Int. J. Chem. Sci.: 6(4), 2008, 1876-1881

IRON (III) CATALYZED BIGINELLI-LIKE THREE COMPONENT CYCLOCONDENSATION REACTION: EFFICIENT SYNTHESIS OF NOVEL 5-SUBSTITUTED 3, 4-DIHYDROPYRIMIDIN-2(1*H*)-ONES

NAINESH N. KANSAGARA, JAGDISH N. GODHASRA, MAHESH C. PATEL and VIRAL R. SHAH*

Department of Chemistry, Kamani Science College, AMRELI – 365601 (Guj.) INDIA

ABSTRACT

The Biginelli reaction, a one-pot condensation of aryl aldehyde, urea and β-dicarbonyl compounds are efficiently catalyzed by iron (III) in acetonitrile to afford the corresponding novel 5-substituted 3, 4-dihydropyrimidin-2-(1*H*)-ones **(2a–i)** in high yields. The first Biginelli-like reactions of urea, aryl aldehydes and ketones were furnished important to synthesize new 3, 4-dihydropyrimidin-2-(1*H*)-ones derivatives suitable for further study. The newly synthesized compounds have been characterized by elemental analysis, IR, ^{1}H NMR and MS spectral data. Some of these compounds showed potential antimicrobial activity.

Key words : Iron (III), Biginelli reaction, Dihydropyrimidines, Antimicrobial activity.

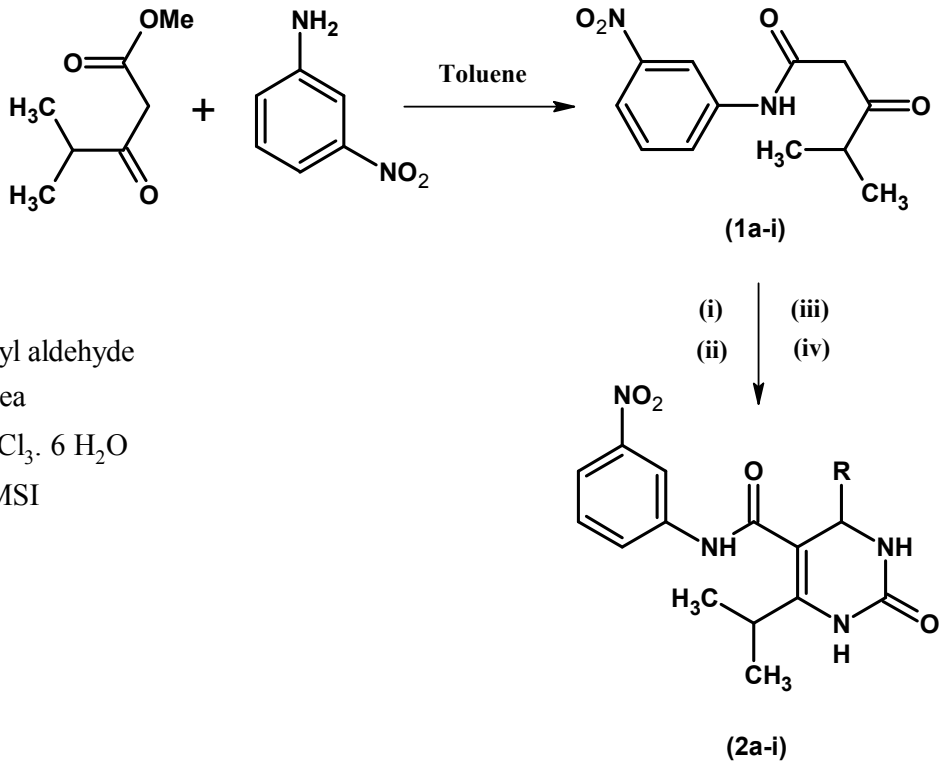
INTRODUCTION

However, in the past decade, the Biginelli reaction has attracted widespread attention because many dihydropyrimidinones and their derivatives have been found to possess various biological activities[1-7] and can be widely used as calcium channel blockers, antihypertensive agents and α-antagonists[8, 9]. In general, Biginelli reactions are simple one-pot but low-yielding condensations of β-dicarbonyl compounds, aldehydes and urea with strong acids and it has been reported that Lewis acids (such as $BF_3.OEt_2$)[10] in combination with transition metals and a proper proton source were effective catalyst for this reaction. Dihydropyrimidinones were also synthesized by using various protic acids such as HCl[11] and AcOH[12] under microwave irradiation. More recently, propane phosphonic acid anhydride[13], ionic liquids[14], montmorillonite KSF[15], polyphosphate ester(PPE)[16] and

* Author for correspondence; E-mail: naineshkansagara@yahoo.co.in

lanthanide triflate[17] as catalysts for the one-pot solvent-free synthesis of dihydro pyrmidinones have also been reported. However, many of these reagents or catalysts are expensive, harmful and difficult to handle especially on a large scale.

