Short communication

A Novel Catalyst for One-Pot Synthesis of Substituted 3,4-Dihydropyrimidin-2-(1*H*)-ones via Biginelli Reaction Under Solvent-Free Conditions

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Abstract

An efficient and simple protocol has been developed for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones by a one-pot three-component cyclocondensation reaction of an aldehyde, β-keto-ester, and urea/thiourea under solvent-free conditions using magnesium(II) nitrate hexahydrate as a catalyst.

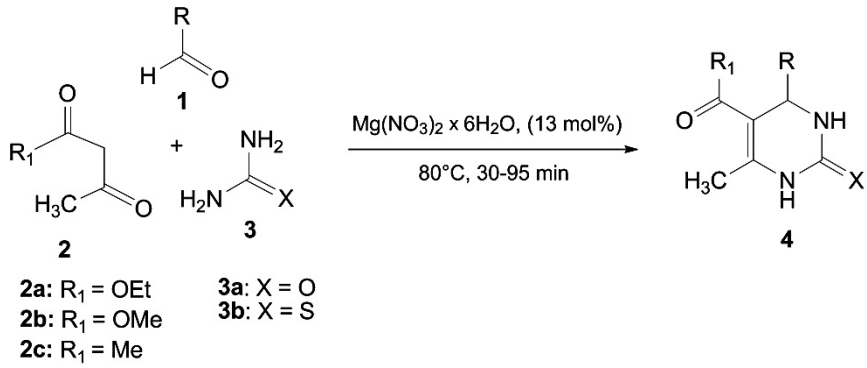
Keywords: Biginelli reaction, multicomponent reaction, dihydropyrimidin-2-(1*H*)-ones, Mg(II) nitrate hexahydrate, solvent-free conditions.

1. Introduction

In the mainstream of the current interest in one-pot multi-component reactions (MCRs),[1] the acid-catalyzed condensation of an aldehyde, β-ketoester and urea (or thiourea), a procedure known as Biginelli reaction,[2] is receiving increased attention.[3] Mostly due to its atom economy feature, the availability and the diversity of the building blocks engaged in this reaction, and the importance of the resulting dihydropyrimidinone products (DHPMs) which exhibit a wide range of biological activities such as antiviral, antitumoral, antibacterial and antihypertensive agents.[3] Moreover, DHPMs have emerged as α-1a-antagonists, neuropeptide Y(NPY) antagonists and as calcium channel modulators.[3b,4] The dihydropyrimidine core unit is also found in nature and in potent HIVgp-120-CD4 inhibitors.[5] Therefore, the synthesis of this heterocyclic core unit is of much current importance.

Several improved procedures for the preparation of DHPMs have recently been reported based on Lewis acids,[6] solid support,[7] or microwave[8] or on reagents like $RuCl_3$,[6e] $LiClO_4$,[9] I_2,[10] $Bi(OTf)_3$,[11] and $PhB(OH)_2$.[12] Recently, a number of procedures under solvent-free conditions using $Yb(OTf)_3$,[13] montmorillonite[14] and ionic liquid[15] as catalysts have been reported. However, despite their potential utility, many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction time, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation, difficulties in handling (especially on a large scale), and the solvents used are not at all acceptable in the context of green synthesis. Thus, a practical and more efficient alternative using an inexpensive and environmentally friendly reagent is still of interest for one-pot synthesis of dihydropyrimidinones and thiones under mild conditions.

In view of the current thrust in catalytic processes, we report in this communication for the first time the catalytic synthesis of DHPMs using $Mg(NO_3)_2.6H_2O$ as catalyst under solvent-free conditions. The synthesis is very simple, high-yielding, and greatly decreases environmental pollution (Scheme 1).



Scheme 1: DHPMs synthesis under solvent-free conditions.

