Catal Lett (2008) 122:310–313
DOI 10.1007/s10562-007-9377-1

Chloroferrate(III) Ionic Liquid: Efficient and Recyclable Catalyst for Solvent-free Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

Xiaofen Chen · Yanqing Peng

Received: 13 November 2007 / Accepted: 29 November 2007 / Published online: 12 December 2007

Abstract A water-tolerant Lewis acidic ionic liquid, [bmim][$FeCl_4$], was found to be an efficient and recyclable catalyst in the synthesis of 4-aryl-dihydropyrimidinones through Biginelli condensation. This method is capable of being scaled up, if desired.

Keywords Biginelli reaction · Dihydropyrimidinones · Ionic liquid · Lewis acid · Green chemistry

1 Introduction

4-Aryl-dihydropyrimidinones (DHPMs) and their derivatives occupy an important place in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties. They have emerged as the integral backbones of several calcium channel blockers [1], antihypertensive drugs [2], α_{1a}-adrenergic antagonists [3] and neuropeptide antagonists [4]. Recently, dihydropyrimidinones have been considered as a new lead for the development of new anticancer drugs [5]. Thus, efficient synthesis of this heterocyclic nucleus has been of great interest in recent years.

The Biginelli reaction, first described more than a century ago and recently reviewed [6], is the most straightforward procedure towards dihydropyrimidine derivatives, involves one-pot three-component condensation of β-dicarbonyl compounds with aldehydes and (thio)ureas under strongly acidic conditions. The formation of title compounds is usually carried out in the presence of a wide range of Brønsted acids (e.g. alcoholic HCl [7], dry acetic acid [8], boric acid [9], amidosulfonic acid [10], tangstophosphoric acid [11] and HBF_4 [12]) and Lewis acids including $FeCl_3$ [13], $LaCl_3$ [14], $CeCl_3$ [15], $ZrCl_4$ [16], $InBr_3$ [17], $InCl_3$ [18], $Cu(OTf)_2$ [19], $Bi(OTf)_3$ [20], $Yb(OTf)_3$ [21], $Ag_3PW_{12}O_{40}$ [22], $CuCl_2/CuSO_4$ [23], CuI [24], $Bi(NO_3)_3$ [25] and so on. However, in spite of their potential utility, most of the reported catalysts suffer from significant drawbacks, such as poor recyclability after work-up procedures. In view of this, there is a need to develop greener methodology for Biginelli reaction.

Room temperature ionic liquids have received a good deal of attention in recent years due to their polar nature, phase behavior, and lack of vapour pressure [26]. Ionic liquids, e.g. [bmim]BF_4 [27], TMGT (1,1,3,3-tetrmethylguanidinium trifluoroacetate) [28] and sulfonic-functionalized ionic liquid [29], were found to be excellent catalysts for Biginelli reaction. Recently, imidazolium chloroferrates [bmim][$FeCl_4$] has been introduced as a new series of Lewis acidic ionic liquids in organic synthesis [30]. These molten salts are reasonably air and moisture stable and are capable of dissolving a wide range of organic compounds.

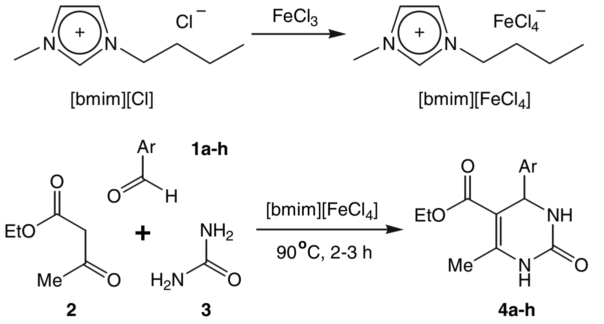
Herein we wish to report a novel [bmim][$FeCl_4$] catalyzed Biginelli reaction applied to one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions, which is not only operationally simple and high-yielding but also safe to scale up (Scheme 1).

