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ORIGINAL PAPER

One-pot three-component Biginelli-type reaction catalyzed by ionic liquids in aqueous media

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Abstract For the first time, 3,4-dihydropyrimidin-2(1*H*)-one and 3,4-dihydropyrimidin-2(1*H*)-thione derivatives have been synthesized in good yields by a modified Biginelli-type reaction with dicationic acidic ionic liquids as catalysts. The products could be separated simply from the catalyst–water system, and the catalysts could be reused at least six times without noticeably reducing catalytic activity.

Keywords Biginelli-type reaction · Dicationic ionic liquid · Catalyst · One-pot reaction

Introduction

3,4-Dihydropyrimidines (DHPMs) and their derivatives are pharmacologically important compounds with broad biological activity, including antiviral, antibacterial, antitumor, and antihypertensive agents, α1a adrenergic antagonists, and neuropeptide Y (NPY) antagonists. Furthermore, these compounds have emerged as the integral backbones of several calcium-channel blockers [1]. 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, dihydropyrimidinones have been considered as a new lead for the development of new anticancer drugs [2, 3]. The simplest and the most straightforward approach for DHPMs reported by Biginelli more than 100 years ago involves a one-pot three-component acid-catalyzed condensation, which is still one of the most often used multi-component reactions (MCRs) [4], but this Biginelli-type reaction suffers from harsh conditions, long reaction times, and, frequently, low yields, and continues to attract 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 of microwave [5, 6] or ultrasound [7, 8] irradiation, and use of Lewis and/or Brønsted acids as catalysts. Many catalysts, for example $FeCl_3$-supported nanopore silica [6], ferric perchlorate [9], polyoxometalate [10], strontium(II) nitrate [11], cerium(III) chloride [12], ytterbium chloride [13], heteropoly acids [14], L-proline [15], silica sulfuric acid [16], TMSCl [17], trifluoroacetic acid [18], and TBAB [19], have been used, and the search for new, readily available, and green catalysts is still being actively pursued.

Nowadays ionic liquids attract much interest as environmentally benign catalysts or excellent alternatives to organic solvents, because of their favorable properties, for example negligible volatility and high thermal stability. Brønsted acidic or basic task-specific ionic liquids (TSILs) are designed to replace traditional acids or bases as catalysts in organic synthetic procedures. In view of the advantages and disadvantages of homogeneous and heterogeneous catalytic reactions, the use of TSILs as reaction medium and/or catalytic system may be a convenient

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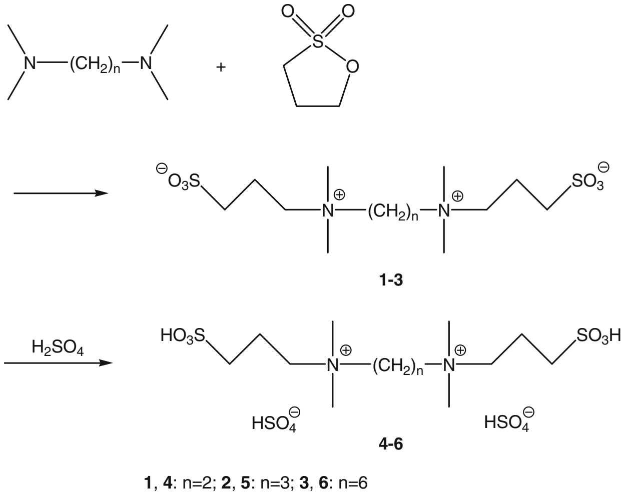
solution to the solvent-emission and catalyst-recycling problems. TSILs have also been used as catalysts for the Biginelli reaction [20–25]. Deng et al. [20, 21] synthesized DHPMs in $BMImBF_4$ or $BMImPF_6$, Shaabani and Rahmati [22] used the room-temperature ionic liquid 1,1,3,3-tetramethylguanidinium trifluoroacetate as catalyst, Li et al. [23] reported an ionic liquid (BMImSac) as catalyst, Zheng et al. [24] used $CMImHSO_4$ as catalyst for a Biginelli-type reaction, and Peng et al. [25] found the Lewis acidic ionic liquid $[bmim][FeCl_4]$ to be an efficient catalyst for synthesis of DHPMs. However, TSILs with imidazole as the cation are relatively expensive, which hinders their industrial application. Furthermore, typical ionic liquids consist of halogen-containing anions (for example $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$, or $[(CF_3SO_2)_2N]^-$) which to some extent limits their “greenness” [26–29]. Therefore, it is necessary to synthesize novel efficient and halogen-free TSILs. In continuation of our study of ionic liquid-catalyzed MCRs in aqueous media [30, 31], we synthesized some dicationic acidic ionic liquids as halogen-free TSILs that bear dialkane sulfonic acid groups in acyclic diamine cations (Scheme 1), and subsequently used these as catalysts in a one-pot, three-component Biginelli-type reaction (Scheme 2). To the best of our knowledge of the open literature, Biginelli-type reactions catalyzed by dicationic ionic liquids have not been reported.



