Res Chem Intermed (2013) 39:1335–1342
DOI 10.1007/s11164-012-0689-4

A novel amino acid functionalized ionic liquid promoted one-pot solvent-free synthesis of 3,4-dihydropyrimidin-2-(1H)-thiones

Parasuraman Karthikeyan · Sythana Suresh Kumar · Aswar Sachin Arunrao · Muskawar Prashant Narayan · Pundlik Rambhau Bhagat

Received: 26 April 2012 / Accepted: 12 June 2012 / Published online: 11 July 2012

Abstract An environmentally benign, cheap and reusable L-amino acid functionalized ionic liquid [L-AAIL]/$AlCl_3$ was found to be an effective catalyst for the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-thione derivatives in good to excellent yield under solvent-free condition. Compared with the classical Biginelli reactions, this method consistently enjoys the advantages of mild reaction conditions, easy work-up, and short reaction time. These one-pot three-component Biginelli products could be separated easily from the catalyst–water system, and the catalyst could be reused at least five times without noticeably reducing catalytic activity.

Keywords Amino acid · Ionic liquid · Thiourea · Reflux

Introduction

Due to the importance of dihydropyrimidinones (DHPMs) as valuable synthons, pharmaceuticals, or precursors, a couple of methods to prepare these compounds have been developed, with the Biginelli reaction gaining particular attention, especially in the last few years [1]. Furthermore, these compounds have emerged as the integral backbones of several calcium-channel blockers. Some marine alkaloids containing the dihydropyrimidine core unit have interesting biological properties: batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors. Recently, DHPMs have been considered as a new lead for the development of new anticancer drugs.

In 1893, Italian chemist Pietro Biginelli [2] reported the simplest and the most straightforward approach to preparation of DHPMs involves a one-pot

P. Karthikeyan · S. S. Kumar · A. S. Arunrao · M. P. Narayan · P. R. Bhagat (✉)
Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore 632 014, Tamilnadu, India
e-mail: drprbhagat111@gmail.com

three-component acid-catalyzed condensation, which is still one of the most often used multi-component reactions. But this Biginelli type reaction suffers from harsh conditions, long duration with organic solvents, low yields, and low purity, and thus this topic continues to attract the attention of researchers seeking a milder and more efficient procedure and efficient catalysts for the synthesis of DHPMs.

In recent years, several synthetic procedures for the preparation of DHPMs have been made to improve and modify this reaction. These include assistance $FeCl_3$-supported nanopore silica [3], ferric perchlorate [4], polyoxometalate [5], transition metals containing halides [6–8], amino acids [9–12], and polymers [13–16] have been used, and the search for new, readily available, and green catalysts is still being actively pursued.

Currently, ionic liquids attract much interest as environmentally benign catalysts or as excellent alternatives to organic solvents, because of their favorable properties, for example, negligible volatility and high thermal stability. Moreover, the past few years, a variety of catalytic reactions have been successfully conducted using ILs as solvents. Task-specific ionic liquids (TSILs) have also been used as catalysts for the Biginelli reaction [17]. Peng and Deng [18] synthesized DHPMs in $BMImBF_4$, Shaabani and Rahmati [19] used the room-temperature ionic liquid 1,1,3,3-tetra methyl guanidinium trifluoroacetate as catalyst, Li et al. [20] reported an ionic liquid (BMImSac) as catalyst, Zheng et al. [21] used $CMImHSO_4$ as catalyst for a Biginelli-type reaction, and Chen and Peng [22] found the Lewis acidic ionic liquid [bmim][$FeCl_4$] to be an efficient catalyst for synthesis of DHPMs. And, moreover, TSILs are those incorporating functional groups designed to exhibit particular properties or reactivates; in recent years, TSILs have attracted considerable attention [23]. Davis et al. reported on TSILs in which the cations were both intrinsically Brønsted acidic and nonvolatile. This was done by covalently tethering an alkane sulfonic acid group to the IL cation [24]. Such sulfonic acid-based TSILs were used simultaneously as solvent and catalyst for Fischer esterification [25], dehydrodimerization of alcohols [26], pinacol–benzopinacol rearrangements [27], and electrophilic substitution of indoles with aldehydes [28]. To the best of our knowledge of the open literature, Biginelli-type reactions catalyzed by amino acid fictionalized ionic liquid [L-AAIL]/$AlCl_3$ (Fig. 1) have not been reported (Scheme 1).

