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WATER-TOLERANT AND REUSABLE CATALYST FOR THE ONE-POT SYNTHESIS OF DIHYDROPYRIMIDIN-2(1*H*)-ONES UNDER SOLVENT-FREE CONDITIONS

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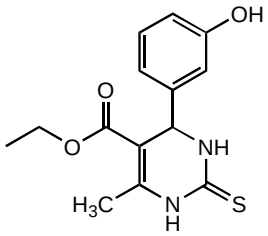
Abstract– An efficient and eco-friendly synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, has been achieved by a three-component condensation reaction of an aldehyde, β-ketoester and urea, in the presence of $K_5CoW_{12}O_{40}.3H_2O$ (0.01 equiv. or 1.0 mol %) as catalyst under solvent-free conditions. The catalyst exhibited remarkable reusable activity. The scope of this method is utilized for the synthesis of mitotic kinesin EG5 inhibitor monastrol.

INTRODUCTION

The generation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery and lead optimization in pharmaceutical research.[1] Multicomponent reactions (MCRs) leading to heterocycles are particularly useful for the creation of diverse chemical libraries, since the combination of $n \geq 3$ small molecular weight building blocks in a single operation leads to high combinatorial efficacy.[1-4] Therefore, solid phase modifications of MCRs are rapidly becoming the cornerstone of combinatorial synthesis of small-molecule libraries.[1-6] One such MCR that has attracted considerable attention is the Biginelli reaction,[5] which involves the one-pot cyclocondensation of a β–ketoester with an aldehyde and an urea derivative.

In recent years, dihydropyrimidines (DHPMs) have attracted considerable attention in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties such as antibacterial, antihypersentive activity as well as behaving as calcium channel blockers, α-1a-antagonists, and neuropeptide Y (NPY) antagonists.[4] Several recently isolated marine alkaloids with interesting biological activities also contain the DHPM's core unit, most notably

among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[7] The scope of this pharmacophore has been further increased by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative (±)-(**4g**) called monastrol,[8] as a novel cell-permeable lead molecule for the development of new anticancer drugs (Figure 1). Monastrol (±)-(**4g**) has been identified as a compound that specifically affects cell division (mitosis) by a new mechanism, which does not involve tubulin targeting. It has been established that the activity of (±)-(**4g**) consists of the specific and reversible inhibition of the motility of the mitotic kinesin Eg5, a motor protein required for spindle bipolarity.



Monastrol

Figure 1

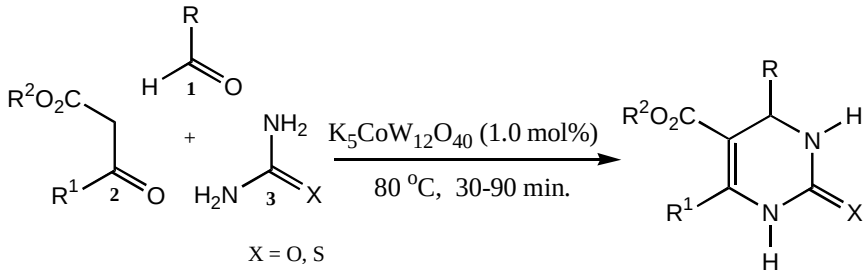
RESULTS AND DISCUSSION

The original Biginelli protocol for the preparation of the DHPMs involves heating a mixture of the three components (aldehyde (**1**), β-keto-ester (**2**), and urea (**3**)) in ethanol containing a catalytic amount of HCl.[6] This procedure leads in one step-one pot to the desired DHPM. The major drawback associated with this protocol is the low yields (20-60 %), particularly for substituted aromatic and aliphatic aldehydes.[7] This has led to the development of multi-step synthetic strategies that produce somewhat higher yields but lack the simplicity of the original one-pot Biginelli protocol.[7, 9]

Recently several improved procedures have been reported,[10] using Lewis acids as well as protic acids as promoters. However, despite their potential utility, many of these methods involve difficulties such as the use of stoichiometric amounts of catalysts, reflux temperatures, the use of metal halides as catalysts, long reaction times, unsatisfactory yields, and incompatibilities with other functional groups. Consequently, there is scope for further modification towards mild reaction conditions, increased variation of the substituents and improved yields. In the course of our studies on the use of heterogeneous catalysis in fine organic chemistry, we developed a method, which allows the ideal route to carry out the Biginelli reaction by using inexpensive and reusable potassium dodecatangestocobaltate trihydrate [$K_5CoW_{12}O_{40}.3H_2O$][11] (0.01 molar equiv. or 1.0 mol %) catalyst in a highly efficient manner. To our knowledge, however, the generality and applicability of $K_5CoW_{12}O_{40}.3H_2O$ to accomplish this reaction have not appeared so far.

