ZIRCONIUM OXYCHLORIDE AS A NEW AND EFFICIENT CATALYST FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDINE-2(1H)-THIONE/ONE UNDER SOLVENT-FREE MICROWAVE IRRADIATION CONDITIONS

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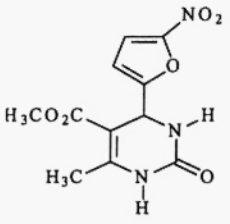
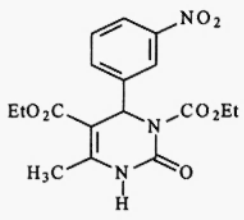
Abstract : $ZrOCl_2$ has been found to be an efficient catalyst for the one-pot synthesis of 3,4-dihydropyrimidine-2(1H)-thione/one, from β-ketoester, aldehyde and (thio)urea under solvent-free microwave irradiation conditions. The beneficial effects of $ZrOCl_2$ / microwave irradiation on the reaction are described. This is the first report on Lewis base catalyzed Biginelli reaction.
Keywords : $ZrOCl_2$ catalyst, dihydropyrimidine-2(1H)-thione/one, solvent-free, microwave irradiation.

4-Aryl-3,4-dihydro-2(1H)-pyrimidone esters of type **4** (DHPMs) represents a heterocyclic system of remarkable pharmacological efficiency[1]. In recent decades a broad range of biological effects including antiviral (e.g. nitracin, **I**)[2], antitumor, antibacterial and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives[1]. Recently appropriately functionalized derivatives have emerged as potent calcium channel modulators (e.g. **II**)[3], orally active antihypertensive agents (e.g. SQ32926, **III**)[4], α-1a-adrenoreceptor-selective antagonists (e.g. **IV**)[5], anticancer (e.g. Monastrol, **V**)[6], neuropeptide Y (NPY) antagonists[7]. Several marine alkaloids containing the DHPMs unit have shown intresting biological properties[8]. Most notably among them are batzelladine alkaloids, which were found to be potent HIVgp-120-CD_4 inhibitors[9]. Therefore the synthesis of DHPMs gained much importance in organic synthesis.



I



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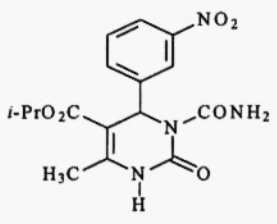

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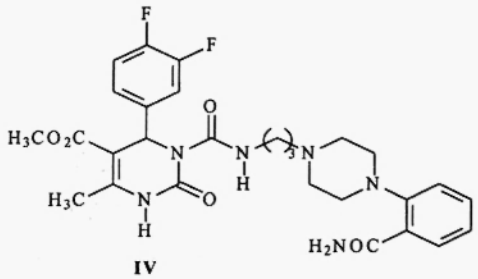

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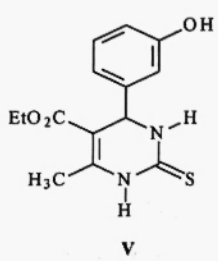
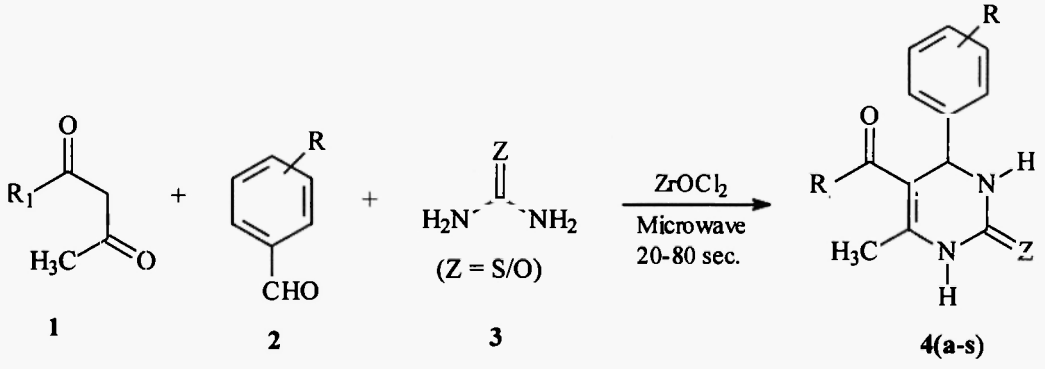


