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Research Article

MICROWAVE ASSISTED SOLID PHASE SYNTHESIS OF 6-METHYL-5-(SUBSTITUTED BENZOYL)-4-(SUBSTITUTED PHENYL)-3,4-DIHYDRO-1-H-PYRIMID-2-ONE/THIONE

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ABSTRACT

Some novel substituted 3,4-dihydropyrimid-2(1H)one / thione derivatives **(IVa-p)** have been synthesized by condensation of corresponding chromones **(i)**, substituted aldehydes **(ii),** and substituted amides **(iii)** in presence of catalytic amount of acetic acid under solid phase condition and microwave irradiation. The structures of the synthesized compounds have been confirmed on the basis of IR, H^1-NMR, UV and Elemental analysis. The purity of compounds has been checked by HPLC technique and new protocol has been set up for newly synthesized compounds.

Keywords: 3, 4-dihydropyrimid-2(1H) one / thione, Chromones, Solid phase, M.W. irradiation.

INTRODUCTION

Nucleic acids are essential component of all cells and thus of living matter. Several pyrimidines have been isolated from the nucleic acids hydrolysates. These are possessing a wide spectrum of biological activities[1] such as antiproliferative[2], antiviral[3], antitumor[4], antiinflammatory[5], analgesic[6], antibacterial[7], antifungal[8], antihistaminic[9], anti-HIV[10], blood platelet disaggregation[11], calcium channel blockers[12], antihyper-tensive[13], for treatment of neurological and psychiatric disorder[14] and hyper uricemia[15] etc. as well as fused pyrimidines are used in a variety of agrochemicals, natural and veterinary products[16]. The first one-step synthesis of substituted 3,4-dihydropyrimid-2-(1H) one / thione by three component condensation of aldehydes, ethyl acetoacetate and urea has been reported by sci. P. Biginelli[17] in 1893.

To overcome the drawbacks of the Biginelli reaction, several protocols, such as use of aluminum trichloride ($AlCl_3$), borontrifluride (BF_3), polyphosphoric acid (PPA), H_3BO_3, NH_4Cl, NBS, triflates of lanthanides and In, Bi, Cu along with microwave irradiation etc. have been tried[18-22] to improve the yield and conditions of Biginelli reaction. It is worth to use catalytic amount of acetic acid to develop a new protocol for the Biginelli reaction.

The diverse nature of chemical universe requires various green strategic pathways in our quest towards attaining sustainability. Interest in search of Green Chemistry, microwave heating is very attractive for chemical applications[23] and has become a widely accepted non-conventional energy source for performing organic synthesis. This statement is supported by the increasing number of related publications in recent years, with the general availability of new and reliable microwave instrumentation. Microwave assisted organic synthesis is characterized by the spectacular accelerations produced in many reactions as a consequence of the heating rate, which cannot be reproduced by classical heating, Higher yields, milder reaction conditions and shorter reaction times can be used and many processes can be improved.

To develop new methodologies in organic reaction, in this communication, a simple and effective Biginnelli reaction that produces high yields of substituted 3,4-dihydropyrimid-2(1H) one/thione in short reaction time is disclosed under solid phase using silica and microwave irradiation condition in presence of a catalytic amount of acetic acid with one spot strategy**.**

MATERIALS AND METHODS

General

Melting points were measured in a open glass capillary and are uncorrected. IR spectra in KBr were recorded on instrument model spectrum one, serial number 68515; H^{1}NMR spectra was recorded on Varian mercury YH-300 MHz ($CDCl_3$) spectrometer using TMS as an internal standard and UV-Spectra on a systronic 119 spectrometer. All reactions were monitored by TLC using silica gel 60-F 254 plates. The reactions were carried out in scientific microwave oven (Scientific Microwave system model-RG31L1, 700W, 2450 MHz). Satisfactory C, H, N analyses were obtained for most of the compounds. Purity of the samples has been checked on HPLC and new protocol has been set up for newly synthesized compounds on a gradient high pressure liquid chromotograph with LC-20ATVP pumps, variable wavelength programmable UV/V1S.Detector SPD-10-AVP Shimadzu and RP-C-18 column (250 mm x 46 mm) was used. Mobile phase component methanol and water was filtered through 0.2 µm membrane filter before use and were pumped from the solvent reserviour at the ratio 80:20% V/V to the column at a flow rate of 1 ml/min. The volume of the newly synthesized sample was 20µl and the retention time was noted.

