection of wool against moths[4]. Later, there was development of nitractin, which showed excellent activity against the viruses of the trachoma group[5-7] and also exhibited antibacterial activity. DABOs, d_4T, 3-TC, AZT, batzelladine β-alkaloids, showed a potent and selective activity against HIV-I[8]. Parlato *et al.*[9] synthesized various dihydropyrimidinone derivatives by modification of the substituents in virtually all the six positions of the pyrimidine nucleus which provided with interesting activity against HIV, ASFV, Sendai virus and Rubella virus. Besides these, substituted pyrimidine derivatives have been used as antihypertensive agents, anticancer agents (Monastrol), antimalarial agents, antiinflammatory agents and also used as calcium channel blockers, neuropeptide γ-antagonists and α-1a-antagonists[10].

Biginelli condensation is an important 'Multicomponent Reaction' for the construction of DHPM's. Traditional Biginelli reactions were conducted under strongly acidic conditions which suffer from poor yields and long reaction duration, especially in the case of substituted aromatic and aliphatic aldehydes. This has led to the development of several new synthetic methodologies which improved the yields compared to the original procedure. These new strategies involve the combinations of Lewis acids and/or transition metal salts *e.g.* BF_3-OEt_2, montmorillonite (KSF), polyphosphate esters and reagents like $InCl_3$ (ref. 11), LiBr (ref. 12), TMSCl/NaI (ref. 13), $LaCl_3.7H_2O$ (Ref. 14), $CeCl_3.7H_2O$ (ref. 15), $Mn(OAc)_3.2H_2O$ (ref. 16), InBr (ref. 17), $FeCl_3$ and HCl (ref. 18), ytterbium triflate[19], Iodine (ref. 20), $ZnCl_2$ (ref. 21), $CoCl_2$ (ref. 22), *etc.*



Scheme I-Reagents and conditions: $CuCl_2.2H_2O$, conc. HCl, grinding

Although, many Lewis acids and transition metal salts have been found to catalyze this reaction, they still have limitations like high cost, limited availability, prolonged reaction duration and the use of strong acids. Therefore, search for a milder and more efficient protocol for the synthesis of dihydropyrimidinone continues to draw the attention of researchers.

Results and Discussion

The current method not only preserved the 'one-pot' protocol of Biginelli condensation but also favours environmentally benign reaction conditions of saving energy consumption. To optimize the amount of catalyst requirement and maximum product yield, various molar ratios of catalyst were tried. The best yields were obtained when the catalyst used was 40 mol% (**Scheme I**). No improvement in yields was observed even by increasing the amounts of catalyst. After completion of the reaction (indicated by TLC) the reaction-mixture was poured into ice-cold water. The precipitate so obtained was filtered, dried and recrystallized from ethanol. This method works well with various functional groups such as Cl, NO_2, OH, OCH_3 *etc*., which establishes the general utility of the procedure. It worked well with aromatic aldehydes possessing either an electron-donating or electron-withdrawing group. Comparing the results shown in **Table I** it is seen that high yields are obtained (85-94%) which is much better as compared to the previous literature[23,24]. Thiourea has been used with similar success to provide the corresponding dihydro-

Table I — Physical characterization data of compounds **4a-j**

Compd	X	Z	Yield (%)	m.p. (°C) Found (Reported)
4a	H	O	95	208-10 (209-10)(Ref. 26)
4b	4-Cl	O	89	209-11 (213-15)(Ref. 27)
4c	4-F	O	94	183-85 (183-85)(Ref. 28)
4d	4-NO_2	O	93	209-10 (209-10)(Ref. 28)
4e	H	S	85	209 (208-10) (Ref. 28)
4f	4-Cl	S	86	193 (192-94) (Ref. 28)
4g	4-F	S	91	192-94 (193-94) (Ref. 29)
4h	4-NO_2	S	89	107-09 (109-11) (Ref. 30)
4i	3-OCH_3, 4-OCH_3, 5-OCH_3	O	92	216-18 (217-19) (Ref. 31)
4j	3-OCH_3, 4-OCH_3, 5-OCH_3	S	94	222-23 (224) (Ref. 32)

Note: Satisfactory C, H, N analyses were observed.

