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Solvent-Free One Pot Multi-Component Synthesis of 3, 4-Dihydropyrimidone Derivatives Catalyzed by Organic White Clay as an cheap and environmentally friendly catalyst

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***Abstract:** The reaction of different aromatic aldehydes, ethyl acetoacetate or acetyl acetone, urea or thiourea (Biginelli reaction) has been performed over organic white clay as the catalyst, under solvent-free conditions using microwave as the energy source, obtaining the corresponding 3, 4- dihydropyrimidones. Powder XRD and SEM-EDX analysis was carried out to characterize the white clay. Cystallite size of clay calculated from XRD spectra. This new method has the advantage of moderate to excellent yields (90-95%). The advantages of this novel protocol include the excellent yield, operational simplicity, short time, and the eco-friendly preparations and the avoidance of the use of organic solvents.*
***Keywords:** 3, 4- dihydropyrimidone, solvent-free, microwave, eco-friendly, white clay*

I. INTRODUCTION

One interesting class of nitrogen heterocycles is the venerable Biginelli dihydropyrimidinones synthesis which exhibits a wide range of biological activity due to their constituent stereogenic centers. For this reason, there have been many years of ongoing research to find an efficient and practical method for DHPM synthesis. One facet of this reaction's promise comes from the fact that it can be carried out under an array of chemical conditions; however, it is not at all without complications. While understanding the 'solvent-free' mechanism and finding a cheap catalyst are of some concerns for this particular approach, the major problem is finding a technique which gives high product yields, has limited drawbacks, and is safe for the environment. Dihydropyrimidines are known to possess therapeutic and pharmacological properties such as antiviral, antibacterial, antioxidant, analgesic, anticonvulsant, anti-coagulant, anti-inflammatory, and anti-HIV activities [1-5, 6]. Therefore, many synthetic methods for preparing such compounds have been developed [7].

Various catalytic process involving catalysis like $AlCl_3$,[8]$[Al(H_2O)_6](BF_4)_3$,[9] $ZnCl_2$,[10] $CuCl_2.2H_2O$ [11] $FeCl_3.6H_2O$,[12] Ziegler–Natta catalyst,[13] polyphosphate ester,[14] Baker's yeast,[15] $LaCl_3 \cdot 7H_2O$,[16] and $LiClO_4$,[17] and heteropoly acids[18] have been developed. Most of these catalysts are expensive, non-recoverable and generate strong acidic wastes [19]. This problem has been addressed to some extent by different heterogeneous methods using zeolites, [20] KSF clay with dry acetic acid under microwave irradiations [21], Nafion-H [22], montmorilonite K10 [17, 23], HCl_4/SiO_2 [24], amberlyst-15 [25] etc. In particular, clays and catalysis seem to have a very promising future, and even if many catalytic application have already been found day by day (in the laboratory & on an industrial scale), with a focus mainly towards establishing new environmentally-friendly technologies. From the literature search it was found that synthetic clay which has origin outside of india such as montmorillionite and KSF clay also have been used for these reactions. Here, we have used white clay which was found in India in western region. Regionwise different clay found which have different colour and properties.

II. EXPERIMENTAL

Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-252 (Merck) plates. All β-keto esters, aldehydes, and urea derivatives were obtained from Aldrich Chemical Co. and used without further purification, with the exception of benzaldehyde, which was distilled in vacuo prior to use. Organic white clay sample were collected from satara region, purified via simple washing and analysed by characterisation techniques. All solid components were employed as grained powders. Infrared spectral studies were carried out using KBr discs on a Perkin Elmer FTIR/4000 spectrophotometer. ^{1}H NMR and ^{13}C spectra were recorded in DMSO-d6 on Bruker Advance II 400 NMR spectrometer. Microwave oven used is of Sineo MAS II Plus. All products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopic studies and by comparison of physical characteristics with authentic samples.