General procedure for the preparation of.6-Methyl-5-(sub-benzoyl)-4-(sub-phenyl)-3,4-dihydro-1-H-pyrimid-2-one/thione (IVa-p)

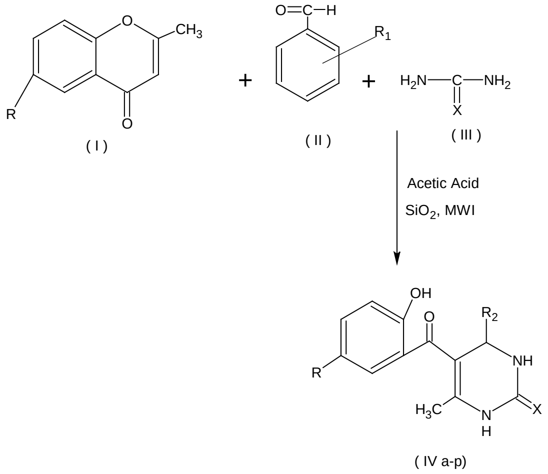
A mixture of substituted chromone (0.01 mol), substituted amide (0.02 mol) and substituted aldehyde (0.015 mol) was dissolved in minimum amount of ethanol. Then few drops of acetic acid were added to the mixture. The complete mixture was absorbed over silica and dried. Mixture in solid phase condition was irradiated to microwave irradiation in a scientific microwave oven for the specific time (2-5 min) at Medium High Power at the interval of 30 sec. Completion of the reaction was monitored by TLC. The reaction content was stirred in acetone and filter to get the desired product in good yield. It was recrystalized in ethanol to afford pure substituted 3,4-dihydro-1-H-pyrimid-2-one/thione **(IVa-p) (Scheme 1).**

6-Methyl-5-(2′-hydroxy-5′-Chlorobenzoyl)-4-(2″-hydroxylphenyl)-3,4-dihydro - 1-H-pyrimid-2-one (IVj)

Yield 92%, yellow, m.p.174–176^{0}C IR (KBr): 3400 cm^{-1} (NH and OH), 3018 cm^{-1} (C-H), 1729cm^{-1} (C=O), 1653cm^{-1} (CONH), 1443 cm^{-1} (-C-O-H bending), 1215 cm^{-1} (-C-O), 755cm^{-1} (-C-Cl),^{1}H-NMR (300 MHz,$CDCl_3$): δ1.75 (S,3H, $-CH_3$), δ4.75 (S,1H, OH), δ5.5 (S,1H,OH), δ 1.95 (S,1H,-CH), δ 7.355 (d,J=3Hz, Ar.1H), δ 7.14 (d, J=3Hz, Ar.1H), δ 6.96-7.015 (dd, J=12 Hz,3Hz, Ar.1H), δ 6.81 (d, J=12Hz,Ar.1H), δ6.65-6.70 (dd,J=12Hz, 6Hz, Ar.1H), δ 6.50-6.54 (dd, J=12Hz, 3Hz, Ar.1H),δ 6.36(d, J=15Hz, Ar.1H), δ 6.22(br,S,1H,-NH), δ 7.52(br,S,1 H,-NH).

The UV-spectrum recorded in $CHCl_3$ showed $\lambda_{max.}$ corresponding to $n\rightarrow\pi^*$ transition.

Analitical Calculation for $C_{18}H_{15}ClN_2O_4$ (358.5); C=60.25%, H=4.21%, N=7.80%. Found C=60.15%, H=4.12%, N=7.66%.