Table II — Spectroscopic characterization data of dihydropyrimidinones **4**

Compd	^{1}H NMR (δ ppm, $CDCl_3$)
4a	9.17(s, N*H*, 1H), 7.68 (s, N*H*, 1H), 7.18-7.28 (m, Ar-*H*, 5H), 5.18 (d, *J* = 3.3 Hz, C*H*, 1H), 4.01 (q, *J* = 7.0 Hz, O$CH_2$$CH_3$, 2H), 2.29 (s, CH_3, 3H), 1.27 (t, *J* = 7.0 Hz, OCH_2CH_3, 3H)
4b	10.33 (s, N*H*, 1H), 9.64 (s, N*H*, 1H), 7.17-7.35 (m, Ar-*H*, 5H), 5.12 (d, *J* = 3.3 Hz, C*H*, 1H), 4.00 (q, *J* = 7.0 Hz, O$CH_2$$CH_3$, 2H), 2.28 (s, CH_3, 3H), 1.09 (t, *J* = 7.0 Hz, OCH_2CH_3, 3H)
4c	10.31 (s, N*H*, 1H), 9.61 (s, N*H*, 1H), 7.19-7.31 (m, Ar-*H*, 5H), 5.10 (d, *J* = 3.3 Hz, C*H*, 1H), 4.01 (q, *J* = 7.0 Hz, O$CH_2$$CH_3$, 2H), 2.27 (s, CH_3, 3H), (t, *J* = 7.0 Hz, OCH_2CH_3, 3H)
4d	9.35 (s, N*H*, 1H), 7.84 (s, N*H*, 1H), 8.23-7.47 (m, Ar-*H*, 4H), 5.23 (d, *J* = 3.3 Hz, C*H*, 1H), 3.92 (q, *J* = 7.0 Hz, O$CH_2$$CH_3$, 2H), 2.21 (s, CH_3, 3H), 1.06 (t, *J* = 7.0 Hz, OCH_2CH_3, 3H)
4e	10.27 (s, N*H*, 1H), 9.61 (s, N*H*, 1H), 7.29-7.36 (m, Ar-*H*, 5H), 5.21 (d, *J* = 3.3 Hz, C*H*, 1H), 4.01 (q, *J* = 7.0 Hz, O$CH_2$$CH_3$, 2H), 2.31 (s, CH_3, 3H), 1.12 (t, *J* = 7.0 Hz, OCH_2CH_3, 3H)
4i	8.25 (s, N*H*, 1H), 6.56 (s, Ar-*H*, 2H), 6.31 (s, N*H*, 1H), 5.31 (d, *J* = 3.3 Hz, C*H*, 1H), 4.10 (q, *J* = 7.0 Hz, 2H, O$CH_2$$CH_3$), 3.83 (s, 3*O$CH_3$, 9H), 2.36 (s, CH_3, 3H), 1.26 (t, *J* = 7.0 Hz, OCH_2CH_3, 3H)

pyrimidin-2(*1H*)-thiones in high yields, which are also of much interest with regard to biological activity.

The present research work from this group has shown that commercially available cupric chloride dihydrate ($CuCl_2.2H_2O$) along with a few drops of conc. HCl is a mild water soluble Lewis acid which functions as a highly efficient catalyst for Biginelli condensation. Further, use of cupric chloride obviates anhydrous conditions. To the best of the knowledge, there is no report on its use in the synthesis of di-hydropyrimidinones using 'Grindstone Chemistry Technique'.

