

Solvent-free and one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones using ionic liquid *N,N*-diethyl-*N*-sulfoethan ammonium chloride {[Et₃N-SO₃H]Cl} as a green catalyst

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Abstract

In this work, the ionic liquid triethylamine-bonded sulfonic acid {[Et₃N-SO₃H]Cl}, *N,N*-diethyl-*N*-sulfoethan ammonium chloride was used as a green acidic homogeneous catalyst in order to synthesis 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones as two categories of heterocycles. The dihydropyrimidineones and dihydropyrimidinethiones derivatives which were synthesized in this method can be regarded as two important categories of heterocyclic compounds with biologic and pharmacologic activity. The ionic liquid that was used in these reactions acts as Bronsted acid and green homogeneous catalyst. It has N-S bond in its cationic fragment and can be easily synthesised. The advantages of our method are as follow: solvent-free conditions, green process and high isolated yield of products.

Keywords: Ionic liquid; Biginelli reaction; green catalyst; 3,4-dihydropyrimidin-2(1H)-ones; *N,N*-diethyl-*N*-sulfoethan ammonium chloride.

Introduction

Dihydropyrimidinones and their derivatives (DHPMs) are an important class of

heterocycles and have been at the focus of attention because of their biological activities and wide pharmacological rolls such as

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calcium channel blockers, antihypertensive agents, anti-inflammatory and antitumor actions [1-4]. Since their first use in 1893 that the Biginelli reaction was reported [5], researchers have studied how to modify these reaction type and they have found some methods and protocols such as solvent-free synthesis with variety catalysts such as silicatriflate [6], Bismuth (III) nitrate [7], *p*-TSA [1], Silica Sulfuric Acid [2], Silica Immobilized Nickel Complex [8], Glycine nitrate [4] and other classic Lewis or Bronsted acid [9]. Recently, Wang and Liu have reported solvent-free and catalyst-free characteristic of this reaction, but their method was limited to some specific substrates and high temperature and long reaction time [10].

Other methods, however, reported different types of catalysts, suffer drawbacks such as harsh solvents, high temperature process, or using heavy metal complexes [9]. In our method, by using *N,N*-diethyl-*N*-sulfoethan ammonium chloride ($[\text{Et}_3\text{N}-\text{SO}_3\text{H}]\text{Cl}$) as a bronsted acidic ionic liquid (Figure 1) and green catalyst [11], throughout the solvent-free process and mild reaction, we obtained good and excellent isolated yields of Biginelli reaction products. After the first report of the application of this ionic liquid [11], we used it to catalyze the

Biginelli reaction between the aromatic aldehydes and ethylacetoacetate and Urea or thiourea and successfully reached the products in solvent-free conditions and green method with very good yields.

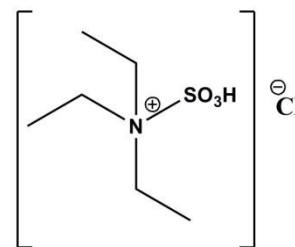


Figure 1. Structure of *N,N*-diethyl-*N*-sulfoethan ammonium chloride

Experimental

Materials and instrumentation

All of the substrates and reagents were purchased from Merk and Sigma Aldrich. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ^1H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) were run on a BrukerAvance DPX. FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Buchi B-545 apparatus in open capillary tubes.

Procedure for the preparation of ionic liquid $[\text{Et}_3\text{N}-\text{SO}_3\text{H}]\text{Cl}$

A solution of triethylamine (0.50 g, 5 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirring solution of chlorosulfonic acid (0.58 g, 5 mmol) in dry CH_2Cl_2 (40 mL) over a

period of 10 min at 10 °C. Afterward, the reaction mixture was allowed to heat to room temperature (accompanied with stirring), and stirred for another 4 h. The solvent was evaporated, and the liquid residue was triturated with t-butylmethyl ether (3×10 mL) and dried under powerful vacuum at 90 °C to give [Et₃N-SO₃H]Cl as a viscous pale yellow oil in 93% yield [11].

General procedure for synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones

A mixture of β -dicarbonyl compound (2 mmol), aldehyde (2 mmol), urea or thiourea (3 mmol) and *N,N*-diethyl-*N*-sulfoethan ammonium chloride (0.02 g) was heated in an oil bath (70 °C) under stirring for 30 min. After completion (monitored by TLC), the mixture was cooled to room temperature, then H₂O (5mL) was added and filtered, the precipitate was washed with water, recrystallized with hot ethanol, then the solvent was evaporated on the reduced pressure and pure products were obtained in good to high yields. The products were analyzed with Ft-IR, ¹HNMR, ¹³CNMR and comparison melting points observed with reported in the literatures.

