An Efficient and High Yielding Protocol for the Synthesis of Substituted Dihydropyrimidin-2(1*H*)-ones and Spiro-fused Heterocycles by Involving Tandem Reactions

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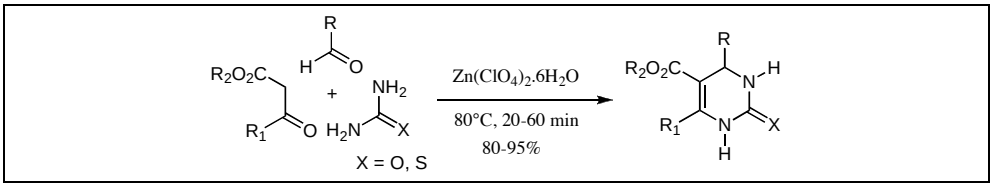

A simple and efficient method has been developed for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by a one-pot three component cyclocondensation reaction of alkyl acetoacetates, aldehyde, and urea in the presence of a catalytic amount of the reusable catalyst zinc per chlorate hexahydrate, $Zn(ClO_4)_2.6H_2O$ (10 mol %) the scope of this protocol is utilized for the synthesis of mitotic Kinesin EG5 inhibitor monastrol and new class of fused heterobicyclic compounds in high yields.

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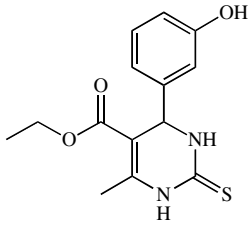
The synthesis of complex natural products is traditionally carried out by a sequence of separate steps, each of which requires its own conditions, catalyst, reagents and solvent. After completion of each step, the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Economic and environmental considerations are now forcing the chemical community to search for more efficient ways of performing chemical transformations [1]. These issues can be addressed by the development of new synthetic methods that, by bringing together simple components, can generate complex structures in one pot, in much the same way as occurs in nature [2]. In this context, the tandem transformations are of considerable interest [3].

Dihydropyrimidines (DHPMs) have attracted considerable attention in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties [4]. They have emerged as integral backbones of several calcium channel blockers, antihypersentive agents, α-1a-antagonists, neuropeptide Y (NPY) antagonists [5] and HIV gp-120-CD4 inhibitors activity in some marine natural products, containing the DHPM skeleton, such as batzelladine alkaloids [6]. The scope of this pharmacophore has been further increased by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative (±)-**4g** called monastrol [7], 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

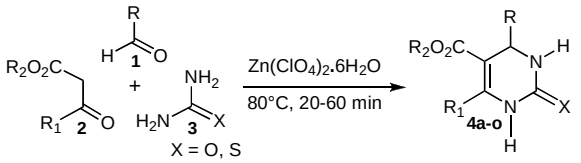
Figure 1

At present several general methods for the preparation of DHPMs exist. The most well known approach is the Biginelli reaction [8], in which aromatic aldehydes **1**, ureas **2** and alkyl acetoacetates **3** are condensed to DHPMs. The classical Biginelli reaction proceeds under relatively harsh conditions (EtOH, HCl, Δ) that are detrimental to sensitive functional groups present in the components used. Further, the use of aliphatic and *o*-substituted aromatic aldehydes or thioureas as starting materials affords the desired DHPMs in only moderate yields (20-60%), particularly for substituted aromatic and aliphatic aldehydes [9]. However, several improved protocols have been reported involving combinations of Lewis acids and transition metal salts, *e.g.* $BF_3.OEt_2$, polyphosphate esters, and reagents like $InCl_3$, trimethylsilyltriflate, $LaCl_3.7H_2O$, $CeCl_3.7H_2O$, $Yb(OTf)_3$,

clays, heterogeneous catalysts including various solid phase modifications suitable for combinatorial chemistry applications [10]. Unfortunately, these methods involve expensive reagents, stoichiometric amount of catalysts, long reaction times, strongly acidic conditions, unsatisfactory yields, and incompatibility with other functional groups. Therefore, the development of a neutral alternative would extend the scope of the Biginelli reaction.