In this communication, is exemplified a simple but effective modification of the Biginelli reaction that produces high yields of dihydropyrimidinones using catalytic amounts of $CuCl_2.2H_2O$ and 5-6 drops of conc. HCl simply by grinding the components together. This technique is superior to the existing methods, since, grinding does not require solvents leading to safe and environmental friendly synthesis. Furthermore, the proposed technique does not require external heating or cooling at any stage, leading to energy efficient synthesis providing high yields of products. A mixture of aromatic aldehyde **1**, ethyl acetoacetate **2**, urea/thiourea **3**, $CuCl_2.2H_2O$ and a few

drops of conc. HCl are ground together in a mortar using pestle for nearly 5 min to give the desired products **4** (**Table I; 4a-j**). A catalytic amount of $CuCl_2.2H_2O$ and friction created by grinding is sufficient to push the Biginelli reaction forward. (**Scheme I**). This process worked well with aromatic aldehydes possessing either an electron-donating or electron-withdrawing group. No solvent is required except for product purification by recrystallization.

In the plausible mechanism catalyzed by $CuCl_2.2H_2O$ and HCl, the initial step is the formation of imine. The Cu^{2+} ion co-ordinates with the nitrogen atom of imine to give an intermediate complex which activtates the C=N bond towards nucleophile. Further, complexation of β-ketoester with Cu^{2+} ion increases the nucleophilicity of α-carbon of enolate, facilitating the attack on imine carbon. Attack of free amidic group to β-carbonyl carbon, results in the formation of six-membered heterocyclic intermediate which on dehydration gives the desired DHPM's. This is in harmony with the mechanism proposed by Kappe *et al*[25].

Experimental Section

All the melting points were determined in open glass capillary tubes and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer 557 grating infrared spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on Jeol AL 300 spectrometer (300 MHz) using $CDCl_3$ as a solvent. TMS was used as internal standard (chemical shift in δ, ppm). The homogeneity of the compounds was checked by TLC using silica gel-G as adsorbent, UV light or iodine accomplished visualisation. Esters, aldehydes, urea and thiourea were all commercial products and were used as received. All liquid reagents were distilled before use. The physical and analytical characterization data are given in **Table I** and **Table II**.

General procedure for the synthesis of dihydropyrimidinones: A mixture of an aromatic aldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea/thiourea (20 mmol), $CuCl_2.2H_2O$ (5 mmol) and few drops (5-6 drops) of Conc. HCl was ground together for 2-5 min using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidifies within 5-20 min. The solid mass was left overnight, then washed with cold water and purified by recrystallization from ethanol. The obtained products were identified by comparison with authentic samples (synthesized by conventional process) and from their spectral (^1H NMR and IR) data and their melting points.

Conclusion

It was found that $CuCl_2.2H_2O$ works as an excellent catalyst for the one-pot three component and solvent-free syntheses of dihydropyrimidinones. This procedure is simpler (preserving the 'one-pot' synthesis), economical, milder, faster, and is also consistent with the green chemistry theme since no solvent is needed and affords excellent yields.

Acknowledgements

One of the authors (Bindu Varshney) is grateful to the University Grants Commission (UGC), New Delhi for award of fellowship. Authors are also thankful to Dr. K.P. Madhusudanan, Deputy Director and Head, SAIF, Central Drug Research Institute (CDRI), Lucknow for providing elemental analyses and spectral data and the Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur for extending laboratory facilities and IR and NMR data.

