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Magnesium Chloride Hexahydrate Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1H)ones Under Solvent-Free Conditions

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Abstract: 3,4-Dihydropyrimidin-2-(1H)-one were prepared by Biginelli condensation of aldehyde, 1,3-dicarbonyl compound and urea under solvent-free condition at 80°C with magnesium chloride hexahydrate as catalyst.

Keywords: Biginelli reaction, dihydropyrimidinones, magnesium chloride hexahydrate, one-pot condensation, solvent-free

3,4-Dihydropyrimidin-2-(1H)-ones (DHPMs, **4**) and related compounds possess diverse biological properties, such as antiviral, antitumor, antihypertensive, and antibacterial effects.^[1] They are potential calcium-channel blockers, and α -adrenergic and neuropetide Y (NPY) antagonists.^[2]

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In addition, several marine alkaloids with interesting biological properties contain 3, 4-dihydropyrimidinone-5-carboxylate moiety.^[3] The simple and direct method for the synthesis of DHPMs reported by Biginelli in 1893 involves the one-pot condensation of aldehyde, β -keto ester, and urea under strongly acidic condition.^[4] This method suffers from low yields, especially in the cases of aliphatic and some substituted aromatic aldehydes. Recently, many improved procedures were reported for the preparation of DHPMs using Bi(OTf)₃,^[5] ZrCl₄,^[6] InCl₃,^[7] LiClO₄,^[8] FeCl₃·6H₂O or NiCl₂·6H₂O,^[9] *p*-TsOH,^[10] LaCl₃·7H₂O,^[11] Bi(OTf)₃,^[12] KHSO₄,^[13] ionic liquids (BMImPF₆ and BMImBF₄),^[14] Mn(OAc)₃·2H₂O,^[15] or TMSOTf^[16] as the catalyst. However, some of the catalysts are expensive, complex or unavailable, and some of these methods require vigorous reactions, prolonged standing and tedious manipulations to isolation the products. Organic solvents are always used. Therefore, the inexpensive and environmentally friendly procedure for the preparation of DHPMs under mild conditions is of prime importance.

The solvent-free Biginelli reaction has attracted much attention and good results were reported recently. Under solvent-free conditions, *N*-butyl-*N*, *N* dimethyl- α -phenylethyl ammonium bromide could catalyze the Biginelli reaction to afford corresponding products in 86~99% yields at 100°C within 1 h.^[17] CuCl₂·2H₂O or CuSO₄·5H₂O as the catalyst gives Biginelli condensation products in 80~99% yields at 100°C for 60~110 min under solvent-free conditions.^[18] However, these procedures involved expensive or environmentally unfriendly catalysts. Ammonium chloride was used as the catalyst under solvent-free conditions,^[19] but the yields are not satisfactory (42~92%) and longer reaction time (3 h) is required. Magnesium chloride has been used to catalyze the acylation of β -keto esters.^[20] Here we would like to report a new economic approach for the synthesis of DHPMs by Beginelli reaction using MgCl₂·6H₂O as the catalyst under solvent-free conditions (Scheme 1).

Biginelli condensation was performed using hydrous Lewis acid as the catalyst, such as $FeCl_3 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, and $LaCl_3 \cdot 7H_2O$ in higher yields in an organic solvent. We studied the Biginelli condensation using hydrous salt as catalyst under solvent-free conditions. Then, we selected



Scheme 1.

3,4-Dihydropyrimidin-2-(1H)Ones

Entry	Catalyst	Time	Isolated yield (%)
1	$NiCl_2 \cdot 6H_2O$	1 h	90
2	FeCl ₃ · 6H ₂ O	1 h	86
3	$MgCl_2 \cdot 6H_2O$	1 h	96
4	none	2 h	81

