Synthesis of fused Azo-linked 1, 2, 4-Triazole-3-Thione derivatives using Ag₂S/RHA-MCM-41 nanocomposite

Zeinab Jafarian¹, Mohammad Nikpassand k, Afshin Pourahmad¹, Leila Zare Fekri¹, ²

¹Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran
²Department of Chemistry, Payame Noor University, Tehran, Iran

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Abstract
Magnetic nanoparticles have received much attention in synthesizing organic compounds due to their unique properties such as high contact surface, recyclability, and easy separation. In this study, Rice husk ash (RHA), an agriculture waste, was used as a silica source for MCM-41 synthesis. Ag₂S/RHA-MCM-41 nanocomposite synthesized and characterized with FT-IR, SEM, and XRD. Prepared nanocomposite used for the synthesis of azo-linked 1, 2, 4-triazole-3-thione derivatives. Our study result showed that Ag₂S/RHA-MCM-41 nanocomposite showed high activity in the synthesis of azo-linked 1, 2, 4-triazole-3-thione derivatives because of good yields and desirable reaction time. The structure of all compounds was determined by FTIR, ¹H-NMR and ¹³C-NMR spectroscopy. In all reactions, the catalyst is easily removable and reusable, and its catalytic activity is maintained after five runs.

Keywords: Ag₂S/RHA-MCM-41; Azo-Linkage; Nanocomposite; Phenylhydrazine; 1, 2, 4-Triazole-3-Thione

INTRODUCTION
Triazoles moiety contains a five-membered ring with three nitrogen atoms and two carbon atoms. These heterocycles compounds are widely used in pharmaceuticals as medicinal agents such as anti-fungal [1,2], anti-tumour [3], antioxidant [4], anti-tuberculosis [5], anti-bacterial [6], anti-malarial [7], and anti-virus [8] properties. On the other hand, 1, 2, 4-triazole-thione derivatives have important biological properties and have been reviewed in the last few years [9, 10]. Pitucha et al. [11] introduced the synthesis of a series of 1, 2, 4-triazolin-5-thione derivatives and reported their CK1γ kinase inhibitors with anticancer activity. Also, A. Aly et al. [12] reported antiviral and anti-inflammatory properties of Mercapto-substituted 1, 2, 4-triazoles derivatives. 1, 2, 4-triazole heterocyclic compounds have been prepared successfully with various methods [13-16], such as the dehydrative cyclization method using various reagents such as sodium hydroxide [17, 18], potassium hydroxide [19], or acidic ionic liquid [20]. Foks et al. [21] reported the synthesis of a series of new derivatives of 1, 2, 4-triazole-3-thiol derivatives from methyl 3-acyldithiocarbazates as starting materials. G. Mahajan et al. [22] synthesized and introduced 1, 2, 4-triazolidine-3-thiones via reaction between aldehydes and thiosemicarbazide in acidic ionic liquid media. Dogukan Dincel et al. [23] reported the synthesis and antimicrobial properties of some 1, 2, 4-triazole-3-thione derivatives from furoic acid hydrazide by a six-step synthesis process. Ahmed A. M. El-Reedy and N. K. Soliman [24] reported the synthesis and biological activity study of novel 1, 2, 4-triazolo [4, 3-b] [1, 2, 4, 5] triazines and 1, 2, 4-triazolo [4, 3-b][1, 2, 4, 5] tetrazines via heterocyclization reaction of 3-substituted-4-amino-5-hydrazino-1, 2, 4-triazoles and 3-substituted-4-amino-5-substituted -amino-1,
2, 4-triazoles with bifunctional compounds. On the other hand, some features of magnetic nanoparticles, such as recyclability and reusability, high contact surface and easy separation, make them valuable and useful compounds in the synthesis of organic compounds [25-28].

Nanocomposites are a high performance material and unique properties. These complex compounds have many applications in the chemical industry, plastic engineering and elastomers, etc., so that they are useful in various fields from catalytic role to biomedical applications. Also, applications of nanocomposites offer new technology and business opportunities for several sectors of the aerospace, automotive, electronics and biotechnology industries [29-31].

