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ZnO-CaO-MgO nanocomposite: efficient catalyst for the preparation of thieno[2,3-d]pyrimidin-4(3H)-one derivatives

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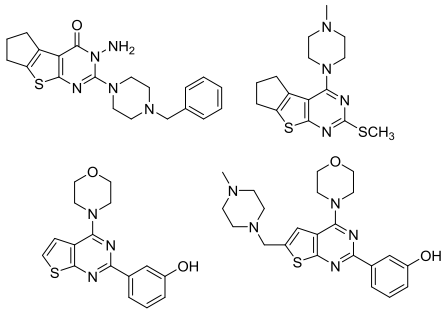
ABSTRACT

The replacement of toxic homogeneous catalysts by reusable heterogeneous catalysts is one of the most important environmentally friendly aspects of green chemistry investigations. In this study a new ZnO-CaO-MgO nanocomposite system was synthesized and characterized using XRD and FE-SEM analysis. The catalyst thus synthesized was studied for its utility in the synthesis of some novel 9-aryl-6,10-dihydro-11H-thiochromeno[4',3':4,5]thieno[2,3-d]pyrimidin-11-one and 9-aryl-6,10-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11(5H)-one derivatives.

Keywords: *ZnO-CaO-MgO nanocomposite; 2-amino-thiophene; thieno[2,3-d]pyrimidin-4(3H)-one.*

1. INTRODUCTION

Thienopyrimidines are attracting the attention of medicinal and organic chemists due to a wide range of biological activities and pharmaceutical significance. The thienopyrimidine core is an integral part of many natural products and agricultural chemicals. Thienopyrimidines are known for their wide range of biological, anti-inflammatory, anti-tumor, antimalarial and antimicrobial activities. Regarding anti-tumor activity, some derivatives of thienopyrimidines act as tyrosine kinases, and other derivatives of these compounds exhibit high biological activity against pathogenic bacteria and humans [1-7]. Scheme 1 shows the examples of medically valuable compounds in which thienopyrimidine core is present in their structure [8-10].



Scheme 1. Chemical structure of some medically valuable thienopyrimidines

Various compounds with a thienopyrimidine core are able to selectively inhibit the Src of tyrosine kinases family as well as the treatment of various diseases including hematologic, osteoporosis and neurological diseases [11]. However, wide approaches to the synthesis of thienopyrimidines have been developed with different features and applications; the simpler of them is based on the condensation of 2-aminothiophenes with an aldehydes, an orthoformate or formamides lead to the formation of thieno[2,3-d]pyrimidin-4(3H)-one derivatives. From the diversity point of view, the development of synthetic methodologies toward thieno[2,3-d]pyrimidin-4(3H)-one is a highly desired goal for organic chemists, as the previously reported methods used hazardous liquid acid catalyst such as HCl, H_2SO_4 and so on [12-17]. And there is no report of the use of heterogeneous catalytic systems under solvent-free conditions.

Considering the importance and wide application of thienopyrimidine derivatives, the provision of new and efficient methods for the synthesis of these compounds is of great importance. In this regard, in continuation of our catalytic investigations [18-43], the present study investigates the synthesis of some thienopyrimidine derivatives using ZnO-CaO-MgO nanocomposite.

2. EXPERIMENTAL SECTION

Chemicals were purchased from Merck and Aldrich and used without further purification. The catalyst characterizations were taken on a HITACHI S-4160 field emission scanning electron microscope (FE-SEM) and a D_8, Advance, Bruker, axs, X-Ray diffractometer (XRD) (Cu-Kα irradiation). The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel Polygram SIL G/UV 254 plates.

2.1. Preparation of ZnO-CaO-MgO nanocomposite. In a 250 mL beaker calcium nitrate (10 mmol), magnesium chloride (10 mmol) and zinc chloride (10 mmol) was dissolved in 100 ml of water (solution A). In a separate beaker, 2-aminoethanol (90 mmol) and glycerol (10 mL) was dissolved in water (100 mL) (solution B). Solution (B) was slowly added dropwise to the solution (A) under vigorous magnetic stirring. The mixture was continuously stirred for another 60 min. The resulting precipitate was filtered, washed with water several times and dried at ambient temperature and finally calcined at 500 °C for 2h.

2.2. Synthesis of 2-amino-4,5-dihydronaphtho[2,1-b]thiophene-1-carboxamide. To a mixture of 3,4-dihydronaphthalen-1(2H)-one (1 mmol) cyanoacetamide (1 mmol) and sulfur (1 mmol) in 5 ml of ethanol, morpholine (1mL) was added. The resulting mixture was refluxed for 10 hours (TLC monitoring). In the end, the mixture was filtered, washed with hot ethanol, cooled and the resultant crystals were purified in ethanol. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.80-2.87 (m, 4H), 4.67 (s, 2H, NH_2), 6.31 (s, 2H, NH_2), 7.08-7.32 (m, 4H) ppm. Elemental Analysis Found: C, 64.08; H, 5.06; N, 11.39; S, 13.03% $C_{13}H_{12}N_2OS$; requires: C, 63.91; H, 4.95; N, 11.47; S, 13.12%.

