Arabian Journal of Chemistry (2012) **5**, 485–488

King Saud University

**Arabian Journal of Chemistry**

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

# An efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by molten $[Et_3NH][HSO_4]$

**Hojatollah Khabazzadeh, Esmat Tavakolinejad Kermani *, Tayebeh Jazinizadeh**

*Department of Chemistry, Shahid Bahonar University of Kerman, 76169 Kerman, Iran*

Received 29 August 2010; accepted 15 September 2010
Available online 19 September 2010

**KEYWORDS**

Triethylammonium hydrogen sulfate;
Ionic liquid;
3,4-Dihydropyrimidin-2(1H)-one;
Biginelli reaction

**Abstract** A simple ammonium salt of sulfuric acid in molten state was used as a cheap and mild acidic ionic liquid for efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones in good to excellent yields.



## 1. Introduction

Evolution of clean and environmentally benign chemical processes using less hazardous catalysts has become a primary goal in synthetic organic chemistry.

Ionic liquids have attracted considerable interest as environmentally friendly or "green" alternatives to conventional molecular organic solvents because they have very low vapor pressure and are non-explosive and thermally stable in a wide temperature range (Sheldon, 2005). Now ionic liquids have been used as environmentally benign solvents or catalysts for a number of chemical processes (Suarez, 2002), such as separations (Esser et al., 2004), reactions (Sheldon, 2001), homogeneous two phase catalysis (Carmichael et al., 1999), and polymerizations (Carlin and Wilkes, 1990). The current emphasis on alternative reaction media is motivated by the need for efficient methods for replacing toxic or hazardous solvents and catalysts. The use of ionic liquids as alternative reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem (Olah et al., 2005).

Notwithstanding the unique advantages of ionic liquids as reaction media and catalysts, currently they have not been widely applied in industry. The reason for this is probably related to the high cost of ionic liquids, the difficulty in separation or recycling, the paucity of data with regard to their toxicity and biodegradability, and so on. Recently, some new ionic liquids have been prepared via a simple and atomeconomic acid–base neutralization reaction. For example, Noda et al. reported the preparation and application of the Brønsted acid–base ionic liquids from imidazole and bis(trifluoromethanesulfonyl) amide (Noda et al., 2003). Han et al. prepared new ionic liquids by neutralization of 1,1,3,3-tetramethylguanidine with different acids (Gao et al., 2004). However, the preparation of simple ammonium ionic liquid via acid–base

* Corresponding author. Tel./fax: +98 341 322 2033.
E-mail address: etavakoly@yahoo.com (E.T. Kermani).



Peer-review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.09.015

Production and hosting by Elsevier

neutralization from cheap amine and acid is absent in the literature. After the announcement of the first industrial process involving ionic liquids by BASF (BASIL11 process) in 2003 the potential of ionic liquids for new chemical processes and technologies is beginning to be recognized.

3,4-Dihydropyrimidin-2-(1H)-ones (Biginelli products) are very important heterocyclic motifs in the realm of natural and synthetic organic chemistry due to their interesting biological and pharmacological activities such as antitumour, antibacterial, antiviral and anti-inflammatory activities (Kappe, 2000). Previously different derivatives of 3,4-dihydropyrimidin-2-(1H)-ones have exhibited calcium channel modulators, $\alpha_{1a}$-antagonists and neuropeptide Y (NPY) antagonist (Atwal et al., 1991). Several alkaloids have been isolated from marine sources which contain the dihydropyrimidine core unit. Most notable among these are the batzelladine alkaloids which were recently found to be potent HIV gp-120-CD4 inhibitors (Atwal et al., 1989).

The classical synthesis of dihydropyrimidines (DHPMs) was first reported by the Italian chemist Pietro Biginelli in 1893, involving a one pot condensation of aldehydes, β-ketoester and urea under strongly acidic conditions. However, this method suffers from low yields (20–40%) of the desired products.

This has led to the recent disclosure of several one-pot methodologies for the synthesis of DHPM derivatives such as [bmim][$FeCl_4$] (Chen and Peng, 2008) [bmim] $BF_4$-immobilized Cu(II) acetylacetonate (Jain et al., 2007), piperidinium triflate (Ramalingan et al., 2010), ammonium carbonate (Tamaddon et al., 2010). However, some of existing methods displayed drawbacks, such as environmental pollution caused by utilization of organic solvents, long reaction time, exotic reaction conditions, high cost catalysts. Therefore, it is urgent to further develop an efficient and convenient method to construct such significant scaffold.