Scheme 1

Results and discussion

The procedure for synthesis of catalyst TSILs was made up of a two-step atom-economic reaction. The zwitterionic-type precursors were prepared by a one-step direct sulfonation reaction. Acidification of the zwitterions was accomplished by mixing with twice the molar amount of sulfuric acid (98%, aq.) to convert the pendant sulfonate group into dicationic halogen-free acidic ionic liquids. The chemical yields for both zwitterion formation and acidification were essentially quantitative, because neither reaction produced byproducts. The fresh new catalysts are somewhat viscous pale yellow liquids at room temperature. All the catalysts produced are entirely miscible with water and soluble or partly soluble in organic solvents.

In the initial catalytic activity experiments, benzaldehyde, ethyl acetoacetate, and urea were employed as the model reactants at 90 °C in TSILs for a length of time to compare the catalytic performance of the TSILs (Table 1). It was shown that no desirable product could be detected when a mixture of benzaldehyde, ethyl acetoacetate, and urea was heated at 90 °C for 60 min in the absence of TSILs (entry 1), which indicated that the catalysts was absolutely necessary for this three-component Biginelli-type reaction. All TSILs proved to be very active. It is clear that the yield was increased by addition of TSILs and the optimum amount of TSILs was 2 mol% (entries 3, 7). A larger amount of the catalysts could not improve the yield. For the purpose of comparison, sulfuric acid as catalyst was tested for this reaction under the same conditions and a yield of 41% was obtained (entry 12). Condensation reaction in TSILs–H_2O gave the same yield as in organic solvents. As a clean and inexpensive solvent, it is important to carry out this reaction in water for environmental and economic reasons.

The recycling performance of the catalysts was also investigated using the above model reaction. After separation of the products, the filtrate containing the catalyst was reused in the next run without further purification.

Scheme 2

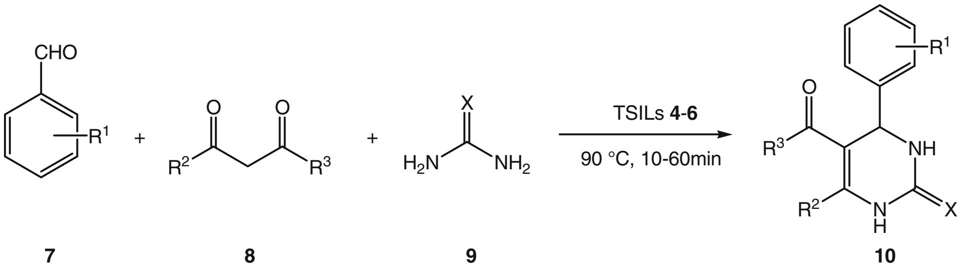


Table 1 Effect of the different catalysts on the Biginelli-type reaction

Entry	Catalyst (mmol)	Isolated yield (%)
1	0	0
2	**4** (0.1)	88
3	**4** (0.2)	96
4	**4** (0.3)	96
5	**4** (0.4)	95
6	**5** (0.1)	86
7	**5** (0.2)	96
8	**5** (0.3)	96
9	**6** (0.1)	84
10	**6** (0.2)	91
11	**6** (0.3)	91
12	H_2SO_4 (0.2)	41

