$Co(OAc)_2$–CATALYZED TANDEM REACTION: SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES/THIONES FROM β-KETO ESTER, SUBSTITUTED ALDEHYDES AND UREA / THIOUREA USING MICROWAVES UNDER SOLVENT FREE CONDITION

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Abstract: Cobalt (II) acetate efficiently catalyzes the three-component coupling of *β*–keto ester, substituted arylaldehyde 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 reactions go to completion within one minute.

Introduction

Multicomponent coupling reactions (Tandem reactions) are emerging as useful tools for the carbon–carbon and carbon–heteroatom bond-forming reactions and for the synthesis of small drug like molecules with several degrees of structural diversity (1). Pioneering work by several research groups in this area has already established the versatility and uniqueness of one–pot multicomponent coupling protocols as a powerful methodology for the synthesis 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 (ref 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 (ref 2). The synthesis of this heterocyclic nucleus is thus important, and the most simple and straightforward procedure reported by Biginelli in 1893 involves one-pot condensation of β-keto ester, benzaldehyde and urea under strongly acidic conditions (3).

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 in ionic liquids, some of them include - Grindstone method (grinding components together) (4a), ZnI_2/CH_3CN (4b), I_2/CH_3CN (4c), I_2/toluene (4d), heteropolyacid - $Ag_3PW_{12}O_{40}$ (4e), use of ceric ammonium nitrate (CAN) under the influence of ultrasound (5a), montmorillonite-KSF (5b), $InCl_3$ (6b), $InBr_3$ (7), $LnCl_3$ (8), $Yb(OTf)_3$ (9), $Cu(OTf)_3$ (10), H_2SO_4 (11a), conc.HCl (11b), Zirconium(IV)chloride (12), Ytterbium(III)-resin (13), 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$)

in ionic liquids (14), $Mn(OAc)_3{\cdot}2H_2O$ (15), polyphosphate ester (PPE) (16a), phosphotungstic acid/EtOH (16b), BF_3-$OEt_2/CuCl/HOAc$ (17), Silica/H_2SO_4 (18), $NiCl_2/FeCl_3$(19a), $FeCl_3/HCl$ (19b), NH_4Cl (20), LiBr (21), $KHSO_4$/glycol (22), $CdCl_2$ (23a-b), $CdSO_4$ (23c) and $SnCl_2{\cdot}2H_2O$ (24) have also been used for the purpose. Many of the existing methods involve use of expensive reagents, require stoichiometric amount of catalyst, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields, incompatibility with other functional groups, and cumbersome product isolation. Therefore, there is a need for versatile and simple 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 and 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 $CuCl_2{\cdot}2H_2O$/ $CuSO_4{\cdot}5H_2O$ (60-120sec) (25a), polyphosphate ester (PPE, 60-90sec) (25b), Amberlyst-15/ Nafion-H/HOAc (120-300secs) (25c) and best our knowledge only one report $Mn(OAc)_3{\cdot}2H_2O$ (ref 15) by C S Reddy *et al* described under reflux condition 2–4 hr in acetonitrile medium.

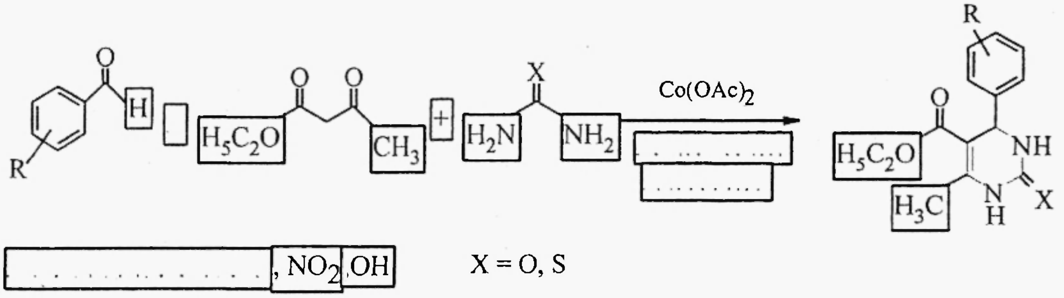
Experimental

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 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 Cobalt (II) acetate (0.89 g, 5 mmoles) was taken in a Pyrex cylindrical tube, heated in a domestic MW oven (160 W). At the end of irradiation (50 sec), after completion monitored by TLC (10% Ethyl acetate: Pet ether) the contents were cooled to room temperature and poured onto crushed ice, 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**.