Results and discussion

Initially, the condensation reaction was carried out in absence of any catalyst and solvent. It was found that no product formed. This shows that the catalyst was

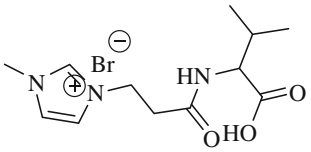
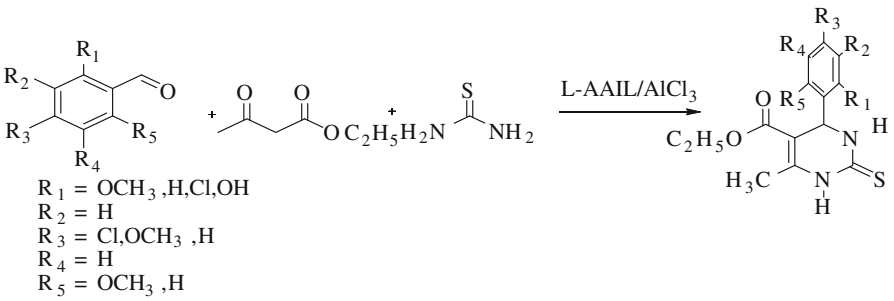


Fig. 1 Molecular structure of 3-(3-(1-carboxy-2-methylpropylamino)-3-oxopropyl)-1-methyl-1H-imidazol-3-ium bromide (L-AAIL)



Scheme 1 Synthesis of 3,4-dihydropyrimidin-2(1-H)-thiones using L-AAIL/ALCl$_3$

necessary for this reaction (Table 1, entry 1). The substrates in the given mole proportion were condensed using L-AAIL/AlCl$_3$ in the absence of solvent for different times at room temperature. It was observed that the formation of the product increases with time duration. This indicates that the catalyst was necessary for the condensation reaction (Table 1, entries 2–6). Subsequently, the effect of temperature on the rate of condensation was studied. The temperature of the reaction was gradually increased from room temperature to 80 °C. The effect of temperature was clearly distinct on the rate of condensation, enhancing it with temperature. The product formation was most desirable at 80 °C in 6 h (Table 1, entries 7–11).

Finally, the effect of the duration of the reaction on the yield of the product was studied at 80 °C by variation of time for the same condensation and also with

Table 1 Optimization reaction using L-AAIL/AlCl$_3$

Sample no.	Catalyst	Solvent	Temperature (0 °C)	Time (h)	Yield (%)
1	NIL	Nil	RT	24	7
2	L-AAIL/AlCl$_3$	Nil	RT	6	30
3	L-AAIL/AlCl$_3$	Nil	RT	8	35
4	L-AAIL/AlCl$_3$	Nil	RT	10	43
5	L-AAIL/AlCl$_3$	Nil	RT	12	45
6	L-AAIL/AlCl$_3$	Nil	RT	24	51
7	L-AAIL/AlCl$_3$	Nil	40	12	70
8	L-AAIL/AlCl$_3$	Nil	50	12	74
9	L-AAIL/AlCl$_3$	Nil	60	12	77
10	L-AAIL/AlCl$_3$	Nil	70	12	80
11	L-AAIL/AlCl$_3$	Nil	80	6	94
12	L-AAIL/AlCl$_3$	Nil	80	5	88
13	L-AAIL/AlCl$_3$	Nil	80	4	87
14	L-AAIL/AlCl$_3$	Nil	80	2	86
15	L-AAIL/AlCl$_3$	Nil	90	2	89
16	L-AAIL/AlCl$_3$	Nil	100	2	95