2. Results and Discussion

Initially, we have studied the Biginelli's one-pot condensation reaction of benzaldehyde (**1a**, R=C_6H_5), ethyl acetoacetate (**2a**) and urea (**3a**) using $Mg(NO_3)_2.6H_2O$ as the sole promoter agent in refluxing acetonitrile. To establish the optimal conditions, we carried out a set of experiments varying the reaction times and the molar ratios of the reagents. The best yield of the corresponding dihydropyrimidinone (**4a**) (89%) was obtained when 13 mol % of $Mg(NO_3)_2.6H_2O$, 1 equivalent of both benzaldehyde (**1a**) and ethyl acetoacetate (**2a**), and 1.4 equivalent of urea (**3a**) were refluxed in acetonitrile for 4 hours. It seems that acetonitrile is a much better solvent in terms of yields than all other tested solvents such as dichloromethane (50%), tetrahydrofuran (56%), and toluene (70%). However, under solvent-free conditions (Scheme 1), the reaction was fast and 90% yield of the DHPM (**4a**) was obtained in 90 minutes (Table 1, entry 1).

Encouraged by these results, and due to the increasing demand in modern organic processes of avoiding expensive purification techniques and large amounts of solvents, we have examined the reactivity of our catalyst under solvent-free conditions.

Thus, with optimal reaction conditions in hand, and to gauge the scope and limitations of this process, series of aromatic and heterocyclic aldehydes were examined and the results from our study are presented in Table 1.

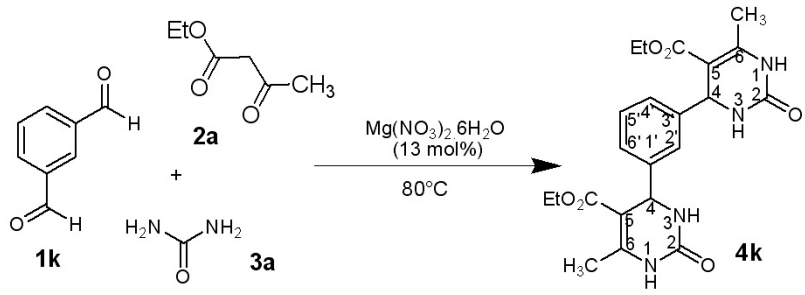
In all cases the reaction proceeded smoothly to give the corresponding DHPM in high yield. All aromatic aldehydes, carrying either electron-donating (Table 1, entries 2, 3, 4, 5 and 14) or electron-withdrawing (Table 1, entries 6, 7) substituent, reacted very well, giving good to excellent yields. Similarly, alkyl-substituted aromatic aldehydes (Table 1, entries 8, 9) reacted very well under optimized conditions giving good yields of the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones.

Even the bifunctional compound containing two dihydropyrimidinone units (**4k**) (Table 1, entry 11) was obtained in a good yield using isophthalaldehyde (**1k**) as a precursor (Scheme 2).

Table 1: $Mg(NO_3)_2.6H_2O$ catalyzed condensation of an aromatic aldehyde, ethyl acetoacetate and urea/thiourea.

Entry	R	X	Product (4)[a]	Time (min)	Yield[b] (%)	M. p. °C Found[c]	M. p. °C Reported[lit.]
1	C_6H_5	O	**4a**	90	90	207–208	206–207[16]
2	4-$(CH_3)_2N$-C_6H_4	O	**4b**	60	80	256–258	256–258[17]
3	4-CH_3O-C_6H_4	O	**4c**	45	90	203–204	203–204[16a]
4	2-CH_3O-C_6H_4	O	**4d**	40	80	258–259	257–258[16a]
5	4-HO-C_6H_4	O	**4e**	55	85	230–233	230–232[18]
6	4-Cl-C_6H_4	O	**4f**	95	88	211–213	212–214[16a]
7	2,4-Cl_2-C_6H_3	O	**4g**	55	89	247–248	248–250[6d,21]
8	4-H_3C-C_6H_4	O	**4h**	30	89	216–218	215–216[16a]
9	2-H_3C-C_6H_4	O	**4i**	55	83	200–204	207–208[19]
10	2-furyl	O	**4j**	95	45	204–206	203–205[20]
11	3-(CHO)-C_6H_4	O	**4k**	60	79	316–318	>300[20]
12	C_6H_5	S	**4l**	70	67	205–206	206–207[19]
13	4-CH_3O-C_6H_4	S	**4m**	72	70	149–151	150–152[18]
14	2-HO-C_6H_4	O	**5**	90	79	201–203	202–203[21]

[a] All products were characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy, and by comparison of physical characteristics with authentic samples. [b] Isolated yields. [c] Melting points are uncorrected.



