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Note

One pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones catalysed by zinc chloride: An improved procedure for the Biginelli reaction using microwaves under solvent free condition

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Zinc chloride efficiently catalyzes the three-component coupling of β-keto ester, substituted aldehyde and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones respectively, the new protocol for the Biginelli reaction under microwave irradiation works in the absence of solvent, the yields are high and the reaction goes to completion within 20-35 sec.

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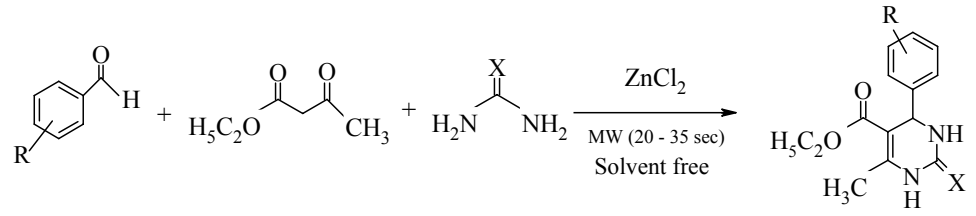
There is considerable interest in the formation of 3,4-dihydropyrimidin-2(1*H*)-ones and related compounds as they exhibit a wide range of biological activities such as antiviral, antitumor, antibacterial and anti-inflammatory properties[1]. These compounds have also emerged as the integral backbones of several calcium channel blockers, antihypertensive agents, and α_{1a}-adrenergic antagonists and neuropeptide antagonists[2]. Several alkaloids containing the 3,4-dihydropyrimidin-2(1*H*)-one unit have been isolated from marine sources and among them are the *batzelladine* alkaloids which are found to be potent HIV gp-120-CD4 inhibitors[2]. The synthesis of this heterocyclic nucleus is thus important, and the most simple and straight forward procedure reported by Biginelli in 1893 involves one-pot condensation of β-keto ester, benzaldehyde and urea under strongly acidic conditions[3].

Recently, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has gained acceptance and popularity among the synthetic chemist community. Numerous synthetic methods for preparing these compounds have been reported by using Lewis acids as well as protic acid promoters and ionic liquids, some of them include-ceric ammonium nitrate (CAN) under the influence of ultrasound[4], montmorillonite KSF[5], $InCl_3$ (ref. 6), $InBr_3$ (ref. 7), $LnCl_3$ (ref. 8), $Yb(OTf)_3$ (ref. 9), $Cu(OTf)_3$ (ref. 10), H_2SO_4 (ref.11a), conc.HCl (ref.11b), zirconium(IV)chloride[12], ytterbium(III)-resin[13], 1-*n*-butyl-3-methylimidazolium tetrafluoro-borate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$) in ionic liquids[14], $Mn(OAc)_3{\cdot}2H_2O$ (ref. 15), polyphosphate ester (PPE)[16a], phosphotungstic acid/EtOH[16b], BF_3-OEt_2/CuCl/HOAc[17], Silica/H_2SO_4 (ref. 18), $NiCl_2/FeCl_3$ (ref. 19), $FeCl_3/HCl$[20], NH_4Cl[21], LiBr[22], $KHSO_4$/glycol [23], $CdCl_2$[24a] and $SnCl_2{\cdot}2H_2O$ (ref. 25). Many of the existing methods involve expensive reagents stoichiometric amount of catalyst, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation and environmental pollution. Therefore, there is a need for versatile, simple and environmentally friendly processes for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. The development of alternative methods would extend the scope of the useful Biginelli reaction.

Currently, microwave irradiation has become a very useful tool in organic synthesis. Microwave technology in organic chemistry has been explored extensively within the last decade. Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, easier work-up matching with green chemistry protocols. There are a few reports on the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation. These methods involve use of $CuCl_2{\cdot}2H_2O/CuSO_4{\cdot}5H_2O$ (60-120 sec)[26a], polyphosphate ester (PPE, 60-90 sec)[26b], Amberlyst-15/Nafion-H/HOAc (120-300 secs)[26c]. In this report we describe a method of synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones **4** under microwave irradiation using catalytic amounts of zinc chloride for a three-component coupling of substituted aldehyde **1**, β-keto ester **2** and urea or thiourea **3**. While the Biginelli reaction with $ZnCl_2$ is known[24b], the reaction takes about 1-2 hr for completion under normal conditions. The new protocol under microwave irradiation works in the absence of a solvent, the yields are high and the reaction goes to completion within 20-35 sec as shown in **Scheme I**.



1 **2** **3** **4a-n**

R = H, F, Cl, OMe, CH_3, NO_2 ,OH X = O, S

Scheme I

Results and Discussion

In our laboratory we have shown that, reduction of different functional groups using metals/metal salts and/or ammonium salts is possible and simple metals such as Al, Zn, Sn can replace expensive and complex reducing agents for the reduction under different reaction conditions[27-33]. In continuation with the search for simple non-hazardous catalysts for transformations in organic synthesis, we are reporting the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones using catalytic amount of $ZnCl_2$ *via* Biginelli reaction under microwave conditions.