R = CH_3, Cl
R_1 = H, 2-OH, 4-OH, 4-NO_2
X = O,S

Scheme 1: General synthetic pathway for the preparation substituted 3,4-dihydro-1-H-pyrimid-2-one/thione (IVa-p).

RESULTS AND DISCUSSION

In recent past, in the synthesis of substituted 3,4-dihydro-1-H-pyrimid-2-one/thione **(IVa-p)** , 1-3diones and their esters had been attracted the researchers as one of the synthon. In this work, substituded 2-methylchromones have been used as starting moiety in Biginelli reaction for the first time. In the synthesis of novel 3, 4 -dihydro-1-H-pyrimid-2-one/thione derivatives, a mixture of substituted 2-methyl-chromones, substituded aldehydes, substituted amides, (1.1:1.5:2.0 molar ratio) and a catalytic amount of acetic acid was irradiated under solid phase and microwave conditions at 360 W for 2 -5 min, which gave **(IVa-p)** with an excellent yield, and the results are summarized in **Table1**. The compound 6-Methyl-5-(2'-hydroxy-5'-chlorobenzoyl)-4-(2"-hydroxyphenyl)-3,4– dihydro -1-H-pyrimid-2-one, **(IVj)** Shows IR absorption for NH and OH stretching Vibrations at 3400 cm^{-1}, an amide showed combine stretching at 1653cm^{-1} due to conjugation of unpaired electrons of nitrogen atom with carbonyl group resulting in increase single bond character and lowering of carbonyl frequency. C-O-H bending vibration at 1443 cm^{-1}, CH_3 bending peak at 1386 cm^{-1}, -C-O stretching at 1215cm^{-1}. The H^1-NMR spectrum of **(IVj)** exhibited a singlet of three protons of methyl group at δ 1.75, a sharp singlet slightly deshielded of N-CH at δ 1.9 ,two characteristic amide NH humps at δ 6.22 and δ 7.52 , phenolic -OH singlets at δ 4.75 and δ 5.55 assigned for chloro-substituated benzoyl -OH group. Multiplets in aromatic range are assigned for seven protons at δ 6.96 – 7.015.

Table 1: Physical data of 6-Methyl-5-(substitutedbenzoyl)-4-(substitutedphenyl)-3,4-dihydro-1-H-pyrimid-2-one/thione (IVa-p)

Entry	R_1	R	X	M.W. Time	Yield (%)*	M.P. (^{0}C)
IVa	H	-CH_3	O	3 min	96	152-154
IVb	2-OH	-CH_3	O	3 min	96	132-134
IVc	4-OH	-CH_3	O	3 min	93	149-151
IVd	4-NO_2	-CH_3	O	2.5 min	94	138-140
IVe	H	-CH_3	S	3.5 min	93	156-158
IVf	2-OH	-CH_3	S	3.0 min	96	138-140
IVg	4-OH	-CH_3	S	3.5 min	95	155-158
IVh	4-NO_2	-CH_3	S	3.5 min	94	158-160
IVi	H	-Cl	O	2.5 min	92	164-167
IVj	2-OH	-Cl	O	2.5 min	92	174-176
IVk	4-OH	-Cl	O	3.0 min	94	167-169
IVl	4-NO_2	-Cl	O	3.0 min	93	159-161
IVm	H	-Cl	S	3.0 min	94	165-167
IVn	2-OH	-Cl	S	3.0 min	89	163-168
IVo	4-OH	-Cl	S	2.5 min	93	167-169
IVp	4-NO_2	-Cl	S	2.5 min	94	158-160

*Isolated yield

CONCLUSION

In summary, we demonstrated an efficient and mild one spot three component and solid phase protocol for the synthesis of substituted 3,4-dihydro-1-H-pyrimid-2-one/thione**(IVa-p)** in presence of catalytic amount of acetic acid under microwave heating which is consistent with the green chemistry theme. The structures of the synthesized compounds have been confirmed on the basis of IR, H^1-NMR, UV and Elemental analysis. The purity of compounds has been checked by new protocol ie. HPLC technique.

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