Scheme 2: Synthesis of the "bifunctional compound"

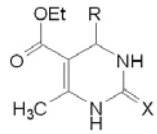
However, the yield drops significantly when an heteroaromatic carboxaldehyde such as furfural was used (Table 1, Entry 10). The usefulness of this methodology has also been successfully extended to thiourea in a similar manner, to give the corresponding dihydropyrimidin-2(1*H*)-thiones in high yields, which are also of much interest with regard to biological activities[22,23] (Table 1, entries 12, 13).

This method is also effective with methyl acetoacetate (**2b**) (Table 2, entries 1–4) and acetylacetone (**2c**) (Table 2, entries 5, 6) as the 1,3-dicarbonyl components.

The results summarized in Tables 1 and 2 clearly indicate generality and scope of the present protocol with respect to variations in all three components, as they have been accommodated very comfortably.

During the course of our studies, we have observed that the condensation product obtained in a standard Biginelli reaction after 30 min using salicylaldehyde (**1t**), urea (**3a**) and ethyl acetoacetate (**2a**), was a mixture of two products as confirmed by ^{1}H NMR spectroscopy: DHPM (**4t**) with the characteristic signal at 5.50 ppm (s, 1H, C4–***H***) and the oxygen-bridged compound (**5**), characteri-

Table 2: $Mg(NO_3)_2.6H_2O$ catalyzed condensation of an aromatic aldehyde, urea and methyl acetoacetate or acetyl acetone.



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Entry	R	R_1	Product (4)[a]	Time (min)	Yield[b] (%)	M.p. °C Found[c]	M.p. °C Reported[lit.]
1	4-CH_3-C_6H_4	OCH_3	**4n**	40	79	203–206	204–206[18]
2	4-CH_3O-C_6H_4	OCH_3	**4o**	45	90	195–197	193–196[19]
3	2,4-Cl_2-C_6H_3	OCH_3	**4p**	85	88	260–262	255–257[24]
4	2-CH_3-C_6H_4	OCH_3	**4q**	40	89	238–240	240–242[16b]
5	C_6H_5	CH_3	**4r**	45	89	233–236	232–235[19]
6	4-CH_3O-$C_6H_4OCH_3$	CH_3	**4s**	45	89	180–182	178–180[19]

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy, and by comparison of physical characteristics with authentic samples. [b] Isolated yields. [c] Melting points are uncorrected.

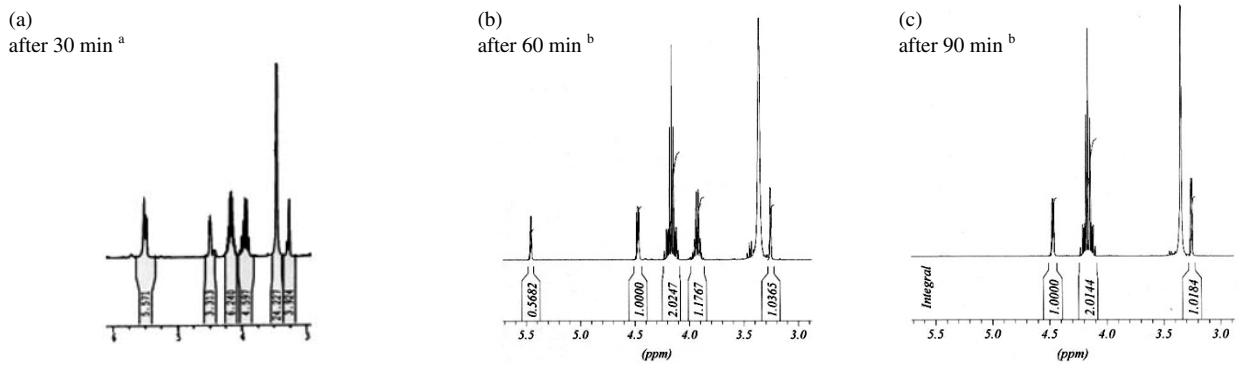
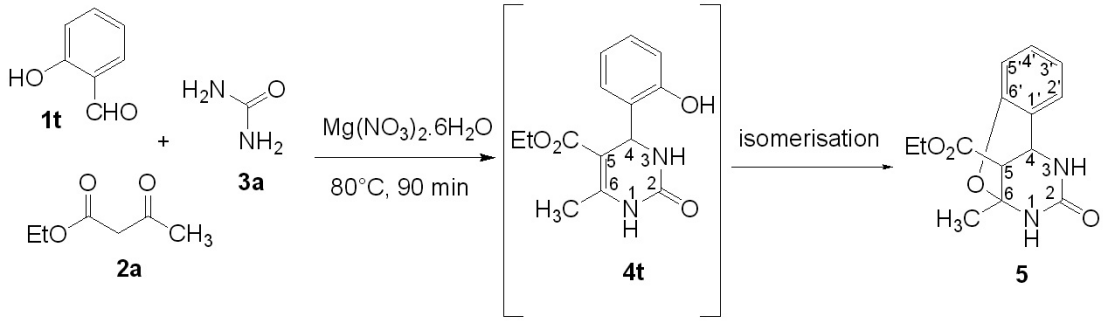


