

Fe(HSO₄)₃ as an Efficient Catalyst for the Preparation of 3,4-Dihydropyrimidin-2(1H)-ones in Solution and under Solvent-Free Conditions

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A one-pot three-component condensation of aromatic aldehydes, β -ketoesters and urea or thiourea, efficiently promoted in the presence of Fe(HSO₄)₃ in solution and under solvent-free conditions, produced 3,4-dihydropyrimidin-2(1H)-ones. The method offers several advantages including simple, easy and clean work-up procedure, relatively short reaction times and good to high yields of the products

Keywords: 3,4-Dihydropyrimidin-2(1H)-ones, Solvent-free conditions, Biginelli reaction, Three-component condensation, Fe(HSO₄)₃

INTRODUCTION

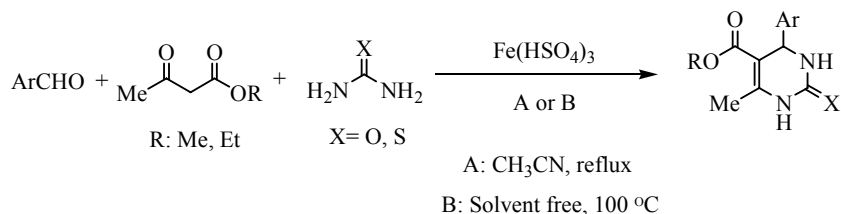
Dihydropyrimidinones (DHPMs) and their derivatives, important classes of compounds in the field of pharmaceuticals [1], exhibit significant biological properties, good for antihypertensive, antibacterials, antivirals, as well as antitumor and anti-HIV agents [2-6]. In 1893, Biginelli reported an important method for the preparation of 3,4-dihydropyrimidin-2(1H)-ones, *via* a one-pot condensation reaction of β -dicarbonyl compounds with aldehydes and urea or thiourea in the presence of an acid catalyst [7]. The strongly acidic conditions and the low to moderate product yields are important drawbacks of Biginelli's method.

In recent years, reported improvements in the Biginelli reaction include several methods and reagents, such as zirconium(IV) chloride [8], ytterbium(III) resin [9], boric acid [10], silica sulfuric acid [11], poly(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex [12], concentrated HCl [13],

N-butyl-N,N-dimethyl- α -phenyl ethyl ammonium bromide [14], samarium iodide [15], ZnCl₂, CuCl₂, NiCl₂ and CoCl₂ doped hydroxyapatite [16], H₂SO₄ [17], silica triflate [18], trichloroisocyanuric acid [19], 12-molybdophosphoric acid [20], covalently anchored sulfonic acid onto silica [21] and propane phosphonic acid anhydride [22]. Most reported methods have shortcomings due to expensive reagents, long reaction times, unsatisfactory yields, and so forth. Therefore, the discovery of an inexpensive, facile, and efficient reagent for the preparation of 3,4-dihydropyrimidin-2(1H)-ones under mild conditions is an active ongoing research topic.

Recently, the use of metal hydrogensulfates in organic reactions has become an important part of our research program [23-27]. In continuation of these studies, we herein report an efficient method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones by the one-pot three-component condensation of aromatic aldehydes, β -keto esters and urea or thiourea in the presence of Fe(HSO₄)₃, both in solution and under solvent-free conditions (Scheme 1).

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Scheme 1

EXPERIMENTAL

Products of the following procedures were characterized by their physical constants, and compared with authentic samples by IR and NMR spectroscopy.

General Procedure for the Synthesis of DHPMs in CH₃CN

A solution of β -keto ester (1.2 mmol), aldehyde (1.0 mmol) and urea or thiourea (1.2 mmol) in 8 cm³ acetonitrile was heated under reflux conditions in the presence of Fe(HSO₄)₃ (0.348 g, 1 mmol) for 2 h. The progress of the reaction was monitored by TLC. The reaction was cooled to room temperature and poured into 30 cm³ ice water. The separated solid was filtered, washed with water and then recrystallized from ethanol to afford the products in 80-95% yields [33].

General Procedure for the Synthesis of DHPMs under Solvent-Free Conditions

A mixture of the substrate (1 mmol), β -keto ester (1.2 mmol) urea or thiourea (1.2 mmol) and Fe(HSO₄)₃ (0.348 g, 1 mmol) was heated in an oil bath (100 °C) for 2 h. After completion (monitored by TLC), the reaction was cooled to room temperature and the mixture was poured onto crushed ice, upon which a solid material was separated and then filtered and recrystallized from ethanol to produce the desired product in 80-95% yields [33].

RESULTS AND DISCUSSION

The optimized conditions for the condensation of benzaldehyde, ethyl acetoacetate and urea are 1 mmol benzaldehyde, 1.2 mmol ethyl acetoacetate and 1.2 mmol urea or thiourea in the presence of 1 mmol Fe(HSO₄)₃ for 2 h in 8

cm³ acetonitrile under reflux conditions. Other substituted aldehydes also reacted well under the same conditions, to give the corresponding dihydropyrimidinones in excellent yields (Table 1).