## 2. Materials and methods

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples and all yields refer to the isolated products. Melting points were determined in a capillary tube and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker 500-DRX Avance instrument at 500 and 125 MHz using TMS as internal standard. [$Et_3NH$][$HSO_4$] was prepared according to a literature method (Wang et al., 2006). All other solvents and reagents were purchased from Merck chemical company and used without any further purification.

### *2.1. General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones*

A mixture of aldehyde (1 mmol), 1,3-dicarbonyl compounds (1.35 mmol), urea (1.35 mmol) and [$Et_3NH$][$HSO_4$] (3 mmol) under solvent-free conditions was heated to 100 °C for the required time which was monitored by TLC. After completion of the reaction, 10 mL of ethanol was added and the reaction mixture was poured into crushed ice and stirred for 5 min. The solid was filtered, washed with cold water and then recrystallized from ethanol to afford the pure product.

Some selected data are as follows:

### *2.2. Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**4a**)*

$^1$H NMR ($CDCl_3$): $\delta$ (ppm) 1.06 (t, $J$ = 7.1 Hz, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$), 3.96 (m, 2H, $CH_2$), 5. 26 (d, $J$ = 2.9 Hz, 1H, CH), 6.51 (s, 1H, NH), 7.12–7.29 (m, 5H, arom), 8.62 (s, 1H, NH). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 14.5, 18.8, 55.7, 60.1, 101.0, 127.0, 127.9, 128.8, 144.7, 147.6, 153.7, 166.2.

### *2.3. Ethyl 4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (**4h**)*

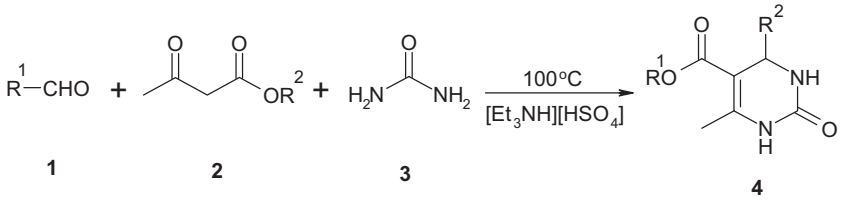
1.05 (t, $J$ = 7.4 Hz, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 3.94 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 5.20 (d, $J$ = 2.9 Hz, 1H, CH), 6.80 (s, 1H, NH), 7.10 (d, $J$ = 8.4 Hz, 2H, arom), 7.29 (d, $J$ = 8.3 Hz, 2H, arom), 8.75 (s, 1H, NH). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 14.5, 18.8, 55.0, 60.2, 100.5, 121.6, 128.8, 131.8, 143.9, 148.1, 153.6, 166.0.

## 3. Results and discussion

Herein, we describe the utility of [$Et_3NH$][$HSO_4$] in molten state (Scheme 1), which is a low cost, mild, non-volatile and non-corrosive acidic ionic liquid, as an efficient Brönsted acid catalyst in solvent-free conditions for the Biginelli reaction.

We began our study with the model reaction of benzaldehyde, ethyl acetoacetate and urea in [$Et_3NH$][$HSO_4$] that was optimized by investigating various parameters such as molar ratios of reactants and conditions. The best results were obtained with 1:1.35:1.35:3 M ratios of benzaldehyde, ethyl acetoacetate, urea and [$Et_3NH$][$HSO_4$], respectively, at 100 °C. Higher amounts of reactants and [$Et_3NH$][$HSO_4$] have no considerable effect on reaction time and yields so we used these ratios and conditions as optimized conditions. In order to study the generality of the procedure, a series of DHPMs having different steric and electronic properties were synthesized using the optimized conditions. In all cases that were studied the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1H)-ones in satisfactory yields. The results are presented in Table 1.

