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Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones by Aluminum Hydrogensulfate

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3,4-Dihydropyrimidin-2(1*H*)-ones are synthesized by the three-component condensation of aromatic aldehydes, β-ketoesters and urea or thiourea in methanol or under solvent-free conditions, using aluminum hydrogensulfate as the catalyst.

Key words: aluminum hydrogensulfate, Biginelli reaction, catalysis, solvent-free, dihydropyrimidinones

Dihydropyrimidinones (DHPMs) and their derivatives exhibit pharmacolgical properties, as the calcium channel blockers, antihypertensive agents, α_{1a}- and neuropeptide Y (NPY) antagonists [1]. More than a century ago, the Biginelli reaction was reported as a one pot condensation reaction of β-dicarbonyl compounds with aldehydes and urea in the presence of HCl to produce dihydropyrimidinones in low yields [2]. Biginelli reaction has already been reviewed [3]. Several improved protocols for the preparation of DHPMs have recently been reported, either by modification of the classical one-pot condensation approach itself [4–9] or by the development of novel, but more complex multi-step strategies [10]. However, some of the reported methods suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedures and making environmental pollutions [4,11–16].

Recently, we have reported the preparation and application of metallic hydrogensulfates, as the source of both protic and metallic Lewis acids, in synthetic methodology [17–20]. They are very cheap and stable acidic reagents with general formula, $M(HSO_4)_n$ (M = Na, Mg, Al, Fe, *etc.*), that could be used as catalysts in many important organic reactions under heterogeneous conditions.

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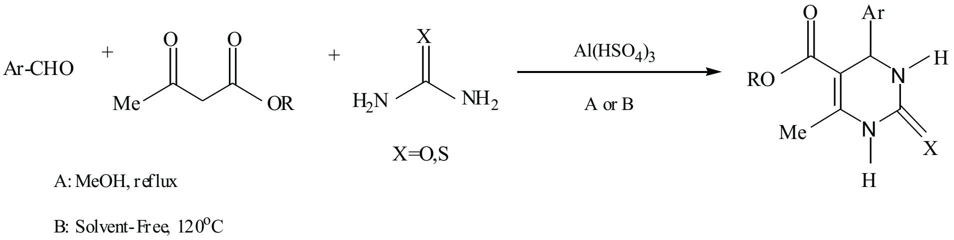
RESULTS AND DISCUSSION

Aluminum hydrogensulfate, $Al(HSO_4)_3$, is a stable solid material that in contrary to $AlCl_3$ is not hygroscopic [21,22]. Herein we wish to report its application as a very mild and efficient reagent for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones by the three component Biginelli condensation (Scheme 1).

Scheme 1



The results are summarized in Table 1. Aromatic aldehydes, alkyl acetoacetates and urea or thiourea were used as strating materials and subjected to the condensation reaction in methanol and also under solvent-free conditions. Thiourea was used with similar success to urea and the corresponding thiones were obtained satisfactorily (entries 16, 17). Another advantage of this method is the mildness of the reagent which permits the survival of acid-sensitive functional groups after several hours (entries 5, 14, 17). Comparison of the last two columns in Table 1 shows that under solvent-free conditions the reactions took place in shorter periods and in most cases in higher yields.

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones by three component condensation of aldehydes, β-ketoesters, and urea or thiourea in MeOH or under solvent-free conditions.

Entry	Ar	R	X	In MeOH		Solvent-free		M.p. (°C)	
				Time (h)	Yield (%)	Time (h)	Yield (%)	Found	Reported
1	C_6H_5	Et	O	35	89	15	90	203–205	202–204[4]
2	4-Cl-C_6H_4	Et	O	45	84	18	86	210–212	213–215[4]
3	4-O_2N-C_6H_4	Et	O	45	87	17	91	209–210	208–211[4]
4	4-Me-C_6H_4	Et	O	35	90	13	94	213–214	213–214[23]
5	4-MeO-C_6H_4	Et	O	35	92	16	93	202–203	201–203[4]
6	4-F-C_6H_4	Et	O	45	85	20	85	182–184	185–186[4]
7	3-Cl-C_6H_4	Et	O	40	81	17	86	195–196	195–196[15]
8	3-O_2N-C_6H_4	Et	O	40	87	20	90	227–228	227–229[10d]

Table 1 (continuation)

9	2-O$_2$N-C$_6$H$_4$	Et	O	35	85	20	90	207–208	206–208^{16}
10	2,4-(Cl)$_2$-C$_6$H$_3$	Et	O	45	76	20	80	248–250	248–250^{14}
11	C$_6$H$_5$	Me	O	30	85	20	80	210–211	209–212^{4}
12	4-Cl-C$_6$H$_4$	Me	O	40	80	20	82	204–206	204–207^{4}
13	4-O$_2$N-C$_6$H$_4$	Me	O	35	90	22	90	234–235	235–237^{4}
14	4-MeO-C$_6$H$_4$	Me	O	35	91	17	92	190–192	192–194^{4}
15	2,4-(Cl)$_2$-C$_6$H$_3$	Me	O	40	75	20	70	252–254	252–253^{12}
16	C$_6$H$_5$	Et	S	35	90	13	89	208–210	209–211^{15}
17	4-MeO-C$_6$H$_4$	Et	S	40	85	12	80	152–154	153–155^{15}

In summary, a convenient modification of the Biginelli dihydropyrimidinone synthesis using Al(HSO$_4$)$_3$ as a catalyst in methanol or under solvent-free conditions is reported, in which the products are obtained in good to excellent yields.

EXPERIMENTAL

Products are known compounds and were characterized by comparison of their spectral data (^{1}H NMR, IR) and melting points with those reported in the literature. Monitoring of the reactions were accomplished by TLC on precoated silica gel 60 F$_{254}$ sheets. Al(HSO$_4$)$_3$ was prepared according to our previously reported procedure [22]. All yields refer to isolated products.

General procedure for the synthesis of dihydropyrimidin-2-ones under solvent-free conditions. Aldehyde (1 mmol), β-ketoester (1 mmol), urea or thiourea (1.5 mmol) and Al(HSO$_4$)$_3$ (0.6 mmol) were mixed thoroughly in a mortar. The mixture was transferred to a flask and capped. The flask was heated at 120°C for the appropriate period of time (Table 1). Hot methanol was added and filtered. The filtrate was concentrated followed by addition of water. The resulting precipitate was filtered and recrystallized from ethyl acetate or ethanol to afford the corresponding DHPMs in 70– 94% yields.

General procedure for the synthesis of dihydropyrimidinones in methanol. To a solution of aldehyde (1 mmol), β-ketoester (1 mmol), and urea or thiourea (1.5 mmol) in methanol (5 ml), Al(HSO$_4$)$_3$ (0.6 mmol) was added. The mixture was stirred under reflux conditions. Progress of the reaction was followed by TLC (eluent: *n*-hexane/EtOAc: 2/1). Solvent was removed under reduced pressure and water was added. The precipitated solid was filtered and recrystallized from ethyl acetate or ethanol to afford the products in 75–92% yields.

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