Spectral data of product

Compounds 4a-m, are reported in the literature and references are given. All products gave satisfactory spectral data and

were compared with authentic samples wherever possible. Some of spectral data are listed below.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

m.p=196-197°C, ¹HNMR (250MHz, DMSO-d₆) δ (ppm): 1.07 (t, ³J_{HH}=6 Hz, 3H, CH₃), 2.17 (s, 3H, CH₃), 3.96 (q, ³J_{HH}=6 Hz, 2H, CH₂), 5.12 (s, 1H), 7.20–7.47 (m, 5H, ArH), 7.76(s, 1H, N-H), 9.25(s, 1H, N-H). ¹³CNMR (62.9 MHz, DMSO-d₆) δ = 14.90, 18.19, 54.40, 59.63, 99.72, 126.68, 127.20, 127.70, 128.99, 133.30, 145.28, 152.67, 160.29 and 165.78 ppm. IR (KBr): ν_{\max} =3440, 3351, 3248, 2979, 1725, 1698, 1648, 1462, 1313, 1291, 1091, 782, 699, 515 cm⁻¹.

Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

m.p= 215-217°C, ¹HNMR (250MHz, DMSO-d₆) δ (ppm): 1.07 (t, ³J_{HH}=7 Hz, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.95 (q, ³J_{HH}=7 Hz, 2H, CH₂), 5.28 (s, 1H), 7.60-7.66 (m, 2H, ArH), 7.88 (s, 1H, N-H), 8.06-8.12 (m, 2H, ArH), 9.36(s, 1H, N-H). IR (KBr): ν =3330, 3217, 3093, 2965, 1707, 1629, 1526, 1456, 1347, 1223, 1088, 900, 739, 602, 526 cm⁻¹.

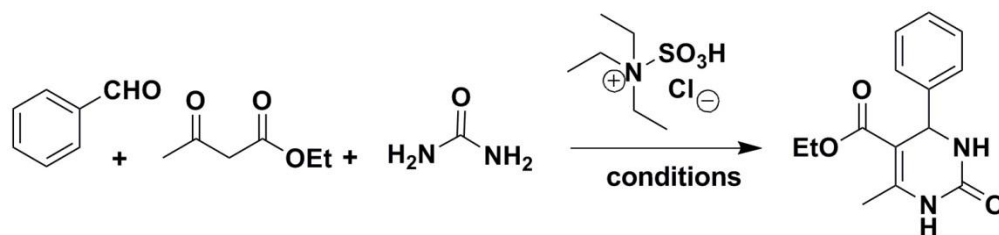
Ethyl-4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

m.p=202-204 °C, ¹HNMR (250MHz,

DMSO-d₆) δ (ppm): 1.02 (t, $^3j_{\text{HH}}=7$ Hz, 3H, CH₃), 2.16 (s, 3H, CH₃), 3.92 (q, $^3j_{\text{HH}}=7$ Hz, 2H, CH₂), 5.10 (s, 1H), 7.13-7.24 (m, 2H, ArH), 7.47 (s, 1H, N-H), 7.64-7.80 (m, 2H, ArH), 9.22 (s, 1H, N-H). IR (KBr): $\nu = 3244, 3116, 2980, 1724, 1705, 1541, 1487, 1289, 1222, 1090, 1009, 781, 656, 519, 483$ cm⁻¹.

Results and discussion

First of all, we select reaction of benzaldehyde (3mmol), urea (4mmol) and ethyl acetoacetate (3 mmol) as a model reaction (scheme 1) and investigate variety of conditions such as different solvents, temperature and amounts of catalysts to optimize conditions of reactions and results provided in Table 1.



Scheme1. The model reaction between benzaldehyde (1mmol), ethyl acetoacetate (1mmol) and urea (1mmol) in the presence of catalyst

According to the results that provided in Table 1, we examined different solvents in the absence of catalyst and in the presence of varying amounts of catalyst. Three different solvents were examined in the absence of catalyst and we observed the low or trace yield of products in those conditions (Table 1, Entries 1-3), then we tested these solvents in the presence of variety amounts of

catalysts and observed by using ethanol as solvent and 20 mol% of catalyst in the reflux conditions. The maximum yield of product which was 86% (Table 1, Entry 8), however, in solvent free conditions the best yield of reaction was obtained. The best amount of ionic liquid used as a catalyst was 10 mol% in solvent-free conditions in the 70 °C (Table 1, Entries 9-11).

Table 1. Optimization of catalyst amount, solvent and temperature of model reaction (Scheme 1)

