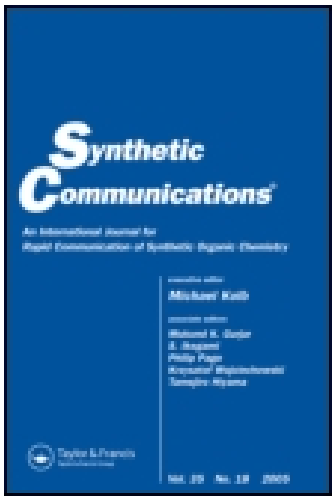

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A Facile and Efficient One-Pot Synthesis of Dihydropyrimidinones Catalyzed by Magnesium Bromide Under Solvent-Free Conditions

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A Facile and Efficient One-Pot Synthesis of Dihydropyrimidinones Catalyzed by Magnesium Bromide Under Solvent-Free Conditions

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ABSTRACT

Magnesium bromide efficiently catalyzes the three-component condensation reaction of aldehyde, β-diketon and urea/thiourea under solvent-free conditions to afford the corresponding dihydropyrimidinones in high yields and short reaction time.

Key Words: One-pot synthesis; Magnesium bromide; Dihydropyrimidinones; Biginelli reaction.

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Dihydropyrimidinone derivatives have attracted considerable interest recently because of their promising activities as calcium channel blockers, antihypertensive agents and α-1a-antagonists.[1] Morever, several alkaloids containing the dihydropyrimidine unit have been isolated from marine sources, and exhibit interesting biological properties.[2,3] Recently several isolated marine alkaloids with biological activities were also found containing the dihydropyrimidinones core. Most notably among them are betzelladine alkaloids, which have been found to be potent HIVgp-120-CD4 inhibitors.[4–6] Thus, synthesis of this heterocyclic nucleus is of much current important. The most simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions.[7]

However, one serious drawback of Biginelli's reaction is low yields obtained in the case of substituted aromatic and aliphatic aldehydes.[8] This has led to the development of multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot synthesis.[9–11]

The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amount of solvents and expensive purification technique, represent a fundamental target of the modern organic synthesis.[12] Thus, Biginelli's reaction for the synthesis of dihydropyrimidinones has received renewed interest. Several improved procedures have recently been reported.[13–25] It has been reported that Lewis acids (such as $BF_3 \cdot OEt_2$)[13] in combination with transition metals and a proper proton source were effective catalyst for this reaction. Dihydropyrimidinones were also synthesized by using various protic acids such as HCl,[23] and AcOH,[19] under microwave irradiation. More recently, ionic liquids,[17] montmorillonite KSF,[20] polyphosphate ester(PPE),[21] and lanthanide triflate,[25] as catalysts for the one-pot solvent-free synthesis of dihydropyrmidinones have also been reported. However, in spite of their potential utility, many of these methods involve expensive reagents, strongly acidic conditions, long reaction time, unsatisfactory yields and cumbersome product-isolation procedures. Consequently, there are scopes for further renovation toward milder reaction conditions, variations of substituents in all three components and better yields.

In recent years magnesium bromide has received considerable attention as a powerful reaction medium for effecting various transformations[26–31] such as condensation reactions, cyclization reaction, polymerization, Diels-Alder reactions, anti-Aldol reactions and acylation of alcohols. The challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents.[32] Reactions under solvent-free or so-called dry media conditions are especially appealing as they provide an opportunity to

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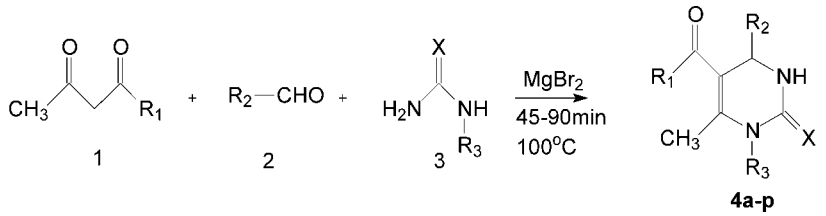

Scheme 1.

work with open vessels, thus avoiding the risk of high pressure development and with the possibility of upscaling the reactions to larger scale.[33–35]

Here, we wish to report a facile and efficient method for the one-pot synthesis of dihydropyrimidinones using magnesium bromide as catalyst under solvent free conditions (Sch. 1).

A wide range of substituted aldehydes and several β-diketones and urea/thiourea were subjected to this procedure to produce the corresponding dihydropyrimidinones (Table 1). The procedure gives the products in good to excellent yields and avoids problems associated with solvent use (cost, handling, safety and pollution). Decreased reaction times are also realized because of the increased reactivity of the reactant in the solid state and the fact

Table 1. Magnesium bromide-catalyzed one-pot synthesis of dihydropyrimidinones under solvent-free conditions at 100°C.