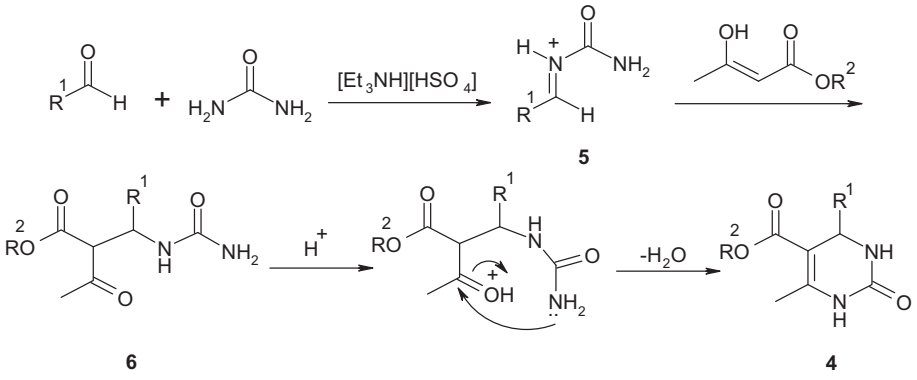
Electron withdrawing groups (such as $NO_2$) or electron donating groups (such as methoxy) on the aromatic ring of benzaldehyde do not have any effects on the yields of the reaction.




**Scheme 1** [$Et_3NH$][$HSO_4$]-catalyzed Biginelli reaction.

**Table 1** [$Et_3NH$][$HSO_4$]-catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones.

| Product | $R^1$ | $R^2$ | Time (min) | Yield (%) | Mp (°C) | | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | Observed | Reported | |
| **4a** | $C_6H_5$ | OEt | 60 | 75 | 194–197 | 198–200 | Yu et al. (2007) |
| **4b** | 4-Cl-$C_6H_4$ | OEt | 80 | 85 | 202–204 | 211–213 | Yu et al. (2007) |
| **4c** | 4-$OCH_3$-$C_6H_4$ | OEt | 60 | 80 | 194–196 | 200–202 | Kumar and Maurya (2007) |
| **4d** | 4-$CH_3$-$C_6H_4$ | OEt | 90 | 75 | 202–205 | 205–206 | Kumar and Maurya (2007) |
| **4e** | 2-Cl-$C_6H_4$ | OEt | 110 | 75 | 206–209 | 211–214 | Khabazzadeh et al. (2008a,b) |
| **4f** | 4-HO-$C_6H_4$ | OEt | 55 | 77 | 213–216 | 209–220 | Zumpe et al. (2007) |
| **4g** | 3-$NO_2$-$C_6H_4$ | OEt | 90 | 80 | 216–218 | 217 | Fazaeli et al. (2006) |
| **4h** | 4-Br-$C_6H_4$ | OEt | 90 | 80 | 195–198 | 197 | Reddy et al. (2003) |
| **4i** | 2,4-di-Cl-$C_6H_3$ | OEt | 120 | 60 | 237–239 | 243–245 | Khabazzadeh et al. (2008a,b) |
| **4j** | 4-$NO_2$-$C_6H_4$ | OEt | 80 | 76 | 196–198 | 202–204 | Khabazzadeh et al. (2008a,b) |
| **4k** | $C_6H_5$ | OMe | 50 | 80 | 202–205 | 208–210 | Kumar and Maurya (2007) |
| **4l** | 4-Cl-$C_6H_4$ | OMe | 60 | 87 | 194–196 | 204–206 | Kumar and Maurya (2007) |
| **4m** | 4-$OCH_3$-$C_6H_4$ | OMe | 65 | 75 | 186–188 | 189–193 | Salehi et al. (2003) |




**Scheme 2** A reasonable mechanism for [$Et_3NH$][$HSO_4$]-catalyzed Biginelli reaction.

According to the mechanism suggested by Kappe (1997), a proposed reaction mechanism for the [$Et_3NH$][$HSO_4$]-catalyzed Biginelli condensation via acyl imine intermediate is presented in Scheme 2. The reaction of the aldehydes and urea generates an acylimine intermediate (**5**). Interception of this iminium ion intermediate by activated 1,3-dicarbonyl compound produces an open-chain ureide (**6**) which subsequently undergoes cyclization and dehydration to afford the corresponding dihydropyrimidinone (**4**).

