Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Brønsted Acidic Ionic Liquid: An Efficient and Reusable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones

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Version of record first published: 21 Aug 2006.

To cite this article: Renwei Zheng, Xiaoxia Wang, Hui Xu & Jingxing Du (2006): Brønsted Acidic Ionic Liquid: An Efficient and Reusable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:11, 1503-1513

To link to this article: http://dx.doi.org/10.1080/00397910600588488

Synthetic Communications®, 36: 1503–1513, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600588488

Brønsted Acidic Ionic Liquid: An Efficient and Reusable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

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Abstract: A novel ionic liquid, 3-carboxymethyl-1-methylimidazolium bisulfate ($CMImHSO_4$), was synthesized and used as a recyclable catalyst for the Biginelli reaction under solvent-free conditions. High yields of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones (or thiones) were obtained. The ionic liquid can be recovered and recycled easily without loss of activity.

Keywords: Biginelli reaction, Brønsted acidic ionic liquid, dihydropyrimidinone, recyclable catalyst

INTRODUCTION

In the past decades, the dihydropyrimidiones (DHPMs) and their derivatives have attracted increasing interest in the realms of natural and synthetic organic chemistry because of their diverse therapeutic and pharmacological properties.[1] These nonplanar heterocyclic compounds have emerged as the integral backbones of calcium channel modulators,[2] antihypertensive agents,[3] α_{1a}-adrenergic receptor antagonists,[4] neuropeptide Y (NPY) antagonists,[5] mitotic kinesin inhibitors,[6] and hepatitis B virus replication inhibitors.[7] In addition, several marine-derived natural products such as Crambine,

Received in Japan September 20, 2005
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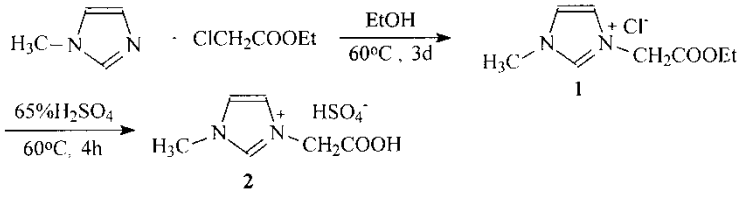
Batzelladine B (potent HIV gp-120CD_4 inhibitors), and Ptilomycalin alkaloids have been reported to contain DHPM moiety.[8] Consequently, synthesis of this heterocyclic core is currently of much importance.

A simple and direct method, first reported by Biginelli in 1893, involves a three-component, one-pot condensation of an aldehyde, a β-ketoester, and urea (or thiourea) under strongly acidic conditions.[9] Though simple, the original Biginelli reaction suffered from low yields (20–50%), especially when substituted aromatic or aliphatic aldehydes were used as the substrates.[10] This has led to the development of multistep strategies that produced relatively higher overall yields but lack the simplicity of the one-pot Biginelli synthesis.[11] As a result, many improved procedures for the preparation of DHPMs have recently been reported, either by modification of the catalyst or by employment of novel experimental techniques. The former involves using such catalysts as Lewis acids,[12] protic acid,[13] triflate,[14] and others.[15] Instead of strong acid, and the latter includes applying microwave irradiation,[14e,16] ultrasound irradiation,[17] solid-phase reaction,[18] and so on. In spite of their respective advantage and potential utility, some of the reported methods suffer from drawbacks such as longer reaction times, higher temperatures, expensive catalysts, unsatisfactory yields, cumbersome product-isolation procedures, and environmental pollution problems.