Product	R_1	R_2	R_3	X	Time (min)	Yield (%)[a]
4a	OMe	C_6H_5	H	O	45	90
4b	OMe	3-(NO_2)-C_6H_4	H	O	90	82
4c	Me	C_6H_5	H	O	60	88
4d	C_6H_5	4-(OMe)-C_6H_4	H	O	90	86
4e	C_6H_5	2,4-$(Cl)_2$-C_6H_3	H	O	90	82
4f	OEt	4-(OH)-C_6H_4	Me	O	90	79
4g	OEt	C_6H_5	H	O	45	92
4h	OEt	4-(OMe)-C_6H_4	H	O	45	94
4i	OEt	2-Furyl	H	O	90	84
4j	OEt	3-(NO_2)-C_6H_4	H	O	90	86
4k	OEt	4-(OH)-C_6H_4	H	O	90	91
4l	OEt	2,4-$(Cl)_2$-C_6H_3	H	O	90	85
4m	OEt	$C_6H_5CH{=}CH$	H	O	90	81
4n	OEt	C_6H_5	H	S	60	90
4o	OEt	4-(OMe)-C_6H_4	H	S	45	91
4p	Me	C_6H_5	H	S	90	86

[a]Isolated yields.

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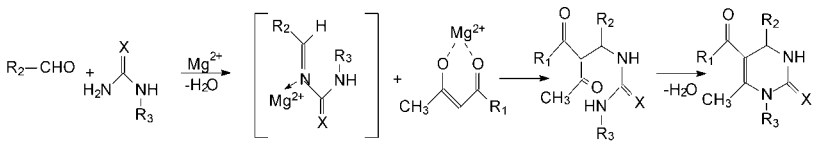
that the other reaction product, water, evaporates at the reaction temperature of 100°C. Most literature examples of the Biginelli variants used simple β-ketoesters in the condensation reaction. Besides the β-ketoester, the β-diketone can also be employed. Thiourea and N-methylurea have been used with similar success to provide the corresponding dihydropyrimidinones, which are also of much interest with regard to biological activity.[1] No additive or protic acid is necessary in this procedure. Another important aspect of this procedure is survival of a variety of functional groups, such as NO_2, Cl, OH, OMe, and C═C under the experimental conditions. Furthermore, aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents all worked well, giving good to excellent yields. In addition, acid sensitive aldehydes, such as furfural reacted well without any side products, which normally reacted either in the presence of portic or Lewis acids. The reaction may proceed through the acylimine intermediate (formed in situ by reaction of the aldehyde with urea), which is stabilized by the magnesium ion, and the subsequent addition of the β-diketon enolate to the acylimine, followed by cyclization and dehydration, affords the corresponding dihydropyrimidinones (Sch. 2).

In conclusion, we developed an environmentally friendly procedure for the synthesis of dihydropyrimidinones by using magnesium bromide as an inexpensive and easily available catalyst under solvent-free conditions. In addition to its simplicity and mild reaction conditions, it tolerates a wide variety of substitutions in all three components. The adopted procedure is convenient, involves simple experimental procedure and product isolation; hence, it is a useful addition to the existing methods.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were run on a Bruker spectrometer and expressed in cm^{-1} (KBr). ^1H and ^{13}C NMR spectra were recorded on a Bruker AVMCE-300 MHz in DMSO-d_6 solutions. Elemental analysis was performed by the Elementar Vario EL-III. High resolution mass spectra were obtained with a Micromass GCT TOF mass spectrometer.



Scheme 2.

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General Procedure for the One-Pot Synthesis of Dihydropyrimidinones Under Solvent-Free Conditions

Representative procedure for 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2 (1H)-one (**4g**). Ethyl acetoacetate (10 mmol), benzaldehyde (10 mmol), urea (15 mmol) and magnesium bromide (1 mmol, 10 mol%) were heated at 100°C under stirring for 45 min. After cooling, the reaction mixture was poured onto crushed ice (50 g) and stirred for 5–10 min. The solid separated was filtered under suction, washed with ice-cold water (2×50 mL) and then recrystallized from ethanol to afford pure product. All the products were characterized by mp, spectral and analytical data. **4e** and **4f** are new compounds.

4a. m.p. 214–216°C. IR (KBr): $\nu = 3333$, 3226, 3106, 2950, 1696, 1668 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 2.24$ (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 5.12 (d, 1H, $J = 3.18$, H-4), 7.21–7.34 (m, 5H, H_{arom}), 7.76 (brs, 1H, NH), 9.22 (brs, 1H, NH). MS: $m/z = 246.09$ (M^+), 231, 214, 187, 169, 137, 77, 43.

