#### **ORIGINAL PAPER**



# Preparation of 2,5-diamino-1,3,4-thiadiazole derivatives using MgO nanoparticles as heterogeneous basic catalysts

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#### Abstract

The synthesis of 2,5-diamino-1,3,4-thiadiazole derivatives was performed via the reaction of dithiocarbamate derivatives and hydrazine sulfate in presence of MgO nanoparticles as heterogeneous catalysts, which were prepared by the sol–gel method. The pure products were produced in a simple and clean method in presence of MgO nanoparticles (5 mg) in the refluxing water (0.5 cm<sup>3</sup>) around 10 h with good-to-excellent yields (up to 95%). The prepared metal oxide nanoparticles were characterized by powder X-ray diffraction, scanning electron microscopy, energy dispersive X-ray, and Fourier transform infrared spectroscopy.

#### **Graphical abstract**



Keywords Nanoparticles · Heterogeneous basic catalysts · Thiadiazole · Metal oxide · Dithiocarbamate derivatives

# Introduction

Today, the development of new procedures and efficient synthesis of biological molecules are necessary and inevitable in chemistry, pharmacology, and biology. Thiadiazole derivatives which have several heteroatoms in their original structures are known as one of the most important functional groups in heterocyclic chemistry. Various drugs have thiazole and thiadiazole moieties as the main group in own structures which are made using these heterocyclic cores [1, 2]. The importance of these medicinal compositions can be

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indicated as anti-microbial, anti-cancer, and anti-bacterial as well as their use to synthesize anti-tubercular drugs, antigenic, anti-hypertension, and anti-hypoglycaemic activity [3–7]. On the other hand, the synthesis of these compounds included methods with multistage reaction conditions that somehow turned too hard [8–10].

To synthesize widely used compounds, using new and more convenient routes has become the key technology in chemistry and extends the functionality of synthetic reactions. As a result, many new routes which are well planned for the synthesis of commercial drug and redesign of productions protocols should be maintained. Among the modern synthesis methods, the use of nanocatalysts as a new class of highly effective materials to facilitate and accelerate synthetic routes has attracted special attention in recent years [11, 12].

Nanocrystalline metal oxides which are stable under harsh process conditions have several applications such as

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nanocatalysts in various organic reactions [13, 14]. Among them, magnesium oxide nanoparticles, due to the surface effect (surface/volume ratio) [15], high melting point [16], and dual character of ions [17] are more reactive to use in many fields spatially in organic reactions as a highly effective heterogeneous basic catalyst, which makes them proper for synthesizing the desired products with high efficiency, in a short time and mild reaction condition [18–21].

To the best of our knowledge, the synthesis of symmetric amino thiadiazoles with aromatic substituted on the amino groups attached to the ring is limited in the literature. Few reports are available that they also have some problems such as using toxic and expensive reagents, low efficiency, long reaction time, and difficulty in the products separation [22–25].

As the biological activity of symmetrical thiadiazoles was known [26], earlier, Ziyaei group reported the preparation of some thiadiazole derivatives in water using of dithiocarbamate derivatives, hydrazine sulfate, and pyridine as a base in water, but the uncyclized products were obtained as the by-products [27]. To overcome this problem, in this work we attempted to use different nanoparticles as heterogeneous basic catalysts to obtain the mild and green reaction condition for preparing these thiadiazole derivatives (Scheme 1).

#### **Results and discussion**

#### The catalytic effect of different nanoparticles on the preparation of 2,5-diamino-1,3,4-thiadiazole derivatives

The optimized reaction conditions were achieved by performing the reaction of benzyl phenylcarbamodithioate (1a) and hydrazine sulfate in water under reflux as a model reaction by varying factors such as different nanoparticles as a catalyst with the various loading, different amount of starting materials, various bases and solvents.

