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Simple and Efficient one Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones and Thiones By Using A Mixture of Ionic Liquid And Graphene Oxide Nanoparticles at Reflux Condition.

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Abstract

A simple and efficient protocol was established for the one-pot Biginelli condensation reaction of aldehydes, β-dicarbonyl compounds, and urea or thiourea by using a mixture of [Hmim]HSO_4 and Graphene oxide nanoparticles as catalyst at reflux condition in ethanol. The advantages of this protocol includes high yields, recyclable catalyst, easy work-up and selectivity towards 3,4-dihydropyrimidin-2(1H)-onesderivatives

Keywords: Biginelli,Ionic liquid, Graphene Oxide nanoparticles , Reflux.

1. Introduction

Dihydropyrimidinones (DHPMs) were found to possess several biological activities such as antimicrobial, antiviral, antimalarial, anticancer, antihypertensive, anti-inflammatory, calcium channel modulators, mitotic kinesin inhibitors and neuropeptide Y(NPY) antagonists (Agrawal 2007; Rajesh 2011; Fewell 2004; Kappe 2000; Atwal 1991). The most simple and straightforward procedure, reported by Biginelli more than 100 years ago (Biginelli 1893; Dondoni 2006) involves the three component acid catalyzed condensation in one-pot, but this reaction suffers from the harsh conditions, long reaction times and frequently low yields.In recent yearsseveral literature citations exist relating to various efforts to develop the Bigineli reaction using alternative catalyst and greener methods such as Ionic liquids,ultrasound irradiation [6], solvent free[7], catalyst free [8], aqueous media [9], metal triflate [10] and PtNPs@GO [11]. Many of these reported methods involve theuse of expensive reagents, hazardous solvents, long reactiontimes and tedious workup procedures. Presently, a mixture of [Hmim]HSO_4 and Graphene oxide has attractive features because of using minimum catalytic amount, reusability, recoverability and tolerable metal

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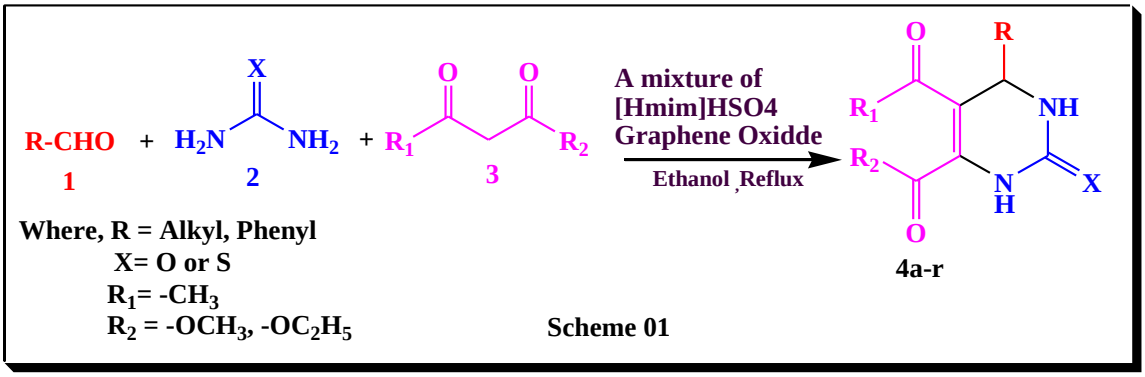
leaching to the solution. So it has been reported to facilitate several organic transformations replacing hazardous chemical reagents[12-18].

Owing to these, here we reported, use of a mixture of [Hmim]HSO_4 and graphene oxide as a metal free catalyst for synthesis of 3,4-dihydropyrimidin-2(1H)-onesderivatives as shown in Scheme 01



Where, R = Alkyl, Phenyl
X= O or S
R_1= -CH_3
R_2 = -OCH_3, -OC_2H_5

Scheme 01

2. Experimental

2.1. Materials and Methods.

Melting points were measured in open glass capillaries on a Veego melting-point apparatus and were uncorrected. ^{1}H NMR was recorded at room temperature on a Bruker Avance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in $CDCl_3$ using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instrument. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. The products were also characterized by comparison of their melting point with literature values.Graphene oxide is prepared by using known procedure and characterized by IR spectra and XRD analysis on X-Ray Diffraction System UltimaIV(Solapur University).

2.2 General Procedure for Synthesis of Graphene Oxide:

Graphene Oxide nanoparticles were prepared by using Hummer's Method(19). The graphite powder (2.5g) and $NaNO_3$ (1.25 g) were added to the concentrated H_2SO_4 (57.5 mL) in an ice bath. $KMnO_4$ (7.5 g) was slowly added to the solution, while maintaining the temperature below 20°C. The mixture was stirred in the ice bath for 30 min and then put in 35^0 C water bath for 30 min. Then 100 mL of hot water was added, followed by 25 mL hydrogen peroxide (25wt %,) solution to terminate the reaction. The mixture was filtered and washed with deionised water many times to remove any excessive acid and inorganic salts. The resulting GO was dried in heating mantle at 60°C.