This method not only preserves the simplicity of Biginelli's reaction but also consistently produces excellent yields of dihydropyrimidine-2(1*H*)-ones (**4a-o)** (Scheme 1). Under these conditions, the yields

were significantly increased; to 80-95% for the classical Biginelli method, and that the reaction time was drastically reduced from 18-48 h to 40 min after the addition of a low catalyst concentration.

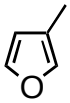


Scheme 1 **4a-o**

Moreover, this procedure 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 that the other reaction product, water, evaporates at the reaction temperature of 80^0C. In order to improve the yields, we performed reactions using different quantities of reagents. The best results were obtained with a 0.01:1:1:1.5 ratio of $K_5CoW_{12}O_{40}$, aldehyde, 1,3-dicarbonyl compound and urea or thiourea. Higher amounts of catalyst $K_5CoW_{12}O_{40}$ did not improve the result to a greater extent. After completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice from which the dihydropyrimidinones were isolated by filtration and recrystallized. Moreover, the catalyst could be quantitatively recovered from the reaction mixture by using simple filtration of the contents and washing with solvent, and could be reused after thermal activation (80 ^{o}C). For example, the catalyst was reused in case of *4*-methoxybenzaldehyde more than three times with no loss of activity. The crude products obtained are of high purity (>95% by ^{1}H NMR). Another important aspect of this procedure is the survival of a variety of functional groups such as NO_2, Cl, OH, OCH_3, and a conjugated C=C double bond under the reaction conditions.

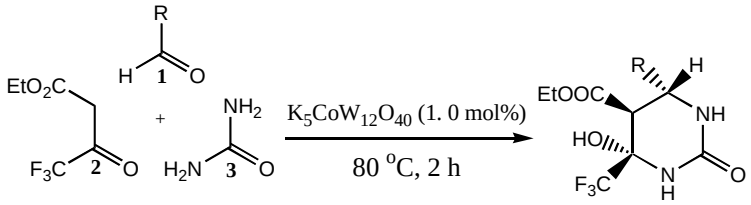
To study the generality of this process, several examples were studied and are summarized in Table 1. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Thiourea has been used with similar success to provide the corresponding dihydropyrimidine-(2*H*)-thiones, which are also of much interest with regard to the biological activity (eg., monastrol (**4g**), 95%). By using classical Biginelli conditions i.e. HCl in ethanol turned out to be not compatible with the thiourea obtained **4g** in much lower yield (17%).[12] Thus, variations in all three components have been accommodated very comfortably. However, under the present reaction conditions β-ketoaldehydes do not produce the corresponding dihydropyrimidinones; instead they lead to multiple products whose identities are yet to be established.

Table 1. $K_5CoW_{12}O_{40}$ (1. 0 mol%)-catalyzed synthesis of Dihydropyrimidinones under solvent-free conditions

Entry	R	R^1	R^2	X	Time (min)	Product (**4**)[a]	Yield (%)[b]	Ref.
1	Ph	CH_3	CH_3	O	30	**4a**	90	10a
2	4-(CH_3O)-C_6H_4	CH_3	C_2H_5	O	40	**4b**	95, 90, 87[c]	10b
3	4-$N(CH_3)_2$-C_6H_4	CH_3	CH_3	O	65	**4c**	88	10f
4	4-$N(CH_3)_2$-C_6H_4	CH_3	CH_3	S	90	**4d**	86	10f
5	2,4-(CH_3O)$_2$-C_6H_3	CH_3	CH_3	O	30	**4e**	95	10f
6	2,4-(CH_3O)$_2$-C_6H_3	CH_3	CH_3	O	30	**4e**	90[d]	10f
7	2,4-(Cl)$_2$-C_6H_3	CH_3	CH_3	O	75	**4f**	90	10f
8	3-(OH)-C_6H_4	CH_3	C_2H_5	S	60	**4g**	90	12
9	3,4-(CH_3O)$_2$-C_6H_3	CH_3	$C(CH_3)_3$	S	45	**4h**	95	10f
10	3,4-(CH_3O)$_2$-C_6H_3	C_2H_5	C_2H_5	O	45	**4i**	91	10f
11	C_6H_5-CH=CH	CH_3	C_2H_5	O	55	**4j**	88	10f
12	$CH_3CH_2CH_2$	CH_3	C_2H_5	O	90	**4k**	83	13
13	$(CH_3)_2CH$	CH_3	C_2H_5	O	70	**4l**	80	13
14	3,4,5-(CH_3O)$_3$-C_6H_2	CH_3	$C(CH_3)_3$	O	45	**4m**	95	10f
15		CH_3	$C(CH_3)_3$	O	30	**4n**	93	10f
16	2-(NO_2)-C_6H_4	CH_3	C_2H_5	O	90	**4o**	82	10d

