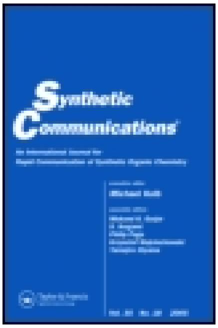

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One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Catalyzed by Acidic Ionic Liquids Under Solvent-Free Conditions

Jianzhou Gui [a] , Dan Liu [a] , Chan Wang [a] , Feng Lu [a] , Jingzhao Lian [a] , Heng Jiang [a] & Zhaolin Sun [a]
[a] College of Chemistry and Materials Science, Liaoning Shihua University, Fushun, Liaoning, China

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Jianzhou Gui, Dan Liu, Chan Wang, Feng Lu, Jingzhao Lian, Heng Jiang, and Zhaolin Sun
College of Chemistry and Materials Science, Liaoning Shihua University,
Fushun, Liaoning, China

Abstract: The acidic ionic liquids were new catalysts for the one-pot Biginelli reaction coupling of aldehyde, 1,3-dicarbonyl compound, and urea to afford the corresponding dihydropyrimidinones in good yields under solvent-free conditions. The catalysts could be recycled and reused five times without a noticeable decrease in catalytic activity.

Keywords: Acidic ionic liquid, Biginelli reaction, synthesis

INTRODUCTION

Dihydropyrimidinone derivatives (DHPMs) have attracted considerable interest because of therapeutic and pharmacological properties. To improve the efficiency of the Biginelli reaction, recently many synthetic methods for preparing these compounds, such as use of heteropoly acids,[1] $CuCl_2 \cdot H_2O$,[2] l-proline,[3] praseodymium methanesulfonate,[4] chloroacetic acid,[5] and so on, have been developed. The search for the new, readily available, and green catalysts is still being actively pursued.

Because of the great potential of room-temperature ionic liquids (ILs) as environmentally benign media for catalytic processes, much

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Address correspondence to Jianzhou Gui, College of Chemistry and Materials Science, Liaoning Shihua University, Fushun 113001, Liaoning, China. E-mail: jzgui@hotmail.com; guijz@lnpu.edu.cn

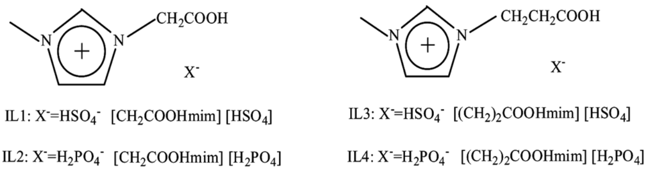
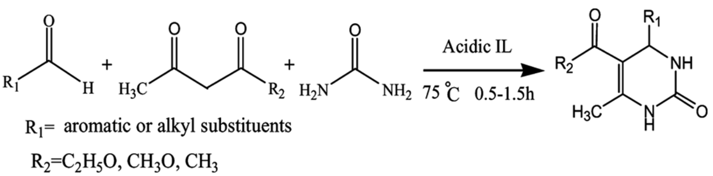


Figure 1. Structure of the acidic liquids in the study.



Scheme 1. The synthesis of 3,4-dihydropyrimidin-2(1H)-ones.

attention has currently been focused on the organic reactions catalyzed with or in ILs, and many organic reactions, especially in the reactions promoted with acid–base catalysts, were performed in ILs. In recent years, the acidic ILs, which were stable and reusable, have emerged as a powerful alternative to conventional chloroaluminate ILs.[6] The acidic ILs have also been used as catalysts for the Biginelli reaction.[7] Some of them are really good; however, some drawbacks still remain. For example, reaction temperature of some catalytic systems is relatively high. Furthermore, the anionic portion consisting of halogen containing anions (such as PF_6^-, BF_4^-, $[CF_3SO_3]^-$, and $[(CF_3SO_2)_2N]^-$) can easily yield white fumes of hydrogen fluoride (HF) or hydrate precipitates. To follow the generally recognized safe rule to avoid toxicological and environmental hazards, there is still much room for the development of more efficient methods.