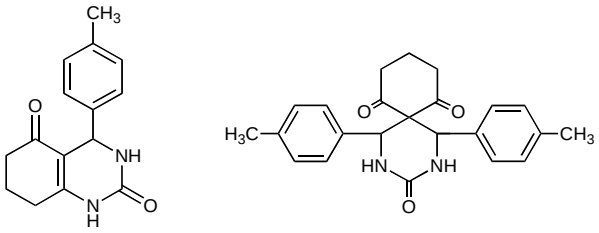
Recently, $Zn(ClO_4)_2.6H_2O$ [11] has emerged as a powerful catalyst in various chemical transformations such as acylation of alcohols with anhydrides, and in the conversion of β-keto esters into β-enamino esters. Since $Zn(ClO_4)_2.6H_2O$ is inexpensive, stable to air and moisture, it could represent a very attractive choice for other Lewis acid-promoted transformations. Therefore we decided to investigate its catalytic activity in a challenging Biginelli condensation (Scheme 1). This method not only preserved the simplicity of Biginelli's one-pot condensation but also remarkably improved the yields (>90%) of dihydropyrimidinones in shorter reaction times (20-60 min) as against the longer reaction times required for other catalysts after the addition of a low catalyst concentration. The procedure gives the products in good 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 that the other reaction product, water, evaporates at the reaction temperature of 80°C. In order to improve the yields, we performed reactions using different quantities of reagents. The best results were obtained with a 0.1:1:1:1.5 ratio of $Zn(ClO_4)_2.6H_2O$, aldehyde, 1,3-dicarbonyl compound and urea or thiourea. Higher amounts of $Zn(ClO_4)_2.6H_2O$ 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. The crude products obtained are of high purity (>95% by ^{1}H NMR). When the filtered solution containing the zinc perchlorate catalyst was reused, only a slight decrease in the yield from 95 to 87% as observed after the third run (entry 2, Table 1). Another important aspect of this procedure is the survival of a variety of functional groups such as NO_2, OH, OCH_3, and a conjugated C=C double bond under the reaction conditions.

Scheme 1



To study the generality of this process, several examples were studied and are summarized in Table 1. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes carrying either electron donating or – 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 biological activity (*eg*., monastrol 4g, 90%) [8]. By using traditional conditions ethanol/HCl 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. Furthermore, we investigated the reaction in the case of cyclic β-diketones, *p*-methyl benzaldehyde and urea under the experimental conditions (80°C/ethylene glycol/90 min), and found interestingly that the formation of spiro-fused heterobicyclic **5b** system exclusively (75 %) instead of expected fused heterobicyclic **5a** system (Scheme 2).

Scheme 2



5a **5b**

It is interesting to note that when ethyl trifluoroacetoacetate is used as the 1,3-dicarbonyl compound in this synthesis, the hexahydropyrimidine (Scheme 3), considered to be an intermediate in the Biginelli reaction, was isolated in good yields (65-70%). This confirms the earlier report by Kappe *et al*. [13] that in the ^{1}H NMR spectrum of **6b** the doublets at δ 3.12 and 4.81 with a coupling constant of 11.0 Hz are assignable to the 4-H and 5-H protons, which are *trans* to each other. The isolation and characterization of this intermediate (**6b**) assumes significance in terms of confirming the mechanism of the reaction. 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.

Table 1

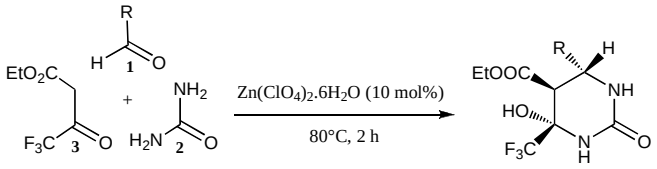
$Zn(ClO_4)_2.6H_2O$ (10 mol%)-catalyzed synthesis of Dihydropyrimidinones under solvent-free conditions

Entry	R	R^1	R^2	X	Time (min)	Product (**4**) [a]	Yield (%)[b]
1	Ph	CH_3	CH_3	O	30	**4a**	90
2	4-(OCH_3)-C_6H_4	CH_3	C_2H_5	O	20	**4b**	95, 90, 87[c]
3	4-$N(CH_3)_2$-C_6H_4	CH_3	CH_3	O	45	**4c**	88
4	4-$N(CH_3)_2$-C_6H_4	CH_3	CH_3	S	60	**4d**	86
5	2,4-$(OCH_3)_2$-C_6H_3	CH_3	CH_3	O	20	**4e**	95
6	2,4-$(OCH_3)_2$-C_6H_3	CH_3	CH_3	O	20	**4e**	90[d]
7	3-(OCH_3)-4-$(OCH_2$-C≡CH)-C_6H_3	CH_3	C_2H_5	S	50	**4f**	90
8	3-(OH)-C_6H_4	CH_3	C_2H_5	S	25	**4g**	90
9	3,4-$(OCH_3)_2$-C_6H_3	CH_3	$C(CH_3)_3$	S	35	**4h**	95
10	3,4-$(OCH_3)_2$-C_6H_3	C_2H_5	C_2H_5	O	30	**4i**	91
11	C_6H_5-CH=CH	CH_3	C_2H_5	O	45	**4j**	88
12	$CH_3CH_2CH_2$	CH_3	C_2H_5	O	60	**4k**	83
13	$(CH_3)_2CH$	CH_3	C_2H_5	O	60	**4l**	80
14	3,4,5-$(OCH_3)_3$-C_6H_2	CH_3	$C(CH_3)_3$	O	25	**4m**	95
15		CH_3	$C(CH_3)_3$	O	20	**4n**	93
16	2-(NO_2)-C_6H_4	CH_3	C_2H_5	O	60	**4o**	82

[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]5 mol% catalyst was used.