2 Experimental

Products obtained are all known compounds and were identified by comparing of their physical and spectra data

---

X. Chen · Y. Peng (✉)
Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science & Technology, Shanghai 200237, P.R. China
e-mail: yqpeng@ecust.edu.cn



Scheme 1

with those reported in the literature. Melting points were measured on a BÜCHI B-540 apparatus and uncorrected. IR spectra were recorded on a Nicolet Nexus 470 spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on Bruker AV 400 spectrometer in DMSO-d_6 with TMS as internal standard. The catalyst, [bmim][$FeCl_4$], was prepared following the procedure reported in the literature [30c] from commercially available butylmethylimidazolium chloride and $FeCl_3 \cdot 6H_2O$.

2.1 General Procedure

A mixture of aldehyde (10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.72 g, 12 mmol) and chloroferrate(III) ionic liquid [bmim][$FeCl_4$] 0.34g (10%mol) was heated with stirring at 90 °C for an appropriate time (Table 3). On completion of reaction (TLC), the solidified reaction mixture was cooled, crushed, and washed with 90% aqueous methanol (3 mL). Crude product thus obtained was collected by filtration and further purified by recrystallization from hot ethanol to afford pure 3,4-dihydropyrimidin-2(1*H*)-ones. The filtrate was concentrated to recover [bmim][$FeCl_4$] which could be reused in the next run.

2.2 Selected Spectral Data

4b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 9.116 (s, 1H, NH), 7.636 (s, 1H, NH), 7.135 (d, $J = 8.4$ Hz, 2H, ArH), 6.860 (d, $J = 8.4$ Hz, 2H, ArH), 5.073 (s, 1H, Ar–CH), 3.965 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.705 (s, 3H, OCH_3), 2.223 (s, 3H, CH_3), 1.089 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3) ppm. IR (KBr): ν_{max} 3,237, 3,111, 2,940, 1,717, 1,699, 1,643, 1,506, 1,446 cm^{-1}.

4g: ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 9.342 (s, 1H, NH), 8.133–8.069 (m, 2H, ArH), 7.877 (s, 1H, NH), 7.694–7.644 (m, 2H, ArH), 5.289 (s, 1H, Ar–CH), 3.983 (t, $J = 6.5$ Hz 2H OCH_2), 2.260 (s, 3H, CH_3), 1.085 (t, $J = 6.9$ Hz, 3H, OCH_2CH_3) ppm. IR (KBr): ν_{max} 3,318, 3,103, 2,955, 1,706, 1,687, 1,617, 1,521 cm^{-1}.

3 Results and Discussion

Initially, the ionic liquid [bmim][$FeCl_4$] was obtained as a dark brown liquid by simply grind crystalline $FeCl_3 \cdot 6H_2O$ with commercially available 1-methyl-3-butyl-imidazolium chloride at room temperature [30c]. With this catalyst in hand, we first investigated the model reaction of ethyl acetoacetate (10 mmol), benzaldehyde (10 mmol) and urea in order to optimize the reaction conditions (reaction time: 2 h). Firstly, the reaction was carried out in the presence of 10 mol% of [bmim][$FeCl_4$] using different amount of urea (Table 1, Entry 1–5). Slight improvement in yield was observed when the amount of urea was increased from 1 to 1.2 equiv. but the similar yields were observed with further increment of urea up to 2 equiv. Hence, 1.2 equiv. of urea (based on benzaldehyde) in the reaction mixture was ideal for achieving the balance between efficiency and economy. In order to find the optimum catalyst-substrate ratio, the model reaction was carried out in the presence of different amount of catalyst, resulting in the isolation of **4a** in 88, 90, 91, and 91% yield respectively (Table 1, Entry 2, 6–8). Higher amount of the catalysts did not improve the result to a greater extent. Thus, 10% mol [bmim][$FeCl_4$] was chosen in followed investigations. It is worthy to note that a control experiment without the catalyst, using the same reagents and conditions, afforded 43% yield of desired product (Table 1, Entry 9).