In our previous work, our group had synthesized and characterized several Brønsted acid sites functionalized ILs.[8] In continuation of our interest in acidic ILs and the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones,[4] in this communication, we describe them (Fig. 1) as catalysts for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions (Scheme 1).

EXPERIMENTAL

All solvents and chemicals in the experiment were commercially available and used without further purification unless otherwise stated. The C, N, and H elemental analyses were performed on an Elementar Vario EL element analyzer. Infrared (IR) spectra were recorded on a PE Spectrum^{TM} GX Fourier transform (FT-IR) spectrometer using liquid film or KBr tablet. ^{1}H NMR (300 MHz) was obtained on Varian Mercury-plus 300BB instruments as solutions in deuterium-substituted reagent. Chemical shifts were reported in parts per million (ppm, d).

Aldehyde (20 mmol), 1,3-dicarbonyl (20 mmol), urea (24 mmol), and ILs (0.3 mmol) were heated to 75°C while being stirred for 0.5–1.5 h, then 5 mL ice–cold water were added. The products were filtered out and washed with ice–cold water to afford pure 3,4-dihydropyrimidin-2-(1*H*)-ones. The IL was reused after removal of water under vacuum (0.01 torr) at 130°C for 3 h.

RESULTS AND DISCUSSION

The catalytic activity of the different acidic liquids was first examined in the model reaction of benzaldehyde, methyl acetoacetate, and urea under the same conditions. It can be seen that all ILs exhibit good catalytic effects with yields greater than 84% (Table 1). The data in entries 1–4 (Table 1) indicate that the yields of DHPMs in IL1 and IL3 are considerably more than those in IL2 and IL4. It is suggested that the IL's anion has a significant impact on its catalytic activity. This phenomenon can be explained in terms of the different Brønsted acidities of the anions.

After reaction, the mixture was poured into ice water. The product 4A that precipitated was isolated by simple filtration. The IL remaining in the aqueous phase was reused after removal of water under vacuum (0.01 torr) at 130°C for 3 h. It is to be noted that IL3 can indeed be reused five times without visible loss of activity (Table 1, entry 5). This indicated that IL3 as catalyst for the Biginelli reaction was recyclable.

Then, three-component Biginelli condensation of aldehyde, 1,3-dicarbonyl, and urea was catalyzed by IL3. In all cases studied, the three-component reaction proceeded smoothly to give the corresponding DHPMs in satisfactory yields.[20] Aromatic aldehydes carrying either electron-donation or electron-withdrawing substituents (functional groups including ethers, nitro, hydroxyl, and halides) afforded good yields of DHPMs in high purity (entries 6–20). Most importantly, aliphatic aldehydes, which usually show extremely poor yields in the Biginelli reaction, afforded good yields of products too (entries 21–29). It showed that aliphatic aldehyde exhibited behavior analogous to that of aromatic aldehydes, which demonstrated IL3 is efficient for the Biginelli reaction.

Table 1. Synthesis of DHPMs catalyzed by acidic ionic liquid under solvent-free conditions[a]