Figure 1: The isomerisation reaction monitored by ^{1}HNMR spectroscopy: (a) at 250 MHz, (b) and (c) at 400 MHz.

zed by signals at 4.50 ppm (d, 1H, C4–***H***) and 3.28 ppm (d, 1H, C5–***H***) (Figure 1a).

In view of this result, the reaction was monitored by ^{1}H NMR spectroscopy and we have observed that as the reaction proceeded, the peaks of **4t** progressively disappeared, as well as the intensity of the signals of **5** increased (figures 1b and 1c).

The reaction was finished in 90 min, when signals of (**4t**) had disappeared. This confirms that the oxygen-bridged pyrimidine[25] was obtained by the isomerisation reaction of the initially formed DHPM (**4t**)[21] (Scheme 3).



Scheme 3: The isomerisation of DHPM (**4t**) to diazatricyclic compound (**5**).

3. Experimental

All products are known compounds and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. IR spectra were obtained as KBr pellets with a Shimadzu FT IR-8201 PC spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance DPX spectrometer. Chemical shifts (δ) are reported in ppm and J values in hertz (Hz).

3. 1. General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones (4a-s)

1,3-Dicarbonyl compound (2.5 mmol), aromatic aldehyde (2.5 mmol), urea/thiourea (3.7 mmol), and magnesium(II) nitrate hexahydrate (13 mol %) were mixed thoroughly in a mortar. The mixture was transferred to a screwed round bottomed flask. The flask was then heated at 80 °C with magnetic stirring, for the appropriate time as mentioned in Tables 1 and 2, during which a solid gradually formed. After completion of the reaction, the resulting solid was crushed, washed with ice-cold water, filtered under suction, and crystallized from hot ethanol to afford the pure 3,4-dihydropyrimidin-2(1*H*)-ones. The aqueous layer was concentrated and the catalyst was recovered.

This procedure was followed for the preparation of all the products listed in Tables 1 and 2 except in the case of (**4k**) where a 1:2:3 molar ratio of isophthalaldehyde (**1k**), ethyl acetoacetate (**2a**), and urea (**3a**) was used, in the presence of 26 mol % of the catalyst $Mg(NO_3)_2.6H_2O$.