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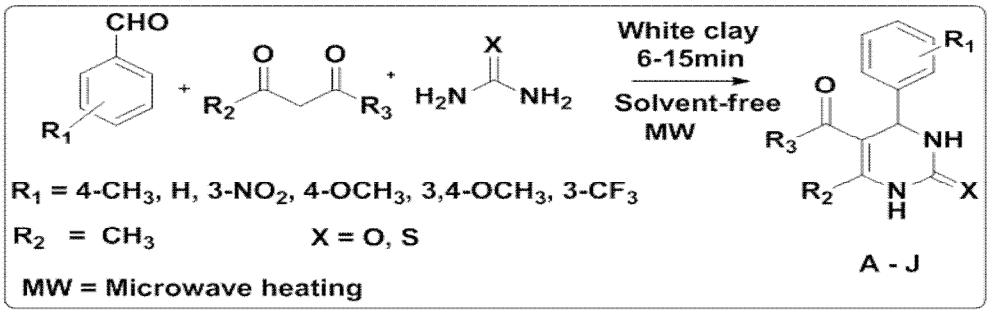
A. One-pot synthesis of 3, 4-Dihydropyrimidone derivatives

A mixture of appropriate aromatic aldehydes (0.01 mol), acetyl acetone/ethyl acetoacetate (0.01 mol, 1.3 g), urea (0.015 mol, 0.9 g) / thiourea (0.01 mol, 0.76 g) and white clay as a catalyst (0.2 g) (**Scheme 1**) was subjected to microwave irradiation for appropriate time without solvent. Cool the reaction mixture and quenched with crushed ice. The solid separated out was filtered, washed with cold water, dried and recrystallized from 95% ethanol to give pure products and structures confirmed by FT-IR, Proton, Carbon spectroscopic studies. The spent catalyst were collected by filtration and then washed with hot ethanol.

Table I
Solvent-free microwave-assisted synthesis of 3, 4-dihydropyrimidin-2(1H)-ones derivatives catalysed by White clay (b)

Entry	R_1	R_2	R_3	X	Product	M.P. (˚C)	Yield (%)	Time (min)	Power (w)
1	4-CH_3	CH_3	OC_2H_5	O	A_1	171-173	90	10	250
2	H	CH_3	OC_2H_5	O	B_1	200-203	95	10	250
3	H	CH_3	CH_3	O	C_1	210-212	93	8	250
4	H	CH_3	OC_2H_5	S	D_1	191-193	86	10	250
5	3-NO_2	CH_3	OC_2H_5	O	E_1	226-229	62	15	250
6	4-OCH_3	CH_3	OC_2H_5	O	F_1	------	----	----	----
7	3,4-OCH_3	CH_3	OC_2H_5	O	G_1	176-177	36	10	250
8	3-CF_3	CH_3	CH_3	O	H_1	313-316	60	8	250
9	3-CF_3	CH_3	OC_2H_5	O	I_1	161-164	76	8	250
10	X	CH_3	CH_3	O	J_1	207-210	54	6	400



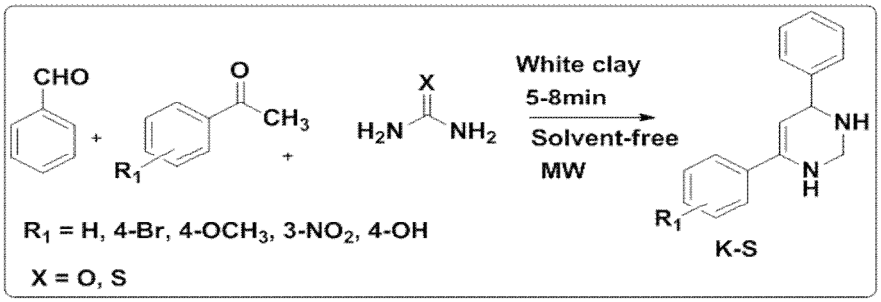
Scheme 1

B. Synthesis of 4, 6-diphenyl-3, 4-dihydropyrimidones Derivatives

A mixture of benzaldehydes (0.01 mol), substituted acetophenone (0.01 mol, 1.3 g), urea (0.015 mol, 0.9 g) / thiourea (0.01 mol, 0.76 g) and white clay (b) as a catalyst (0.2 g) (**Scheme 2**)was subjected to microwave irradiation for appropriate time without solvent. Cool the reaction mixture and quenched with crushed ice. The solid separated out was filtered, washed with cold water, dried and recrystallized from 95% ethanol to give pure products. The spent catalysts were collected by filtration and then washed with hot ethanol.