Entry	DHPMs	R1	R2	IL	Time (h)	Yield (%)[b]	Mp (°C)	
							Found	Reported
1	4A	C_6H_5	CH_3O	IL1	0.5	87.5		
2	4A	C_6H_5	CH_3O	IL2	0.5	84.6		
3	4A	C_6H_5	CH_3O	IL3	0.5	88.7	210–212	210[9]
4	4A	C_6H_5	CH_3O	IL4	0.5	85.2		
5[c]	4A	C_6H_5	CH_3O	IL3	0.5	88.0		
6	4B	4-(CH_3O)-C_6H_4	CH_3O	IL3	1	94.6	191–193	191–193[10]
7	4S	4-(NO_2)-C_6H_4	CH_3O	IL3	1	88.8	236–238	237–238[11]
8	4De	4-(Cl)-C_6H_4	CH_3O	IL3	1	96.5	205–208	206–208[12]
9	4E	2,4-$(Cl)_2$-C_6H_3	CH_3O	IL3	1	90.5	253–256	254–255[13]
10	4F	4-OH-3-(OMe)-C_6H_3	CH_3O	IL3	0.5	67.4	249–251	/
11	4G	2-(OH)-C_6H_4	CH_3O	IL3	1	77.6	229–231	/
12	4H	C_6H_5	C_2H_5O	IL3	1	97.0	205–207	201–203[14]
13	4I	4-(CH_3O)-C_6H_4	C_2H_5O	IL3	1	97.8	201–203	201–202[15]
14	4J	4-(NO_2)-C_6H_4	C_2H_5O	IL3	0.5	96.4	206–208	208–209[16]
15	4K	2,4-$(Cl)_2$-C_6H_3	C_2H_5O	IL3	1	94.8	237–239	238–240[17]
16	4M	C_6H_5	CH_3	IL3	1	85.1	235–237	235–236[9]
17	4N	4-(CH_3O)-C_6H_4	CH_3	IL3	1	83.7	164–166	165–168[11]
18	4O	4-(NO_2)-C_6H_4	CH_3	IL3	1	78.1	227–229	227–229[11]
19	4P	4-(Cl)-C_6H_4	CH_3	IL3	0.5	92.9	214–216	215–216[18]
20	4Q	2,4-$(Cl)_2$-C_6H_3	CH_3	IL3	1	94.5	228–230	/
21	4R	CH_3	C_2H_5O	IL3	1.5	83.0	186–189	186–188[19]
22	4S	CH_3CH_2	C_2H_5O	IL3	1	90.0	180–183	179–181[9]
23	4T	n-$CH_3(CH_2)_2$	C_2H_5O	IL3	1	89.0	158–159	155–157[19]
24	4U	CH_3	CH_3O	IL3	1.5	73.2	168–170	/
25	4V	CH_3CH_2	CH_3O	IL3	1	84.6	184–186	184–185[9]
26	4W	n-$CH_3(CH_2)_2$	CH_3O	IL3	1	89.3	172–175	174–175 [9]
27	4X	CH_3	CH_3	IL3	1.5	74.1	186–188	/
28	4Y	CH_3CH_2	CH_3	IL3	1.5	73.7	174–176	/
29	4Z	n-$CH_3(CH_2)_2$	CH_3	IL3	1.5	77.5	149–151	151–152 [9]

[a] Aldehyde, 20 mmol; 1,3-dicarbonyl, 20 mmol; urea, 24 mmol; and ILs, 0.3 mmol. Reactions were run in a thermostated oil bath at 75°C, variation ±2°C.

[b] Isolated yields.

[c] IL3 was reused five times.

CONCLUSION

In summary, an efficient procedure for synthesizing DHPMs from aromatic and aliphatic aldehydes catalyzed by acidic ILs was developed. After the reaction, the catalyst can be easily recovered and reused without distinct decrease in reactive activity. The procedure is free of organic solvent, has a short reaction time, and requires a low reaction temperature. Therefore, it is a useful and environmentally friendly process.

Spectral Data for Selected Compounds

5-Methoxycarbonyl-6-methyl-4-(4-hydroxy-3-methoxyphenyl)-3,4-dihydropyrimidin-2-(1H)-one (**4F**)

IR (KBr) ν/cm^{-1}: 3258, 1675, 1649; ^{1}H NMR (DMSO-d_6) 9.18 (s, 1H), 8.92 (s, 1H), 7.62 (s, 1H), 6.83 (d, $J = 1.7$ Hz, 1H), 6.69–6.67 (d, $J = 8.1$ Hz, 1H), 3.74 (s, 3H), 3.54 (s, 3H), 2.24 (s, 3H). $C_{14}H_{16}O_5N_2$ (292.16) calcd.: C, 57.55; H, 5.48; N, 9.58. Found: C, 57.70; H, 5.41; N, 9.52.

