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Research Article

One pot Solvent free Synthesis of Biginelli Type Derivatives using $Ag_2O/GO/TiO_2$ Composite Nanostructure and evaluation of biological activity

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ABSTRACT

The Biginelli Reaction is a one-pot acid catalysed cyclocondensation of -keto ester, urea and aromatic aldehyde which leads to the synthesis of functionalised 3,4-dihydro-2(H)-pyrimidinones (DHPMs). This three-component reaction for the synthesis of dihydropyrimidinone and corresponding dihydropyrimidinethiones has now been known for more than a century since first reported in 1893. The classical reaction has been modified in the recent past by using various catalysts and several structural variants in different solvents to synthesize large number of Biginelli type compounds. Also, these DHPMs (synthetic and natural) possess a wide range of pharmacological activities.

Keywords: Dihydropyrimidinone, dihydropyrimidinethione, multicomponent reactions, $Ag_2O/GO/TiO_2$

1. Introduction

With the development of nanotechnology, catalysts made of transition metals have drawn a lot of attention due to their application in various areas including catalytic

hydrogenation, rechargeable batteries, and wastewater treatment [1]. Transition metals (Co, Fe, Ni, Mo, Mn, and Zn, etc.) exhibit significant advantages such as being inexpensive, non-toxic, and abundant in the earth [2]. In this regard, Bonin et al. reviewed recent developments of electrochemical and photochemical CO_2 reduction molecular catalysis with a metal-based Fe and Co complex [3]. He *et al*. increased atomic utilization and electronic regulation for promoting ORR catalysis and proposed a practicable strategy for the Pt-Fe intermetallic catalysts'synthesis[4]. Youn *et al*. described the morphological evolution of Fe-Mo bimetallic catalysts for the vertically aligned carbon nanotubes' diameter and density features modulation [5]. The applications of N^O (ethylimino-methyl) phenol Fe(II) and Co(II) complexes in ethylene oligomerization catalysis and their structural elucidation were studied by Ngcobo et al. [6]. In artificial photosynthetic systems, hydrogen is generated with molecular catalysts of Co, Ni, Fe, and Mo[7]. Du *et al*. carried out theoretical and experimental studies on metal-organic framederived (M=Fe, Ni, Zn, and Mo) which were doped into Co_9S_8 nanoarrays as an efficient electrocatalyst for water splitting [2].

Recently, noticeably growth in the applications of heterogeneous catalysis in organic reactions to carry out synthetic transformations as a consequence of its significance in terms of enviro-economical and practical aspects. [8]

At the other hand, there has been interested in the use of inorganic solid acids in the organic synthesis [9–12]. Among these catalysts, nanoparticles (MNPs) have emerged as a new class of heterogeneous nano catalyst for organic transformations and organic synthesis. Among the various solid acid catalysts, zeolites have received an increasing attention because of their suitable acidity, thermal stability and low cost. [13]

The Biginelli reaction is one of the well-designed methodologies used for the synthesis of dihydropyrimidinone (DHPM) or thione derivatives, an important family of compounds known for their diverse pharmacological properties, which can act as antibacterial, antiviral,

and calcium channel modulators as well as anticancer and antihypertensive agents. The reported biological activities of DHPMs encourage research groups to produce structurally diverse libraries of bioactive heterocycles. [14-17]

This great biological importance of these heterocyclic compounds has prompted the development of new improved methodologies for Biginelli reaction, including transition metal Lewis acid catalysis, [18] solid phase synthesis, [19] ionic liquids, [20] activation with certain additives, [21] microwave-assisted synthesis technique, [22] ultrasound irradiation, [23] solvent-free techniques,[24] grinding techniques,[25] and many new catalysts. [26]

Nevertheless, most protocols have severe limitations, for example, low yields, high cost and catalyst loadings, and low catalyst recovery and recyclability.