Normally it requires prolonged reaction time and high temperature with moderate yield and hence, there has been considerable interest to explore mild, rapid and higher yielding protocol at ambient temperature. In continuation of interest in the use of Lewis acid catalyst or reagent and our interest in the preparation of new 3, 4-dihydropyrimidin-2-(1*H*)-one derivatives, an attempt has been made for the extension of this versatile reaction to other substrates.



(i) Aryl aldehyde
(ii) Urea
(iii) $FeCl_3$. 6 H_2O
(iv) TMSI
R- Aryl

Scheme 1

EXPERIMENTAL

The melting points were determined by using capillary method and are uncorrected. The IR spectra were recorded on a Simadzu FTIR -8400 instrument in KBr pellets and peaks are defined (cm^{-1}). ^1H NMR spectra were recorded on a Bruker

spectrometer 400 MHz using TMS as an internal standard and chemical shift were measured in δ ppm. Mass spectrum was recorded on a Jeol D-300 spectrometer. The purity of compounds was checked by TLC. All the synthesized compounds gave satisfactory elemental analysis as recorded on a Carlo Erba 1108 Analyzer.

General procedure for the preparation of 4-aryl-6-isopropyl-5-[N-(m-nitro phenyl) amino carbonyl]-3, 4-dihydro pyrimidine-2(1*H*)-ones (2a-i)

A mixture of urea 1.2 g (0.02 mol), aryl aldehyde (0.01 mol), 4-methyl-N-(3-nitrophenyl)-3-oxopentanamide 2.50g (0.01 mol), $FeCl_3.6H_2O$ 0.27g (0.001 mol) and TMSI 0.44 g (0.002 mol) in 25 mL of acetonitrile was refluxed for 10 hrs. The solution was allowed to stand for 1 h at room temperature. The reaction mass poured into chilled water and solid product was filtered and dried. The product was recrystallized from isopropyl alcohol.

The physical data of all synthesized compounds are recorded in Table 1.

Table 1. The physical data of all synthesized compounds (2a-i)

Compd.	R	Mol. formula	mp (°C)	Yield (%)	Nitrogen (%) Calcd (Found)
2a	C_6H_5-	$C_{20}H_{20}N_4O_4$	>250	65	14.73 (14.76)
2b	4-OCH_3-C_6H_4-	$C_{21}H_{22}N_4O_5$	240	68	13.65 (13.62)
2c	3, 4-$(OCH_3)_2$-C_6H_3	$C_{22}H_{24}N_4O_6$	131	74	13.52 (13.55)
2d	4-OH-C_6H_4-	$C_{20}H_{20}N_4O_5$	220	72	14.14 (14.20)
2e	2-OH-C_6H_4-	$C_{20}H_{20}N_4O_5$	192	74	14.14 (14.12)
2f	4-F-C_6H_4-	$C_{20}H_{19}FN_4O_4$	202	81	14.07 (14.10)
2g	4-Cl-C_6H_4-	$C_{20}H_{19}ClN_4O_4$	155	85	13.52 (13.40)
2h	2-Cl-C_6H_4-	$C_{20}H_{19}ClN_4O_4$	200	73	13.52 (13.50)
2i	3-Br-C_6H_4-	$C_{20}H_{19}BrN_4O_4$	102	80	12.20 (12.18)

The spectral data of the compound 4-(4-methoxy phenyl)-6-isopropyl-5-[N-(m-nitro phenyl) amino carbonyl]-3, 4-dihydropyrimidine-2(1H)-one are given below :

IR (KBr disc) cm^{-1} : 1677 (C=O Str.), 3306 (Amide NH Str.), 3285 (Pyrimidine

NH Str.), 1500 (C=C Str.), 2977 (CH_3 Str.), 3077 (Aromatic ring Str.).

^{1}H NMR (DMSO-d_6) δ ppm : 1.54 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 3.68 (m, 1H, CH), 3.79 (s, 3H, OCH_3) 4.96 (d, 1H, Chiral-H, J = 4Hz)

4-Methoxy aromatic ring - 6.83 – 6.85 and 7.24 – 7.26 (double doublet, 4H, Ar H, J = 8.6Hz)

3-Nitro aromatic ring - 7.49-7.53(t, 1H, Ar-H5), 7.90-7.93(d, 1H, Ar-H6, J = 8.1), 8.05-8.07 (d, 1H, Ar-H4, J = 8.2), 8.60 (s, 1H, Ar-H2), 7.71-7.72 (s, 1H, NH CO), 9.74-9.75 (d, 1H, NH near chiral center, J = 3.04Hz), 7.173 (s, 1H, -NH near isopropyl).

MS m/z value : 410, 395, 380, 293, 273, 245 and 204.