Table II
Solvent-free microwave assisted synthesis of 4, 6-diphenyl-3, 4 dihydropyrimidin-2(1H)-one derivatives by White clay (b)

Entry	R_1	X	Product	M.P. (˚C)	Yield (%)	Time (min)	Power (w)
10	H	O	K_1	208-210	43	5	400
11	4-Br	O	L_1	181-183	61	8	400
12	H	S	M_1	152-155	45	7	400
13	4-OCH_3	O	N_1	214-217	42	6	400
14	4-NO_2	O	O_1	226-228	65	8	400
15	3-NO_2	O	P_1	210-212	45	6	400
16	4-OH	O	Q_1	----	----	-----	-----
17	4-Br	S	R_1	146-148	48	7	400
18	4-NO_2	S	S_1	116-119	53	6	400



Scheme 2

III.RESULT AND DISCUSSION

From the above Table 1 it was clear that compound Ethyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate(A_1), Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4- tetrahydropyrimidine-5-carboxylate (B_1), and 5-(acetyl)-6-methyl-4-(phenyl)-3,4- dihydropyrimidin-2(1H)-one (C_1) obtained excellent yield (90-95%). Compound 5-(Ethoxycarbonyl)-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-thione(D_1) having sulphur obtained excellent yield (86%) in presence of white clay as a catalyst. Compound Ethyl-6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (E_1) obtained good yield (62%). It is clear that electronic effect of substitutent affects the yield of the products. As compound G_1 having 3,4-dimethoxy substituent has low yield (36%) as compared to compound B_1 and C_1 having H as substituent (90-95%).

From the above Table 2 it is clear that the compound K_1, M_1, N_1 and P_1 obtained low yield (43-48%) in presence of white clay. Compound L_1 having bromo at para position and O_1 having nitro group at para position obtained good yield (61%-65%) as compared to other compounds. Other compound R_1 having bromo substitutent at para position but having X= S obtained in low yield (48%). In compound P_1 having nitro group at meta position obtained in low yield (45%). In **Scheme 2** it was observed that compounds having electron withdrawing substituent such as bromo and nitro group obtained the good yield as compared to other compounds and also substitutent at X position affected the yield.

A. Characterisation of Organic White Clay

X-ray diffraction (XRD) pattern of organic white clay was recorded using an X-ray Diffractometer (Rigaku; model Miniflex –II) with monochromatic Cu K-α radiation (λ = 1.54178 A^o). The XRD data was collected with a scan rate of 3^o per minute. Energy dispersive x-ray analyzer (EDXA), Oxford instrument was used in conjuction with SEM (Scanning Electron Microscope) model JEOL JSM-6010 to measure the elemental composition of clay. To check the pH of clay Digital Equiptronics (Model EQ - 610) pH meter was used.

B. Analysis of White clay

To test the recovery of catalyst model reaction was carried out with organic white clay (0.2 g) for synthesis of product **A_1**. There is negligible loss (less than 0.02g) was found with 3 cycle of reaction. The pH of organic white clay was calculated by using pH meter (Digital Equiptronics, Model EQ - 610) which is 5.2 (acidic).

C. EDX study of White Clay

Elemental composition of organic red clay determined by EDS pattern recorded in the binding energy region of 1-10 KeV was shown in Fig. 1.