In recent years, ionic liquids (ILs) have been widely used for various organic reactions.[19] The increased interest of the researchers lies mainly in their green characteristics, such as being chemical and thermal stable, nonvolatile, designable, nonflammable, etc.[20] In addition, they can facilitate the isolation of products and are readily recycled. Recently, Peng and Deng[21] reported that 1-n-butyl-3-methyl-imidazolium tetrafluoroborate ($BMImBF_4$) and hexfluorophosphorate ($BMImPF_6$) were effective catalysts for the Biginelli reaction. More recently, Shaabani and Rahmati[22] also reported that 1,1,3,3-tetramethyl-guanidinium trifluoroacetate (TMGT) is a very efficient promoter for this reaction. Herein, we report a simple and effective approach to the Biginelli condensation reaction using a reusable catalyst, 3-carboxymethyl-1-methylimidazolium bisulfate ($CMImHSO_4$, **2**), a new Brønsted acidic ionic liquid. The route for its synthesis is shown in Scheme 1.



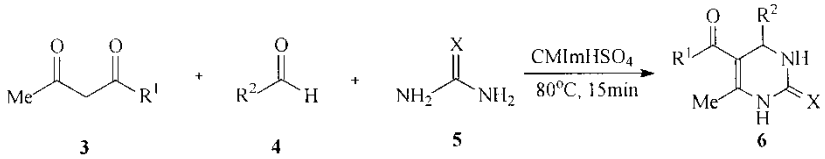
Scheme 1.

$CMImHSO_4$ (compound **2**), melting at about 45°C, was obtained as a pale yellow liquid of low viscosity in the synthetic procedure reported here. It represents a new Brønsted acidic ionic liquid and was easily available from *N*-methylimidazole, chloro ethylacetate, and sulfuric acid under mild reaction conditions. It can dissolve in water, ethanol, DMSO, and DMF, can partly dissolve in dichloromethane, and is insoluble in diethyl ether, acetone, THF, ethyl acetate, cyclohexane, and chloroform. Therefore, the acidic ionic liquid is separated readily from the insoluble product in cold water.

The Biginelli reaction catalyzed by the ionic liquid **2** afforded an excellent yield of DHPMs under solvent-free conditions (Scheme 2 and Table 1).

It can be concluded from Table 1 that when aromatic aldehydes were used as substrates, satisfactory yields could always be obtained, though aromatic aldehydes with a strong electron-withdrawing group (such as nitro group) required relatively longer time (25 min) for the reaction to be complete (entries **6b**, **6l**, **6p**). Aromatic aldehydes carrying electron-donating substituents (entries **6d**–**g**) produced excellent yields of DHPMs even more smoothly, and thus pharmacologically relevant substitution patterns on the 4-aryl group can be introduced efficiently. Aliphatic aldehydes such as butanal and isobutanal also react well with β-ketoester compounds (entries **6i**, **6j**) and urea in the presence of $CMImHSO_4$, giving the corresponding DHPMs in high yields, though longer reaction time and more amount of catalyst were required. However, such aldehydes normally afforded extremely poor yields in the Biginelli reaction,[9] which shows that aliphatic aldehydes exhibit analogous activity to that of aromatic aldehydes here. Thiourea has been used with the same success to provide the corresponding dihydro-pyrimidin-2(1*H*)-thiones (entries **6k**–**n**, **6t**), which are also of much interest with regard to biological activity.[1] The scope of the methodology was demonstrated as a variety of 1,3-dicarbonyl compounds proved effective with this protocol (entries **6o**–**t**). Another important aspect of the procedure is the survival of a variety of functional groups such as NO_2, Cl, OH, and OCH_3 and a conjugated C=C bond under the reaction conditions.

The catalyst is reusable and can be applied several times without any decrease in the yield of the reaction. Take the synthesis of **6a**, for example. $CMImHSO_4$ was reused five times to get the yields of **6a** in 93%, 90%,



3 4 5 6

Scheme 2.