3. 2. Spectral section

Spectral data for selected compounds are presented below:

4j) M.p. 204–206 °C, yield 45%. IR (í, cm^{-1}) 3317 (N–H, ureide), 3116 (C–H furan), 1725 (C=O, ester), 1639 (C=O, cyclic ureide); ^{1}H NMR (250 MHz, DMSO-d_6, TMS): δ 9.26 (s, 1H, N1–H), 7.77 (s, 1H, N3–H), 7.64 (m, 1H, H3', furan), 6.36 (m, 1H, H4', furan), 6.11 (m, 1H, H5', furan), 5.22 (s, 1H, H4), 4.02 (q, *J* = 7.04 Hz, 2H, OCH_2), 2.43 (s, 3H, CH_3), 1.09 (t, *J* = 7.04 Hz, 3H, CH_3 ester); ^{13}C NMR (62.9 MHz, DMSO-d_6, TMS): δ 165.9 (C=O, ester), 156.2 (C=O, amide), 152.8 (C2', furan), 150.0 (C6), 142.6 (C5', furan), 110.7 (C4', furan), 105.7 (C3', furan), 97.0 (C5), 58.0 (OCH_2–), 51.3 (C4), 20.9 (CH_3), 18.1 (CH_3, ester).

4k) M.p. 316–318 °C, yield 79%. IR (í, cm^{-1}) 3247 (N–H, ureide), 3050 (C–H, aryl), 1721 (C=O, ester), 1637 (C=O, cyclic ureide), 805 (aromatic); ^{1}H NMR (250 MHz, DMSO-d_6, TMS): δ 9.17 (s, 2H, 2N1–H), 7.85 (s, 2H, 2N2–H), 7.21 (m, 1H, H5'), 7.15 (m, 3H, H2', H4'and H6'), 5.10 (s, 2H, 2H4), 3.98 (q, *J* = 7.06 Hz, 4H, 2 OCH_2), 2.15 (s, 6H, 2 CH_3), 1.10 (t, *J* = 7.06 Hz, 6H, 2CH_3 ester); ^{13}C NMR (62.9 MHz, DMSO-d_6, TMS): δ 165.65 (2 C=O, esters), 152.50 (2 C=O, amide), 148.78 (2 C6), 145.48 (C1', C3'), 128.92 (C5'), 125.75 (C4', C6'), 124.52 (C2'), 99.62 (2 C5), 59.58 (2 OCH_2), 54.38 (C4), 18.14 (2 CH_3), 14.50 (2 CH_3, ester).

5) M.p. 201–203 °C. yield 79%. IR (í, cm^{-1}) 3220 (N–H, ureide), 3085 (C–H, aryl), 1745 (C=O, ester), 1690 (C=O, cyclic ureide), 1210 (Ph–O–C, bridge); ^{1}H NMR: (250 MHz, DMSO-d_6, TMS): δ 9.83 (s, 1H, N1–H), 9.12 (br s, 1H, N3–H), 7.28–6.62 (m, 4H, Ar), 4.50 (d, *J* = 2.97 Hz, 1H, H4), 4.15 (q, *J* = 7.0 Hz, 2H, OCH_2), 3.28 (d, *J* = 2.97 Hz, 1H, H5), 1.78 (s, 3H, CH_3), 1.22 (t, *J* = 7.0 Hz,

3H, CH_3 ester); ^{13}C NMR (62.9 MHz, DMSO-d_6, TMS): δ 168.5 (C=O, ester), 155.2 (C=O, amide), 150.5 (C6'), 129.5 (C2'), 128.6 (C4'), 125.3(C1'), 121.0 (C3'), 116.5 (C5'), 83.5 (C6), 61.0 (C5), 48.0 (OCH_2), 44.2 (C4), 23.9 (CH_3), 14.3 (CH_3, ester).

4. Conclusions

We have developed a simple, efficient, economic and ecologically clean procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones, employing $Mg(NO_3)_2.6H_2O$ as a novel promoter.

The use of solvent-free conditions, short reaction times, excellent yields, easy work-up, compatibility with various functional groups, recovery of the catalyst, and commercially available or readily accessible aromatic aldehydes, β-ketoesters and urea, will make the present catalytic reaction an environmentally acceptable method for the synthesis and generation of combinatorial dihydropyrimidinone libraries.

5. Acknowledgments

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6. References

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Povzetek

Avtorji v prispevku podajajo enostaven in učinkovit protokol za sintezo 3,4-dihidropirimidin-2-(1*H*)-onov z enostopenjsko trikomponentno kondenzacijsko reakcijo aldehidov, β-keto estrov in uree/tiouree, brez topila in z uporabo magnezijevega(II) nitrata heksahidrata kot katalizatorja.