[HMim]HSO_4 was synthesized according to the previous work [29-31]. All yields refer to the isolated products after purification.

2.3General procedure for synthesis of 3,4-dihydropyrimidones derivatives.

Benzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea or thiourea (1.2mmol), and 0.05gm a mixture of [Hmim] HSO_4 and Graphene oxide were added to a 50 ml round bottom flask by using ethanol as solvent. Reaction mixture was heated at reflux for the appropriate time as mentioned in Table 04. After the completion of reaction, as indicated by TLC, the reaction mixture was filtered to remove catalyst and poured onto crushed ice and stirred for 10 to15 minutes. The yellow solid separated was filtered under suction and washed with ice-cold water. The crude

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reaction product thus obtained was collected and further purified by recrystallization with hot ethanol to afford pure 3,4-dihydropyrimidin-2-one/-thione. The filtrate so obtained was concentrated under reduced pressure to recover ionic liquid which could be reused in subsequent experiments

3. Result and discussion

3.1 Charecterization of Graphene Oxide:

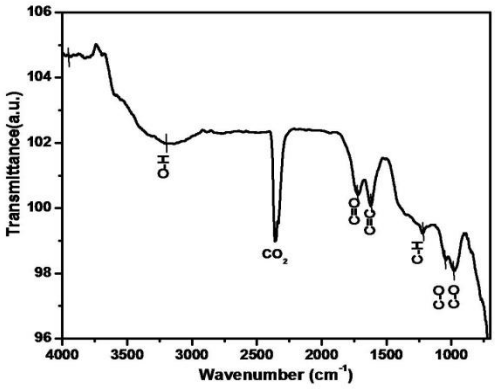

Fig. 1 FTIR spectra of GO nanoparticles

The nature of the chemical functionalities was characterized by FTIR [Fig. 1]. An intense and broad peak appeared at 3350 cm^{-1},corresponds to the stretching mode of an O–H bond, reveals the abundance of hydroxyl groups in graphene oxide. The strong band at 1735cm^{-1} represents carboxylic acid and carbonyl groups. The bands at 1224 $cm^{-1}$and 1053 cm^{-1}suggest the stretching mode of C–H and C–O (epoxy) bonds of GO, respectively

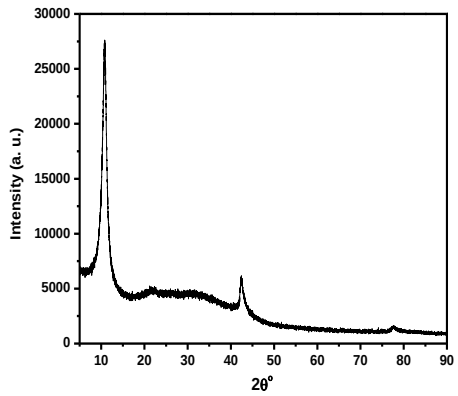

Fig. 2 XRD pattern of GO nanoparticles

Fig.2 shows the XRD patterns obtained for graphene oxide powder. In this figure graphene oxide nanopowder shows intense (002) centered at 10.84^0, corresponding to an interlayer spacing of 0.82 nm. Interlayer spacing can be calculated using Bragg's law ($n\lambda = 2d \sin\Theta$, here $\lambda = 0.154$ nm). On the contrary, the literature value for interlayer distance of the (002) peak for graphite is 0.337 nm (20). It may conclude that the incorporation of oxygenated functional groups due to oxidation of graphite powder to GO enhances its interlayer spacing attached on both sides and the edges.

3.2 Optimization of Reaction

In recent years, Ionic liquid and Graphene Oxides NPs catalysts have gained importance in several organic transformations due to their interesting reactivity as well as for economic and environmental reasons. Keeping in view environmentally benign conditions we tried to develop green and efficient routes for synthesis of biologically active heterocyclic compounds by using , a mixture of [Hmim] HSO_4 and Graphene oxide in ethanol solvent.
As our work on use of different catalyst in heterocyclic synthesis, here we use a mixture of [Hmim] HSO_4 and Graphene oxide for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones derivatives under solvent free and reflux condition.
For our initial studies the effect of solvent on the reaction were studied at reflux conditions with different reaction times with model reaction of Benzaldehyde, ethylacetoacetate and urea. The best results were obtained in ethanol shown in Table 01.

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Table 01. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones using different solvents.

Entry	Solvent used	Time in Hours	Yield (%)
1	Chloroform	3.5	78
2	Ethanol	2.5	86
3	Water	3.6	74
4	Acetonitrile	2.9	72

However the generality of reaction was also checked with different reaction conditions by using a mixture of [Hmim] HSO_4 and Graphene oxide. The best result was obtained for reflux condition at 120^{o}C as it gives high yield at shorter reaction time summarized in Table 02. Even increase in reaction temperature from 120 to 140 the corresponding 3,4-dihydropyrimidin-2(1H)-ones gives the same yield.

Table 02. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones using different reaction conditions .