4b. m.p. > 250°C. IR (KBr): $\nu = 3357$, 3219, 3101, 2957, 1695, 1642, 1535 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 5.29 (d, 1H, $J = 3.19$, H-4), 7.62–7.70 (m, 2H, H_{arom}), 7.93 (brs, 1H, NH), 8.08–8.15 (m, 2H, H_{arom}), 9.40 (brs, 1H, NH). MS: $m/z = 291.08$ (M^+), 274, 232, 186, 169, 137, 58, 43.

4c. m.p. 242–244°C. IR (KBr): $\nu = 3260$, 2923, 1702, 1675, 1599 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 2.10$ (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 5.25 (brs, 1H, H-4), 7.25–7.32 (m, 5H, H_{arom}), 7.83 (brs, 1H, NH), 9.19 (brs, 1H, NH). MS: $m/z = 230.1$ (M^+), 229, 215, 211, 187, 153, 144, 115, 110, 77.

4d. m.p. 236–238°C. IR (KBr): $\nu = 3351$, 3282, 2926, 1709, 1673, 1632 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.66$ (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 5.23 (d, 1H, $J = 2.91$, H-4), 6.84 (d, 2H, $J = 8.64$, H_{arom}), 7.09 (d, 2H, $J = 8.64$, H_{arom}), 7.42–7.53(m, 5H, H_{arom}), 7.72 (brs, 1H, NH), 9.13 (brs, 1H, NH). MS: $m/z = 322.1$ (M^+), 321, 307, 291, 217, 215, 185, 105, 77, 43.

4e. m.p. 232–234°C. IR (KBr): $\nu = 3290$, 1697, 1655, 1615, 1592 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.67$ (s, 3H, CH_3), 5.70 (d, 1H, $J = 2.6$, H-4), 7.40–7.52 (m, 8H, H_{arom}), 7.73 (brs, 1H, NH), 9.24 (brs, 1H, NH). ^{13}CNMR (DMSO-d_6): $\delta = 18.6$, 52.8, 107.5, 127.7, 127.8, 128.6, 128.9, 130.6, 131.6, 132.6, 140.0, 140.8, 146.1, 151.4, 193.8. Anal. Calcd. For $C_{18}H_{14}N2Cl_2O_2$: C, 59.85; H, 3.90; N, 7.75; Found: C, 59.74; H, 3.92; N, 7.83. MS: $m/z = 361.03$ (M^+), 325, 255, 241, 215, 105, 77.

4f. m.p. 178–180°C. IR (KBr): $\nu = 3280$, 3098, 2985, 1703, 1667, 1626 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.11$ (t, 3H, $J = 6.96$, CH_3), 2.46 (s, 3H, CH_3), 3.08 (s, 3H, NCH_3), 4.02 (q, 2H, $J = 7.08$, CH_2), 5.03 (d, 1H, $J = 3.21$, H-4), 6.66 (d, 2H, $J = 8.19$, H_{arom}), 6.98 (d, 2H, $J = 8.34$, H_{arom}), 7.83 (brs, 1H, NH), 9.34 (s, 1H, OH). ^{13}CNMR (DMSO-d_6): $\delta = 14.0$, 16.0, 18.5, 29.6,

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51.9, 56.0, 59.4, 102.9, 115.0, 127.2, 134.6, 149.9, 153.1, 156.6, 165.6. Anal. Calcd. For $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.64; Found: C, 61.93; H, 6.27; N, 9.44. MS: m/z = 290.1 (M^+), 275, 261, 217, 197, 169, 151, 94, 56.

4g. m.p. 206°C. IR (KBr): $\nu = 3245$, 3118, 2978, 1725, 1701, 1649 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.06$ (t, 3H, $J = 6.84$, CH_3), 2.24 (s, 3H, CH_3), 3.94 (q, 2H, $J = 6.75$, CH_2), 5.13 (d, 1H, $J = 3.06$, H-4), 7.21–7.37 (m, 5H, H_{arom}), 7.73 (brs, 1H, NH), 9.19 (brs, 1H, NH). MS: m/z = 260.1 (M^+), 232, 231, 213, 187, 183, 155, 137, 115, 102, 77.

4h. m.p. 198–200°C. IR (KBr): $\nu = 3436$, 3247, 3113, 2929, 1724, 1705, 1649 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.10$ (t, 3H, $J = 7.08$ CH_3), 2.17 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.96 (q, 2H, $J = 7.14$, CH_2), 5.07 (d, 1H, $J = 2.97$, H-4), 6.85 (d, 2H, $J = 8.49$, H_{arom}), 7.12 (d, 2H, $J = 8.55$, H_{arom}), 7.67 (brs, 1H, NH), 9.15 (brs, 1H, NH).