Results and Discussions

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 (26). Recently in our group, we have reported the preparation α–iodoacetates from alkenes by using Cobalt (II) acetate (26f) In our research work and in continuation with the search for simple catalysts for transformations in organic synthesis, we are reporting the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones using catalytic amount of Cobalt(II)acetate *via* Biginelli reaction under microwave irradiation from benzaldehyde, β-keto ester and urea. While the Biginelli reaction takes about 3–4 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 40–50 secs as shown in **Scheme-I**.



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

Scheme-I

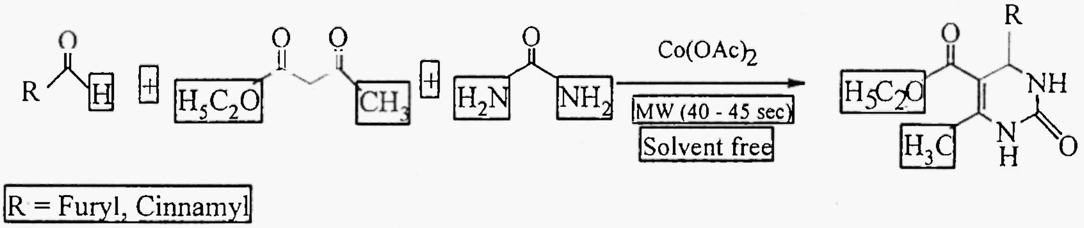
In a typical general experimental procedure, a solution of β-keto ester, an aldehyde, urea and catalytic amount of metal acetate was irradiated under microwave irradiation for 40-50 secs to get 3,4-dihydropyrimidin-2(1*H*)-ones in high yields (**Tables I & II**). It is clear from Table I that, a wide 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-2, 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-2, entry 2). Thiourea has been used with similar success to provide the corresponding thio-derivatives of 3,4-dihydropyrimidin-2(1*H*)-ones (Table-1, entries 10–14), which are also of much interest with respect to their biological activity. This 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.

Table-1: Synthesis of 3,4-dihydro pyrimidin-2(1*H*)-ones-thiones

	1	2		3		4(a-n)	
Entry	1	3	Time	Product[a]	Yield[b]	Melting points (°C)	
	R	X	(sec)	4	(%)	Found	Reported[c]
1	H	O	50	a	98	201-203	202-203
2	4-NO$_2$	O	50	b	92	209-210	208-210
3	2-CH$_3$	O	45	c	90	209-210	208-210
4	4-CH$_3$	O	45	d	90	214-215	215-216
5	4-Cl	O	40	e	93	211-212	210-212
6	4-OCH$_3$	O	40	f	94	200-201	199-201
7	2-Cl	O	40	g	93	217-218	216-218
8	4-OH	O	40	h	90	227-228	227-229
9	4-F	O	40	i	93	183-185	185-186
10	H	S	45	j	95	209-210	208-210
11	4-OCH$_3$	S	40	k	94	151-152	150-152
12	3-NO$_2$	S	40	l	93	204-206	206-207
13	4-Cl	S	40	m	92	192-194	192-195
14	3-OH	S	40	n	94	183-185	184-186

[a] All the products are 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, 23).

Table-2: Synthesis of 3,4-dihydro pyrimidin-2(1*H*)-ones.



1 2 3 4

Entry	1	3	Time	Product 4	Melting points (°C)	
	R	X	(sec)	Yield (%)	Found	Reported[a]
1	2-furyl	O	40	94	204-206	204-205
2	C$_6$H$_4$-CH=CH	O	45	92	232-233	232-235

[a] reference 23.

Conclusions

We have developed a rapid, efficient and environmental friendly method for the synthesis of 3,4–dihydropyrimidin–2(1*H*)–ones/thiones under microwave irradiation using catalytic amounts of cobalt (II) acetate for a three-component coupling of substituted arylaldehyde, β–keto ester and urea or thiourea, the reaction works in the absence of a solvent, the yields are high and goes to completion within one min. This method has the ability to tolerate a wide variety of substitutions in the components. We believe, our procedure will find important applications in the synthesis of dihydropyrimidinones to cater the needs of academia as well as pharmaceutical industries.

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