Furthermore, questions about the efficacy of solvent-free and/or catalyst-free reactions and the effect of solvent versus solvent free conditions still lead to discussions in the scientific community. To overcome these drawbacks, which have thrown chemists toward the search of new, better, and benign conditions for the Biginelli reactions. Transition metal nanoparticles have received a great deal of attention due to a viable alternative to conventional materials in the field of catalyst. Such a new nano catalysts for biginelli reaction are Nano-$Ticl_4.SiO_2$ [27], Fe_3O_4 nanoparticle supported Ni(II) complexes [28], Niobium Nanocatalyst, [29] Fe_3O4-MWCNT nanocomposite [30], Mesoporous ZnO/AlSBA-15 (7) Nanocomposite [31], Magnetic core–shell Carrageenan moss/Fe_3O_4, [32] Mesoporous Silica Nanocomposite, [33] Fe_3O_4@ PVA polymeric magnetic nanocomposite [34].

A combination of metallic and acidic sites in a single nanocomposite material has been good idea for catalytic application for several decades. High thermal stability, high acidity, and unique nanometric porous network of the zeolites made them the best candidates for introducing an acidic function. There are several catalytic reactions where metal-zeolite composite materials have been efficiently used. [35]

In recent years, several researchers have sought the effect of trimetallic catalysts made of transition metals on catalytic capabilities. However, no studies have been found which survey the synthesis of $Ag_2O/GO/TiO_2$ nanostructures.

In continuation of our interest in the synthesis of new nanostructure compounds, [36-38] herein, we report the preparation of $Ag_2O/GO/TiO_2$ structures on zeolite materials and the catalytic activity of this new nanocatalyst was evaluated for the synthesis of a wide range of DHPM derivatives with high structural diversity through the Biginelli reaction. A comparison of the efficiency of this new nanocatalyst with that of other known transitionmetal nanocatalysts has revealed interesting and promising results.

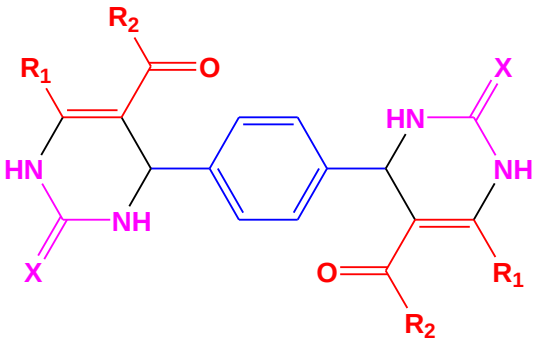

Fig.1 Bis (dihydropyrimidinone) derivatives

2. Experimental

2.1. Materials and instruments

Reagents like ethylacetoaceat, ammonium acetat, titanium dioxide (TiO_2), Ammonium heptamolybdate tetrahydrate $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, and aromatic aldehydes were purchased from Merck company and used without any purifications. Distilled Water was used for these synthesis methods.

The crystalline phase of the as-synthesized sample was identified by X-ray diffraction (XRD) measurements by the means of Ultime IV Multipurpose X-ray diffractometer equipped with Cu $K\alpha_1$ ($\lambda = 0.15406nm$) radiation. Fourier transform infrared (FT-IR) spectrum was

obtained using Perkin Elmer BX-II spectrophotometer. Surface morphology was determined from field emission scanning electron microscopy (FESEM, Zeiss SIGMA VP-500) equipped with side detectors including energy-dispersive X-ray spectroscopy (EDS) and high-resolution elemental mapping to examine elemental compositions. The morphological features of the sample were investigated with a Zeiss (EM10C-Germany) transmission electron microscope (TEM) operating at 100 kV. All yields refer to the isolated products. Products were characterized by comparing their physical data, such as IR, ^{1}H NMR and ^{13}C NMR spectra with authentic samples. Using TMS as internal standard, NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX 250 MHz spectrometer. Determination of the products' purity in the course of the reaction were monitored by TLC on silica gel poly gram SILG/UV 254 plates. Mass spectra were recorded on the MS model 5973 Network apparatus at ionization potential of 70 eV.