Table 1. $CMImHSO_4$ (5 mol%)-catalyzed synthesis of dihydropyrimidinones

Entry[a]	R^1	R^2	X	Product	Yield (%)[b]	Mp(°C) Found	Mp(°C) Reported
1	EtO	C_6H_5	O	**6a**	66[c],87[d],90[e]	201–203	202.4[23]
2	EtO	C_6H_5	O	**6a**	93, 90[f], 92, 89, 91	201–203	202.4[23]
3	EtO	4-$NO_2C_6H_4$	O	**6b**[g]	91	206–207	207–208.5[23]
4	EtO	4-ClC_6H_4	O	**6c**	89	210–212	213–215[23]
5	EtO	2-HOC_6H_4	O	**6d**	92	201–203	201–202[23]
6	EtO	4-$CH_3OC_6H_4$	O	**6e**	96	199–201	201–202[23]
7	EtO	4-$CH_3C_6H_4$	O	**6f**	94	170–172	172–173[12a]
8	EtO	2-HO-3-$CH_3OC_6H_4$	O	**6g**	89	232–233	—
9	EtO	PhCH=CH	O	**6h**	88	238–240	238–239.5[23]
10	EtO	n-Pr	O	**6i**	89[h]	156–157	151–152[23]
11	EtO	i-Pr	O	**6j**	85[h]	191–193	195–196[24]
12	EtO	C_6H_5	S	**6k**	90	206–207	206–207[24]
13	EtO	4-$NO_2C_6H_4$	S	**6i**[g]	93	209–212	210–213[23]
14	EtO	4-ClC_6H_4	S	**6m**	88	180–181	180–182[23]
15	EtO	2-HOC_6H_4	S	**7b**	93	178–179	—
16	EtO	4-$CH_3OC_6H_4$	S	**6n**	96	138–140	136–138[23]
17	CH_3	C_6H_5	O	**6o**	93	232–234	233–236[25]
18	CH_3	4-$NO_2C_6H_4$	O	**6p**[g]	91	228dec	230dec[25]
19	CH_3	4-ClC_6H_4	O	**6q**	90	224–226	226–227[22]
20	CH_3	4-$CH_3OC_6H_4$	O	**6r**	95	181–182	178–180[25]
21	CH_3	2-HO-3-$CH_3OC_6H_4$	O	**6s**	93	235–236	—
22	CH_3	4-ClC_6H_4	S	**6t**	87	224–226	224–225[23]
23	CH_3	2-HOC_6H_4	S	**7a**	91	242–243	—

[a]Typical reaction conditions were used unless otherwise specified: 5 mol% $CMImHSO_4$ relative to aldehyde; 80°C; 15 min, and no solvent. The molar ratio of aldehyde/β-ketoester of β-dicarbonyl compound/urea or thiourea = 1:1:1.5.

[b]Isolated yield.

[c]Compound **1** as catalyst, 80°C, 40 min.

[d]10 mL of ethanol was added as solvent.

[e]10 mL of H_2O was added as solvent.

[f]Isolated yield with reused catalyst.

[g]5 mol% catalyst, 80°C, 25 min.

[h]10 mol% catalyst, 80°C, 40 min.

92%, 89%, and 91%, respectively, exhibiting the same catalytic activity (entry **2**). It should be noted that only 66% isolated yield could be produced when compound **1** were used as a catalyst in ethanol (entry 1). From entry 1, although water and ethanol as solvent afforded also the product in high

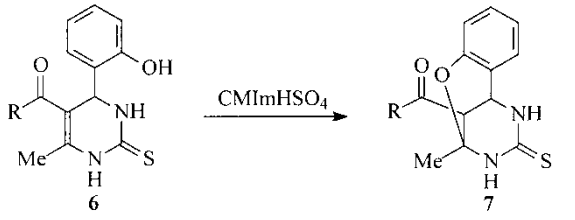
yields, solvent-free conditions were employed for more environmental acceptability. We studied also the effect of the amount of catalyst on the yields of product. Use of just 5 mol% of $CMImHSO_4$ relative to the amount of aldehyde is sufficient to push the reaction forward. High amounts of the catalyst did not improve the result to a large extent.

In the course of our studies, we found that the products derived from the condensation reaction involving salicylaldehyde, acetylacetone (or ethyl acetoacetate), and thiourea gave an NMR spectrum different from that of the expected dihydropyrimidinthione **6**. The exact structures were characterized by IR, NMR, and elemental analysis to be diazatricyclo structures **7a** and **7b**, which are formed from further intramolecular Michael addition of the hydroxyl to the electron-deficient C═C existing in compound **6** under $CMImHSO_4$ catalysis (Scheme 3).