Reaction conditions: aldehyde (10.0 mmol), β-dicarbonyl compound (10.0 mmol), thiourea (12.0 mmol) and L-AAIL/AlCl$_3$ (0.05 mmol), 80 °C under solvent-free conditions

increases in temperature from 80 to 100 °C. It was found that there was not much appreciable change in yield even when the reaction was carried for 2 h and at higher temperature (Table 1, entries 12–16). With the optimized conditions, the derivatives of the 3,4-dihydropyrimidine-2(1-H)-thione were synthesized using L-AAIL/$AlCl_3$. The formation of the product was confirmed by characterization of the representative compound.

In order to test the substrate generality of [L-AAIL]/$AlCl_3$ catalyzed 3,4-dihydropyrimidin-2(1-H)-thiones, the condensation of various aldehyde with ethyl acetoacetate and thiourea were studied under the optimized conditions. The results are summarized in Table 2. It can be noticed that a wide range of aldehyde can efficiently contribute in the Biginelli reaction. However, the benzaldehyde-bearing electron-withdrawing substituents furnished the Biginelli reaction with excellent yields. On the other hand, longer reaction times were required for aldehyde containing an electron-donating group to give comparatively inferior yields. This can be explained by the electron-withdrawing groups improving the electrophilicity of the carbonyl carbons aldehyde, which facilitates the reaction, while electron-donating groups reduce the electrophilicity.

Reusability of the catalyst was next checked by the model reaction under optimized condition. Indeed, the catalytic activity of L-AAIL/$AlCl_3$ is comparable to its parent salt $FeCl_3$ in Biginelli condensation. It is worth noting, however, that the L-AAIL/$AlCl_3$ are much moe robust and water-tolerant in comparison with ferric chloride, especially in the presence of hot water. After work-up procedure, the catalyst L-AAIL/$AlCl_3$ remaining in the filtrate can be recovered by removing the water through heating and then drying under vacuum for 1 h. As shown in Table 3, the catalytic ionic liquid could be reused at least five successive runs for the synthesis of dihydrohydropyridimin-2(1-H)-thiones without significant loss of activity. The yields remained around 86–75 % clearly illustrate the reusability of the catalysts (Table 3).

The above experiments throw some light on the mechanism with the L-AAIL/$AlCl_3$ catalyst. Even though a detailed mechanistic scheme is not yet known, the reaction is catalyzed most likely by L-AAIL/$AlCl_3$ cation of the ionic liquid complex. From that above mechanism, we can observe that addition of the carbanion takes place in the form of a Michael addition. Here, we notice that L-AAIL act as both the Brønsted acid and base (Scheme 2).

Conclusion

In conclusion, we have described an efficient protocol for the Biginelli reaction catalyzed by the functionalized ionic liquid, L-AAIL/$AlCl_3$. The methodology has the advantages of short reaction time, lack of organic solvent, and easy work-up for isolation of the products in good yield with high purity. The reusability of this novel catalyst gave good yield even after being used five times. All these characteristics make this protocol applicable for an industrial purpose.