[a]All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. [b]Isolated and unoptimized yields.[c]catalyst was reused at least three times. [d] 0·5 mol% catalyst was used.

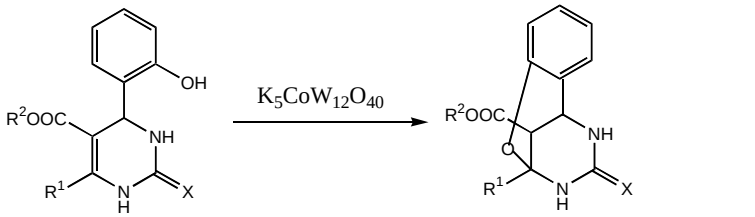
It is interesting to note that when ethyl trifluoroacetoacetate is used as the 1,3-dicarbonyl compound in this synthesis, the hexahydropyrimidine as the only isolable product in diastereomerically pure form (Scheme 2), considered to be an intermediate in the Biginelli reaction, was isolated **5a**-**5b** in good yields (65-70%). In the ^{1}H NMR spectrum of **5b** the doublets at δ 3.12 and 4.81 with a coupling constant of 11.0Hz are assignable to the 4-H and 5-H protons, which are *trans* to each other. The isolation and characterization of this intermediate (**5b**) for the first time assumes significance in terms of confirming the mechanism of the reaction earlier proposed by Kappe *et al.*[10d] It may be presumed that the OH group at C-6 may be *cis* to 5-H, thereby the elimination of water requires drastic conditions (*p*-TsOH, refluxing dry toluene).



Scheme 2

5a: R = C_6H_5
5b: R =4-(CH_3O)-C_6H_4

During the course of our studies, we have observed that the products derived from the condensation reactions involving 2-hydroxybenzaldehyde showed NMR spectra inconsistent with the expected DHPM structure (**4**). However, the product isolated from the reaction was diazatricyclo compound (**6b**), which was confirmed by IR, NMR and mass spectroscopy. The production of compounds (**6a-b**) (60-65% yield) can be explained by the isomerization reaction of DHPMs (**4**), which were initially formed (Scheme 3).



4

6

a: $R^1 = CH_3$; $R^2 = C_2H_5$; X = O
b: $R^1 = CH_3$; $R^2 = C_2H_5$; X = S

Scheme 3. The isomerization of DHPMs to diazatricyclic compounds.

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of dihydropyrimidinones with high yields and short reaction times, which involves the use of inexpensive catalyst potassium dodecatangestocobaltate under solvent-free conditions. Furthermore, the present procedure is readily amenable to parallel synthesis and the generation of combinatorial DHPMs libraries.

EXPERIMENTAL

1. General

Reagents and all solvents were analytically pure grade and were used without further purification. Anhydrous conditions were not required for this reaction. ^{1}H NMR spectra were recorded on Varian FT-200MHz (Gemini) in $CDCl_3$. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70eV on Finnigan Mat 1020B mass spectrometer. Melting points were recorded on Buchi 535 and are uncorrected. Elemental analyses were performed on elemental analyzer Vario EL. Column chromatography was carried out using 60-120 mesh silica gel. Thin-layer chromatography was performed on Merck 60 F-254 silicagel gel plates.