In summary, we have developed a simple, convenient, and one-pot atom economical synthesis of dihydropyrimidine derivatives and a novel spiro-fused heterocycle *via* the zinc perchlorate catalyzed three component coupling of urea, alkylacetoacetate with various aldehydes, involving tandem construction of C-N and C-O bonds. Furthermore, the present procedure is readily amenable to parallel synthesis and the generation of combinatorial DHPMs libraries.

Scheme 3



6a: R = C_6H_5
6b: R =4-(OCH_3)-C_6H_4

EXPERIMENTAL

General Procedure for the Preparation of 3,4-Dihydropyrimidin-2(1*H*)-ones. To a mixture of 4-methoxybenzaldehyde (272 mg, 2.0 mmol), urea (120 mg, 2.0 mmol), ethyl acetoacetate (260 mg, 2.0 mmol) was added $Zn(ClO_4)_2.6H_2O$ (37.2 mg, 0.01 mmol) at 80°C. After being stirred for 20 min. at the same temperature (monitored by TLC) the resulting mixture was poured onto crushed ice (10 g) and stirred for 5-10 min. The resulting solid was collected by suction filtration (water aspirator), washed with ice-cold water (10 mL) and then recrystallized from hot ethanol to afford pure product (0.58 g, 95%). The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The catalyst was recovered and reused in subsequent reactions, three times without losing any significant activity (reaction yields 95%, 90% and 87%).

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

Selected data, **4f**: mp 165-167°C; ir (KBr): 3310, 3180, 2900-2600, 2120, 1680, 1651, 1570 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$, TMS): δ 1.09 (t, *J* = 7.5 Hz, 3H), 2.38 (s, 3H), 2.45 (s, 1H), 3.85 (s, 3H), 4.16 (q, *J* = 7.5 Hz, 2H), 4.74 (s, 2H), 5.38 (s, 1H), 5.22 (d, *J* = 3.5 Hz, 1H), 6.82 (s, 1H), 6.88 (d, *J* = 4.5 Hz, 1H), 7.62 (br s, N1-H), 8.10 (br s, N3-H). ^{13}C nmr (75 MHz, $CDCl_3$) δ = 174.3, 165.3, 149.8, 146.8, 142.7, 136.5, 118.8, 114.5, 111.0, 103.0, 96.1, 75.9, 60.4, 56.8, 55.9, 55.6, 18.2, 14.1. fabms: 361 (M^++1). *Anal*. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 59.95; H, 5.57; N, 7.73.

Selected data, **4g**: mp 185-187°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 (75 MHz, 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.

Selected data, **6b**: mp 98-100°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 (75 MHz, DMSO-d_6) 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 $C_{15}H_{17}F_3N_2O_5$: C, 49.71; H, 4.70; N, 7.74. Found: C, 49.85; H, 4.63; N, 7.76.

Preparation of Spiro-fused Heterocyclic Compound (5b). $Zn(ClO_4)_2.6H_2O$ (74.4 mg, 0.01 mmol) was added to a stirred mixture of *p*-methylbenzaldehyde (480 mg, 2.0 mmol), urea (240 mg, 2.0 mmol), 1,3-cyclohexanedione (448 mg, 2.0 mmol) in ethyleneglycol (3mL) at 80°C. After being stirred for 60 min. at the same temperature (monitored by TLC) the resulting mixture was poured onto crushed ice (10 g) and stirred for 5-10 min. The resulting solid was collected under suction filtration (water aspirator), washed with ice-cold water (10 mL) and then recrystallized from ethanol/H_2O to afford pure product (1.13 g, 75%). mp 188-190°C; ir (KBr): 3425, 2930, 1685, 1650, 1520, 1200 cm^{-1}; ^{1}H nmr: (300 MHz, DMSO-d_6, TMS): δ 0.55 (t, J = 6.0 Hz, 2H), 1.55 (t, J = 6.2 Hz, 2H), 1.85 (t, J = 6.2 Hz, 2H), 2.22 (s, 6H), 5.10 (s, 2H), 6.85 (d, J = 7.5Hz, 4H), 7.15 (d, J = 7.5Hz, 4H). ^{13}C nmr (75 MHz, DMSO-d_6) δ = 211.0, 206.5, 155.5, 139.0, 133.5, 131.0, 130.0, 128.6, 125.8, 67.2, 62.4, 43.7, 42.0, 22.5, 14.6. hrms Calcd for $C_{23}H_{24}N_2O_3$: 377.1860 $[M+H]^+$; found: 377.1858. *Anal*. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.45; H, 6.39; N, 7.38.

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[11] *Caution*: Hazard properties of $Zn(ClO_4)_2.6H_2O$. May cause fire when hot and in contact with oxidising matter. Corrosive to skin, eyes and mucous membranes. Toxicity is low. [a] G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi L. Sambri, *Eur, J Org. Chem*, 4611 (2003); [b] G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, P. Melchiorre, L. Sambri, *Synlett*, 239 (2004).

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