Table 2 Derivative of Biginelli reaction in presence of L-AAIL/$AlCl_3$

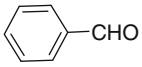
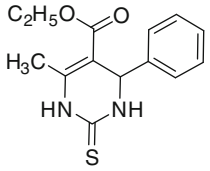
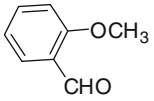
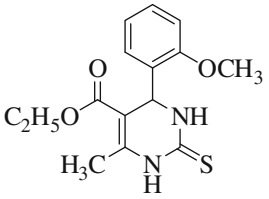
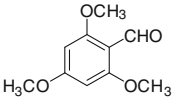
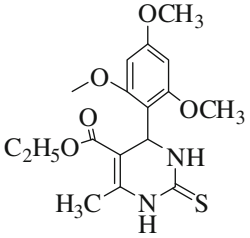
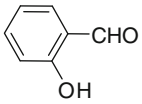
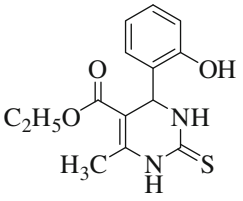
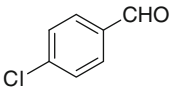
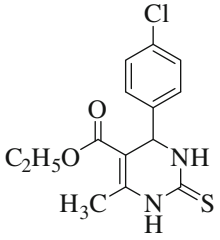
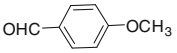
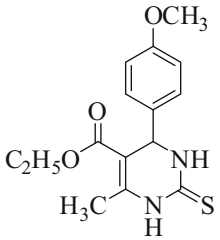
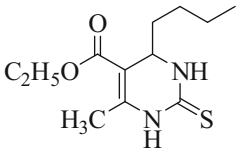
Sample no.	Reactant	Product	Yield (%)	MP (°C)
1			85	208–212
2			88	189–193
3			95	226–228
4			95	182–188
5			89	180–185

Table 2 continued

Sample no.	Reactant	Product	Yield (%)	MP (°C)
6			98	150–156
7	n-$CH_3CH_2CH_2CHO$		96	165–169

Reaction conditions: aldehyde (10.0 mmol), β-dicarbonyl compound (10.0 mmol), thiourea (12.0 mmol) and L-AAIL/$AlCl_3$ (0.05 mmol), 80 °C under solvent-free conditions

Table 3 Recycling of L-AAIL/$AlCl_3$ system for the one-pot three-component synthesis of dihydrohydropyridimin-2(1-H)-thiones

Entry	Cycle	Conversion (%)	Yield (%)
1	0	100	86
2	1	100	84
3	2	95	81
4	3	92	77
5	4	88	75

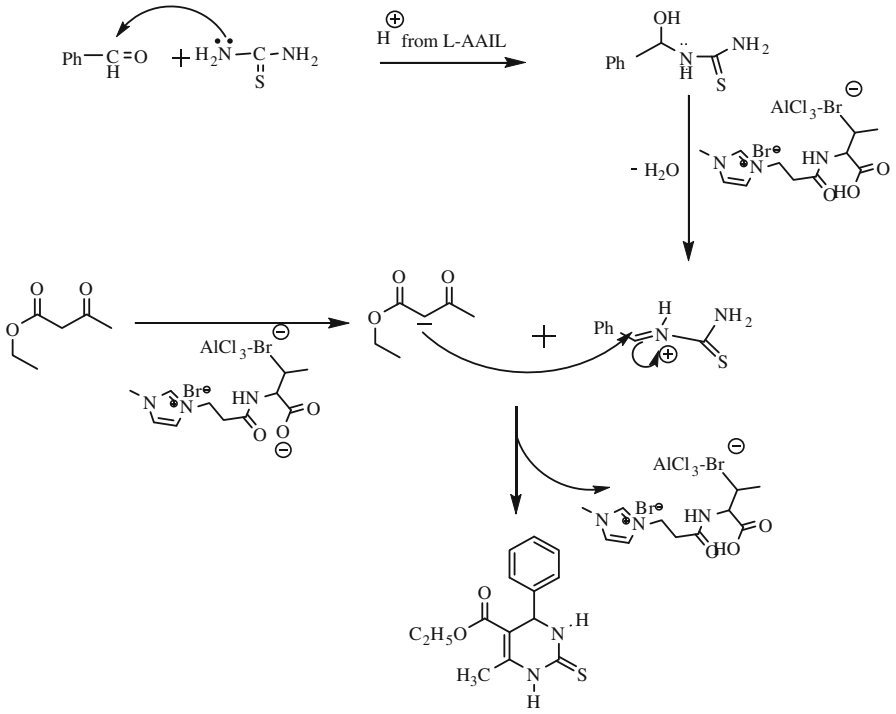
Reaction conditions: aldehyde (10.0 mmol), β-dicarbonyl compound (10.0 mmol), thiourea (12.0 mmol) and L-AAIL/$AlCl_3$ (0.05 mmol), 80 °C under solvent-free conditions