Reaction conditions: 10 mmol benzaldehyde, 10 mmol ethyl acetoacetate, 10 mmol urea, 0.2 mmol TSILs, 90 °C, 10 min

Table 2 Reuse of the dicationic ionic liquid catalysts

Run	Isolated yield (%)		
	4	**5**	**6**
1	96	96	91
2	96	96	91
3	95	94	90
4	94	95	91
5	94	93	88
6	94	92	89

Reaction conditions: 10 mmol benzaldehyde, 10 mmol ethyl acetoacetate, 10 mmol urea, 0.2 mmol TSILs, 90 °C, 10 min. After separation of the product by filtration, the recovered solvent containing the catalyst was reused directly

A mixture of benzaldehyde, ethyl acetoacetate, and urea in stoichiometric ratio was added to the filtrate and stirred under the same conditions. The data listed in Table 2 show that the TSILs could be reused six times without a decrease of catalytic activity. Compared with the traditional solvents and catalysts, the easy recycling performance is also an attractive property of the TSILs for environmental protection and economic reasons.

This condensation reaction with various aldehydes, 1,3-dicarbonyl compounds, and urea (or thiourea) in the presence of TSIL **1** as the catalyst was then explored under the optimized reaction conditions described above; the results are presented in Table 3. It can easily be seen that this three-component Biginelli-type condensation was complete within 10–60 min. Compared with the classical Biginelli method, one additional important feature of the present procedure is the ability to tolerate variations in all three components simultaneously.

Table 3 Three-component Biginelli-type reaction catalyzed by dicationic **4**

Entry	R^1	R^2	R^3	X	Time (min)	Yield (%)[a]	Ref.
10a	H	CH_3	OC_2H_5	O	10	96	[19]
10b	H	CH_3	OC_2H_5	S	30	84	[9]
10c	H	CH_3	OCH_3	O	10	92	[22]
10d	H	CH_3	OCH_3	S	30	80	[22]
10e	H	CH_3	CH_3	O	10	93	[22]
10f	4-CH_3O	CH_3	OC_2H_5	O	10	95	[25]
10g	4-CH_3O	CH_3	OC_2H_5	S	30	91	[19]
10h	4-CH_3	CH_3	OC_2H_5	O	10	90	[25]
10i	4-NO_2	CH_3	OC_2H_5	O	30	86	[19]
10j	4-NO_2	CH_3	OCH_3	O	30	87	[22]
10k	3-NO_2	CH_3	OC_2H_5	O	45	76	[19]
10l	4-Cl	CH_3	OC_2H_5	O	15	92	[19]
10m	2,4-Cl_2	CH_3	OC_2H_5	O	60	83	[25]
10n	3-Br	CH_3	OC_2H_5	O	15	90	[25]
10o	3,4-$(CH_3O)_2$	CH_3	OC_2H_5	O	45	88	[16]
10p	2-OH	CH_3	CH_3	O	10	85	[14]
10q	2-Furyl	CH_3	OC_2H_5	O	30	81	[9]
10r	H	C_6H_5	OC_2H_5	O	15	90	[16]

Reaction conditions: 10 mmol aldehyde, molar ratio of aldehyde, acetoacetate, and urea (or thiourea) 1:1:1, 0.2 mmol **4**, 90 °C

[a] Isolated yield based on carbonyl compounds

Besides the β-ketoester, β-diketones can also be employed without any decrease in yields (entries 5, 16). Thiourea was used as one of the substrates to provide the corresponding DHPMs in reasonable to good yields (entries 2, 4, 7). It is of great importance that many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced without any interruption in efficiency. Also important is the survival of a variety of functional groups, for example as ethers, esters, nitro, hydroxyl, and halides under these reaction conditions. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents could afford good yields of DHPMs in high purity.