Reusability of the catalyst was next checked by the model reaction under optimized condition. Indeed, the catalytic activity of chloroferrate(III) ionic liquid is comparable to its parent salt $FeCl_3$ in Biginelli condensation. It is worthy to note that, however, the chloroferrate(III) ionic liquid is much robust and water-tolerant in comparison with ferric chloride, especially in the presence of hot

Table 1 Optimization of reaction conditions (reaction time: 2 h)

Entry	Urea (mmol)	Catalyst (mmol)	Yield (%)
1	10	1	88
2	12	1	90
3	15	1	91
4	17	1	91
5	20	1	90
6	12	0.5	88
7	12	1.5	91
8	12	2	91
9	12	0	43

Table 2 Reusability of the catalyst

Run	1	2	3	4	5	6
Yield (%)	90	85	89	92	92	90

Table 3 [bmim][$FeCl_4$]-catalyzed synthesis of 4-aryl-dihydropyrimidinones

Entry	Ar	Product	Time (h)	Yield (%)	Mp (°C) (Obs.)	Mp (°C) [reference]
1	C_6H_5	**4a**	2	90	209–211	209–210 [31]
2	4-CH_3O–C_6H_4	**4b**	2	90	208–209	208–209 [32]
3	4-CH_3–C_6H_4	**4c**	2	92	216–218	215–216 [17]
4	4-Cl–C_6H_4	**4d**	2	91	216–218	214–216 [33]
5	3-Br–C_6H_4	**4e**	2	85	195–196	185–186 [13]
6	3,4-(CH_2OCH_2)–C_6H_3	**4f**	2	83	186–188	187–188 [34]
7	3-NO_2–C_6H_4	**4g**	3	68	232–234	229–231 [35]
8	2,4-Cl_2–C_6H_3	**4h**	3	71	251–253	248–250 [36]

water. This feature is superior over many metal–salt Lewis acids and facilitates the recovery and reuse procedures. After work-up procedure, the catalyst [bmim][$FeCl_4$] remaining in the filtrate (90% aqueous methanol) can be recovered by removing the solvent through heating and then drying under vacuum for 1 h. As shown in Table 2, the catalytic ionic liquid could be reused at least five successive runs for the synthesis of **4a** without significant loss of activity. The yields remained around 90% clearly illustrate the reusability of the solvent.

To study the generality of this process, several examples illustrating this method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones were studied. Aromatic aldehydes containing electron-donating as well as withdrawing groups afford satisfactory to excellent yields of corresponding products (Table 3). Most aromatic aldehydes carrying either electron-donating (**4b** 90%, **4c** 92%, and **4f** 83% yield) or electron-withdrawing (**4d** 91%, and **4e** 85% yield) substituents all reacted very well, giving excellent yields.

In comparison with classical Lewis acidic ionic liquid such as [bmim][$AlCl_4$], the advantages of [bmim][$FeCl_4$] involve hydrolytic stability, reduced oxophilicity and good solvating ability. From the environmental viewpoints, [bmim][$FeCl_4$] is superior over ionic liquids such as [bmim][BF_4] in some aspects. Firstly, ferric (or ferrous) salts are accepted as environmentally friendly materials. Secondly, in contrast to [bmim][BF_4], chloroferrate ionic liquids were synthesized from [bmim]Cl and $FeCl_3$ in 100% atom economy, without any waste salt stream. In addition, [bmim][$FeCl_4$] is much less corrosive than Brønsted acidic ionic liquid reported in the literature [29].

4 Conclusion

In conclusion, we have developed a simple, high-yielding, time-saving method for the Biginelli dihydropyrimidinones synthesis using chloroferrate(III) ionic liquid as catalyst under solvent-free reaction conditions. The method offers several advantages including good yields, simple experimental workup procedure, facile recovery and reuse of catalyst, which makes it a useful process for the synthesis of dihydropyrimidinones.

Acknowledgments Financial support for this work from the National Basic Research Program of China (2003CB114402), National Key Technology R&D Program of China (2006BAE01A01-8), and Shanghai Educational Committee are gratefully acknowledged.