V

The most straight forward protocol to synthesize DHPMs **4** involve three component, one-pot condensation of a β-ketoester **1** with an aldehyde and (thio) urea **3** under strongly acidic conditions (Biginelli condensation)[10], suffers from low yields of products. For instance, the reaction of urea and ethylacetoacetate with aliphatic aldehyde resulted ethyl-4-alkyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in yield less than 40%[11]. Subsequently, multistep synthesis afforded high yields but lack of simplicity of original Biginelli one-pot protocol. Therefore, Biginelli reaction for the synthesis of DHPMs has received renewed interest and several improved procedures have been reported such as conc. HCl[12], H_2SO_4[13], $InBr_3$[14], VCl_3[15], $SnCl_2.2H_2O$-LiCl[16], $KHSO_4$[17], Amberlyte-15 or Nafron-H[18], PTSA[19], $Ag_3PW_{12}O_{40}$[20], Polyaniline-bismoclite[21], Silica-sulfuric acid[22], soluble polymer supported liquid phase synthesis[23], TMSCl/NaI[24], PPE[25]. However, most of these methods involved expensive and toxic catalysts, strongly acidic conditions, longer reaction times, high temperature, difficulties in work up, unsatisfactory yields and incompatibility with other functional groups. Thus, there is scope for further improvement towards the milder reaction conditions, high yields, high speed method and variation of substituents in all the three components with commercially available reagents.

In recent years, the development of more economical and environmental friendly conversion process is gaining interest in the chemical community. With the aim of simplification of the procedure, especially to avoid the expensive and unsafe synthetic routes and in continuation of our interest in developing novel methodologies using zirconium salts[26] herein we report an efficient, practical, environmentally benign and high yielding, high speed method for the Biginelli three component, one-pot synthesis of DHPMs using $ZrOCl_2$ as catalyst under solvent-free microwave irradiation conditions (Scheme 1). This is the first report in this direction using a Lewis base catalyst.



1 **2** **3** **4(a-s)**

Scheme-1

In order to be able to carryout such Biginelli condensation in a faster and more efficient way we used microwave irradiation of the neat mixture of β-ketoester **1**, aldehyde **2**, (thio)urea **3** and $ZrOCl_2$. The conditions employed are; 1.1 : 1.0 : 2.0 molar ratio of β-ketoester **1**, aldehyde **2**, and (thio)urea **3**, using $ZrOCl_2$ (~5 mol%) as a reaction mediator. In a typical experiment the four reaction components are simply mixed in a glass beaker and irradiated in an unmodified house hold microwave oven at 360 W for appropriate time (see Table 1). During microwave irradiation the reaction vessel is placed inside a large container filled with allumina, which acts as a heat sink. After cooling, water was added to the reaction mixture which hydrolyzed $ZrOCl_2$, dissolved excess (thio) urea and precipitated the solid DHPMs. The important features of microwave / $ZrOCl_2$ mediated Biginelli protocol are : in majority

of cases the product obtained is atleast 95% purity, high yields, survival of a variety of functional groups such as methoxy (**4b**, **4o**), halides (**4c**), nitro (**4f**, **4h**). Another aspect of this method is that, aliphatic aldehydes (**4l**, **4m**, **4q** and **4r**) also reacted well with β-ketoester to give the DHPMs in good yields. At the same time the reaction time is reduced from 4-8 hours reflux (traditional heating) to a few seconds (microwave irradiation). Finally, usefulness of this methodology has also been extended with thiourea in similar manner to provide the corresponding dihydropyrimidine-2(1H)-thiones (**4p**, **4q**, **4r** and **4s**) in high yields, which are more important biologically active molecules. The isolated products were characterized by IR, ^{1}H NMR and mass spectroscopy, and compared with the literature data for known compounds.