2.2 Synthesis of Ag_2O Nanoparticles

In a typical synthesis process, 80 mL of a 0.005 M silver nitrate ($AgNO_3$) aqueous solution was heated 60 ˚C. After that, 20 *mL* of a 0.025 *M* sodium hydroxide aqueous solution was added drop by drop to the prepared $AgNO_3$ solution under continuous magnetic stirring at 60 ˚C for 2 *h*. After cooling down to the room temperature, the formed precipitate was collected by a centrifuge with a speed of 3000 *rpm*, washed with ethanol several times, and dried at a constant temperature of 40 ˚C at 24 *h*.

2.3. Synthesis of $Ag_2O/GO/TiO_2$ Composite Nanoparticles

$Ag_2O/GO/TiO_2$ composite nanoparticles were synthesized through the sol-gel method according to the process reported by Xiao et al. [38] as follows: Firstly, 5 *g* of cetyltrimethylammonium bromide (CTAB) as the precursor of TiO_2 was added to 30 *mL* of ethanol and kept under continuous stirring. Secondly, 25 *mL* of a butyl titanate solution was separately dissolved in 5o *mL* of absolute ethanol and added to the obtained CTAB solution

at the rate of one drop every 3 *s*. Thirdly, a solution containing 7 *mg* of as-synthesized Ag_2O nanoparticles in 5 *mL* of absolute ethanol, and another solution containing 20 *mg* of as-purchased graphene oxide in 10 *mL* of ethanol were prepared and slowly added to the above solution after 1 *h*. The resultant mixture was stirred for 2 *h* to reach a titanium dioxide gel. The obtained product was finally dried at 65 ˚C for 12 *h* and calcined at 450 ˚C for 2 *h*.

2.4 Typical procedure for the preparation of 1,4 dihydropyridine derivatives (4a-4g)

A mixture of ethyl acetate (0.26 g, 2 mmol), ammonium acetate (0.154 g, 2 mmol), aryl aldehyde (1 mmol) in the presence of graphene oxide nanocomposite (0.02 g) in a test tube at 90 °C in Conditions without solvent and placed in an oil bath. The progress of the reaction was assessed by TLC. After completion of the reaction observed by TLC, hot ethanol was added to the reaction mixture and the catalyst was separated by filter paper. The product was then crystallized with ethanol and water with a yield of 87 to 97%.

All products was characterized by comparison of melting points of synthesized compounds with reported literatures. (4a-j)

2.5 Typical procedure for the preparation of bis (dihydropyrimidone) derivatives (4a-4g)

A mixture of the aldehyde (2 mmol), 1, 3 dicarbonyl (2 mmol), urea (3 mmol), ethanol (5 drops) and catalyst (0.1 mmol) was taken in a round bottom flask, heated at 80˚C. The reaction is monitored by Thin Layer Chromatography. After completion, ethanol added and the catalyst was separated by filtration and the solvent was evaporated to obtain the solid product. It is then recrystallized from ethanol. The yield of product was calculated from re-crystallized weight, based on aldehyde. The product was characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and mass spectroscopy.