Another important feature of this procedure is survival of a variety of functional groups, such as ether, nitro, methoxy, and halides under reaction conditions.

## 4. Conclusion

In conclusion, we successfully developed a simple and efficient method for the one pot three-component synthesis of dihydrohydropyridiminone derivatives using commercially available substrates in the presence of a triethyl ammonium hydrogen sulfate under solvent-free conditions. The advantages, such as milder conditions, simplicity of the reactions, good product yields, rapid reaction rates, absence of organic solvents or unrequired products, and the easy procedure involved in the reaction, make the inexpensive [$Et_3NH$][$HSO_4$] a powerful catalyst for the synthesis of dihydrohydropyridiminone derivatives.

## Acknowledgments

The author gratefully acknowledges the financial support from the Research Council of Shahid Bahonar University of Kerman.

## References

Atwal, K.S., Rovnyak, G.C., O'Reilly, B.C., Schewartz, J., 1989. J. Org. Chem. 54, 5898.
Atwal, K.S., Swanson, B.N., Unger, S.E., Floyd, D.M., Mereland, S., Hedberg, A., O'Reilly, B.C., 1991. J. Med. Chem. 34, 806.
Carlin, R.T., Wilkes, J.S., 1990. J. Mol. Catal. A: Chem. 63, 125.
Carmichael, A.J., Earle, M.J., Holbrey, J.D., McCormac, P.B., Seddon, K.R., 1999. Org. Lett. 1, 997.
Chen, X., Peng, Y., 2008. Catal. Lett. 122, 310.
Esser, J., Wasserscheid, P., Jess, A., 2004. Green Chem. 6, 316.
Fazaeli, R., Tangestaninejad, S., Aliyan, H., Moghadam, M., 2006. Appl. Catal. A: Gen. 309, 44.
Gao, H., Han, B., Li, J., Jiang, T., Liu, Z., Wu, W., Chang, Y., Zhang, J., 2004. Synth. Commun. 34, 3083.
Jain, S.L., Joseph, J.K., Sain, B., 2007. Catal. Lett. 115, 52.
Kappe, C.O., 1997. J. Org. Chem. 62, 7201.
Kappe, C.O., 2000. Eur. J. Med. Chem. 35, 1043.
Khabazzadeh, H., Saidi, K., Sheibani, H., 2008a. Bioorg. Med. Chem. Lett. 18, 278.
Khabazzadeh, H., Saidi, K., Sheibani, H., 2008b. Arkivoc 15, 34.

Kumar, A., Maurya, R.A., 2007. J. Mol. Catal. A: Chem. 272, 53.
Noda, A., Susan, M., Kudo, K., Mitsushima, S., Hayamizu, K., Watanabe, M., 2003. J. Phys. Chem. B 107, 4024.
Olah, G.A., Mathew, T., Goeppert, A., Torok, B., Bucsi, I., Li, X.Y., Wang, Q., Marinez, E.R., Batamack, P., Aniszfeld, R., Prakash, G.K.S., 2005. J. Am. Chem. Soc. 127, 5964.
Ramalingan, C., Park, S.J., Lee, I.S., Kwak, Y.W., 2010. Tetrahedron 66, 2987.
Reddy, K.R., Reddy, C.V., Mahesh, M., Raju, P.V.K., Narayana Reddy, V.V., 2003. Tetrahedron Lett. 44, 8173.
Salehi, P., Dabiri, M., Zolfigol, M.A., Bodaghi Fard, M.A., 2003. Tetrahedron Lett. 44, 2889.
Sheldon, R., 2001. Chem. Commun., 2399.
Sheldon, R., 2005. Green Chem. 7, 267.
Suarez, P.A.Z., 2002. Chem. Rev. 102, 3667.
Tamaddon, F., Razmi, Z., Jafari, A.A., 2010. Tetrahedron Lett. 51, 1187.
Wang, C., Guo, L., Li, H., Wang, Y., Weng, J., Wu, L., 2006. Green Chem. 8, 603.
Yu, Y., Liu, D., Liu, C., Luo, G., 2007. Bioorg. Med. Chem. Lett. 17, 3508.
Zumpe, F.L., Flßü, M., Schmitz, K., Lender, A., 2007. Tetrahedron Lett. 48, 1421.