In summary, the present procedure for the synthesis of dihydropyrimidinones by a novel Brønsted acidic ionic liquid ($CMImHSO_4$)–catalyzed condensation provides an efficient modification of the original Biginelli reaction. Moreover, this method offers several advantages including high yields, short reaction times, simple workup procedures, solvent-free conditions, and reusable catalyst. It is a useful addition to the existing methods.

EXPERIMENTAL

Melting points were measured on an electrothermal digital melting-point apparatus and are uncorrected. NMR spectra were recorded on a Brucker AC-400 instrument at 400 MHz for ^1H and 100 MHz for ^{13}C using d_6-DMSO or D_2O as solvent. Chemical shifts (σ) are reported in ppm and coupling constants (J) are given in Hz. IR spectra were obtained as KBr plates on a Bruker Vector-22 infrared spectrometer. Elemental analyses were performed on an EA-1110 instrument. The reaction was routinely monitored by thin-layer chromatography (TLC) on silica-gel plates.



a: R= Me; b: R= EtO

Scheme 3.

Typical Procedure for the Preparation of $CMImHSO_4$ Ionic Liquid

Methylimidazole (8.2 g, 0.1 mol), anhydrous ethanol (100 mL), and ethyl chloroacetate (18.4 g, 0.15 mol) were added to a 250 mL round-bottom flask containing a stirring bar. After stirring at 60°C (water-bath temperature) for 3 days (TLC monitoring), ethanol was then removed under reduced pressure; the residue was purified by washing with dry diethyl ether and toluene repeatedly and then dried in vacuum to obtain a pale yellow liquid (compound **1**: 3-ethoxycarbonylethyl-1-methyl-imidazolium chloride) (13.7 g, 62%). ^{1}H NMR (D_2O): δ (ppm) 1.20 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 3.86 (s, 3H, CH_3), 4.21 (q, 2H, $J = 7.2$ Hz, CH_2CH_3), 5.08 (s, 2H, CH_2), 7.36 (m, 2H, arom CH), 8.63 (s, 1H, arom CH). ^{13}C NMR (D_2O): δ 13.2, 35.9, 51.6, 63.6, 123.5, 123.6, 137.4, 168.2.

A stoichiomeric amount of 65% sulfuric acid was added to compound **1** and stirred for at least 4 h at 50°C. The solution was evaporated at the rotary evaporator under reduced pressure to remove ethanol and water. The ionic liquid phase was then washed repeatedly with toluene and ether to remove nonionic residue and dried in vacuum to give a pale yellow liquid with low viscosity (compound **2**: 3-carboxymethyl-1-methylimidazoliurn bisulfate). ^{1}H NMR (d_6-DMSO): δ (ppm) 3.90 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 7.70 (m, 1H, arom CH), 7.78 (m, 1H, arom CH), 9.13 (s, 1H, arom CH), 10.15 (s, 1H, HSO_4), 12.90 (s, 1H, COOH). ^{13}C NMR (d_6-DMSO): 36.3, 501, 123.6, 124.2, 138.1, 168.6.

General Procedure for the Preparation of DHPMs

A mixture of β-ketoester or β-dicarbonyl compound **3** (25 mmol), aldehydes **4** (25 mmol), urea or thiourea **5** (37.5 mmol), and $CMImHSO_4$ **2** (1.25 mmol, 5 mol% with respect to aldehyde) was heated with stirring at 80°C for 15 min (monitored by TLC). During the reaction process, a solid product spontaneously formed. After cooling, the solid product was poured into ice water (30 mL) and stirred for 5–10 min. The separated solid was suction filtered, washed with ice water, and recrystallized from hot ethanol to obtain the pure product **6**. The water layer was washed with ethyl ether several times to remove unreacted starting materials and other organic contaminations. The water was then evaporated under reduced pressure. The ionic liquid thus recovered can be reused.