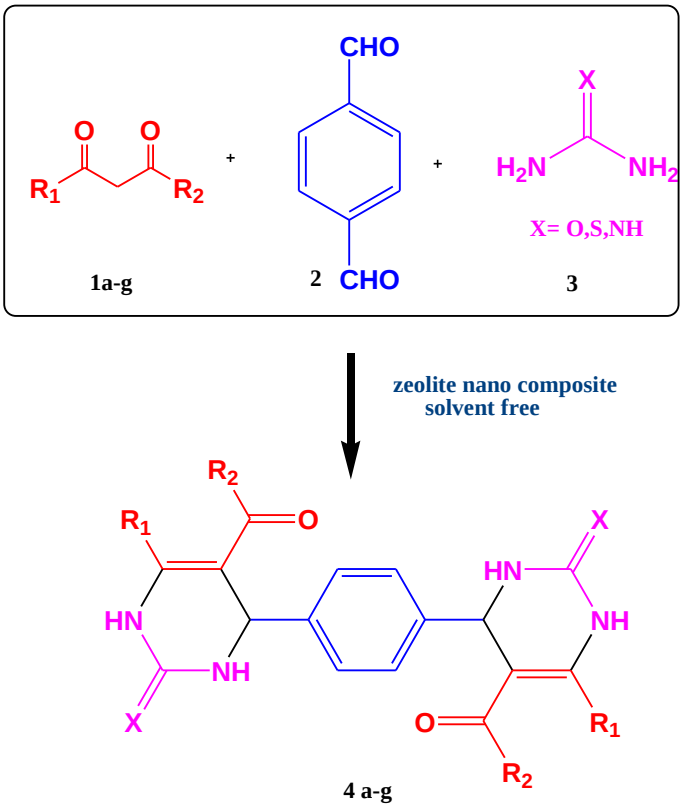

Fig. 2 Schematic of bis(dihydropyrimidon) benzene synthesis reaction

Table. 1 One- pot synthesis of compounds (4a-g) with nano catalyst

Compd[a]	R^1	R^2	X	Time (min)	Yields[b] (%)
4a	Me	Me	O	30	90
4b	Me	Me	S	25	85
4c	Me	Me	NH	35	82
4d	Me	OEt	O	48	90
4e	Me	Ph	O	50	91
4f	CF_3	Me	O	55	83
4g	CF_3	2-thienyl	O	40	87

2.6 Spectral data

4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one) ***4a:***, m.p. 315-317 °C (dec). IR (KBr): λ_{max} = 3279, 3103, 2923, 1706, 1601, 1326 cm^{-1}. ^1H NMR (DMSO-d_6) □: 9.17 (sbr, 2H, NH), 7.78 (sbr, 2H, NH), 7.18 (s, 4H, Ar), 5.21 (d, J=3 Hz, 2H, CH), 2.27 (s, 6H, COMe), 2.10 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) □: 195.0, 152.9, 148.9, 144.3,

127.4, 110.5, 54.3, 31.3, 19.7. MS: (m/z) (%) 382 (M^+,7), 354(10), 259(17), 183(100), 155(45), 43(95).

1,1'-(4,4'-(1,4-phenylene)bis(6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5,4-diyl)) diethanone **4b:** m.p. 310-312 °C (dec). IR (KBr): λ_{max} = 3384, 3176, 2981, 1615, 1447 cm^{-1}. ^1H NMR (DMSO-d_6) □: 10.23 (s, 2H, NH), 9.66 (s, 2H, NH), 7.17 (s, 4H, Ar), 5.24 (s, 2H, CH), 2.29 (s, 6H, COM), 2.16 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) □: 193.5, 174.6, 148.9, 144.2, 127.4, 110.6, 54.5, 31.2, 19.80. MS: (m/z) (%) 414 (M^+,6), 325(11), 314(17), 274(19), 140(94), 59(100).

1,1'-(4,4'-(1,4-phenylene)bis(2-imino-6-methyl-1,2,3,4-tetrahydropyrimidine-5,4-diyl)) diethanone ***4c:*** *m.p. 298-300°C* (dec). IR (KBr): λ_{max} = 3353, 3220, 2973, 1694, 1606, 1374 cm-^{1}. ^1H NMR (DMSO-d_6) □: 9.99 (sbr, 2H, NH), 7.95 (s 2H, NH), 7.21 (s, 4H, Ar), 6.28 (sbr, 2H, NH), 5.23 (s, 2H, CH), 2.23 (s, 6H, COMe), 2.06 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) □: 193.4, 178.2, 154.3, 144.6, 127.6, 109.5, 53.2, 31.1, 20.1. MS: (m/z) (%) 380 (M^+,9), 351(11), 307(19), 267(25), 183(78), 59(81), 43(100).