2.2. Synthesis of 2-amino-4H-thieno[2,3-c]thiochromene-1-carboxamide. To a mixture of thiochroman-4-one (1 mmol) cyanoacetamide (1 mmol) and sulfur (1 mmol) in 5 ml of ethanol, morpholine (1mL) was added. The resulting mixture was refluxed for 10 hours (TLC monitoring). In the end, the mixture was filtered, washed with hot ethanol, cooled and the resultant crystals were purified in ethanol. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.78 (s, 2H), 5.06 (s, 2H, NH_2), 6.30 (s, 2H, NH_2), 7.26-7.54 (m, 5H) ppm. Elemental Analysis Found: C, 55.07; H, 3.97; N, 10.60; S, 24.37% $C_{12}H_{10}N_2OS$; requires: C, 54.94; H, 3.84; N, 10.68; S, 24.44%.

2.3. Synthesis of 9-phenyl-6,10-dihydro-11H-thiochromeno [4',3':4,5] thieno [2,3-d] pyrimidin-11-one. To a mixture of benzaldehyde (1 mmol) and 2-amino-4H-thieno[2,3-c]thiochromene-1-carboxamide (1 mmol), 0.05 g of ZnO-CaO-MgO nanocomposite was added, and the reaction mixture was heated at 140 °C until the reaction was complete (The reaction was followed by TLC, *n*-hexane: EtOAc 9: 1). After completion, the reaction mixture is cooled to ambient temperature and combined with boiling ethanol. The insoluble catalyst is separated off by the filter paper and the pure product is obtained by recrystallization in ethanol. **9-phenyl-6,10-dihydro-11H-thiochromeno[4',3':4,5]thieno[2,3-d]pyrimidin-11-one (Table 2, 1c):** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.68 (s, 2H), 7.19-7.57 (m, 5H), 7.69 (t, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 8.1 Hz, 1H), 12.26 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 36.9, 117.4, 121.6, 126.8, 126.9, 127.1, 127.7, 128.4, 129.1, 129.3, 129.6, 131.4, 136.3, 138.7, 146.3, 160.5, 164.6; Elemental Analysis Found: C, 65.61; H, 3.55; N, 7.93; S, 18.34% $C_{19}H_{12}N_2OS_2$; requires: C, 65.49; H, 3.47; N, 8.04; S, 18.40%.

9-(*p*-tolyl)-6,10-dihydro-11H-thiochromeno [4',3':4,5] thieno [2,3-d] pyrimidin-11-one (Table 2, 2c): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 4.68 (s, 2H), 7.16-7.47 (m, 5H), 7.97 (d, *J* = 7.8 Hz, 2H), 8.25 (d, *J* = 8.0 Hz, 1H), 12.46 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.2, 36.9, 117.2, 121.3, 126.0, 126.3, 127.0, 127.6, 128.9, 129.7, 129.8, 131.9, 135.8, 138.8, 139.2, 145.3, 160.8, 163.0; Elemental Analysis Found: C, 66.39; H, 3.96; N, 7.69; S, 17.64% $C_{20}H_{14}N_2OS_2$; requires: C, 66.27; H, 3.89; N, 7.73; S, 17.69%.

9-(4-methoxyphenyl)-6,10-dihydro-11H-thiochromeno [4',3':4,5] thieno [2,3-d] pyrimidin-11-one (Table 2, 3c): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.91 (s, 3H, OCH_3), 4.67 (s, 2H), 7.15-7.47 (m, 5H), 7.95 (d, *J* = 7.9 Hz, 2H), 8.24 (d, *J* = 8.0 Hz, 1H), 12.67 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 36.8, 55.7, 115.8, 117.9, 121.8, 126.5, 126.9, 127.7, 128.2, 128.5, 129.3, 131.3, 136.3, 138.7, 146.2, 160.7, 161.4, 165.5; Elemental Analysis Found: C, 63.42; H, 3.68; N, 7.32; S, 16.85% $C_{20}H_{14}N_2O_2S_2$; requires: C, 63.47; H, 3.73; N, 7.40; S, 16.94%.

9-(4-chlorophenyl)-6,10-dihydro-11H-thiochromeno[4',3':4,5]thieno[2,3-d]pyrimidin-11-one (Table 2, 4c): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.68 (s, 2H), 7.19-7.55 (m, 5H), 8.11 (d, *J* = 7.9 Hz, 2H), 8.27 (d, *J* = 8.1 Hz, 1H), 12.75 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 36.9, 117.9, 121.7, 126.5, 126.9, 127.6, 128.2, 128.5, 129.0, 129.4, 131.4, 136.3, 136.6, 139.3, 146.8, 160.6, 165.7; Elemental Analysis Found: C, 59.55; H, 2.84; N, 7.23; S, 16.70% $C_{19}H_{11}ClN_2OS_2$; requires: C, 59.60; H, 2.90; N, 7.32; S, 16.75%.