First, we evaluated the effect of different bases such as pyridine, sodium hydroxide, potassium hydroxide, and triethylamine on the model reaction. The obtained results

showed that pyridine had better effect on the reaction rate, but no remarkable effect on the yield of the desired product (Table 1, compare entries 2 with 3–5). On the other hand, using various metal oxide nanoparticles as heterogeneous catalysts led to good chemical yield and none of the acyclic product was observed after 10 h. As presented in Table 1, the rate of cyclization was considerably enhanced in the presence of different metal oxide nanoparticles such as TiO<sub>2</sub>, SiO<sub>2</sub>, CuO, MgO, Al<sub>2</sub>O<sub>3</sub>, and ZnO in comparison with the uncatalyzed reaction which gave acyclic product also (Table 1, entries 6-11). Among the investigated nanocatalysts, MgO nanoparticles have shown better efficiency (Table 1, entry 9). On the other hand, according to entry 12, it is considered that the use of MgO nanoparticles and pyridine as an external base simultaneously gave an insignificant increase in the yield. It could be due to the presence of basic sites in MgO nanoparticles [28] which enable the preformation of the reaction even in the absence of the external base. The usage of MgO was also investigated, but the reaction resulted in lower yields of MgO NPs (entry 13).

The results presented in Table 2 show that the time and yield of the reaction were also affected by the amount of MgO nanoparticles. The best results were obtained when the loading of MgO NPs was 5 mg (Table 2, entry 2).

Effect of various solvents was also investigated on the model reaction. The results obtained showed that the yield was increased with increasing polarity of the solvents. As shown in Table 3, the effect of water and ethanol was nearly the same (entries 5 and 6). Due to the green and environmentally friendly and economic purposes, we have selected water as the best solvent to continue the reaction.

In order to show the generality of the reaction, the scope of this process was explored under the optimized reaction conditions (Scheme 2). The starting material was prepared using a range of aromatic carbamodithioate bearing electron-donating as well as electron-withdrawing groups and benzyl halides or acrylonitrile, which reacted quite general with hydrazine sulfate to afford 2,5-diamino-1,3,4-thiadiazole derivatives in good-to-high yields (Table 4, 64–95% yields). The obtained results showed that the –CN group was not affected in yields remarkably.



#### Table 1 The effect of the various bases or nanoparticles on the model reaction



| 1  | —                 | -                | _               |
|----|-------------------|------------------|-----------------|
| 2  | Pyridine          | _                | 45              |
| 3  | NaOH              | _                | 30 <sup>b</sup> |
| 4  | КОН               | -                | 23 <sup>b</sup> |
| 5  | Et <sub>3</sub> N | _                | 51 <sup>b</sup> |
| 6  | _                 | TiO <sub>2</sub> | 42              |
| 7  | _                 | $SiO_2$          | 44              |
| 8  | _                 | CuO              | 63              |
| 9  | _                 | MgO              | 80              |
| 10 | -                 | $Al_2O_3$        | 65              |
| 11 | -                 | ZnO              | 72              |
| 12 | Pyridine          | MgO              | 85              |
| 13 |                   | MgO              | 55 <sup>c</sup> |

Reaction conditions: benzyl phenylcarbamodithioate (0.2 mmol), hydrazine sulfate (0.1 mmol), bases (0.1 mmol), 5 mg nanoparticles, and  $0.5 \text{ cm}^3$  water for 10 h under reflux

<sup>a</sup>Isolated yield

Entry

<sup>b</sup>The reaction was not complete after 10 h

<sup>c</sup>MgO was used

#### Table 2 Effect of the amount of MgO nanoparticles on model reaction

|       | NHSO4 -              | MgO Nanoparticles<br>H <sub>2</sub> O (0.5 cm <sup>3</sup> ), reflux | S N                  |
|-------|----------------------|--|----------------------|
| Entry | MgO nanoparticles/mg | Time/h   | Yield/% <sup>a</sup> |
| 1     | 2.5                  | 24   | 45                   |
| 2     | 5                    | 10   | 80                   |
| 3     | 7.5                  | 16   | 70                   |
| 4     | 10                   | 20   | 65                   |
|       |                      |  |                      |

Reaction conditions: benzyl phenylcarbamodithioate (0.2 mmol), hydrazine sulfate (0.1 mmol), MgO nanoparticles, and 0.5 cm<sup>3</sup> water under reflux

<sup>a</sup>Isolated yield

#### **Characterization of catalysts**

Nanocrystalline MgO was synthesized by a sol-gel method and characterized through Fourier transform infrared (FT-IR), scanning electron microscopy (SEM), X-ray powder diffraction (XRD), and energy dispersive X-ray (EDX).