Materials and methods

Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and reported uncorrected. ^{1}H NMR spectra were recorded on Bruker (500 MHz) and mass spectra were recorded on JEOL GC MATE II HR-MS (EI) spectrometer. FT-IR was recorded on AVATRA 330 Spectrometer with DTGS detector. All solvents and chemicals were commercially available and used without further purification unless otherwise stated.

Preparation of catalysts (L-AAIL)

A mixture of Boc-valine (11.0 mmol) and triethyl amine (22.0 mmol) in DMF was cooled in an ice-bath. The 1-carboxy ethyl-3-methyl imidazolium bromide



Scheme 2 Tentative mechanism for the L-AAIL/$AlCl_3$ catalyzed 3,4-dihydropyrimidin-2(1-H)-thiones

[Cemim]Br (10.0 mmol) was added and agitation continued at ambient temperature for 24 h. After completion of the reaction, the mixture was extracted with ether and poured into water. The unreacted Boc-valine was removed by centrifugation. The aqueous layer was concentrated using a rotary evaporator and the ionic liquid was dried under vacuum at 70 °C for 6 h. The Boc-3-(3-(1-carboxy-2-methylpropylamino)-3-oxopropyl)-1-methyl-1H-imidazol-3-ium bromide was deprotected using 50 % TFA in dichloromethane (5 mL) for 1 h at 25 °C. After evaporation of the solvent from the mixture, TFA was removed by triturating the residue with 5 mL of methanol (saturated with ammonia). The resulting mixture was concentrated using rotary evaporator, and the ionic liquid 3-(3-(1-carboxy-2-methylpropylamino)-3-oxopropyl)-1-methyl-1H-imidazol-3-ium bromide (L-AAIL) was dried under vacuum 80 °C 3 h. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.9 (d, 6H), 1.8 (m, 1H), 2.4 (d, 2H), 3.4 (s, 3H), 4.3 (s, 1H), 5.2 (s, 2H), 6.8 (d, 1H), 7.2 (d, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 10.2 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.97, 23.02, 36.56, 54.45, 65.96, 127.93, 128.30, 128.90, 140.65, 177.01, 184.35. Microanalytical data: Cal (C: 43.13; N: 12.57; H: 6.03), found: (C: 43.09; N: 12.54; H: 5.99).

A typical experimental procedure for Biginelli type reaction

Aldehyde (10.0 mmol), β-dicarbonyl compound (10.0 mmol), thiourea (12.0 mmol), and L-AAIL/$AlCl_3$ (0.05 mmol) were successively charged into a 100-mL

round-bottomed flask with a magnetic stirring bar. Then, the reaction proceeded at 80–100 °C in oil bath for 2–6 h, while the product formation was monitored by TLC. After the completion of the reaction, the resulting solid product was poured into ice-cold water followed by addition of chloroform (3 × 5 mL). Then, the organic layer was separated, dried over anhydrous Na_2SO_4, and the chloroform was removed under reduced pressure to get the solid product. The resulting product was recrystallized to get white pure crystals with little amount of ethanol.

Data for representative product

Ethyl 1,2,3,4-tetra hydro-4-(4-methoxy phenyl)-6-methyl-2-thioxo pyrimidine-5-carboxylate: ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.047–7.069 (d, $J = 8.8$ MHz, 2H), 6.821–6.843 (d, $J = 8.8$ MHz, 2H), 10.229 (s, 1H), 9.539 (s, 1H), 3.656 (s, 3H), 5.038 (s, 1H), 3.907–3.960 (q, $J = 21.2$ MHz 2H), 1.020–1.056 (t, $J = 14.4$ MHz, 3H), 2.216 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.66, 165.13, 158.70, 144.70, 135.66, 127.57, 113.85, 100.94, 59.51, 55.06, 53.40, 18.51, 17.09. HR-MS (ESI): 306.4066.

