



Short Communication

1-Methylimidazolium hydrogen sulfate/chlorotrimethylsilane: An effective catalytic system for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and hydroquinazoline-2,5-diones

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ABSTRACT

Brønsted acidic ionic liquid, 1-methylimidazolium hydrogen sulfate, in the presence of catalytic amount of chlorotrimethylsilane has been used as an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones and hydroquinazoline-2,5-diones under thermal and solvent-free conditions. High yields of the products were obtained in a few minutes by using this new catalysis system.

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1. Introduction

Biginelli reaction is ranked as one of the most powerful routes for the synthesis of complex heterocyclic scaffolds for therapeutic and pharmacological properties [1–3]. Classical Biginelli reaction involves one-pot condensation of an aldehyde, a β -ketoester, and urea under strongly acidic conditions [4].

In recent decades, the scope of the original Biginelli reaction was extended by variation of the 1,3-dicarbonyl compound building blocks. Many groups have elegantly demonstrated the synthetic versatility of numerous 1,3-dicarbonyl compounds, including β -ketoester and cyclic β -diketones [5–34]. However, in spite of their potential utility, all of the reported synthetic methods suffer from limitations such as the use of expensive reagents, strong acidic conditions, low yields and long reaction times. Also, the requirement for the use of stoichiometric amount of catalyst and un-recoverability of strong acids or solvents as well as harsh reaction conditions are of the other limitations of these reports. Therefore, to avoid these limitations, introducing milder and more efficient methods are needed.

Due to environmental concerns, the use of benign solvents as alternatives to volatile organic solvents is of much interest to organic chemists. The use of ionic liquids as reaction media and catalyst can offer a solution to solvent emission and catalyst recycle problems [35,36].

Ionic liquids possess the advantages like negligible vapor pressure, reasonable thermal stability and recyclability. They dissolve many organic and inorganic substrates and are tunable to specific chemical tasks [37]. Recently, ionic liquids have been successfully employed as solvents with catalytic activity for a variety of reactions [38].

In this study, in continuation of our effort to develop applicability of Biginelli reaction [39,40], an efficient, facile and solvent-free procedure was introduced for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (Table 1) and hydroquinazoline-2,5-diones/thiones (Table 2). For this purpose, the reaction of aromatic aldehydes, cyclic or acyclic ketones and urea/thiourea using Brønsted acidic ionic liquid (1-methylimidazolium hydrogen sulfate, [Hmim]HSO₄), in the presence of catalytic amount of chlorotrimethylsilane (TMSCl) (Schemes 1, 2) as an effective catalytic system was investigated for the first time. The procedure presented here not only gives the desired products in good yields, but also avoids the problems associated with conventional solvents such as cost, handling, safety and pollution, and moreover the reaction times are reduced to a few minutes.

2. Experimental

All reagents were purchased from Merck and Fluka and used without further purification. Melting points were obtained in open capillary tubes and were measured on an Electro-thermal IA 9100 apparatus. IR spectra were recorded on KBr pellets on a Shimadzu FT-IR 8600 spectrophotometer. ¹H and ¹³C NMR spectra were determined on a Bruker 500 DRX Avance instrument at 500 and 125 MHz.

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Table 1
Synthesis of 3,4-dihydropyrimidin-2(1H)-ones and comparison of efficiency 1-methylimidazolium hydrogen sulfate/chlorotrimethylsilane catalytic system with other catalysts and methods^a.

Products	R ¹	R ²	R ³	X	Found			Reported			
					m.p. (°C)	Time (min)	Yield (%)	m.p. (°C)	Time (min)	Yield (%)	Ref.
4a	3-NO ₂	Ph	Ph	O	221–223	40	96(95,92,90) ^b	222–224	7	96	[39] ^c
4b	4-NO ₂	Ph	Ph	O	256–258	25	96	–	–	–	–
4c	3-OMe	Ph	Ph	O	191–193	35	87	191–193	7	91	[39] ^c
4d	3-Br	Ph	Ph	O	201–203	50	88	–	–	–	–
4e	4-Me	Ph	Ph	O	236–238	60	80	–	–	–	–
4f	H	Ph	Ph	S	260–261	45	94	259–261	5	97	[39] ^c
4g	3-Cl	Ph	Ph	S	263–264	50	92	263–265	5	95	[39] ^c
4h	4-Cl	Ph	Ph	S	284–286	35	89	–	–	–	–
4k	4-NO ₂	Ph	Ph	S	276–277	35	96	–	–	–	–
4l	2,4-diCl	Me	COOEt	O	253–255	25	91	–	–	–	–
4m	H	Me	COOEt	O	204–205	30	92	206–208	240	97	[27]
4n	3-NO ₂	Me	COOEt	O	230–232	20	96	230–232	240	94	[27]
4o	3-OMe	Me	COOEt	O	210–211	25	91	206–208	240	94	[27]
4p	2-OMe	Me	COOEt	O	260–261	35	86	–	–	–	–
4q	H	Me	COOEt	S	205–206	30	90	207–208	240	92	[27]
4r	2-OMe	Me	COOEt	S	193–195	25	92	–	–	–	–
4s	3-NO ₂	Me	COOEt	S	205–207	25	94	206–207	240	92	[27]

^a Reaction condition: aromatic aldehyde (1 mmol), ketone or β -ketoester (1 mmol), urea (2 mmol) or thiourea (2 mmol), [Hmim]HSO₄ (0.5 mmol), TMSCl (0.5 mmol) in an oil bath at 80 °C.

