Research Article

Bi-SO₃H Functionalized Ionic Liquid Based on DABCO: New and Efficient Catalyst for Facile Synthesis of Dihydropyrimidinones

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A simple and efficient method for the one-pot Biginelli condensation reaction of aldehydes, β -dicarbonyl compounds, and urea or thiourea employing [DABCO](SO₃H)₂Cl₂ as a novel ionic liquid catalyst is described.

1. Introduction

Over the past decade, ionic liquids have attracted extensive interest in organic synthesis, which has been recognized by a number of articles covering various aspects of ionic liquids as the catalyst or as dual catalyst-solvent in synthetic organic chemistry [1, 2]. With increasing environmental concerns, the design of simple, easily separable, nontoxic, and low-cost acidic ionic liquids has become an important research field [3–5]. In this context, ionic liquids as homogenous acid catalyst have attracted a great deal of attention due to their outstanding properties such as simple preparation, undetectable vapor pressure, nonflammability and high thermal stability. Introduction of functional groups, especially the SO₃H-functional group, obviously enhanced their acidity and water solubility. These functionalized ILs are designed for a special use and are referred to as “task-specific ILs.”

Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three different substrates join through covalent bonds, have steadily gained importance in synthetic organic chemistry. MCRs allow the creation of several bonds in a single operation and offer remarkable advantages like simple procedure, high bond forming efficiency, time and energy saving, extraction and purification processes, and hence minimize waste generation [6–10]. MCRs are useful for the expedient creation of chemical

libraries of drug-like compounds with high levels of molecular complexity and diversity, thereby facilitating identification/optimization in drug discovery programmes [11–16]. Therefore, researchers have made great efforts to develop new MCRs with green procedure, especially in the areas of drug discovery, organic synthesis, and material science [17, 18].

In this paper, a novel bi-SO₃H functionalized ionic liquid based on DABCO was designed as a simple and powerful acid catalyst and applied for synthesis of dihydropyrimidinones in mild reaction condition.

2. Materials and Methods

2.1. Procedure for the Preparation of Ionic Liquid. A round-bottomed flask (100 mL) was charged with a solution of 1,4-diazabicyclo[2.2.2]octane, DABCO (0.56 g, 5 mmol) in dry CH₂Cl₂ (50 mL), and then chlorosulfonic acid (1.21 g, 10.4 mmol) was added dropwise over a period of 10 min at room temperature. After the addition was completed, the reaction mixture was left for 1 hour. In this period of time, a white solid was produced. Afterward, the CH₂Cl₂ was decanted. The residue was triturated with dry diethylether and dried under vacuum to give [DABCO](SO₃H)₂Cl₂ as a very viscous colorless oil at 98% yield.

Spectral data of [DABCO](SO₃H)₂Cl₂: ¹H NMR (300 MHz, DMSO-d₆): δ (ppm) 3.5 (s, 6H), 7.32 (s, 1H);

SCHEME 1: Synthesis of brnsted acidic ionic liquid.

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ (ppm) 43.2; MS: $m/z = 346$ ($\text{M}^+ + 1$), 345 (M^+). IR (KBr, cm^{-1}) ν_{max} : 3500-2800 (broad), 1319 (N-SO₂), 1179 (N-SO₂). Calcd. For $\text{C}_6\text{H}_{14}\text{N}_2\text{S}_2\text{O}_6\text{Cl}_2$: C, 20.86; H, 4.05; N, 8.11. Found: C, 20.63; H, 4.31; N, 7.89.

2.2. General Procedure for the Synthesis of Dihydropyrimidinones Derivatives. Aldehydes (1 mmol), ethyl acetoacetate (1 mmol), and urea or thiourea (1.5 mmol) were dissolved in 4 mL of ethanol containing $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$ (0.07 mmol, 0.024 g). The mixture was heated under reflux. After completion of the reaction, as monitored by TLC, water (10 mL) was added to the reaction mixture. The solid product was filtered, dried, and recrystallized from EtOH to give the pure product.

3. Results and Discussion

In continuation with our interest in developing efficient and environmental benign synthetic methodologies [19–21], we have prepared a new type of brnsted acidic ionic liquid catalyst based on DABCO, and found that it is highly active for the synthesis of dihydropyrimidinones.

To prepare the brnsted acidic ionic liquid, $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$, chlorosulfonic acid (2 equiv.) was added dropwise to a solution of DABCO (1 equiv.) in dry CH_2Cl_2 at room temperature (Scheme 1).

For identification of structure of ionic liquid, we have studied the ^1H NMR spectra of $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$. The presence of sulfonate groups causes a significant downfield shift of the hydrogens of ionic liquid (3.5 δ) compared with DABCO (2.7 δ). Acidic hydrogens of SO_3H groups were observed in 7.32 ppm that confirmed the sulfur atoms in the catalyst were connected to nitrogen atoms of DABCO [5]. Furthermore, according to the literature reports, in the reaction of triethylamine, 1-methyl imidazole, or imidazole with chlorosulfonic acid, the nitrogen atoms of amines act as a nucleophile (not base) and attack the sulfur atom of ClSO_3H [22].