In this research, in continuing our previous studies for the synthesis of heterocyclic compounds using nanocatalysts [32-34], we reported the synthesis of new Azo-linked 1, 2, 4-triazole-3-thione derivatives with Ag₂S/RHA-MCM-41 nanocomposite.

**Experimental**

**Materials and instruments**

All chemicals and solvents were purchased from Merck Company. Reaction progress was followed by thin-layer chromatography (TLC). A Cam scan Mv2300 scanning electron microscope was used to study the morphology and particle size. FT-IR spectra with IR-470 spectrometer and ¹H NMR and ¹³C NMR core magnetic resonance spectra recorded with 100 and 400 MHz Broker in DMSO-­⁶ solvent. A Jeol-JSM-5610 LV scanning electron microscopy (SEM) was used for the surface morphology of the samples. The X-ray diffraction patterns (XRD) were recorded in a Philips PW 3830 diffractometer.

**General procedure for the synthesis of Ag₂S/RHA-MCM-41 nanocomposite**

Ag₂S/RHA-MCM-41 nanocomposite was synthesized with the method described in previous work Ref. [37]. Briefly, 1.0 g of RHA-MCM-41 powder was added to 50 mL solution of 0.05 mol L⁻¹ Ag(NO₃) and stirred for 5 h at room temperature. The resulting solution was then washed with deionized water, and Ag₂S/RHA-MCM-41 precipitate was dried at room temperature.

**General procedure for the synthesis of new Azo-linked 1, 2, 4-triazole-3-thione derivatives using Ag₂S/RHA-MCM-41 nanocomposite**

A solution of synthesized azo-linked salicylic acid 1a-h (1 mmol) and phosphoryl chloride (1 mmol) in dichloromethane (10 mL) was stirred for 3 h at room temperature. After completion of the reaction, chlorinated form of the azo compound was prepared. Then potassium thiocyanate (1 mmol), phenylhydrazine (1 mmol), and 0.1 g of the Ag₂S/RHA-MCM-41 nanocatalyst were added to the reaction mixture and was stirred at room temperature for desired time (Table 3). After completion of the reaction, the residue was filtered, and the crude product was recrystallized from ethanol to produce new azo-linked 1, 2, 4-triazole-3-thione derivatives 4a-h. The structure of the synthesized products 3a-h was confirmed by FT-IR, ¹H NMR, and ¹³C NMR spectroscopy.

5-(5-(2-p-tolyldiazenyl)-2-hydroxyphenyl)-1, 2-dihydro-1-phenyl-1, 2, 4-triazole-3-thione (4a)

m.p. 225-227 °C; FT-IR (KBr) (υ max cm⁻¹): 3055 (CH-Ar), 2976 (CH-Aliphatic), 1245 (C=S); ¹H NMR (400 MHz, CDCl₃) δ: 12.01 (s, 1H, O-H), 8.51 (d, J = 2.4 Hz, 2H), 8.13 (dd, J = 8.9, 2.4 Hz, 2H), 7.81 (d, J = 8.2 Hz, 4H), 7.31 (d, J = 8.1 Hz, 4H), 7.12 (d, J = 8.9 Hz, 2H), 2.44 (s, 3H, CH₃) ppm; ¹³C NMR (100 Hz, CDCl₃) δ: 205.2, 164.5, 157.9, 146.3, 135.1, 133.2, 132.4, 132.3, 131.7, 131.4, 127.7, 127.5, 129.6, 125.7, 123.2, 121.5, 21.1 (CH₃) ppm.

5-(5-(2-(2-bromophenyl) diazenyl)-2-hydroxyphenyl)-1, 2-dihydro-1-phenyl-1, 2, 4-triazole-3-thione (4b)

m.p. 258-260 °C; FT-IR (KBr) (υ max cm⁻¹): 3055 (CH-Ar), 2976 (CH-Aliphatic), 1245 (C=S); ¹H NMR (400 MHz, CDCl₃) δ: 12.00 (s, 1H, O-H), 8.13 (d, J = 10.8 Hz, 2H), 8.04 (d, J = 12 Hz, 3H), 7.81-7.85 (m, 3H), 7.56-7.60 (m, 3H), 7.43-7.47 (m, 2H) ppm; ¹³C NMR (100 Hz, CDCl₃) δ: 212.1, 164.5, 157.9, 146.3, 135.1, 133.2, 132.4, 132.3, 131.7, 131.4, 127.7, 127.5, 129.6, 125.7, 123.2, 121.5, 21.1 (CH₃) ppm.