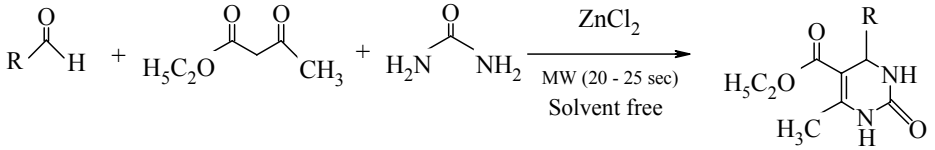
In a typical general experimental procedure, a solution of β-keto ester, an aldehyde, urea and catalytic amount of zinc chloride was irradiated under microwave irradiation for 20-35 sec to get 3,4-dihydropyrimidin-2(1*H*)-ones in high yields (**Table I**). It is clear from **Table I** that, a wide range of structurally varied araldehydes, β-keto ester and urea are coupled together by this procedure to produce the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones. It is also clear that, araldehydes carrying either electron-withdrawing or electron-donating substituents also afford high yields of products with high purity, and another important feature of this procedure is that of the survival of a variety of functional groups such as halides, nitro, hydroxy, ether etc. Acid sensitive aldehyde like 2-furaldehyde also worked well without formation of side products (**Table II**, entry 1) and α,β-unsaturated aldehydes also produce good yields of the product, there is no decomposition or polymerization under our reaction conditions (**Table II**, entry 2). Thiourea has been used with similar success to provide the corresponding thio-derivatives of 3,4-dihydropyrimidin-2(1*H*)-ones (**Table I**, entries 10-14), which are also of much interest with respect to their biological activity. This

Table I — Zinc chloride-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones from substituted benzaldehydes

Entry	**1** (R=)	**3** (X=)	Time (sec)	Product[a] **4**	Yield[b] (%)	m.p. (°C) Found	m.p. (°C) Reported[c]
1	H	O	35	**a**	95	201-03	202-03
2	4-NO_2	O	35	**b**	92	209-10	208-10
3	2-CH_3	O	30	**c**	90	209-10	208-10
4	4-CH_3	O	30	**d**	90	214-15	215-16
5	4-Cl	O	35	**e**	93	211-12	210-12
6	4-OCH_3	O	30	**f**	94	200-201	199-201
7	2-Cl	O	30	**g**	93	217-18	216-18
8	4-OH	O	35	**h**	90	227-28	227-29
9	4-F	O	35	**i**	93	183-85	185-86
10	H	S	35	**j**	95	209-10	208-10
11	4-OCH_3	S	35	**k**	94	151-52	150-52
12	3-NO_2	S	35	**l**	93	204-06	206-07
13	4-Cl	S	35	**m**	92	192-94	192-95
14	3-OH	S	35	**n**	94	183-85	184-86

[a] All the products known, characterized by IR spectral analysis and by comparison of their physical properties with those of the authentic compounds.
[b] Isolated yields.
[c] Melting points of compounds are consistent with reported values (references 10-16, 26).

Table II — Zinc chloride-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from other araldehydes



1 **2** **3** **4**

R = Furyl, Cinnamyl

Entry	**1** (R=)	Time (sec)	Product **4** Yield (%)	m.p (°C) Found	m.p (°C) Reported[a]
1	2-furyl	20	91	204-06	204-05
2	Cinnamyl	25	90	232-33	232-35

[a] References 10-16, 26.

method utilizes readily available low cost reagents affords high yields of different substituted 3,4-dihydropyrimidin-2(1*H*)-ones/or-thiones in short reaction times.

Experimental Section

All the chemicals were purchased from BDH/MERCK and used as received. Reactions were monitored on TLC by comparison with the authentic samples. For the microwave irradiation experiments described below a conventional (unmodified) household microwave oven was used (LG Microwave oven, Electronics India Private Limited). Yields refer to the isolated yields of the products. The IR spectra of the products were recorded on a NICOLET 400D FT-IR spectrophotometer. M.ps were determined on a Buchi melting point apparatus.

General procedure for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. A mixture of benzaldehyde (**1a**, 1.06 g, 10 mmoles), ethyl acetoacetate (**2**, 1.30 g, 10 mmoles), urea (**3**, 0.6 g, 10 mmoles) and zinc chloride (0.65 g, 5 mmoles) was taken in a Pyrex cylindrical tube and heated in a domestic MW oven (160 W). At the end of irradiation (20-35 sec), after completion [monitored by TLC (10% ethyl acetate-pet. ether)] the contents were cooled to room temperature and poured onto crushed ice and filtered through a sintered funnel. The crude product was further purified by recrystallization (EtOH or *i*-PrOH) to afford pure 3,4-dihydropyrimidin-2(1*H*)-one **4a**.