5-Aceto-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2-(1H)-one (**4O**)

IR (KBr) ν/cm^{-1}: 3255, 1673, 1607; ^{1}H NMR (DMSO-d_6) δ: 9.36 (s, 1H), 8.21–8.20 (d, $J = 8.5$ Hz), 8.0 (s, 1H), 7.51–7.50 (d, $J = 8.2$ Hz, 2H), 5.39–5.38 (d, 3.6, 1H), 2.30 (s, 3H), 2.16 (s, 3H). $C_{13}H_{13}O_4N_3$ (275.16) calcd.: C, 56.74; H, 4.72; N, 15.27. Found: C, 56.70; H, 4.80; N, 15.21.

5-Aceto-6-methyl-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidin-2-(1H)-one (**4Q**)

IR (KBr) ν/cm^{-1}: 3340, 1713, 1668; ^{1}H NMR (DMSO-d_6) δ: 9.31(1H, s), 7.81 (s, 1H), 7.61 (d, $J = 2.1$ Hz, 1H), 7.41–7.39 (q, $J = 10.5$ Hz, 1H), 7.26–7.24(d, $J = 8.4$ Hz, 1H), 5.65 (d, $J = 3.1$ Hz, 1H), 2.35 (s, 3H), 2.07 (s, 3H). $C_{13}H_{12}O_2N_2Cl_2$ (315.05) calcd.: C, 49.56; H, 3.81; N, 8.89. Found: C, 49.50; H, 3.87; N, 8.88.

5-Ethoxycarbonyl-6-methyl-4-propyl-3,4-dihydropyrimidin-2-(1H)-one (**4T**)

IR (KBr) ν/cm^{-1}: 3251, 1720, 1647; ^{1}H NMR (DMSO-d$_6$) δ: 8.93 (s, 1H), 7.33 (s, 1H), 4.10–4.04 (q, $J = 4.7$ Hz, 3H), 2.16 (s, 3H), 1.26–1.40 (m, $J = 4.7$ Hz, 4H), 1.21–1.16 (t, $J = 3.2$ Hz, 3H), 0.87–0.83 (t, $J = 6.9$ Hz, 3H). $C_{11}H_{18}O_3N_2$ (226.13) calcd.: C, 58.42; H, 7.96; N, 12.39. Found: C, 58.41; H, 8.01; N 12.31.

5-Methoxycarbonyl-4,6-dimethyl-3,4-dihydropyrimidin-2-(1H)-one (**4U**)

IR (KBr) ν: 3248, 3115, 2954, 1710, 1658 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.08 (s, 1H), 7.23 (s, 1H), 4.18 (q, $J = 6.3$ Hz, 1H), 3.66 (s, 3H), 2.18 (s, 3H), 1.17 (t, $J = 6.5$ Hz, 3H). $C_8H_{12}N_2O_3$ (184.1) calcd.: C, 52.19; H, 6.52; N, 15.22. Found: C, 52.15; H, 6.59; N, 15.26.

5-Aceto-4,6-dimethyl-3,4-dihydropyrimidin-2-(1H)-one (**4X**)

IR (KBr) ν: 3308, 3090, 2978, 1698, 1615 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.07 (s, 1H), 7.32 (s, 1H), 4.25 (m, 1H), 2.20 (s, 3H), 2.17 (s, 3H), 1.07 (t, $J = 6.3$ Hz, 3H). $C_8H_{12}N_2O_2$ (168.1) calcd.: C, 57.18; H, 7.20; N, 16.59. Found: C, 57.22; H, 7.24; N, 16.53.

5-Aceto-6-methyl-4-ethyl-3,4-dihydropyrimidin-2-(1H)-One (**4Y**)

IR (KBr) ν: 3246, 3122, 2974, 1707, 1682 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.94 (s, 1H), 7.40 (s, 1H), 4.08 (t, $J = 5.3$ Hz, 1H), 2.20 (s, 6H), 1.39 (m, $J = 6.4$, 2H, $J = 7.4$ Hz), 0.81 (t, 3H, $J = 7.4$ Hz). $C_9H_{14}N_2O_2$ (182.11) calcd.: C, 59.32; H, 7.54; N, 15.43. Found: C, 59.23; H, 7.69; N, 15.44.

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