^b The yields of reaction with recycled ionic liquid after three successive runs.

^c Reaction carried out under microwave irradiation.

2.1. Preparations of 1-methylimidazolium hydrogen sulfate, [Hmim]HSO₄, as Brønsted acidic ionic liquid

The ionic liquid of [Hmim]HSO₄ was prepared by reported procedure [41]. 1-Methylimidazole (1.59 mL, 20 mmol) and acetonitrile (5 mL) were charged into a 25 mL round-bottom flask. Then, the mixture was stirred at 0 °C for 1 min. Stoichiometric amount of concentrated sulfuric acid (97%, 1.03 g/mL) was added dropwise and the mixture stirred for 1 h at 0 °C and then stirred for 2 h at room temperature. The [Hmim]HSO₄ was washed repeatedly with diethyl ether (2.5 mL) to remove non-ionic residues and then it was dried in a vacuum evaporator.

2.2. General procedure for preparation of 4a-s and 7a-p

A mixture of aldehyde (1 mmol), cyclic or acyclic ketone (1 mmol), urea or thiourea (2 mmol), [Hmim]HSO₄ (0.5 mmol) and TMSCl (0.5 mmol) was heated at 80 °C for the appropriate time according

to Tables 1, 2. After completion of reaction, as indicated by TLC, the reaction mixture was allowed to cool to room temperature. Then, 5 mL distilled water was added into the beaker and stirred. The obtained precipitate was filtered off. The crude product was recrystallized from ethanol and dried to afford powder compounds of 4a-s, 7a-p.

The filtrate was concentrated under reduced pressure and washed with diethyl ether. Then, it was dried in a vacuum evaporator to recover the ionic liquid for subsequent use.

3,4-Dihydro-4-(4-NO₂-phenyl)-5,6-diphenylpyrimidine-2(1H)-one (4b). White powder; mp: 256–258 °C; IR (KBr) ν_{\max} : 3232, 3097, 2928, 1702, 1651, 1530 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ_{H} : 5.35 (d, $J = 4.2$ Hz, 1H), 6.80–7.26 (m, 10H), 7.61 (d, $J = 8.6$ Hz, 2H), 8.25 (d, $J = 8.6$ Hz, 2H), 8.58 (s, 1H, NH), 9.46 (s, 1H, NH); ¹³C NMR (125 MHz, DMSO-d₆) δ_{C} : 58.1, 110.2, 124.9, 127.3, 128.7, 128.8, 129.2, 129.4, 129.9, 130.5, 134.3, 134.7, 137.4, 147.9, 150.2, 153.4.

3,4-Dihydro-4-(3-Br-phenyl)-5,6-diphenylpyrimidine-2(1H)-one (4d). White powder; mp: 201–203 °C; IR (KBr) ν_{\max} : 3220, 3091, 2918, 1689, 1595, 1471 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ_{H} :

Table 2
Synthesis of hydroquinazoline-2,5-diones/thiones and comparison of efficiency 1-methylimidazolium hydrogen sulfate/chlorotrimethylsilane catalytic system with other catalysts.

Products	R ¹	R ²	R ³	X	Found			Reported			
					Time (min)	Yield (%)	m.p.(°C)	Time (h) ^a	Yield (%) ^b	m.p.(°C)	Ref.
7a	3-NO ₂	H	H	O	15	94	308–310	–	–	–	–
7b	2-NO ₂	H	H	O	15	85	271–273	–	–	–	–
7c	2-Cl	H	H	O	15	84	299–301	–	–	–	–
7d	3,5-Cl	H	H	O	15	82	324–326	–	–	–	–
7e	4-Br	H	H	S	15	78	306–308	–	–	–	–
7f	H	H	H	O	15	86	307–308	10, 6.5	70, 94	308–309	[23,34]
7g	2-Br	H	H	O	15	88	289–290	10	66	291–292	[23]
7h	3-Br	H	H	O	15	95	302–303	10	68	304–305	[23]
7i	4-NO ₂	H	H	O	15	82	299–300	10, 6.5	67, 81	302–303	[23,34]
7j	4-Cl	H	H	O	15	93	285–287	10, 6	76, 88	287–288	[23,34]
7k	4-OMe	H	H	O	15	68	277–278	10	74	279–280	[23]
7l	4-Cl	CH ₃	CH ₃	O	10	91	296–297	2, 10	94, 72	296–297	[33,23]
7m	2-Cl	CH ₃	CH ₃	O	10	87	276–288	0.42	75	277–279	[24]
7n	H	CH ₃	CH ₃	O	10	89	286–288	1.5, 2.5, 0.33	95, 92, 73	287–290	[33,34,24]
7o	4-Cl	CH ₃	CH ₃	S	10	86	271–274	0.5	52	271–274	[24]
7p	3-NO ₂	CH ₃	CH ₃	S	10	82	251–253	0.58	46	250–252	[24]

^a Numbers of this column refer to reported time (h) in literatures that are shown in the reference column, respectively.

^b Numbers of this column refer to reported yield in literatures that are shown in the reference column, respectively.

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