Thermogravimetric analysis (TGA) was used to study the thermal stability of the acid catalyst (Figure 1). The catalyst is stable up to 250°C and it is safe to carry out the reaction at 80–140°C, which is sufficient for organic reaction.

To investigate the efficiency and applicability of the new catalyst, its role as brnsted acidic ionic liquid was evaluated for synthesis of dihydropyrimidinones (DHPMs) derivatives in EtOH under mild heating (Scheme 2).

For optimization of the reaction condition, ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), and urea (1.5 mmol)

FIGURE 1: The TGA curve of $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$.

were heated under refluxing EtOH in the presence of $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$ (0.07 mmol) to afford ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate in 98% yield (Table 1, Entry 1). To check the real effect of the catalyst, the reaction was performed without $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$. The yield of catalyst-free reaction was lower than 12%. Further, we carried out the above reaction with ClSO_3H as catalyst (0.14 mmol, 0.07 g) in the same reaction condition; it leads to several very close spots on TLC, and the desired product could not be isolated.

The promising results obtained with $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$ prompted us to further investigate the effect of solvents on Biginelli reactions. So, the model reaction was performed in various solvents, such as EtOH, MeOH, acetonitrile, THF, and CH_2Cl_2 under reflux, and it was found that EtOH provided the best solvents because of yield, reaction rate, cost, and environmental acceptability. Further experiments revealed the optimum amount of catalyst to be 0.07 mmol.

Structural varieties of arylaldehydes have been successfully utilized for this transformation, and in most cases, good yields were obtained (Table 1).

The reaction in refluxing ethanol alone gave poor yields. It is also a well-established fact that brnsted ionic liquids produced H^+ . Based on these two facts, a possible mechanism is depicted in Scheme 3 [23].

Table 2 compares the efficiency of the present method for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones with other reported catalysts in the literature. As can be seen, $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$ acts as a highly effective catalyst in terms of time, temperature, and yield of the reaction.

4. Conclusion

In summary, a novel and highly efficient methodology for the synthesis of DHPMs in the presence of catalytic amounts of novel ionic liquid, $[\text{DABCO}](\text{SO}_3\text{H})_2\text{Cl}_2$, under reflux conditions is reported. This protocol describes a nonmetal catalyst, safe and easy work-up procedure for the synthesis

SCHEME 2: Application of [DABCO](SO₃H)₂Cl₂ (IL) in the Biginelli reaction.

SCHEME 3: A plausible mechanism.

TABLE 1: [DABCO](SO₃H)₂Cl₂-catalyzed synthesis of dihydropyrimidinones derivatives in EtOH.

Entry	Ar	X	R	Time (min)	Yield (%) ^a	Mp (Lit.) ^c
1	C ₆ H ₅	O	Et	35	98	203–204 (202–204) [24]
2	4-F-C ₆ H ₄	O	Et	70	87	181–183 (183–185) [25]
3	4-MeO-C ₆ H ₄	O	Et	70	90	206–208 (206–208) [24]
4	3-MeO-C ₆ H ₄	O	Et	80	88	207–209 (207–208) [26]
5	2-Cl-C ₆ H ₄	O	Et	80	83	220–222 (222–224) [26]
6	4-Cl-C ₆ H ₄	O	Et	50	85	211–216 (208–211) [27]
7	4-MeC ₆ H ₄	O	Et	75	83	214–216 (215–217) [27]
8	3-NO ₂ -C ₆ H ₄	O	Et	55	91	228–232 (229–231) [27]
9	4-NO ₂ -C ₆ H ₄	O	Et	45	93	208–211 (208–210) [24]
10	C ₆ H ₅	S	Et	55	89	206–207 (206–207) [27]
11	4-NO ₂ -C ₆ H ₄	S	Et	120	75	110–113 (109–111) [27]
12	C ₆ H ₅	O	Me	40	93	209–210 (206–208) [27]
13	4-MeO-C ₆ H ₄	O	Me	75	82	190–192 (190–192) [27]
14	4-NO ₂ C ₆ H ₄	O	Me	55	82	213–215 (214–215) [27]

^aIsolated yields.^bProducts were characterized by comparison of their spectroscopic data (¹H NMR, IR) and melting points with those reported in the literature.TABLE 2: Comparison of the results obtained for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones catalyzed by [DABCO](SO₃H)₂Cl₂ with other recently reported catalysts.

Catalyst	Condition	Time	Yield (%)	References
Sulfonated carbon	Neat/140°C	15–30 min	80–92	[26]
[Hmim]HSO ₄	Neat/80°C	25–50 min	88–96	[28]
Bioglycerol-based carbon catalyst	Neat/75–80°C	4–4.5 h	80–91	[29]
HClO ₄ -SiO ₂	Neat/100°C	75–180 min	83–91	[30]
<i>p</i> -sulfonic acid calixarenes	EtOH/reflux	6 h	56–92	[31]
L-pyrrolidine-2-carboxylic acid-4-hydrogen sulfate supported on silica gel	EtOH/reflux	6 h	80–98	[32]
[DABCO](SO ₃ H) ₂ Cl ₂	EtOH/reflux	35–120 min	75–98	This work

of these products. In addition, simplicity and ease of preparation of the catalyst are promising points for the presented methodology.

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