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Contributed Paper

An Efficient Protocol for the Synthesis of 3,4-Dihydropyrimidine-2-(1H)-ones Catalyzed by Functionalized Ionic Liquid [DDPA][HSO_4]

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ABSTRACT

An environmentally benign aqueous Biginelli protocol for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones (DHPMs) using a functionalized ionic liquid, 3-(N,N-dimethyldodecylammonium) propanesulfonic acid hydrogen sulfate ([DDPA][HSO_4]) as a catalyst has been achieved. High yields of the products, short reaction times, mild reaction conditions and simple experimental procedure make this protocol complementary to the existing methods. The catalyst can be reused without obvious loss of the catalytic activity.

Keywords: 3,4-dihydropyrimidine-2-(1H)-one, Biginelli reaction, ionic liquid, catalyst.

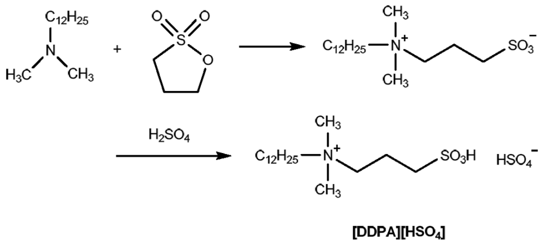
1. INTRODUCTION

3,4-Dihydropyrimidine-2-(1H)-ones (DHPMs) have received considerable attention due to the interesting pharmacological properties associated with this heterocyclic scaffold [1-5]. These compounds can readily be assembled by the so called Biginelli reaction, a one-pot condensation using β-dicarbonyl compounds with aldehydes (aromatic and aliphatic aldehydes) and urea or thiourea. Since Biginelli [6] first reported this method under strongly acidic conditions, improvements in such syntheses have been sought continuously in order to keep the simplicity of the original one-pot Biginelli protocol and to simultaneously overcome its drawbacks such as low yields, especially in the case of substituted aromatic and aliphatic aldehydes [7].

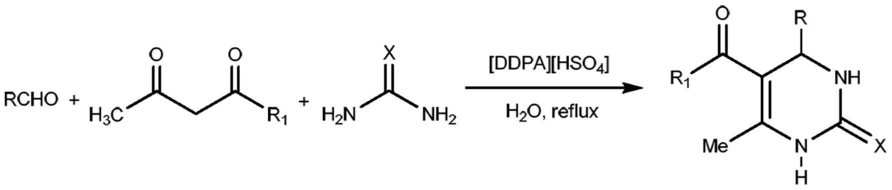
Recently, much work on improving the yields and reaction conditions has been actively pursued. For example, modification and improvements include using Lewis acids as well as Brønsted acids/bases, primary amine, chlorotrimethylsilane and hexaaquaaluminium (□) tetrafluoroborate as promoters [8-16]. Many other synthetic methods have been reported including classical conditions with microwave [17,18] and ultrasound irradiation [19-21]. However, the search for the new readily available and green catalysts is still being actively pursued.

Ionic liquids have attracted extensive interest as excellent alternatives to organic solvents, due to their favorable properties. Combining the useful characteristics of solid acids and mineral acids, Brønsted acidic task-specific ionic liquids (TSILs) are designed to replace traditional mineral liquid acid catalysts, such as sulfuric acid and hydrochloric acid in chemical processes [22,23]. However, TSILs with imidazole as the cation are relatively expensive, which hinders their industrial applications. Furthermore, typical ionic liquids consist of halogen containing anions (such as $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO_2)_2N]^-$) which in some regard limit their "greenness" [24]. Therefore, it is necessary to synthesize less expensive and halogen-free TSILs. Some SO_3H-functional halogen-free acidic ionic liquids have been prepared and their catalytic activities for acid-catalyzed reactions have also been investigated [25-27].