Data

5-Ethoxycarbonyl-6-methyl-4-(2-hydroxyl-3-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (6g): pale brown solid, mp: 232–233°C; ^{1}H NMR: δ 9.08 (s, 1H,OH), 8.72 (brs, 1H, NH), 7.05 (brs, 1H, NH), 6.84 (dd, *J* 8.0 Hz, 1H, arom CH), 6.69 (q, 1H, *J* 7.7 Hz, arom CH), 6.61 (q, 1H, *J* 7.7 Hz, arom CH), 5.51 (d, 1H, *J* 2.8 Hz, CH), 3.93 (q, 2H, *J* 6.8 Hz,

OCH_2), 3.94 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 1.04 (t, 3H, *J* 6.8 Hz, OCH_2CH_3); ^{13}C NMR: 165.9, 152.6, 148.9, 148.0, 144.0, 131.0, 119.5, 119.0, 111.3, 98.5, 59.4, 56.3, 49.2, 18.1, 14.5. ν_{max}(KBr)/cm^{-1}: 3536, 3343, 3113, 2975, 1689, 1643, 1479. Anal. calcd. for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.75; H, 5.90; N, 9.03.

5-Acetyl-6-methyl-4-(2-hydroxy-3-methoxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-one (6t): white solid, mp 235–236°C; ^1H NMR: δ 9.10 (5, 1H, OH), 8.93 (brs, 1H, NH), 7.70 (brs, 1H, NH), 6.85–6.58 (m, 3H, arom CH), 5.16 (d, 1H *J* 3.1 Hz, CH), 3.73 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C NMR: 195.0, 152.5, 148.1, 147.9, 146.4, 135.6, 118.9, 115.8, 111.7, 109.7, 56.1, 54.2, 30.5, 19.2. ν_{max}(KBr)/cm^{-1}: 3320, 3220, 3115, 2968, 1700, 1617, 1524. Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.92; H, 5.79; N, 10.18.

13-Acety-9-methyl-11-thio-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene (7a): red–brown solid, mp 242–243°C; ^1H NMR: δ 9.05 (brs, 1H, NH), 9.00 (brs, 1H, NH), 7.21–6.82 (m, 4H, arom CH), 4.75 (m, 1H, CH), 3.43 (d, 1H, *J* 3.0 Hz), 2.28 (s, 3H, CH_3), 1.68 (s, 3H, CH_3); ^{13}C NMR: 203.9, 177.0, 151.1, 130.1, 129.4, 127.7, 121.1, 116.9, 82.0, 48.5, 47.9, 29.6, 23.3. ν_{max}(KBr)/cm^{-1}: 3228, 3147, 2955, 1715, 1609, 1565. 1511. Anal. calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.44; H, 5.35; N, 10.73.

13-Ethoxycarbonyl-9-methyl-11-thio-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2.7}$] trideca-2,4,6-triene (7b): pale brown solid, mp 197–198°C; ^1H NMR: δ 9.80 (brs, 1H, NH), 9.15 (brs, 1H, NH), 7.24–6.72 (m, 4H, arom CH), 4.58 (d, 1H, *J* 2.4 Hz CH), 4.16 (q, 2H, *J* 7.6 Hz, CH_2), 3.30 (d, 1H, *J* 2.2 Hz), 1.78 (s, 3H, CH_3), 1.23 (t, 3H, *J* 7.6 Hz, CH_2CH_3); ^{13}C NMR: 76.5, 167.9, 150.5, 129.7, 128.8, 123.8, 120.9, 116.5, 81.4, 60.8, 48.2, 42.3, 23.4, 14.0. ν_{max}(KBr)/cm^{-1}: 3416, 3326, 3013, 2960, 1722, 1665, 1508. Anal. calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.60; H, 5.54; N, 9.50.

ACKNOWLEDGMENT

We are grateful to the Education Foundation of Zhejiang Province (Project No. 20040847) for financial support.

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