In summary, an efficient procedure for synthesis of DHPMs via one-pot three-component Biginelli-type reaction catalyzed by dicationic ionic liquids was developed. The methodology has the advantages of short reaction time, lack of organic solvent, recyclability of catalysts, and easy work-up for isolation of the products in good yield with high purity.

Experimental

Melting points were determined by use of an X_6-Data microscope apparatus. The IR spectra were run on a Bruker Vectter 22 spectrometer and results are expressed in cm^{-1}

(KBr). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX300 spectrometer at 300 and 75.5 MHz in D_2O. Elemental analyses were performed with a Perkin–Elmer C elemental analyzer, and the results agreed favorably with calculated values. Mass spectra were obtained with an automated Finnigan TSQ Quantum Ultra AM (Thermal) LC–MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

N,N,N′,N′-Tetramethylethylenediammonium-bis(propanesulfonate) (**1**, $C_{12}H_{28}N_2O_6S_2$)

To a solution of 11.6 g tetramethylethylenediamine (0.10 mol) in 20 cm^3 1,2-dichloroethane was added 24.4 g 1,3-propanesulfone (0.20 mol), in portions, within 15 min. The mixture was then stirred under nitrogen for 2 h at 55–60 °C. The white precipitate thus formed was cooled to room temperature, then isolated by filtration and washed with petroleum ether. The product was recrystallized from a mixture of water, ethanol, and diethyl ether to give 98% yield of white solid product, m.p.: 298–300 °C (dec). ^{1}H NMR (300 MHz): $\delta = 2.12$–2.20 (m, 2× 2H, N–C–CH_2–C–SO_3), 2.88 (t, 2× 2H, $J = 6.9$ Hz, N–C–C–CH_2–SO_3), 3.14 (s, 4× 3H, N–CH_3), 3.49–3.52 (m, 2× 2H, N–CH_2–C–C–SO_3), 3.87 (s, 4H, N–CH_2–CH_2–N) ppm; MS: $m/z = 361.06$ (M^+).

N,N,N′,N′-Tetramethyl-1,3-propandiyldiammonium-bis(propanesulfonate) (**2**, $C_{13}H_{30}N_2O_6S_2$)

Synthesized by the same process as **1** except that the reaction was carried out for 4 h at 35–40 °C. White solid, yield 96%, m.p.: 292–294 °C (dec). ^{1}H NMR (300 MHz): $\delta = 2.06$–2.14 (m, 2× 2H, N–C–CH_2–C–SO_3), 2.18–2.20 (m, 2H, N–C–CH_2–C–N), 2.85 (t, 2× 2H, $J = 6.8$ Hz, N–C–C–CH_2–SO_3), 3.03 (s, 4× 3H, N–CH_3), 3.30 (t, 2× 2H, $J = 8.0$ Hz, N–CH_2–C–C–SO_3), 3.41 (t, 4H, $J = 8.3$ Hz, N–CH_2–C–CH_2–N) ppm; MS: $m/z = 374.30$ ($M^+ -1$).

N,N,N′,N′-Tetramethyl-1,6-hexandiyldiammonium-bis(propanesulfonate) (**3**, $C_{16}H_{36}N_2O_6S_2$)

Synthesized by the same process as **1** except that the reaction was carried out for 2 h at 55–60 °C. White solid, yield 95%, m.p.: 300–303 °C (dec). ^{1}H NMR (300 MHz): $\delta = 1.30$ (s, 4H, N–C–C–CH_2–CH_2–C–C–N), 1.66 (s, 4H, N–C–CH_2–C–C–CH_2–C–N), 2.04–2.10 (m, 2× 2H, N–C–CH_2–C–SO_3), 2.84 (t, 2× 2H, $J = 7.1$ Hz, N–C–C–CH_2–SO_3), 2.96 (s, 4× 3H, N–CH_3), 3.20 (t, 2× 2H, $J = 8.4$ Hz, N–CH_2–C–C–SO_3), 3.33 (t, 4H, $J = 8.5$ Hz, N–CH_2–C–C–C–C–CH_2–N) ppm; MS: $m/z = 417.13$ (M^+).