diethyl4,4'-(1,4-phenylene)bis(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) **4d:** m.p. 315-317 °C (dec). IR (KBr): λ_{max} = 3326, 3105, 2975, 1702, 1236 cm^{-1}. ^1H NMR (DMSO-d_6) □: 9.09 (sbr, 2H, NH), 7.67 (s, 2H, NH), 7.16 (s, 4H, Ar), 5.11 (d, J=3.3 Hz, 2H, CH), 3.87 (q, J=7.2 Hz, 4H, $OC\underline{H}_2CH_3$), 2.21 (s, 6H, Me), 1.05 (t, J=7.2 Hz , 6H, $OCH_2C\underline{H}_3$). ^{13}C NMR (DMSO-d_6) □: 166.2, 152.9, 149.2, 144.7, 127.2, 100.1, 60.1, 51.5, 18.6, 14.9. MS: (m/z) (%) 442 (M^+,7), 398(9), 296(21), 256(54), 183(73), 59(100).

*(4,4'-(1,4-phenylene)bis(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5,4-diyl))bis (phenylmethanon*e) **4e:** m.p. 295-298 °C (dec). IR (KBr): λ_{max} = 3312, 3110, 2923, 1702, 1667 cm^{-1}. ^1H NMR (DMSO-d_6) □: 9.15 (s, 2H, NH), 7.75 (sbr, 2H, NH), 7.49-7.38 (m, 10H,

COPh), 7.13 (s, 4H, Ar), 5.23 (d, J=2.5 Hz, 2H, CH), 1.64 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) □: 195.1, 152.9, 146.5, 144.1, 141.9, 132.3, 129.4, 128.5, 127.2, 110.2, 55.7, 19.3. MS: (m/z) (%) 506 (M^+,5), 450(7), 410(100), 318(71), 242(85), 126(31), 116(41), 57(26).

4,4'-(1,4-phenylene)bis(5-acetyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1H)-one) **4f:** m.p. 328-330 °C (dec). IR (KBr): λ_{max} = 3324, 2962, 1710, 1645, 1231 cm^{-1}. ^{1}H NMR (DMSO-d_6) □: 9.48 (s, 2H, NH), 7.76 (s, 2H, NH), 7.31 (s, 4H, Ar), 5.14 (s, 2H, CH), 2.25 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) □: 193.9, 152.6, 144.4, 132.5, 129.1, 125.9, 107.8, 50.5, 27.6. MS: (m/z) (%) 490 (M^+, 11), 256(100), 69(85), 57(81), 43(63).

*4,4'-(1,4-phenylene)bis(5-(thiophene-2-carbonyl)-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1H)-on*e) **4g:** m.p. 218-220 °C (dec). IR (KBr): λ_{max} = 3157, 3089, 2912, 1658, 1603, 1205 cm^{-1}. ^{1}H NMR (DMSO-d_6) □: 9.92 (s, 2H, NH), 7.89(d, J=4.5 Hz, 2H, thienyl), 7.78 (d, J=3.9 Hz, 2H, thienyl), 7.69 (s, 2H, NH), 7.50(s, 4H, Ar), 7.16 (dd, J=3.9, 4.5 Hz, 2H, thienyl), 5.61 (s, 2H, CH). ^{13}C NMR (DMSO-d_6) □: 182.3, 154.5, 146.1, 142.4, 140.9, 138.9, 137.0, 130.7, 129.3, 123.2, 104.5, 54.6. MS: (m/z) (%) 626 (M^+,5), 542(11), 446(15), 397(21), 350(50), 268(71), 222(55), 111(100), 69(91).

3. Results and discussion

In order to carry out the synthesis of 1,4- dihydropyridine under environmentally benign conditions, Initially, the synthesis of 2,6-dimethyl4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (2 mmol) in the presence of various amount of Ag_2O/GO/TiO_2 composite nanostructure at different temperatures under solvent free conditions. The shortest time and best yield were achieved in the presence of 0.02 gr of

catalyst at 90 °C. In order to elucidate the role of the $Ag_2O/GO/TiO_2$ composite nanostructure as catalyst, a control reaction was set up using benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (2 mmol) in the absence of catalyst. The control reaction ended up with the formation of 10% of corresponding Hantzsch ester. However the test reaction set up with the same substrate, using 0.02 g of $Ag_2O/GO/TiO_2$ composite nanostructure at 90 °C under solvent free conditions afforded the product in 95% yield in 15 min.