9-(4-nitrophenyl)-6,10-dihydro-11H-thiochromeno[4',3':4,5]thieno[2,3-d]pyrimidin-11-one (Table 2, 5c): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.71 (s, 2H), 7.19-7.44 (m, 3H), 7.71 (d, *J* = 8.0 Hz, 2H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 13.21 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 36.9, 117.9, 121.7, 126.6, 127.0, 127.8, 128.2, 128.5, 129.1, 129.6, 131.4, 136.3, 136.6, 139.3, 146.8, 161.6, 165.8; Elemental Analysis Found: C, 57.91; H, 2.77; N, 10.63; S, 16.26% $C_{19}H_{11}N_3O_3S_2$; requires: C, 58.00; H, 2.82; N, 10.68; S, 16.30%.

2.4. Synthesis 9-phenyl-6,10-dihydronaphtho [1',2':4,5] thieno [2,3-d] pyrimidin-11(5H)-one. To a mixture of benzaldehyde (1 mmol) and 2-amino-4,5-dihydronaphtho[2,1-b]thiophene-1-carboxamide (1 mmol), 0.05 g of ZnO-CaO-MgO nanocomposite was added, and the reaction mixture was heated at 140 °C until the reaction was complete (The reaction was followed by TLC, *n*-hexane: EtOAc 9: 1). After completion, the reaction mixture is cooled to ambient temperature and combined with boiling ethanol. The insoluble catalyst is separated off by the filter paper and the pure product is obtained by recrystallization in ethanol. **(Table 2, 1d):** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.78-3.09 (m, 4H), 7.19-7.58 (m, 5H), 7.69 (t, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 1H), 12.46 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 28.9, 30.3, 117.7, 124.4, 126.8, 127.2, 127.5, 128.4, 128.9, 129.6, 129.9, 131.7, 132.5, 135.4, 138.8, 146.2, 160.3, 164.5 ppm; Elemental Analysis Found: C, 72.82; H, 4.36; N, 8.44; S, 9.66% $C_{20}H_{14}N_2OS$; requires: C, 72.70; H, 4.27; N, 8.48; S, 9.70%.

9-(4-nitrophenyl)-6,10-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11(5H)-one (Table 2, 5d): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.79-3.12 (m, 4H), 7.19-7.44 (m, 3H), 7.72 (d, *J* = 8.1 Hz, 2H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 13.36 (s, 1H, NH) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.5, 117.8, 124.3, 124.8, 126.9, 127.3, 128.2, 128.5, 129.4, 131.9, 132.6, 136.4, 138.6, 143.7, 146.8, 161.3, 164.8; Elemental Analysis Found: C, 63.87; H, 3.45; N, 11.17; S, 8.50% $C_{20}H_{13}N_3O_3S$; requires: C, 63.99; H, 3.49; N, 11.19; S, 8.54%.

3. RESULTS SECTION

Figure 1 shows the XRD pattern of ZnO-CaO-MgO nanocomposite. The XRD pattern states that nanocomposites consist of three phases: zinc oxide, calcium oxide and magnesium oxide. Zinc oxide is well crystallized in hexagonal phase with characteristic peaks of 31.7, 34.4, 36.2, 47.5, 56.5, 62.8, 67.9, and 69.0 [2θ°]. Calcium oxide crystallized in tetragonal phase with characteristic peaks of 43.1, 47.5, 49.6, 51.6, 57.2, 62.7, 66.9, and 74.3 [2θ°]. Finally, magnesium oxide crystallized in cubic phase with characteristic peaks of 36.7, 42.8, 62.2, and 78.4 [2θ°].

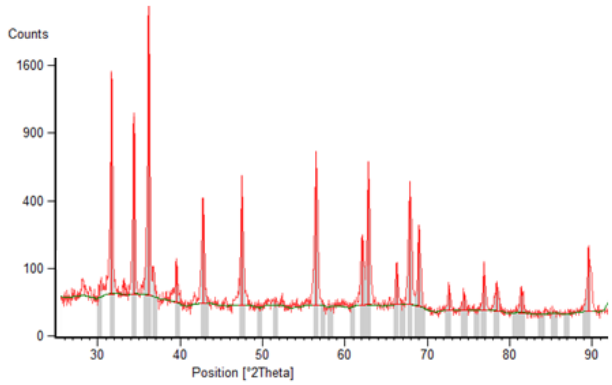


Figure 1. XRD pattern of ZnO-CaO-MgO nanocomposite.