References

1 Toda F, Tanaka K & Sekikawa A, *J Chem Soc, Chem Commun*, **1987**, 279.
2 Bose A K, Pednekar S, Ganguly S N, Chakraborty G & Manhas S M, *Tetrahedron Lett*, 45, **2004**, 8351.
3 Kappe C O, Kumar D & Varma R S, *Synthesis*, **1999**, 1799.
4 Hentrich W & Schepss W (I. G. Farbenindustrie) DRP **1930**, 547, 057; *Fortsch Teerfarbenfabr Verw Industriezweige*; edited by Friedlander E 25, **1932**, 2590.
5 Hull R (ICI Ltd.) *Brit Patent* **1965**, 984, 365; *Chem Abstr*, 62, **1965**, 13159f.
6 Hurst E W & Hull R, *J Med Pharm Chem*, 3, **1961**, 215.
7 Hurst E W, *Ann N Y Acad Sci*, 98, **1962**, 275.
8 Patil A D, Kumar N V, Kokke W C, Bean M F, Freyer A J, DeBrosse C, Mai S, Truneh A, Faulkner D J, Carte B, Breen A L, Hertzberg R P, Johnson R K, Westley J W & Potts B C M, *J Org Chem*, 60, **1995**, 1182.
9 Parlato M C, Mugnaini C, Renzulli M L, Corelli F & Botta M, *Arkivoc*, 5, **2004**, 349.
10 (a) Atwal K S, Rovnyak G C, O' Reilly B C & Schwartz J, *J Org Chem*, 54, **1989**, 5898; (b) Kappe C O, Fabian W M F & Semones M A, *Tetrahedron*, 53, **1997**, 2803.
11 Ranu B C, Hajra A & Jana U, *J Org Chem*, 65, **2000**, 6270.
12 Partha P B, Sunil G, Dipak P & Jagir S S, *Chem Lett*, 10, **2002**, 1038.
13 Sabitha G, Kiran Kumar Reddy G S, Srinivas Reddy Ch & Yadav J S, *Synlett*, **2003**, 858.
14 Lu J, Bai Y, Wang Z, Yang B & Ma H, *Tetrahedron Lett*, 41, **2000**, 9075.
15 Subhas Bose D, Fatima Liyakat & Hari Babu M, *J Org Chem*, 68, **2003**, 587.
16 Kumar K A, Kasthuraiah M, Reddy C S & Reddy C D, *Tetrahedron Lett*, 42, **2001**, 7873.

17 Martins A P M, Teixeira M V M, Cunico W, Scapin E, Mayer R, Pereira C M P, Zanatta N, Bonacorso H G, Peppe C & Yuan Y-F, *Tetrahedron Lett*, 45, **2004**, 8991.

18 Lu J & Ma H, *Synlett*, 1, 2000, 63.

19 Ma Y, Qian C, Wang L & Yang M, *J Org Chem*, 65, **2000**, 3864.

20 Bhosale R S, Bhosale S V, Bhosale S V, Wang T & Zubaidha P K, *Tetrahedron Lett*, 45, **2004**, 9111.

21 Xue S, Shen Y C, Li Y L, Shen X M & Guo Q X, *Chin J Chem*, 20, **2002**, 385.

22 Narsaiah AV, Basak A K & Nagaiah K, *Synthesis*, 8, **2004**, 1253.

23 Balalaie S, Arabanian A & Hashtroudi M S, *Monatshefte fur Chemie*, 131, **2000**, 945.

24 Kappe C O, *Acc Chem Res*, 33, **2000**, 879.

25 Kappe C O, *J Org Chem*, 62, **1997**, 7201.

26 Sun Q, Wang Y-Q, Ge Z-M, Cheng T-M & Li R-T, *Synthesis*, 7, **2004**, 1047.

27 Hu E H, Sidler D R & Dolling U H, *J Org Chem*, 63, **1998**, 3454.

28 Afzal Md P & Jayshankar V P, *Indian J Heterocyclic Chemistry*, 14, **2005**, 261.

29 Zhu Yulin, Pan Yuanjiang & Huang Shenlin, *Synth Commun*, 34, **2004**, 3167.

30 Wang Ji-Tao & Peppe Clovis, *Tetrahedron*, 58, **2002**, 4801.

31 Singh K, Singh J, Deb Prasant K & Singh H, *Tertrahedron*, 55, **1999**, 12873.

32 Bozsing D, Sohar P, Gigler G & Kovacs G, *Eur J Med Chem Chim Ther*, 31, **1996**, 663.