In order to establish the true effectiveness of the nanostructure of catalyst, the condensation reaction was also tested using $Ag_2O/GO/TiO_2$ composite nanostructure under the same reaction condition. It clearly shows that although the reaction proceeded in the presence of $Ag_2O/GO/TiO_2$ composite (45%, 75 min), the best result was obtained in the presence of $Ag_2O/GO/TiO_2$ composite nanostructure. This may be due to considerable ratio of surface to volume in nanoparticles.

3.1 Cytotoxic effect on cancer cell lines

The half-maximal inhibitory concentration (IC_{50}) and (IC_{16}) are the most widely used and informative measure of a drug's efficacy. They indicate how much drug is needed to inhibit a biological process by 50 and 16 percentage, thus providing a measure of potency of an antagonist drug in pharmacological research. Most approaches to determine IC_{50} and IC_{16} of a pharmacological compound are based on assays that utilize whole cell systems.

The in vitro cytotoxic activities for 10 1,4 dihydropyridine derivatives are shown in Table 2. All the compounds under study showed superior cytotoxic activity on the Raji cells. Scheme 2 (Entry 3 –Table 2) showed higher cytotoxicity in all of the tested cells. This indicated that chlore as an electron withdrawing acceptor groups is a favorable structure for designing cytotoxic agents. This pathway may also be seen for other similar compounds (entry 2-6 – table 2) for Raji cell line. These compounds possess electron withdrawing halogen atoms

(F,Cl,Br) on their aryl rings. It seems that halogen atoms can have an appropriate interaction with Raji cell receptors.

Table 2. Cytotoxic activity of some bis dihydropyrimidone derivatives

Compound	HeLa cells		LS-180 cells		Raji cells	
	IC_{16} (µM)	IC_{50} (µM)	IC_{16} (µM)	IC_{50} (µM)	IC_{16} (µM)	IC_{50} (µM)
4 a	56±10.12	> 100	> 100	> 100	17.51 ±4.91	> 100
4 b	15.65 ±5.12	> 100	22.34±6.74	> 100	20.2 ±3.22	> 100
4 c	18.5 ±7.8	> 100	> 100	> 100	37.7 ±2.2	> 100
4 d	8.1 ±1,5	85.1 ±34.53	12.32 ±1.74	> 100	19.2 ±18.32	> 100
4 e	21.5 ±6.54	> 100	54.32 ±15.65	> 100	23.51 ±12.8	> 100
4 f	31.7 ±6.7	> 100	> 100	> 100	20.72 ±13.43	> 100
4 g	27.2 ±7.3	> 100	25.12±4.34	> 100	> 100	> 100
DOX	62.7 ±17.45	> 100	6.5 ±6	86.6 ±31.6	64 ±6.5	> 100
Cisplatin	2.3 ±0.65	8.6 ±2.1	6.6 ±1.95	35.8 ±13.1	2.7 ±0.3	11.3 ±1.25

4. Conclusion

In conclusion, we successfully developed a simple and efficient method for preparation of a variety of 1,4-dihydropyridines by the one pot three-component reactions of different aromatic, hetero aromatic aldehydes, β-keto compounds and ammonium acetate in the presence comparing the performance of the present work with of a catalytic amount of $Ag_2O/GO/TiO_2$ Composite Nanostructure under solvent free conditions. 1, 4 dihydropyrimidone derivatives bearing heterocyclic substituents were synthesized and identified by comparing with instrumental analyses and reported literatures. All the tested compounds showed higher cytotoxic effect on Raji cancer cell lines compared to LS180 and Hela cancer cells. Electron withdrawing groups along with heterocyclic rings bearing more hetero atoms seemed to be necessary factors in providing higher cytotoxic activities in Raji cell lines.

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