FE-SEM analysis investigated the surface morphology of ZnO-CaO-MgO nanocomposite, and the result is shown in Figure 2. FE-SEM images indicate that nanocomposite consist of uniform particles, and metal oxides are homogeneously distributed in the sample. The results also demonstrate that the nanocomposite has an average particle size of less than 100 nm.

The catalytic activity of ZnO-CaO-MgO nanocomposite was examined in the synthesis of 9-aryl-6,10-dihydro-11H-thiochromeno[4',3':4,5]thieno[2,3-d]pyrimidin-11-one and 9-aryl-6,10-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11(5H)-one derivatives.

To find optimal conditions for the synthesis of thieno[2,3-d]pyrimidin-4(3H)-one derivatives, the reaction between benzaldehyde (1 mmol) and 2-amino-4H-thieno[2,3-c]thiochromene-1-carboxamide (1 mmol) was selected as the model. This reaction was studied under solvent-free conditions, and in a solvent medium at different temperatures (Table 1).

The obtained results show that the reaction at room temperature does not lead to the product and states that the heat is necessary for the product formation. Based on the results, the following condition was selected as optimal conditions: catalyst amount (0.05 g), temperate (140 °C) and in solvent-free conditions. The results show that the conditions at which the reaction temperature is less than 100 °C will not be productive. For this reason, the use of solvents whose boiling point is less than 100 °C such as ethanol, ethyl acetate, hexane, dichloromethane, diethyl ether, and acetonitrile was not effective. As it was shown in Table 1, a systematic reduction of catalyst will result in a regular reduction in reaction time and yield. The further increase in catalyst content will not have a significant effect on the product yield. The efficacy and generality of this catalytic system were investigated by the use of various derivatives of aromatic aldehydes containing electron-donating and electron-withdrawing groups. The results are summarized in Table 2. As see, aromatic aldehydes containing electron-withdrawing groups are more reactive in reaction to their electron-donating groups.

Table 1. Optimization of the reaction condition for the synthesis of thieno[2,3-d]pyrimidin-4(3H)-ones.

Entry	Catalyst (g)	T (°C)	Solvent (5 mL)	Yield (%) [a]
1	0.05	Reflux	*n*-Hexane	-
2	0.05	Reflux	CH_2Cl_2	-
3	0.05	Reflux	Et_2O	-
4	0.05	Reflux	EtOAc	-
5	0.05	Reflux	Toluene	-
6	0.05	Reflux	MeOH	-
7	0.05	Reflux	EtOH	-
8	0.05	Reflux	H_2O	-
9	0.05	140	-	89
10	-	140	-	-
11	0.025	140	-	79
12	0.075	140	-	81
13	0.1	140	-	65
14	0.05	100	-	15
15	0.05	80	-	-

[a] Isolated Yields; Time: 1 h

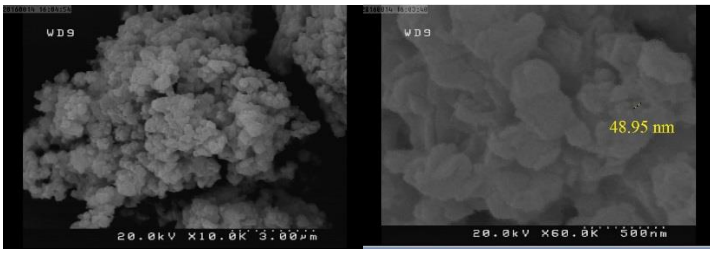


Figure 2. FE-SEM photographs of ZnO-CaO-MgO nanocomposite.

Table 2. Preparation of thieno[2,3-d]pyrimidin-4(3H)-one derivatives using ZnO-CaO-MgO nanocomposite.

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Entry	Product	Aldehyde (b)	Time (h)	Yield (%)*
1	**1c**	Benzaldehyde	1	89
2	**2c**	4-methylbenzaldehyde	3	82
3	**3c**	4-methoxybenzaldehyde	3	77
4	**4c**	4-chlorobenzaldehyde	1	86
5	**5c**	4-nitrobenzaldehyde	1	90
6	**1d**	Benzaldehyde	1	87
7	**2d**	4-methylbenzaldehyde	3	80
8	**3d**	4-methoxybenzaldehyde	3	87
9	**4d**	4-chlorobenzaldehyde	1	89
10	**5d**	4-nitrobenzaldehyde	1	93

* Isolated yield

4. CONCLUSIONS

The catalytic synthesis of some novel thieno[2,3-d]pyrimidin-4(3H)-one derivatives over ZnO-CaO-MgO nanocomposite as an efficient catalyst was reported. The catalyst was characterized by XRD, and FE-SEM analysis. The procedure is efficient as the products were obtained in good to excellent yields.

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6. ACKNOWLEDGEMENTS

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