Table 1. Biginelli condensation of benzaldehyde, ethyl acetoacetate, and urea under different conditions

inexpensive and available NiCl₂·6H₂O, MgCl₂·6H₂O, and FeCl₃·6H₂O (20 mol%) as catalysts to the three-component Biginelli condensation under solvent-free conditions at 80°C, and the results obtained are exhibited in Table 1. Entry **3** shows that magnesium chloride hexahydrate gave the best results among the three salts. To optimize the reaction conditions, the condensation reaction of benzaldehyde, ethyl acetoacetate, and urea was selected as a model to examine the effects of the catalyst (0, 10, 20, and 30 mol%) and

Table 2. Magnsium chloride hexahydrate catalyzed solvent-free synthesis of 3,4-dihydropyrimidin-2-(1H)-one at 80° C

DHMP ^a	R ₁	R ₂	Time (min)	Yield $(\%)^b$	Mp (°C)	Lit. mp (°C)
4a	EtO	C ₆ H ₅	60	96	203-204	200-202 ^[18]
4b	EtO	$4-(MeO)-C_6H_5$	50	95	200-202	198-200 ^[18]
4c	EtO	3-(HO)-4-(MeO)-C ₆ H ₅	40	92	185-187	185-187 ^[21]
4d	EtO	4-(HO)-3-(MeO)-C ₆ H ₅	60	89	230-232	231-232 ^[22]
4 e	EtO	4-(HO)-C ₆ H ₅	60	90	228-230	227-229 ^[25]
4f	EtO	4-(Cl)-C ₆ H ₅	45	93	213-215	209-212 ^[23]
4g	EtO	3,4-(2-Cl)-C ₆ H ₅	60	95	223-225	222-223 ^[24]
4h	EtO	$4-(F)-C_6H_5$	30	96	183-186	$182 - 184^{[23]}$
4i	EtO	2-(NO ₂)-C ₆ H ₅	60	97	207-209	205-206 ^[26]
4j	EtO	2-furyl	90	85	210-212	208-209 ^[18]
$4\mathbf{k}^{c}$	EtO	Me	40	88	190-191	186-188 ^[19]
4l ^d	EtO	$(CH_3)_2CH$	50	90	195-196	190-192 ^[18]
4m	Me	C_6H_5	60	94	229-230	229-231 ^[23]
4n	Me	4-(MeO)-C ₆ H ₅	90	92	173-174	170-172 ^[23]
40	Me	$4-(F)-C_6H_5$	50	91	217-218	
4p	Me	2-furyl	90	90	212-213	210-212 ^[7]

^aAll products were characterized by IR, ¹H NMR, and MS spectral data.

^bIsolated yield.

^cRoom temperature.

^{*d*}50°C.

quantities of reagents at different reaction temperature (50, 80, and 100° C). The best results were obtained with a 1:1:1.5:0.2-mol ratio of aldehyde, ethyl acetoacetate, urea, and magnesium chloride hexahydrate under solvent-free conditions at 80°C for 1 h.

In a typical procedure, a mixture of ethyl acetoacetate (0.65 g, 5 mmol), benzaldehyde (0.503 g, 5 mmol), urea (0.45 g, 7.5 mmol), and magnesium chloride hexahydrate (0.20 g, 1 mmol) was heated to 80°C for 1 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperture and poured into water (30 mL). The solid was separated by filtration, washed with water, and then recrystallized from ethanol to afford **4a**, mp 203~204°C (lit.^[18] mp 200~202°C) in 96% yield. Similarly, substituted aldehyde, and 1,3-dicarbonyl compound were together heated with urea to give the corresponding 3,4-dihydropyrimidin-2-(1H)-ones, which were purified by recrystallizing from ethanol or washing three times with cool ethyl acetate. The results are summarized in Table 2. Apparently, the procedure gave the products in high yields ($85\sim97\%$) within 1.5 h at 80° C and solvent was not necessary. Moreover, the separation and purification of the products is simple.

In conclusion, an economically and environmentally friendly procedure for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones using magnesium chloride hexahydrate as catalyst was developed. The synthetic procedure provides an efficient and attractive method to synthesize DPHMs by Biginelli condensation in good to excellent yields under solvent-free conditions.

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