Recently, a novel SO_3H-functional halogen-free Brønsted acidic ionic liquid 3-(N,N-dimethyldodecylammonium) propanesulfonic acid hydrogen sulfate ([DDPA][HSO_4]) (Scheme 1) has been successfully applied to catalyze the Mannich reaction [28]. The versatility of this ionic liquid encouraged us to study its utility for Biginelli reaction. To the best of our knowledge in the open literature, Biginelli reactions catalyzed by [DDPA][HSO_4] have not yet been reported. Herein, we have discovered that this functionalized ionic liquid effectively promoted Biginelli reactions under relatively mild conditions (Scheme 2).



Scheme 1. Sructure of the ionic liquid [DDPA][HSO_4].



Scheme 2. Synthesis of 3,4-Dihydropyrimidine-2-(1H)-ones by Biginelli reactions in the presence of [DDPA][HSO_4].

2. MATERIALS AND METHODS

Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. The IR spectra were recorded with a Bomem Michelson model 102 FTIR. ^{1}H NMR spectra were recorded on Bruker DRX (500 MHz) spectrometer. Elemental analyses were performed on a Yanagimoto MT3CHN recorder. All starting chemicals (AR grade) were purchased from commercial suppliers and used without further purification.

The functionalized ionic liquid, [DDPA][HSO_4] was prepared by the procedures given in Refs [28].

2.1 General Procedure for Biginelli reactions

A mixture of aldehyde (10mmol), ethyl acetoacetate (10mmol), urea (12mmol), [DDPA][HSO_4] 0.2 mmol, and 15mL H_2O were stirred at reflux temperature for the appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was poured onto crushed ice, cooled and left overnight. The products were filtered out, washed with ice-cold water, and then recrystallized with alcohol to afford pure 3, 4-DHPMs. The products were identified by ^{1}H NMR, IR data and physical data (mp) by comparison with literature data. The ionic liquid was remaining in the aqueous media and could be reused in the next run without further purification.

3. RESULTS AND DISCUSSION

In the initial catalytic activity experiments, different solvents were screened for Biginelli reaction. Herein the reaction of benzaldehyde, methyl-acetoacetate and urea was selected as model. The results are summarized in Table 1. It was shown that Biginelli reactions could proceed effectively in polar organic solvents, for example enthanol and acetonitrile (entries 2, 3). The chemical industry is under considerable pressure to replace many of the volatile organic compounds (VOCs) that are currently used as solvents in organic synthesis. As a clean and cheap solvent, it is important to carry out Biginelli reaction in water (entry 1) for the environmental and economic reasons.

Table 1. Effect of the [DDPA][HSO_4]/solvent on the Biginelli reaction.

Entry	Catalyst/solvent	Yield (%)[b]
1	[DDPA][HSO_4]/H_2O	90
2	[DDPA][HSO_4]/C_2H_5OH	88
3	[DDPA][HSO_4]/CH_3CN	91
4	[DDPA][HSO_4]/CH_2Cl_2	81

[a] Reaction conditions: benzaldehyde (10 mmol), methyl-acetoacetate (10mmol), urea (12 mmol), [DDPA][HSO_4] (0.2 mmol), reflux, reaction time (20min).

[b] Isolated yield.

Subsequently, the same reaction of benzaldehyde, methyl-acetoacetate and urea was employed as the model reaction to screen the effect of the catalytic amount of [DDPA][HSO_4] on the Biginelli reaction. The results showed that no desirable product could be detected when a mixture of benzaldehyde, methyl-acetoacetate and urea was heated at a reflux temperature for 20min without any catalyst (entry 1), which indicated that the catalyst should be absolutely necessary for the reaction. With the amount of [DDPA][HSO_4] increased, a ramp in the yield was clearly observed. The optimum amount of [DDPA]

Table 2. Effect of amount of [DDPA] [HSO_4] on the reaction.

Entry	Catalyst (mmol)	Yield (%)[b]
1	0	0
2	0.1	84
3	0.2	90
4	0.3	90
5	0.4	91

[a] Reaction conditions: benzaldehyde (10 mmol), methyl-acetoacetate (10mmol), urea (12 mmol), reflux, reaction time (20min).

[b] Isolated yield.