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References

1 Kappe C O, *Tetrahedron*, 49, **1993**, 6937 and references cited therein.
2 (a) Kappe C O, *Eur J Med Chem*, 35, **2000**,1043.
(b) Kappe C O, Shishkin O V, Uray G & Verdin P, *Tetrahedron*, 56, **2000**,1859.
(c) Patil A D, Kumar N V, Kokke W C, Bean M F, Freyer A J, Brosse C D, Mai S, Truneh A, Faulkner D J, Carte B, Breen A L, Hertzberg R P, Johnson R K, Westly J W & Potts B C, *J Org Chem*, 60, **1995**, 1182.
3 Biginelli P, *Gazz Chim Ital*, 23, **1893**, 360.
4 Yadav J S, Reddy B V S, Reddy K B, Raj K S & Prasad A R, *J Chem Soc Perkin Trans 1*, 42, **2001**, 7975.
5 Bigi F, Carloni S, Frullanti B, Maggi R & Sartori G, *Tetrahedron Lett*, 40, **1999**, 3465.
6 Ranu B C, Hajra A & Jana U, *J Org Chem*, 65, **2000**, 6270.
7 Fu N Y, Yuan Y F, Cao Z, Wang S W, Wang J T & Peppe C, *Tetrahedron*, 58, **2002**, 4801.
8 Lu J, Bai Y, Wang Z, Yang B & Ma H, *Tetrahedron Lett*, 41, **2000**, 9075.
9 Ma Y, Qian C, Wang L & Yang M, *J Org Chem*, 65, **2000**, 3864.
10 Paraskar A S, Dewkar G K & Sudalai A, *Tetrahedron Lett*, 44, **2003**, 3305.
11 (a) Bussolari J C & McDonnell P A, *J Org Chem*, 65, **2000**, 6777.
(b) Atwal K S, O'Reilly B C, Gougoutas J Z & Malley M F, *Heterocycles*, 26, **1987**, 1189.
(c) Atwal K S, O'Reilly B C & Schwartz J, *J Org Chem*, 54,**1985**, 5898.
12 Reddy C V, Mahesh M, Raju P V K, Babu T R & Reddy V V N, *Tetrahedron Lett*, 43, **2002**, 2657.
13 Dondoni A & Massi A, *Tetrahedron Lett*, 42, **2001**, 7975.
14 Peng J & Deng Y, *Tetrahedron Lett*, 42, **2001**, 5917.
15 Kumar K A, Kasthuraiah M, Reddy C S & Reddy C D, *Tetrahedron Lett*, 42, **2001**, 7873.
16 (a) Kappe C O & Falsone S F, *Synlett*, **1998**, 718.

(b) Jin T S, Xiao J C, Chen Y X & Li T S, *J Chem Res (S)*, 3, **2004**, 190.
17 Hu E H, Sidler D R & Dolling U H, *J Org Chem*, 63, **1998**, 3454.
18 Salehi P, Dabiri M, Zolfigol M A & Fard M A B, *Tetrahedron Lett*, 44, **2003**, 2889.
19 Lu J & Bai Y, *Synthesis*, 4, **2002**, 466.
20 Lu J & Ma H, *Synlett*, 1, **2000,** 63.
21 Shaabani A, Bazgir A & Teimouri F, *Tetrahedron Lett*, 44, **2003**, 857.
22 Maiti G, Kundu P & Guin C, *Tetrahedron Lett*, 44, **2003**, 2757.
23 Tu S, Fang F, Zhu S, Tuanjie L, Zhang X & Zhuang Q, *Synlett*, 3, **2004**, 537.
24 (a) Narsaiah A V, Basak A K & Nagaiah K, *Synthesis*, **2004**,1253.
(b) Sun Q, Wang Y Q, Ge Z M, Cheng T M & Li R T, *Synthesis*, **2004**, 1047.
25 Kumar S, Saini A & Sandhu J S, *Indian J Chem*, 43B, **2004**,1485.
26 (a) Gohain M, Prajapati D & Sandhu J S, *Synlett*, 2, **2004**, 235.
(b) Kappe C O, Kumar D & Verma R S, *Synthesis*, **1999**, 1799.
(c) Yadav J S, Reddy B V S, Reddy E J & Ramalingam T, *J Chem Res (S)*, 5, **2004**, 354.
27 Nagaraja D & Pasha M A, *Tetrahedron Lett*, 40, **1999**, 7855.
28 Pasha M A & Jayashankara V P, *J Chem Res (S)*, 4, **2004**, 282.
29 Pasha M A & Jayashankara V P, *Ultrason Sonochem*, **2004** (04J21- available online).
30 Pasha M A & Jayashankara V P, *Indian J Chem*, 43B, **2004**, 2464.
31 Pasha M A & Nanjundaswamy H M, *J Chem Res (S)*, **2004** (04/2585-In press)
32 Pasha M A & Ramesh N, *Indian J Chem*, 44B, **2005**, 778.
33 Myint Y Y & Pasha M A, *J Chem Res (S)*, 5, **2004**, 333.