Similar reactions were also performed under solvent-free conditions in an oil bath at 100 °C, although this did not change the reaction times and the yields considerably.

In order to show the merit of this method, Table 2 compares some of our results with some of the aforementioned methods for the synthesis of Biginelli-type 3,4-dihydropyrimidin-2(1H)-ones [20-22,29].

In conclusion, we have described a simple and efficient method for the synthesis of dihydropyrimidinones using a reusable Fe(HSO₄)₃ both in solution and under solvent-free conditions. The method offers several advantages including simple, easy and clean work-up procedure, relatively short reaction times and good to high yields of the products, which make it a useful addition to the present methodologies for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones.

ACKNOWLEDGEMENTS

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Table 1. Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Thiones in the Presence of Fe(HSO₄)₃^a

Entry	Ar	R	X	In CH ₃ CN		Solvent-free		M.P. (°C)	
				Time (h)	Yield (%) ^b	Time (h)	Yield (%) ^b	Found	Reported
1	C ₆ H ₅	Et	O	1.5	86	2.0	90	201-203	202-204 [10]
2	C ₆ H ₅	Et	S	2.0	90	1.5	90	208-210	209-211 [10]
3	C ₆ H ₅	Me	O	1.5	81	2.0	83	231-233	233-236 [10]
4	C ₆ H ₅	Me	S	2.0	95	2.0	93	228-229	229-231 [10]
5	4-ClC ₆ H ₄	Et	O	2.0	83	2.0	85	210-213	213-215 [10]
6	4-ClC ₆ H ₄	Et	S	1.5	89	2.0	90	191-193	192-195 [30]
7	4-ClC ₆ H ₄	Me	O	2.0	81	2.0	83	205-206	204-207 [10]
8	3-ClC ₆ H ₅	Et	O	1.5	85	2.0	87	193-195	195-196 [31]
9	4-MeOC ₆ H ₄	Et	O	2.0	90	2.0	90	202-203	201-203 [10]
10	4-MeOC ₆ H ₄	Me	O	1.5	91	2.0	95	191-193	192-194 [10]
11	2-MeOC ₆ H ₄	Et	O	1.5	85	2.0	87	260-261	261-262 [10]
12	4-O ₂ NC ₆ H ₄	Et	O	2.0	83	1.5	90	208-210	208-211 [32]
13	4-O ₂ -C ₆ H ₄	Me	O	1.5	90	1.5	90	233-235	235-237 [32]
14	3-O ₂ NC ₆ H ₄	Et	O	2.0	87	2.0	90	226-228	227-229 [10]
15	3-O ₂ NC ₆ H ₄	Et	S	1.5	80	2.0	80	204-206	206-207 [10]
16	2-O ₂ NC ₆ H ₄	Et	O	2.0	85	2.0	85	207-208	206-208 [10]
17	PhCH=CH	Et	O	1.5	80	1.5	85	231-233	232-235 [10]

^aProducts were characterized by their physical constants, and compared with authentic samples by IR and NMR spectroscopy. ^bIsolated yields.

Table 2. Efficiencies of Present and Previously Reported Methods for the Synthesis of Biginelli-Type 3,4-Dihydropyrimidine-2(1*H*)-ones^a

Method	Time (h)/Yield (%)		
	Ph	4-MeO-C ₆ H ₄	PhCH=CH ₂
Present	1.5/86	2/90	1.5/80
12-Molybdophosphoric acid [20]	5/80	4/70	-
Sulfonic acid ^b [21]	18/90	7/92	9.5/87
Propane phosphonic acid anhydride [22]	6/77	6/59	-
Montmorillonite KSF [29]	48/82	48/79	48/79

^aR² = ethanol; X = oxygen. ^bCovalently anchored on silica.

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 Entry 1. FT-IR (KBr), ν (cm^{-1}): 3440 (m), 3240 (m), 3105 (w), 2990 (w), 1725 (s), 1700 (s), 1640 (s), 1450 (s), 1415 (s), 1310 (m), 1285 (m), 1220 (m), 1085 (s), 780-755 (s), 700 (w), ^1H NMR (CDCl_3), δ (ppm): 1.19-1.21 (t, 3H), 2.39 (s, 3H), 4.09-4.15 (m, 2H), 5.44-5.45 (d, 1H), 5.57 (bs, 1H), 7.29-7.55 (m, 5H), 7.55 (bs, 1H).
 Entry 9. FT-IR (KBr), ν (cm^{-1}): 3470 (m), 3240 (m), 3105 (w), 2980 (w), 1725 (s), 1700 (s), 1640 (s), 1460 (s), 1425 (s), 1310 (m), 1285 (m), 1220 (m), 1080 (s), 755 (s), ^1H NMR (CDCl_3), δ (ppm): 1.20 (t, 3H), 3.82 (s, 3H), 4.10 (m, 2H), 5.39 (d, 1H), 5.66 (bs, 1H), 6.86 (dd, 2H), 7.27 (dd, 2H), 7.39 (bs, 1H).