[HSO_4] was 0.2mmol (2 mol% based on benzaldehyde) (entry 3), and increasing the amount of catalyst beyond this led to no substantial improvement in the yield.

Compare with traditional solvents and catalysts, ionic liquids are easily reused, which is superior to the conventional solvents and catalysts. When optimizing the reaction condition, the recycling performance of [DDPA][HSO_4] in the same model Biginelli reaction was investigated. After the reaction, the products were isolated from the catalytic system by filtration. The filtrate (containing the catalyst) was reused in the next run without further purification. As shown in Figure 1, the catalyst could be reused at least five times without significant decrease in catalytic activity.

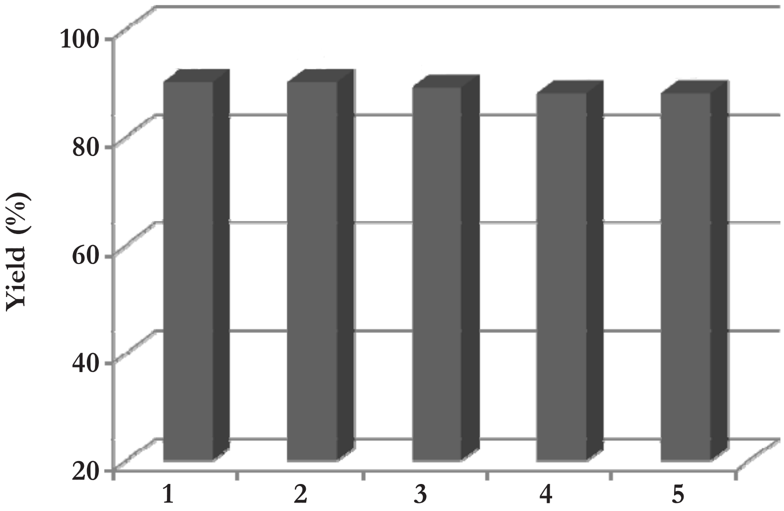


Figure 1. Reusability of [DDPA] [HSO_4].

With optimize conditions in hand we decided to explore the scope of this method. Thus, series of Biginelli 3,4-DHPMs with significant steric, electron withdrawing and donating substituent, were synthesized and the obtained results are summarized in Table 3. It can be seen that the condensation of a series of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea catalyzed by [DDPA][HSO_4] proceeded smoothly to give the corresponding products in high yields. Compared to the classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate variation in all three components simultaneously.

4. CONCLUSIONS

In conclusion, we have described an efficient protocol for the Biginelli reaction catalyzed by the functionalized ionic liquid, [DDPA][HSO_4]. High yields of the products, short reaction times, mild reaction conditions and simple experimental procedure make this protocol complementary to the existing methods. Further, the catalyst can be reused without obvious loss of the catalytic activity. This approach could make a valuable contribution on the synthesis of 3,4-DHPMs.

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Table 3. Biginelli reactions catalyzed by [DDPA] [HSO_4].

Entry	R	R_1	X	Time(min)	Yield (%)[b]
1	C_6H_5	OMe	O	20	91
2	C_6H_5	OMe	S	30	79
3	C_6H_5	OEt	O	20	92
4	C_6H_5	OEt	S	30	81
5	C_6H_5	Me	O	20	93
6	C_6H_5	Me	S	30	84
7	3-OH-C_6H_4	OEt	O	20	89
8	4-OH-C_6H_4	OEt	O	20	88
9	4-CH_3O-C_6H_4	OMe	O	20	92
10	4-CH_3O-C_6H_4	OEt	O	20	93
11	4-CH_3O-C_6H_4	Me	O	20	90
12	4-Cl-C_6H_4	OMe	O	20	88
13	4-Cl-C_6H_4	OEt	O	20	90
14	4-NO_2-C_6H_4	OMe	O	20	83
15	4-NO_2-C_6H_4	OEt	O	20	84

[a] All products were characterized by IR, ^{1}H NMR, and their mp were in comparison with that of previous literatures.

[b] Isolated yield

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