4i. m.p. 206–208°C. IR (KBr): $\nu = 3342$, 3242, 3117, 2985, 1700, 1645 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.05$ (t, 3H, $J = 7.08$, CH_3), 2.22 (s, 3H, CH_3), 3.98 (q, 2H, $J = 6.99$, CH_2), 5.19 (d, 1H, $J = 3.0$, H-4), 6.08 (d, 1H, $J = 2.94$, H_{arom}), 6.35 (s, 1H, H_{arom}), 7.55 (s, 1H, H_{arom}), 7.76 (brs, 1H, NH), 9.25 (brs, 1H, NH). MS: m/z = 250.09 (M^+), 233, 221, 205, 177, 176, 124.

4j. m.p. 226–228°C. IR (KBr): $\nu = 3422$, 3104, 2964, 1708, 1690, 1630, 1526 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.08$ (t, 3H, $J = 7.02$, CH_3), 2.27 (s, 3H, CH_3), 3.98 (q, 2H, $J = 4.57$, CH_2) 5.30 (d, 1H, $J = 2.69$, H-4), 7.63-7.72 (m, 2H, H_{arom}), 7.93 (brs, 1H, NH), 8.09–8.16 (m, 2H, H_{arom}), 9.40 (brs, 1H, NH). MS: m/z = 305.1 (M^+), 289, 288, 276, 260, 232, 183, 155, 137, 110.

4k. m.p. 232°C. IR (KBr): $\nu = 3511$, 3278, 3123, 2975, 1686, 1647 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.07$ (t, 3H, $J = 6.90$, CH_3), 2.22 (s, 3H, CH_3), 3.93 (q, 2H, $J = 6.98$, CH_2) 5.03 (d, 1H, $J = 2.76$, H-4), 6.67 (d, 2H, $J = 8.25$, H_{arom}), 7.01 (d, 2H, $J = 8.32$, H_{arom}), 7.62 (brs, 1H, NH), 9.12 (brs, 1H, NH), 9.32 (brs, 1H, OH).

4l. m.p. 248–250°C. IR (KBr): $\nu = 3359$, 3220, 3105, 2971, 1698, 1644, 1590 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.04$ (t, 3H, $J = 7.04$, CH_3), 2.28 (s, 3H, CH_3), 3.87 (q, 2H, $J = 6.99$, CH_2), 5.59 (brs, 1H, H-4), 7.29 (d, 1H, $J = 8.26$, H_{arom}), 7.39 (d, 1H, $J = 8.27$, H_{arom}), 7.55 (brs, 1H, H_{arom}), 7.77 (brs, 1H, NH), 9.33 (brs, 1H, NH). MS: m/z = 300, 299, 293, 263, 257, 255, 183, 155, 137, 110, 58, 43.

4m. m.p. 240–242°C. IR (KBr): $\nu = 3247$, 3115, 2928, 1720, 1701, 1652 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.17$ (t, 3H, $J = 7.05$, CH_3), 2.19 (s, 3H, CH_3), 4.06 (q, 2H, $J = 7.17$, CH_2) 4.72 (brs, 1H, H-4), 6.20 (dd, 1H, $J = 5.86$, $J = 6$, =CH), 6.33 (d, 1H, $J = 15.86$, =CH), 7.22–7.41 (m, 5H, H_{arom}), 7.56 (brs, 1H, NH), 9.15 (brs, 1H, NH). MS: m/z = 286.1 (M^+), 258, 257, 240, 213, 211, 183, 155, 137, 104, 103, 91, 78.

4n. m.p. 206–208°C. IR (KBr): $\nu = 3328$, 3173, 3104, 2979, 1670, 1573, 1465 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.07$ (t, 3H, $J = 7.08$, CH_3), 2.28

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(s, 3H, CH_3), 3.97 (q, 2H, $J = 7.02$, CH_2) 5.15 (d, 1H, $J = 3.57$, H-4), 7.20–7.35 (m, 5H, H_{arom}), 9.66 (brs, 1H, NH), 10.34 (brs, 1H, NH).

4o. m.p. 152°C. IR (KBr): $\nu = 3445$, 3315, 3175, 2965, 1667, 1617, 1575, 1510 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.08$ (t, 3H, $J = 6.93$ CH_3), 2.28 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.96 (q, 2H, $J = 7.17$, CH_2), 5.10 (d, 1H, $J = 3.6$, H-4), 6.87 (d, 2H, $J = 8.64$, H_{arom}), 7.09 (d, 2H, $J = 8.64$, H_{arom}), 9.60 (brs, 1H, NH), 10.28 (brs, 1H, NH).

4p. m.p. 236–238°C. IR (KBr): $\nu = 3296$, 3203, 2994, 1610, 1577, 1462 cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 2.15$ (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 5.28 (d, 1H, $J = 3.57$, H-4), 7.21–7.37 (m, 5H, H_{arom}), 9.76 (brs, 1H, NH), 10.29 (brs, 1H, NH). MS: $m/z = 246.08$ (M^+), 245, 231, 203, 169, 144, 77, 43.

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