The FT-IR spectrum of MgO NPs is presented in Fig. 1. The broad absorption peaks at about  $3413 \text{ cm}^{-1}$ 

and 1618 cm<sup>-1</sup> are related to the stretching and bending of water, respectively. The absorption peak at 1386 cm<sup>-1</sup> is due to the bending vibration of the hydroxyl group (OH). The peaks at around 623.5 and 481.1 cm<sup>-1</sup> correspond to the Mg–O stretching vibrations [31, 32].

The morphology of the MgO nanoparticles is determined using scanning electron microscopy (SEM). As shown in Fig. 2, the spherical particles are agglomerated and their size is around 15–60 nm. Table 3 Effect of different solvents on the model reaction



| Entry | Solvent          | Yield/% <sup>a</sup> |
|-------|------------------|----------------------|
| 1     | Dimethyl sulfide | 65                   |
| 2     | Acetone          | 60                   |
| 3     | Dichloromethane  | 70                   |
| 4     | Chloroform       | 50                   |
| 5     | Water            | 80                   |
| 6     | Ethanol          | 78                   |

Reaction conditions: benzyl phenylcarbamodithioate (0.2 mmol), hydrazine sulfate (0.1 mmol), 5 mg MgO nanoparticles for 10 h under reflux <sup>a</sup>Isolated yield

Scheme 2



EDX analysis demonstrated the presence of Mg and O in the synthesized sample. According to the EDX spectrum (Fig. 3), the elemental percentages of Mg and O are 58.6 and 41.4 wt%, respectively.

The XRD pattern of MgO NPs (Fig. 4) reveals diffraction peaks at  $2\theta = 36.72^{\circ}$ ,  $42.83^{\circ}$ ,  $62.10^{\circ}$ ,  $74.43^{\circ}$ , and  $78.33^{\circ}$  are assigned to (111), (200), (220), (311), and (222) planes, respectively, which confirm the formation of MgO nanoparticles. No other peaks are observed in the XRD pattern that establishes the purity of the produced nanoparticles. The average size of magnesium oxides nanoparticles is estimated at about 65 nm using the Scherrer equation [33].

# Proposed mechanism

Proposed mechanism for the catalytic formation of substituted 2,5-diamino-1,3,4-thiadiazole derivatives is presented in Scheme 2. As indicated, hydrazine sulfate salt is converted to hydrazine in presence of water. Both nitrogen atoms of hydrazine attack thiocarbonyl groups of dithiocarbamates which were coordinated to MgO nanoparticles. Intermediate **B** is obtained leaving –SR groups from intermediate **A**. Then cyclization of intermediate **B** via nucleophilic attack of sulfur on the thiocarbonyl group converts it to cyclic intermediate **C**. In continues, basic oxygen site of nanoparticles abstract the N-H proton that led the coordinated -SH group release and product **3** produces after aromatization. 
 Table 4
 The scope of the reaction

$$Ar_{N} \stackrel{S}{\Vdash} s^{-}R + NH_{2}NH_{3}HSO_{4} \xrightarrow{MgO NPs (5 mg)} H_{2}O, (0.5 cm^{3}), reflux \xrightarrow{N-N} H^{-N} S^{-}N^{-}N$$

| Entry | Ar                                 | R                                   | Yield/% <sup>a</sup> | M.p./°C | Reported M.p./°C     |
|-------|------------------------------------|-------------------------------------|----------------------|---------|----------------------|
| 1     | Ph                                 | -CH <sub>2</sub> Ph                 | 80                   | 234–237 | 239–242 <sup>b</sup> |
| 2     | $4-ClC_6H_4$                       | $-CH_2Ph$                           | 85                   | 252-256 | 256–258 <sup>c</sup> |
| 3     | $4-BrC_6H_4$                       | $-CH_2Ph$                           | 91                   | 231-236 | 234-236 <sup>b</sup> |
| 4     | $4-\text{MeC}_6\text{H}_4$         | $-CH_2Ph$                           | 84                   | 231-236 | 251-256 <sup>b</sup> |
| 5     | 4-MeOC <sub>6</sub> H <sub>4</sub> | $-CH_2Ph$                           | 84                   | 251-254 | 235-238 <sup>b</sup> |
| 6     | Ph                                 | -CH <sub>2</sub> CH <sub>2</sub> CN | 72                   | 237–242 | 239-242 <sup>b</sup> |
| 7     | $4-ClC_6H_4$                       | -CH <sub>2</sub> CH <sub>2</sub> CN | 90                   | 256-258 | 256–258°             |
| 8     | $4-BrC_6H_4$                       | -CH <sub>2</sub> CH <sub>2</sub> CN | 95                   | 231-233 | 234-236 <sup>b</sup> |
| 9     | $4-\text{MeC}_6\text{H}_4$         | -CH <sub>2</sub> CH <sub>2</sub> CN | 86                   | 251-258 | 251-256 <sup>b</sup> |
| 10    | $4-MeOC_6H_4$                      | -CH <sub>2</sub> CH <sub>2</sub> CN | 64                   | 234–237 | 235-238 <sup>b</sup> |