Entry	Reaction condition used	Time in Hours	Yield (%)
1	Room Temperature	120	68
2	60^{0}C	104	70
3	80^{0}C	100	70
4	100^{0}C	90	74
5	120^{0}C	75	88
6	140^{0}C	75	88

With above optimized reaction conditions, in order to study the generality of the reaction using different aldehydes containing both electron donating and electron withdrawing groups underwent the conversion smoothly and gave the products in good to excellent yields (Table 04). Similarly, we have studied the condensation of aldehyde, ethyl acetoacetate and thiourea. The reaction of thiourea proceeded at lower rate to give S-DHPMs.

Table 03. Reuse of catalyst for the synthesis 3,4-dihydropyrimidin-2(1H)-ones.

Cycle	Fresh	1st	2nd	3rd	4th	5th
Yield (%)	86	80	76	71	65	62

The reuse of the catalyst is a major factor in a new synthetic green procedure. The ionic liquid and grapheme oxide can be reused after simple distillation to remove water and remaining ionic liquids was dried under vacuum and reuse for further reactions. To test this, a series of five consecutive runs of the reaction Benzaldehyde, ethylacetoacetate and urea with catalyst were carried out. The results, however, demonstrated decrease in the activity of the catalyst (Table 03). This method offers some advantages in terms of low reaction times, simplicity of performance, low cost and use of catlyst which follow along the line of green chemistry.

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Table 04. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones derivatives by using a mixture of [Hmim]HSO_4 and Graphene Oxide NPs at reflux condition

Entry	R_1	R_2	X	Time(Min.)	Yield(%)[a]	M.P.(^{0}C)
a	-C_6H_5	-OEt	O	75	86	197-199
b	4-NO_2-C_6H_4	-OEt	O	90	83	198-200
c	4-Cl-C_6H_4	-OEt	O	87	82	202-204
d	4-Br-C_6H_4	-OEt	O	88	85	196-198
e	4-HO-C_6H_4	-OEt	O	96	81	214-216
f	4-OCH_3-C_6H_4	-OEt	O	65	80	198-200
g	3-NO_2-C_6H_4	-OEt	O	95	85	218-220
h	4-CH_3-C_6H_4	-OEt	O	90	78	203-205
i	2,4-$(OCH_3)_2$-C_6H_3	-OEt	O	70	84	175-177
j	-C_6H_5	-OMe	O	55	80	204-206
k	4-Cl-C_6H_4	-OMe	O	60	86	195-197
l	4-OCH_3-C_6H_4	-OMe	O	65	78	183-185
m	4-NO_2-C_6H_4	-OMe	O	65	79	214-216
n	-C_6H_5	-OEt	S	60	82	206-208
o	4-NO_2-C_6H_4	-OEt	S	120	84	110-112
p	4-CH_3-C_6H_4	-OEt	S	110	85	192-194
r	4-OCH_3-C_4H_4	-OEt	S	90	84	208-210

[a]Yields refer to the pure isolated product.

3.3. Spectral data of compounds.

1.5-Ethoxycarbonyl-6-methyl-4-(3-methylphenyl)-1,3-dihydropyrimidin-2-thione (4r):

IR (KBr):υ_{max}= 3314, 1722, 1645, 1560cm^{-1}; ^{1}HNMR ($CDCl_3$):δ= 1.12 (t, J= 7.1 HZ, 3H), 2.47 (s, 3H), 2.38 (s, 3H), 4.31 (q, J=7.1 HZ, 3H), 5.27 (s, 1H), 7.1-7.4 (m,4H,Ar), 7.8(s, 1H, NH), 8.4 (s,1H, NH) ; ^{13}CNMR ($CDCl_3$): δ= 15.5, 20.26, 24.51, 58.18, 61.24, 106.64, 123.44, 127.45, 128.82, 130.15, 136.64, 141.91, 143.1, 167.7, 178.5 ppm

2.5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4f):

IR (KBr):υ_{max}= 3254, 1745, 1688 cm^{-1}; ^{1}HNMR ($CDCl_3$):δ= 1.19 (t, *J* = 6.8Hz, 3H), 2.34 (s, 3H), 3.74 (s, 3H), 4.2 (q, J=6.8 HZ, 2H), 5.27 (s, 1H), 6.9-7.1(m,4H,Ar), 7.6 (s, 1H, NH), 9.3 (s,1H, NH) ; ^{13}CNMR ($CDCl_3$): δ= 14.6, 18.6, 56.67, 55.56, 59.64, 99.7, 117.2, 126.8, 146.4, 148.3, 160.8, 165.8 ppm.

4. Conclusion

In conclusion, developed an efficient method for the synthesis of fused 3,4-dihydropyrimidin-2(1 H)-ones and thiones by using a mixture of [Hmim]HSO_4 and Graphene Oxides NPs at reflux condition. The method offers several advantages such as catalyst reusability, high yield of product, short reaction time, simple work-up procedure and easy isolation. We believe this methodology is useful to existing methodologies for the synthesis of fused 3,4-dihydropyrimidin-2(1 H)-ones and thiones.

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