Acknowledgments We gratefully acknowledge the management of VIT University for providing the required facilities and SAIF (IITM) for providing the spectral data.

References

1. C.O. Kappe, Tetrahedron **49**, 6937 (1993)
2. P. Biginelli, Gazz. Chim. Ital. **23**, 360 (1893)
3. B.J. Ahn, M.S. Gang, K. Chae, Y. Oh, J. Shin, W. Chang, J. Ind. Eng. Chem. **14**, 401 (2008)
4. X.L. Zhang, Y.P. Li, C.J. Liu, J.D. Wang, J. Mol. Catal. A **253**, 207 (2006)
5. J.T. Li, J.F. Han, J.H. Yang, T.S. Li, Ultrason. Sonochem. **10**, 119 (2003)
6. M.M. Heravi, F.K. Behbahani, H.A. Oskooie, Chin. J. Chem. **26**, 2203 (2008)
7. R. Fazaeli, S. Tangestaninejad, H. Aliyan, M. Moghadam, Appl. Catal. A **309**, 44 (2006)
8. C. Liu, J. Wang, Y. Li, J. Mol. Catal. A **258**, 367 (2006)
9. D.S. Bose, L. Fatima, H.B. Mereyala, J. Org. Chem. **68**, 587 (2003)
10. H. Zhang, Z. Zhou, Z. Xiao, F. Xu, Q. Shen, Tetrahedron Lett. **50**, 1622 (2009)
11. E. Rafiee, F. Shahbazi, J. Mol. Catal. A **250**, 57 (2006)
12. M. Gohain, D. Prajapati, J.S. Sandhu, Synlett. **2**, 235 (2004)
13. P. Salehi, M. Dabiri, M.A. Zolfigol, M.A.B. Fard, Tetrahedron Lett. **44**, 2889 (2003)
14. Y.L. Zhu, S.L. Huang, J.P. Wan, L. Yan, Y.J. Pan, A. Wu, Org. Lett. **8**, 2599 (2006)
15. D. Shobha, M.A. Chari, K.H. Ahn, Chin. Chem. Lett. **20**, 1059 (2009)
16. B. Ahmed, R.A. Khan, K.M. Habibullah, Tetrahedron Lett. **50**, 2889 (2009)
17. D. Fang, D.Z. Zhang, Z.L. Liu, Monatsh. Chem. **141**, 419 (2010)
18. J.J. Peng, Y.Q. Deng, Tetrahedron Lett. **42**, 5917 (2001)
19. A. Shaabani, A. Rahmati, Catal. Lett. **100**, 177 (2005)
20. M. Li, W.S. Guo, L.R. Wen, Y.F. Li, H.Z. Yang, J. Mol. Catal. A **258**, 133 (2006)
21. R.W. Zheng, X.X. Wang, H. Xu, J.X. Du, Synth. Commun. **36**, 1503 (2006)
22. X. Chen, Y. Peng, Catal. Lett. **122**, 310 (2008)
23. J.H. Davis, A. Wierzbicki, *Proceedings of the Symposium on Advances in Solvent Selection and Substitution for Extraction*, New York, 2000
24. A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes, J.H. Davis, J. Am. Chem. Soc. **124**, 5962 (2002)
25. J.H. Davis, Chem. Lett. **33**, 1072 (2004)
26. D.C. Forbes, K.J. Weaver, J. Mol. Catal. A **214**, 129 (2004)
27. H.P. Zhu, F. Yang, J. Tang, M.Y. He, Green Chem. **5**, 38 (2003)
28. D.G. Gu, S.J. Ji, Z.Q. Jiang, M.F. Zhou, T.P. Lo, Synlett. **7**, 959 (2005)