N,N,N′,N′-Tetramethyl-N,N′-bis(3-sulfopropyl)ethylenediammonium bis(hydrogensulfate) (**4**, $C_{12}H_{32}N_2O_{14}S_4$)

To a solution of 36.1 g **1** (0.10 mol) in 10 cm^3 water was added 20.0 g sulfuric acid solution (98%, 0.20 mol). The mixture was then stirred for 2 h at 80 °C. The water was then removed under vacuum at 100 °C and the product was washed repeatedly with diethyl ether to remove unreacted material and again dried under vacuum. TSIL **4** was obtained quantitatively and in high purity as a colorless oil. ^{1}H NMR (300 MHz): $\delta = 1.85$–1.95 (q, 2× 2H, $J = 7.65$ Hz, N–C–CH_2–C–SO_3), 2.64 (t, 2× 2H, $J = 6.9$ Hz, N–C–C–CH_2–SO_3), 2.89 (s, 4× 3H, N–CH_3), 3.24 (t, 2× 2H, $J = 8.4$ Hz, N–CH_2–C–C–SO_3), 3.60 (s, 4H, N–CH_2–CH_2–N) ppm; ^{13}C NMR (75.5 MHz): $\delta = 18.71$, 47.48, 51.72, 56.30, 64.18 ppm; MS: $m/z = 556.89$ (M^+), 361.07 (M^+- $2H_2SO_4$, 100).

N,N,N′,N′-Tetramethyl-N,N′-bis(3-sulfopropyl)-1,3-propandiyldiammonium bis(hydrogensulfate) (**5**, $C_{13}H_{34}N_2O_{14}S_4$)

Synthesized by the same process as **4**, quantitative yield of pale yellow oily product. ^{1}H NMR (300 MHz): $\delta = 2.01$–2.11 (m, 4H+2H, N–C–CH_2–C–SO_3, N–C–CH_2–C–N), 2.72–2.81 (m, 2× 2H, N–C–C–CH_2–SO_3), 2.92 (s, 4× 3H, N–CH_3), 3.21–3.32 (m, 4H+4H, N–CH_2–C–C–SO_3, N–CH_2–C–CH_2–N) ppm; ^{13}C NMR (75.5 MHz): $\delta = 17.14$, 19.09, 48.10, 52.33, 61.15, 63.77 ppm.

N,N,N′,N′-Tetramethyl-N,N′-bis(3-sulfopropyl)-1,6-hexandiyldiammonium bis(hydrogensulfate) (**6**, $C_{16}H_{40}N_2O_{14}S_4$)

Synthesized by the same process as **4**, quantitative yield of pale yellow oily product. ^{1}H NMR (300 MHz): $\delta = 1.13$ (s, 4H, N–C–C–CH_2–CH_2–C–C–N), 1.49 (s, 4H, N–C–CH_2–C–C–CH_2–C–N), 1.88–1.90 (m, 2× 2H, N–C–CH_2–C–SO_3), 2.64–2.68 (m, 2× 2H, N–C–C–CH_2–SO_3), 2.79 (s, 4× 3H, N–CH_3), 3.00–3.02 (m, 2× 2H, N–CH_2–C–C–SO_3), 3.13–3.15 (m, 4H, N–CH_2–C–C–C–C–CH_2–N) ppm; ^{13}C NMR (75.5 MHz): $\delta = 17.92$, 21.42, 24.74, 47.15, 50.40, 61.85, 63.84 ppm.

General procedure for the three-component Bigineli-type reaction catalyzed by ***4***

To a mixture of an aromatic aldehyde **7** (10 mmol), acetoacetate **8** (10 mmol), and urea **9** (thiourea or guanidine) (10 mmol) in 10 cm^3 H_2O was added 0.2 mmol **4**. The mixture was stirred at 90 °C until TLC indicated the starting materials had disappeared. The resulting mixture was cooled and left to stand overnight. After filtration the crude product was then purified by recrystallization from alcohol to afford pure 3,4-dihydropyrimidines **10**. All products were characterized by IR and ^{1}H NMR, and their m.p.s were in agreement with reference values [9, 19, 25].

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