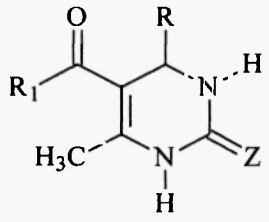
In conclusion, we have developed a simple in-expensive, efficient and solvent-free microwave induced method for the Biginelli condensation using cheap, less toxic and commercially available ziroconium oxychloride catalyst. The advantages of this environmentally benign and safe protocol include a simple reaction-setup, high yields, shorter reaction times, simple work-up procedure and also have the ability to tolerate a wide variety of substituents in all the three components which makes it a useful process for the synthesis of DHPMs.

Experimental

Melting points were uncorrected and were determined in open glass capillaries on Fisher-Johns apparatus. IR spectra (KBr) were recorded on a Perkin-Elmer spectrum BX series FT-IR 5000 Infrared spectrometer. ^{1}H NMR spectra were obtained on a varian Gemini (200 MHz) spectrometer and TMS was used as an internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a VG-micromass 7070H spectrometer. $ZrOCl_2$ is procured from Aldrich Company. All the aldehydes, β-ketoesters, (thio) urea (Analar grade) are commercially available; β-ketoester was employed after redistillation under vacuum. For the microwave irradiation, a conventional house hold microwave oven was used (LG Electronics India Private Limited).

Typical Procedure: A mixture of ethylacetoacetate (1.33 g, 1.1 mmol), benzaldehyde (1.06 g, 1 mmol) and urea (1.2 g, 2 mmol) was mixed with $ZrOCl_2$ (70 mg, 0.21 mmol, ~5 mol %). The mixture was taken in a glass beaker and the beaker was placed in an alumina bath inside an unmodified house hold microwave oven and subjected to microwave irradiation for the specified time (see Table 1) at 360 W, with mechanical stirring to avoid macroscopic hot spots. On completion of the reaction (as determined by TLC), the reaction mixture was cooled and stirred with water to dissolve $ZrOCl_2$ and excess urea. The solid product separated was filtered and recrystallized from ethanol to afford pure, 5-(ethoxycarbonyl)-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4a**. All the other compounds (4b-s) were prepared by the similar procedure and the physical data are given in Table 1.

Table-1: $ZrOCl_2$ catalyzed solvent-free synthesis of DHPMS.



DHPM[a]	R	R_1	Z	Time (sec)	Yield (%)[b]	m.p. °C	
						Obs.	Lit.
4a	C_6H_5	OEt	O	30	96	201-203	202-204
4b	4-(OMe)-C_6H_4	OEt	O	30	98	198-200	200-201
4c	4-Cl-C_6H_4	OEt	O	60	87	209-211	213-215
4d	4-Me-C_6H_4	OEt	O	40	92	170-172	172
4e	4-(NMe_2)C_6H_4	OEt	O	80	89	229-230	230-232
4f	4-(NO_2)C_6H_4	OEt	O	80	90	209-210	208-211
4g	3,4-(OCH_2O)C_6H_3	OEt	O	45	92	185-186	187-189
4h	3-(NO_2)C_6H_4	OEt	O	60	88	226-228	228
4i	C_6H_5-CH=CH-	OEt	O	40	96	230-232	232-235
4j	2-Furfuryl	OEt	O	60	89	204-206	205
4k	2-Thienyl	OEt	O	50	91	220-221	221-222
4l	CH_3-	OEt	O	25	94	192-193	193-194
4m	CH_3-CH_2-	OEt	O	35	90	181-183	186-187
4n	C_6H_5	OMe	O	30	94	209-211	209-212
4o	4-(OMe)C_6H_4	OMe	O	30	97	189-191	192-195
4p	4-(Me)C_6H_4	OEt	S	40	92	151-153	150-151
4q	H	OEt	S	20	96	236-237	236-237
4r	CH_3-CH_2	OEt	S	30	92	148-149	149-151
4s	C_6H_5	OEt	S	30	91	211-212	212-213

[a]All the products were well characterized by ^{1}H NMR, IR and Mass spectrometry and compared with authentic compounds.
[b]The yields refer to the isolated products and melting points were uncorrected.

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