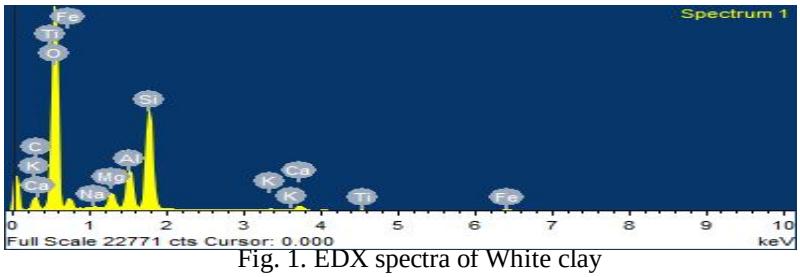


Fig. 1. EDX spectra of White clay

From the EDX spectra Fig.4 it was cleared that white clay contains Oxygen (O), Aluminium (Al), Silicon (Si), Iron (Fe) elements in large percentage as compared to other elements. (Main Element Composition). Results are summerised in Table III.

Table III
Elemental analysis (EDX) of Organic clays

Elements	White clay (Wt%)
Oxygen(O)	47.29
Sodium (Na)	---
Magnesium (Mg)	1.44
Aluminium (Al)	3.19
Silicon (Si)	23.14
Potassium (K)	0.86
Titanium (Ti)	0.66
Iron (Fe)	7.39

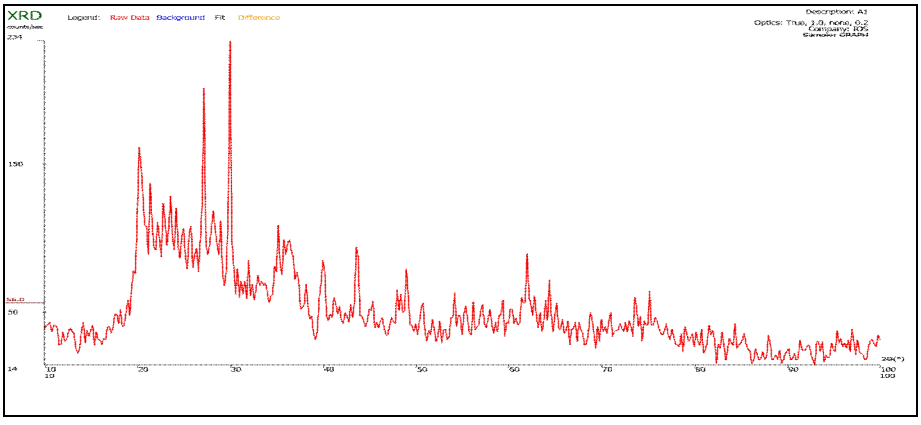


Fig. 2: XRD spectra of Organic White Clay

Fig. 2 shows XRD Spectra of Organic white clay. The sharpness of peaks determined the degree of crystallinity. Strong sharp peaks indicate good crystallinity of white clay. XRD plot Fig. 2 shows average well defined peak at $2\Theta = 29.98^{o}$ which indicate crystallinity.

From XRD pattern, crystallite size of the white clay is calculated by using Debye-Scherrer equation,

$$D = 0.90\ \lambda / \beta \cos\theta \qquad \textit{Equation 1}$$

Where, β = broadening of the diffraction line (Bragg peak) measured at full width at half of its maximum intensity (FWHM) (in radian), λ = wavelength of target, D = diameter of the crystal particle, θ = angle of diffraction

The average crystallite size distribution can be determined independently from X-ray diffraction line broadening which for the organic white clay is 30.60 nm.

Size of clay particles has effect on it's surface area. As the surface area increases the size of the clay particles decreases. Surface area and the pore volume in the clay structure also add to the efficiency of the catalyst. Because of their large surface area and the presence of surface defects and dislocations, nanoparticles in soil are very reactive towards external solute molecules.

IV. CONCLUSION

We have developed the new method for the synthesis of substituted dihydropyrimidinones /thiones catalyzed by organic white as a catalyst under solvent-free conditions. Moderate to excellent yields of the corresponding DHPMs derivatives were obtained from readily available starting materials. Average crystallite size of white clay was 30.60 nm which is obtained from XRD spectral analysis. pH of white clay is found to be 5.2. It was also observed that electronic effect of substituents present on the reactants also affect (increase or decrease) the yield of final product. This improved reaction condition allows the preparation of wide variety of substituted dihydropyrimidones in good yields under mild reaction conditions.