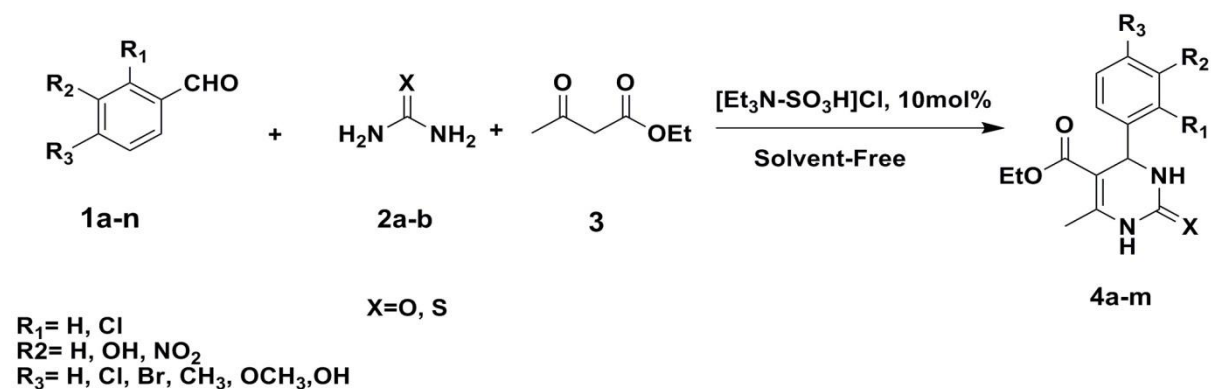
Entry	Solvent	Amount of Catalyst (%mol)	Temp. (°C)	Time (h)	Yield (%) ^a
1	CH ₂ Cl ₂	0	Reflux	4	6

2	CH ₃ CN	0	Reflux	4	trace
3	EtOH	0	Reflux	4	14
4	CH ₂ Cl ₂	5	Reflux	10	20
5	CH ₃ CN	5	Reflux	7	10
6	EtOH	5	Reflux	6	35
7	EtOH	10	Reflux	5	85
8	EtOH	20	Reflux	5	86
9	Solvent free	5	70	3	70
10	Solvent free	10	70	1	93
11	Solvent free	10	80	1.5	93

^aIsolated yields

Therefore, by selecting these conditions, other reactions with aromatic aldehydes and urea and thiourea were carried out (Scheme

2) and results of these reactions were provided in Table 2.



Scheme 2. Solvent free Biginelli reaction between aromatic aldehydes, urea or thiourea and ethylacetoacetate in optimized conditions

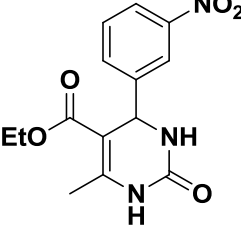
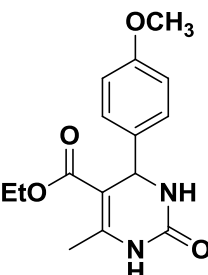
Table 2. Results of reaction between aromatic aldehydes, urea or thiourea and ethylacetoacetate in optimized conditions

Entry	R ₁	R ₂	R ₃	X	Product	Yield (%)	Time (h)	M.P (°C)	M.P (°C) reported [ref]
1	H	H	H	O	4a	93	1	196-197	206 [2]
2	H	NO ₂	H	O	4b	97	0.5	215-217	229-230 [6]
3	H	OH	H	O	4c	85	2	164-165	167-170[11]
4	H	H	Br	O	4d	97	0.5	202-204	--
5	H	H	OCH ₃	O	4e	82	1.5	199-200	205-207 [2]
6	Cl	H	Cl	O	4f	92	0.5	224-226	--
7	H	H	OH	O	4g	84	2	228-229	231-233[12]
8	H	H	CH ₃	O	4h	80	2	216-217	218-219[13]
9	H	H	H	S	4i	86	1	198-199	205-206 [1]
10	H	NO ₂	H	S	4j	95	0.5	196-197	203-205 [6]
11	H	H	OCH ₃	S	4k	81	1	147-148	153-155 [2]
12	H	OH	H	S	4l	87	2	185-186	183-184[11]
13	H	H	OH	S	4m	85	1.5	195-196	198-200[12]

For the investigation of efficiency of catalyst used in our method and comparison with previously reported protocols we

provided Table 3. According to the Table 3, we observed good and high yields of products in very mild and green conditions.

Table 3. Comparison between our method with some previous reported methods in Biginelli reaction

Entry	product	Time	Temperature (°C)	Catalyst (%mole)	Solvent	Yield (%)	Ref.
1		5 h	100	NH ₄ H ₂ PO ₄ /SiO ₂	H ₂ O	74	[14]
		8.5 h	reflux	MPA-supported HY	CH ₃ CN	95	[15]
		15min	110	[Hmim]HSO ₄ (10 mol%)	Solvent-free	90	[16]
		30 min	70	[Et ₃ N-SO ₃ H]Cl (10 mol%)	Solvent-free	97	Our method
2		30 min	110	[Hmim]HSO ₄ (10 mol%)	Solvent-free	92	[16]
		7.5 h	reflux	MPA-supported HY	CH ₃ CN	95	[15]
		1.5 h	70	[Et ₃ N-SO ₃ H]Cl (10 mol%)	Solvent-free	82	Our method

Conclusion

In conclusion, we described a new method for the synthesis of two categories of useful heterocyclic compounds, by using new ionic liquid involving N-S bond in cationic fragment that act as bronsted acid and catalyze one important multi-component reaction. The solvent free conditions, high isolated yield of products, reusability of catalyst and high purity of products are the advantages of this method.

Supporting Information

More experimental details and copies of

NMR spectra (¹H and ¹³C NMR spectra) and Ft-IR spectra of some products, provided in supporting information file 1.

Acknowledgements

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