7-(2-(3-bromophenyl)diazenyl)-3, 4-dihydro-3, 3-dimethyl-9-phenyl acridin-1(2H)-one (4c)

m.p. 268-270 °C; FT-IR (KBr) (υ max cm⁻¹): 3402 (OH), 3055 (CH-Ar), 1228 (C=S), 694 (C-Br), 121.8 ppm.
NMR (400 MHz, CDCl₃) δ: 12.15 (s, 1H, O-H), 3.71 (s, 3H, OMe) ppm; 13C NMR (100 MHz, CDCl₃) δ: 200.2, 167.99, 159.92, 150.36, 141.52, 135.41, 132.20, 131.42, 130.88, 130.40, 129.94, 129.32, 128.72, 125.95, 119.80, 118.3, 114.0 ppm.

RESULTS AND DISCUSSION

Characterization of synthesized Ag₂S/RHA-MCM-41 nanocomposite

The successful preparation of Ag₂S/RHA-MCM-41 nanocomposite was checked by FT-IR spectra (Fig. 1). The band at 3432-3469 cm⁻¹ attributed to the O-H stretching vibrations (Figs. 1b and 1c). Also, the Ag–S–Ag stretching vibrations appeared at 1074-1090 cm⁻¹, and Si-O-Si bending vibrations appeared at 466 cm⁻¹. Asymmetric Si-O-Si stretching vibration appeared at 3432 cm⁻¹ and 669 cm⁻¹ (Fig. 1c). The XRD patterns obtained for MCM-41/Ag₂S-RHA is shown in Fig. 2. The characteristic XRD peaks at 2θ = 26.0°, 29.0°, 31.5°, 33.6°, 34.4°, 36.8°, 37.7°, 40.7°, 43.5°, 46.2°, 47.7°, 48.9°, 53.3°, and 63.8°, corresponding to the typical reflections of (-111), (111), (-112), (120), (-121), (-103), (031), (200), (-123), (-212), (014), (-213), and (-134) crystallographic planes of Ag₂S (Fig. 2).

The SEM scanning electron microscopy was applied to recognize the morphology of the Ag₂S/RHA-MCM-41. As shown in Fig. 3, the diameters of small spherical particles of RHA-MCM-41 are 70 nm (Fig. 3).

Fig. 4 indicates the elemental mapping of Ag₂S/RHA-MCM-41 sample. The result shows that there are all elements Si, O, Ag and S in nanocomposite.

Optimization of reaction conditions

Continuing our extending research on the synthesis and study of heterocyclic and pharmaceutical compounds and efforts in the field.
Fig. 1. The FT-IR spectrum of (a) RHA, (b) RHA-MCM-41, and (c) Ag$_2$S/RHA-MCM-41.

Fig. 2. XRD patterns of Ag$_2$S/RHA-MCM-41.

Fig. 3. The SEM images of Ag$_2$S/RHA-MCM-41.
of efficient synthetic processes, improving activity and decreasing reaction time, by-products, and the number of separation steps [33-39], in this work, the first synthesis of some azo-linked 1, 2, 4-triazole-3-thiones from various of synthesized azo-linked salicylic acid, phenylhydrazine and potassium thiocyanate, and Ag$_2$S/RHA-MCM-41 as a catalyst is reported (Fig. 5).

To study this reaction and optimize the different reaction conditions, we selected the one-pot reaction of synthesized azo-linked salicylic acid 1a, phenylhydrazine and potassium thiocyanate in EtOH (10 mL) as a model reaction. At first, to determine the optimal conditions, various catalysts were used. The results are shown in Table 1.