References

1. Rovnyak GC, Kimball SD, Beyer B, Cucinotta G, Dimarco JD, Gougoutas J, Hedberg A, Malley M, McCarthy JP, Zhang R, Moreland S (1995) J Med Chem 38:119
2. Rovnyak GC, Atwal KS, Hedberg A, Kimball SD, Moreland S, Gougoutas J, O'Reilly BC, Schwartz J, Malley M (1992) J Med Chem 35:3254
3. Sidler DR, Larsen RD, Chartrain M, Ikemoto N, Roberge CM, Taylor CS, Li W, Bills GF (1999) PCT Int Appl WO 99 07695
4. Bruce MA, Pointdexter GS, Johnson G (1998) PCT Int Appl WO 98 33791
5. Mayer TU, Tapoor TM, Haggarty SJ, King RW, Schreiber SL, Mitchison TJ (1999) Science 286:971
6. Kappe CO (1993) Tetrahedron 49:6937
7. Gupta R, Gupta AK, Paul S, Kachroo PL (1995) Indian J Chem, Sect B 34B:151
8. Yadav JS, Reddy BVS, Reddy EJ, Ramalingam T (2000) J Chem Res (S) 354
9. Tu S, Fang F, Miao C, Jiang H, Feng Y, Shi D, Wang X (2003) Tetrahedron Lett 44:6153
10. Li J-T, Han J-F, Yang J-H, Li T-S (2003) Ultrason Sonochem 10:119
11. Amini MM, Shaabani A, Bazgir A (2006) Catal Commun 7:843
12. Chen W, Qin S, Jin J (2007) Catal Commun 8:123
13. Lu J, Ma H (2000) Synlett 63
14. Lu J, Bai Y, Wang Z, Yang B, Ma H (2000) Tetrahedron Lett 41:9075
15. Bose DS, Fatima L, Mereyala HB (2003) J Org Chem 68:587
16. Reddy ChV, Mahesh M, Raju PVK, Babu TR, Reddy VVN (2002) Tetrahedron Lett 43:2657
17. Fu N-Y, Yuan Y-F, Cao Z, Wang S-W, Wang J-T, Peppe C (2002) Tetrahedron 58:4801
18. Ranu BC, Hajra A, Jana U (2000) J Org Chem 65:6270
19. Paraskar AS, Dewkar GK, Sudalai A (2003) Tetrahedron Lett 44:3305
20. Varala R, Alam MM, Adapa SR (2003) Synlett 67
21. Ma Y, Qian C, Wang L, Yang M (2000) J Org Chem 65:3864

22. Yadav JS, Reddy BVS, Sridhar P, Reddy JSS, Nagaiah K, Lingaiah N, Saiprasad PS (2004) Eur J Org Chem 552
23. Gohain M, Prajapati D, Sandhu JS (2004) Synlett 235
24. Kalita HR, Phukan P (2007) Catal Commun 8:179
25. Banik BK, Reddy AT, Datta A, Mukhopadhyay C (2007) Tetrahedron Lett 48:7392
26. Welton T (1999) Chem Rev 99:2071
27. Peng J, Deng Y (2001) Tetrahedron Lett 42:5917
28. Shaabani A, Rahmati A (2005) Catal Lett 100:177
29. Fang D, Luo J, Zhou X, Ye Z, Liu Z (2007) J Mol Catal A: Chem 274:208
30. (a) Valkenberg MH, deCastro C, Hölderich WF (2001) Appl Catal A 215:185. (b) Alexander MV, Khandekar AC, Samant SD (2004) J Mol Catal A: Chem 223:75. (c) Bica K, Gaertner P (2006) Org Lett 8:733
31. Badaoui HE, Bazi F, Tamani S, Boulaajaj S, Zahouily M, Lazrek HB, Sebti S (2005) Synth Commun 35:2561
32. Bose AK, Pednekar S, Ganguly SN, Chakraborty G, Manhas MS (2004) Tetrahedron Lett 45:8351
33. Foroughifar N, Mobinikhaledi A, Jirandehi HF (2003) Phosphorus Sulfur Silicon Relat Elem 178:495
34. Folkers K, Harwood HJ, Johnson TB (1932) J Am Chem Soc 54:3751
35. Fu NY, Yuan YF, Cao Z, Wang SW, Wang JT, Peppe C (2002) Tetrahedron 58:4801
36. Khodaei MM, Salehi P, Zolfigol MA, Sirouszadeh S (2004) Pol J Chem 78:385