V. ACKNOWLEDGMENT

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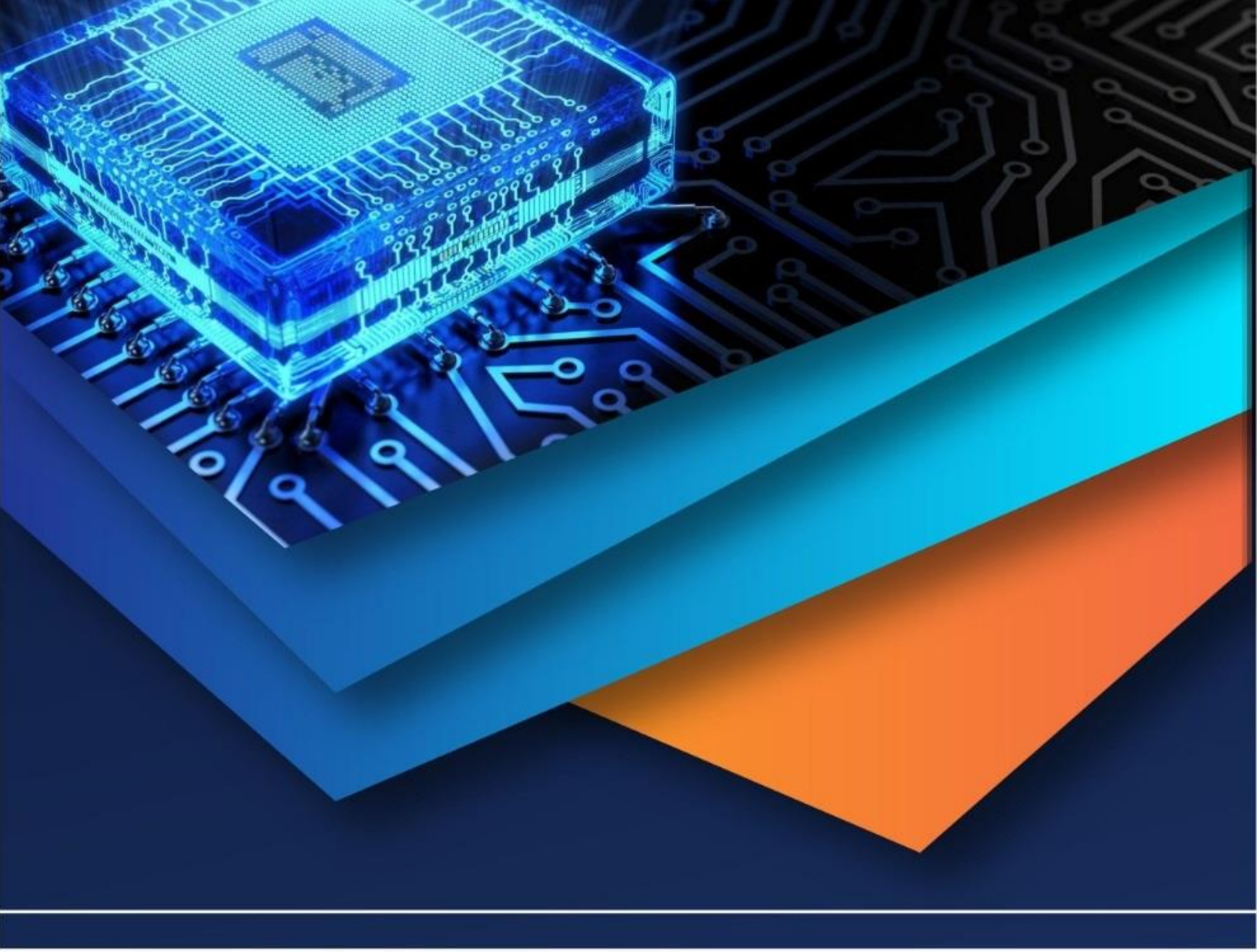

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