The results of the study showed that the use of Ag$_2$S/RHA-MCM-41 nanocomposite (entry 6) has better yields (88%) and shorter time (2h) than other reaction conditions. Also, the effect of the amount of catalyst on the synthesis process of 4a was investigated (Table 2). The best quantity of Ag$_2$S/RHA-MCM-41 nanocomposite was determined based on the results in Table 2, 0.1g/mmol. Under these conditions, product 4a was obtained with a higher yield (88%) and shorter time (2 h).

According to this data, we synthesized other azo-linked 1, 2, 4-triazole-3-thione derivatives using 0.1g of Ag$_2$S/RHA-MCM-41 nanocomposite, was shown in Table 3. To test the generality and
Table 1. Effect of catalyst for the synthesis of 4a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>nano-SiO₂</td>
<td>24</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>K10</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>nano-Fe₃O₄</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>GO-ZnO</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>Ag₂S/RHA-MCM-41</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>7^b</td>
<td>[DBU]Br</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>8^b</td>
<td>[DBU]OAc</td>
<td>6</td>
<td>85</td>
</tr>
</tbody>
</table>

^a The amount of catalyst in these reactions was 0.1 g. In these reactions, 10 mL of ethanol was used as the solvent. b. For ionic liquids, 2 mL ionic liquid was used and the conditions are without solvent.

Table 2. Effect of catalyst amount of Ag₂S/RHA-MCM-41 for the synthesis of 4a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst amount (g/nmol)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>0.03</td>
<td>10</td>
<td>71</td>
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<tr>
<td>3</td>
<td>0.05</td>
<td>2.5</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>2</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 3. Synthesis of Azo-linked 1, 2, 4-triazole-3-thiones using Ag₂S/RHA-MCM-41 nanocomposite 4a-h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Structure</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>1.5</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>1.5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>1.5</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>1.5</td>
<td>95</td>
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<td>8</td>
<td>4h</td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>1.5</td>
<td>92</td>
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efficiency of Ag₅S/RHA-MCM-41 nanocomposite, we checked some aldehydes with electron withdrawing and electron donating substituents (Table 3). The rate of nucleophile attack of thiocyanate on aldehydes was faster for aldehydes with electron withdrawing groups. Even so, overall yields were about the same. All of the synthesized compounds in Table 3 are new and were characterized by spectroscopic methods (IR, ¹H NMR and ¹³C NMR) and elemental analysis.

The results of catalyst reusability are shown in Fig. 5. After completion of the reaction, the residue was filtered and the crude product was dissolved in ethanol and separated from Ag₅S/RHA-MCM-41 nanocomposite which remained insoluble, and washed three times with 30
mL (H₂O : EtOH). As shown in Fig. 5, after five successive runs, the recycled catalyst didn’t show any significant decrease in efficiency concerning reaction time and yield. That confirmed the advantage of this method for the synthesis of azo-linked 1, 2, 4-triazole-3-thione derivatives (Fig. 6).

A proposed mechanism for the synthesis of 1, 2, 4-triazole-3-thione is shown in Fig. 6. Initially, Ag₂S/RHA-MCM-41 nanocomposite appears to activate aldehyde by forming a hydrogen bond with the carbonyl functional group. Next, the reaction continues with acetylation and then substitution of nulceophilic reaction of thiocyanate. Then, after a rearrangement and formation of isothiocyanate 9 followed by addition of phenylhydrazine 2 to generate 10. Subsequent cyclization of intermediate 10 generates 11, which is converted into product 12 by dehydration (Fig. 7).

CONCLUSION

In this study, new derivatives of 5-(5-(2-phenyl diazenyl)-2-hydroxyphenyl)-1, 2-dihydro-1-phenyl-1, 2, 4-triazole-3-thiones were produced in the reaction of different synthesized azo-linked salicylic acids, potassium thiocyanate, and phenylhydrazine using Ag₂S/RHA-MCM-41 nanocomposite and the reaction products were obtained in 1.5-2 h with an efficiency of 88-95%. High reaction efficiency and short reaction time indicate the high efficiency of this method. In all reactions, the Ag₂S/RHA-MCM-41 nanocomposite can be easily removed and reused without any significant activity decrease.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

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