RESULTS AND DISCUSSION

In the present work, we have synthesized 3, 4-dihydropyrimidin-2(1H)-ones by iron (III) catalyzed cyclocondensation of aryl aldehyde, β-dicarbonyl compounds and urea **(Scheme 1)**. It represents an excellent example of the utility of one-pot multiple component condensation reaction. In the primary study, we have used $FeCl_3.6\ H_2O$[18] as a catalyst in this reaction and get products with low yield. However, the addition of TMSl accelerated the Biginelli-like reaction and gave good results. For example, the TMSl mediated Biginelli-like reaction of β-dicarbonyl compound, aryl aldehyde and urea gave corresponding product in high yields. The role of TMSl is not completely understood, it may be explained in terms of hard–soft acid, which activates the carbonyl group (ketone)[19].

Antimicrobial screening

The antimicrobial activity was carried out by using the cup-plate agar diffusion method[20] by measuring the zone of inhibition in millimeter. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strain such as *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli* and Fungi *Aspergillus niger* using dimethyl sulfoxide solvent at 40 μg concentration. Standard drugs like amoxicillin, benzyl penicillin, ciprofloxacin, erythromycin and griseofulvin were used for comparison purpose.

The screening data indicated that among dihydropyrimidin-2-(1H)-one derivatives tested compounds **2c**, **2d**, **2g** and **2i** showed greater degree of antibacterial activity against *S. aureus*. However, the compounds **2b**, **2c**, **2d**, **2f**, **2g**, **2h** and **2i** showed greater degree of

antibacterial activity against *B. subtilis*, The compounds **2a**, **2b**, **2e**, **2f**, **2i** and **2c**, **2d**, **2f**, **2h** showed greater degree of antibacterial activity against *E. coli* and *P. aeruginosa*, respectively. The compounds **2a**, **2b**, **2c**, **2e** and **2i** showed greater degree of antifungal activity against *A. niger*.

ACKNOWLEDGEMENTS

The authors are thankful to Principal and Head, Chemistry Department of Kamani Science College, Amreli for providing laboratory facilities and we are also thankful to Department of Chemistry, Saurashtra University, Rajkot for MS spectral analysis. Authors are also thankful to RSIC, Chandigarh for providing ^{1}H NMR spectral analysis of the compounds.

REFERENCES

1. C. O. Kappe, Eur J. Med. Chem., **35**, 1043–1052 (2000).
2. A. O. Bryzgalov, M. P. Dolgikh, I. V. Sorokina, T. G. Tolstikova, V. F. Sedova and O. P. Shkurko, Bioorg. Medi. Chem. Lett., **16**, 1418-1420 (2006).
3. B. Schnell, U. T. Strauss, P. Verdino, K. Faber and C. O. Kappe, Tetrahedron, Asymmetry, **11,** 1449-1453 (2000).
4. R. Garg and D. Patel, Bioorg. Medi. Chem. Lett., **15**, 3767-3770 (2005).
5. C. Blackburn, B. Guan and J. Brown, Bioorg. Medi. Chem. Lett., **16**, 3504-3509 (2006).
6. K. S. Atwal, B. N. Swanson, S. E. Unger and D. M. Floyd, J. Med. Chem., **34**, 806 (1991).
7. D. Russowsky, F. S. Romulo, Bioorg. Chem., **34**, 173-182 (2006).
8. K. S. Atwal, G. C. Rovnyak, B. C. O'reilly and J. Schwartz, J. Org. Chem., **54**, 5898–5907 (1989).
9. C. O. Kappe, W. M. F. Fabian and M. A. Semones, Tetrahedron, **53**, 2803–2816 (1997).
10. E. H. Hu, D. R. Sidler and U. H. Dolling, J. Org. Chem., **63**, 3454–3457 (1998).
11. R. Gupta, A. K. Gupta, S. Paul and P. L. Kachroo, Ind. J. Chem., **34b**, 151 (1995).
12. J. S. Yadav, B. V. S. Reddy, E. J. Reddy and T. J. Ramalingam, Chem. Res. (S) **7**, 354 (2000).

13. F. L. Zumpe, M. Flüß, K. Schmitz and A. Lender, Tetrahedron Letters, **48**, 1421-1423 (2007).

14. J. Peng and Y. Deng, Tetrahedron Lett., **42**, 5917 (2001).

15. F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, Tetrahedron Lett., **40**, 3465 (1999).

16. C. O. Kappe, D. Kumar and R. S. Varma, Synthesis, **10**, 1799 (1999).

17. M. Yun, Q. Changtao, W. Limin and Y. Min, J. Org. Chem., **65**, 3864–3868 (2000).

18. Li-Wen Xu, Zong-Ting Wang, Chun-Gu Xia, Lyi Li and Pei-Qing Zhao, Helv. Chimi. Acta, **87**, 2608 (2004).

19. E. Nakamura, S. Matsuzawa and I. Kuwajima, Tetrahedron Lett., **27**, 4092 (1986),

20. P. Ho Lee, H. Ahn, K. Lee, Sun-Young Sung and S. Kim, Tetrahedron Lett., **42**, 37 (2001).

21. A. L. Barry, the Antimicrobial Susceptibility Test, Principle and Practices, I. Les and Febiger (Eds.) Philadelphia Pa, Usa (1976) P. 180 Biol Abstr, **64**, 25183 (1976).

Accepted : 01.11.2008