1. **2. Typical experimental procedure for 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (entry 2):** To a mixture of 4-methoxybenzaldehyde (2.72 g, 20 mmol), urea (1.80 g, 30 mmol), ethyl acetoacetate (2.60 g, 20 mmol) was added $K_5CoW_{12}O_{40}{\cdot}3H_2O$ (0.640 g, 0.20 mmol, 1.0 mol %) at 80 ^oC. After being stirred for 40 min at the same temperature (monitored by TLC) the resulting mixture was poured onto crushed ice (100 g) and stirred for 5-10 min. The resulting solid was filtered under suction (water aspirator) that was refluxed in EtOH (25 mL) and filtered to separate the catalyst. The ethanol solution was then cooled to room temperature to afford pure product (5.80 g, 95%). The filtered catalyst was reactivated by heating in oven at 80 ^oC for 2 h and reused at least for three times.

The known compounds have been identified by comparison of spectral data and mp with those reported. The mp, and analytical data of the new compounds have been presented below in order of their entries.

4i: mp 185-187^{0}C; IR (KBr): 3300, 3180, 2900-2600, 1680, 1651, 1570 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 1.10 (t, J = 7.5 Hz, 3H), 2.36 (s, 3H), 4.08 (q, J = 7.5 Hz, 2H), 5.22 (d, J = 3.5 Hz, 1H), 6.64-6.78 (m, 3H), 7.02-7.15 (m, 1H), 8.90 (s, 1H, OH), 9.18 (br s, N1-H), 9.82 (br s, N3-H). ^{13}C NMR (75MHz, DMSO-d_6) δ 174.1, 165.3, 157.1, 144.4, 144.0, 129.0, 117.4, 113.6, 101.4, 111.0, 59.5, 54.7, 17.4, 13.8. EIMS: m/z (%) 292 (M^+, 80), 263 (45), 219 (41), 199 (100), 171(35). Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.43, H, 5.55, N, 9.42.

5b: mp 98-100^{0}C; IR (KBr): 3420, 3105, 3045, 1600, 1520 cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6, TMS): δ 0.90 (t, J = 7.5 Hz, 3H), 3.12 (d, 1H, J = 11.0 Hz), 3.82 (s, 3H), 3.92-4.03 (m, 2H), 4.81(d, 1H, J = 11.0 Hz), 5.35 (br s, 1H, NH), 5.58 (s, 1H, OH), 5.90 (br s, 1H, NH), 6.82-6.93 (m, 2H), 7.21-7.36 (m, 2H). ^{13}C NMR (75MHz, DMSO-d_6) δ δ 167.0, 159.1, 153.8, 129.8, 128.6, 113.2, 111.8, 102.7, 95.5, 60.0, 54.6, 52.8, 50.2, 23.4, 13.3. EIMS: m/z (%) 362 (M^+). Anal. Calcd for $C_{15}H_{17}N_2O_5F_3$: C, 49.71; H, 4.70; N, 7.74. Found: C, 49.85, H, 4.63, N, 7.76.

6a: mp 200-202^{0}C; IR (KBr): 3220, 3085, 1745, 1690 cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6, TMS): δ 9.83 (br s, N1-H), 9.12 (br s, N1-H), 7.28-6.62 (m, 4H), 4.53 (d, J = 2.1 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.28 (d, J = 2.1 Hz, 1H), 1.78 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75MHz, DMSO-d_6) δ 168.5, 155.2, 150.5, 129.5, 128.6, 125.3, 121.0, 116.5, 83.5, 61.0, 48.0, 44.2, 23.9, 14.3. EIMS: m/z (%) 276 (M^+, 62), 247 (81), 229 (97), 203 (71), 183 (100). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.84; H, 5.84; N, 10.14. Found: C, 60.78, H, 5.90, N, 10.16.

6b: mp 203-205^{0}C; IR (KBr): 3365, 3175, 3085, 1745, 1590, 1565 cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6, TMS): δ 9.75 (br s, N1-H), 9.22 (br s, N1-H), 7.21-6.88 (m, 4H), 4.57 (d, J = 2.2 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.32 (d, J = 2.2 Hz, 1H), 1.76 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75MHz, DMSO-d_6) δ 175.5, 167.7, 150.5, 129.8, 128.6, 123.5, 121.0, 116.5, 82.5, 60.8, 48.2, 42.4, 23.6, 14.2. EIMS: m/z (%)

292 (M^+, 100), 263 (67), 219 (51), 199 (71). Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.49; H, 5.52; N, 9.59. Found: C, 57.65, H, 5.61, N, 9.43.

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