Reaction conditions: benzyl phenylcarbamodithioate (0.2 mmol), hydrazine sulfate (0.1 mmol), 5 mg MgO nanoparticles for 10 h under reflux <sup>a</sup>Isolated yield

<sup>b</sup>Ref. [29]

<sup>c</sup>Ref. [30]





## Conclusion

In this work, we have introduced a simple and green route for the synthesis of thiadiazoles derivatives using magnesium oxide nanoparticles as heterogeneous basic catalysts. The symmetrical 2,5-diamino-1,3,4-thiadiazoles derivatives were afforded in good-to-excellent yield and no acyclic product was observed. It should be maintained the hazardous organic solvents and toxic bases or catalysts were not used in this protocol. Besides, the heterogeneous nanocatalysts could be recycled and reused in four reactions.



Fig. 2 SEM images of MgO NPs

## Experimental

Nearly all of the chemical materials were purchased from Merck and Aldrich and used as received. Dithiocarbamates derivatives were synthesized according to the literature [34]. The metal oxide nanoparticles were prepared according to the reported procedures [35].

Melting points were measured by an Electrothermal 9100 apparatus. Fourier transform infrared (FT-IR) spectrum was recorded on a Bruker Vector 22 spectrometer using pressed KBr pellets. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker 300 MHz spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) or CDCl<sub>3</sub> as an internal reference. The SEM image was taken using VEGA\\TESCAN. X-ray diffraction patterns were obtained on an STOE diffractometer with Cu K $\alpha$  radiation.

Column chromatography was performed using silica gel 60  $(230 \pm 400 \text{ mesh})$  eluting with ethyl acetate and *n*-hexane.

#### Synthesis of MgO NPs

MgO NPs were prepared using magnesium methoxide as the precursor by the sol–gel method according to the literature [29]. In order to prepare magnesium methoxide, initially, 10 g magnesium ribbon and 100 cm<sup>3</sup> dried methanol were reacted in the presence of a small amount of iodine under reflux condition in an inert atmosphere. After completion of the reaction, the solution was filtered to remove unreacted magnesium. The magnesium methoxide was crystallized from filtrated at -20 °C and collected by filtration in an inert atmosphere using a frit-filter. After drying the filtrated crystals under reduced pressure, white magnesium methoxide was exposed to air at room temperature for 24 h, and the afforded gel was calcined at 400 °C for 3 h.

# General procedure for preparation of substituted 2,5-diamino-1,3,4-thiadiazoles

In a Schlenk tube, carbamodithioate derivative (0.2 mmol), 13 mg hydrazine sulfate salt (0.1 mmol), and 5 mg MgO nanoparticles were added to  $0.5 \text{ cm}^3$  water. The mixture was heated under reflux condition while stirring for 10 h. After the completion of the reaction, the nanoparticles were filtered, and the filtrate was extracted with diethyl ether and washed with water (two times). Subsequently, the organic phase was evaporated, and then the obtained crude product was purified by column chromatography (ethyl acetate/*n*hexane, 3:1) to afford the substituted 2,5-diamino-1,3,4thiadiazoles as white solid.



Fig. 3 The EDS spectrum of MgO NPs







Fig. 5 The effect of catalyst recycling on the yield of the product 3a

#### The recycling of MgO nanocatalysts

In this work, the recycling of MgO nanocatalysts was accomplished and the recycled catalyst was used in another reaction run. As presented in Fig. 5, the catalytic activity continuity has been reached for four sequences with very little decrease. After the reaction, MgO NPs were simply filtered, washed with methanol, dried under reduced pressure, and reused. The FT-IR spectra were confirmed the preservation of the structure of MgO nanocatalysts after third-time recycling.

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