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Short Communication

One-Pot Facile Synthesis of New 1, 2, 4-Triazolidine Derivatives Using Sodium Borohydride and Fe_3O_4 Magnetic Nanoparticles (MNPs)

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Abstract

One-pot reaction of aldehydes with thiosemicarbazide was performed using $NaBH_4$ and Fe_3O_4 magnetic nanoparticles (MNPs). The reaction mixture of thiosemicarbazide and carbonyl compounds was stirred under reflux condition in the present of Fe_3O_4 MNPs and $NaBH_4$. The optimum amount of Fe_3O_4 MNPs was 5 mol% in ethanol. The precipitate was appeared immediately to obtain 1,2,4-triazolidine. The reflux continued 20 min after addition of $NaBH_4$ to complete the reaction. 1,2,4-triazolidines were obtained in good to excellent yields. All products were identified by GC-Mass, NMR, FT-IR spectra and physical data with those of authentic samples. The magnetically recoverable iron oxide nanoparticles are found to be efficient for synthesis of 1,2,4-triazolidine derivatives. The Fe_3O_4 MNPs were simply recovered by external magnetic field and exhibited exceptionally high catalytic activity in green chemistry and enhanced reaction speed without pollution. Fe_3O_4 MNPs could be successfully recovered and reuse. This method is easier and less expensive than the other methods.

Keywords: *Fe_3O_4 magnetic nanoparticles, Thiosemicarbazone, 1,2,4-triazolidine, $NaBH_4$.*

1. INRODUCTION

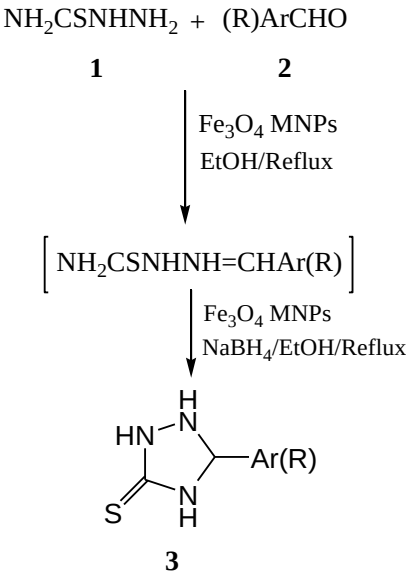
A large number of heterocyclic compounds containing 1,2,4-triazoles have *attracted* the *interest* of chemists for wide variety of chemical properties, synthetic versatility [1-4], and pharmacological activities such as antifungal [5-6], anticonvulsant [7], anticancer [8-10], antibacterial properties [11] and anti-inflammatory [12-13]. Some 1,2,4-triazole derivatives are well known as drugs, for example, fluconazole [14], Triadimefon [15], Mycobutanil [16], anastrozole [17], loreclezole [18], Rizatriptan [19] and Alprazolam [20]. Moreover, the 1,2,4-triazole compounds carrying sulfone moiety or imine bond have been reported as antibacterial and antifungal, antihypertensive, analgesic, anti-inflammatory, or antitumoral agents [21−23].

Recently, superparamagnetic iron oxide nanoparticles (SPIONs) have been intensively investigated because of their super paramagnetic properties, excellent catalytic activity in organic synthesis, complete magnetically recoverable facile catalyst and low Curie temperature [24-28]. In addition to these characteristics, Fe_3O_4 MNPs are also environmentally friendly, economical and relatively non-toxic compounds [29-31]. Because of the mentioned facts and in continuation of our research on synthesis of heterocyclic compounds, we herein report the synthesis of some new 1,2,4-triazolidine derivatives using $NaBH_4$ and Fe_3O_4 MNPs. However,

a few studies have been reported on synthesis of 1,2,4-triazolidines. The aim of this research is to highlight the application of Fe_3O_4 magnetic nanoparticles as an *eco-friendly*, *recyclable* and highly efficient catalyst for synthesis of 1,2,4-triazolidine derivatives in good yields and under mild reaction conditions.

2. RESULTS AND DISCUSSION

In this article, it was reported, that nano Fe_3O_4 is a highly efficient and ecofriendly catalyst for synthesis of 1,2,4-triazolidine derivatives in the presence of $NaBH_4$. The reaction mixture of thiosemicarbazide and carbonyl compounds was stirred under reflux condition in the present of Fe_3O_4 MNPs and monitored by TLC in *n*-hexane:ethyl acetat (4:1). The thiosemicarbazone intermediate was obtained after 20 min. Then $NaBH_4$ was added, the precipitate was appeared immediately to obtain 1,2,4-triazolidine. The reflux continued 20 min after addition of $NaBH_4$ to complete the reaction (Scheme 1). All products were identified by GC-Mass, NMR, FT-IR spectra and physical data with those of authentic samples.



Scheme 1. *One-pot synthesis of of 1,2,4-triazolidine, catalyzed by $NaBH_4$ /Fe_3O_4 Magnetic Nanoparticles.*

Fe_3O_4 MNPs were prepared by a simple, low cost and convenient method from the reaction of $FeCl_2.4H_2O$ and $FeCl_3.6H_2O$ in ammonia solution. The FT-IR spectra of prepared Fe_3O_4 nanoparticles are shown in Figure 1.

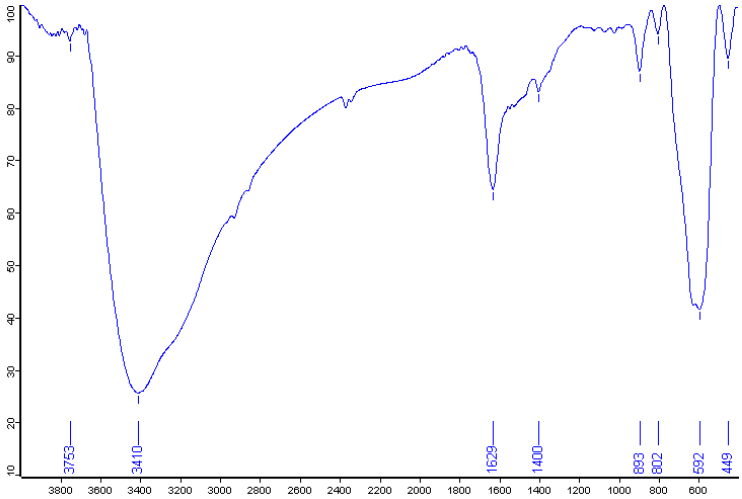


Figure 1. *FT-IR spectra of Fe_3O_4 Magnetic Nanoparticles.*

The results in this spectra show that the data are the same as reported in literature. A strong peak at around 592 cm^{-1} is related to Fe-O stretching frequency. The broad band at around 3000–3500 cm^{-1} is attributed to adsorbed water [32-33]. Nano-Fe_3O_4@SiO_2 was synthesized according to a previously published literature method [33-34].

Transmission electron microscopy (Figure 2) shows the transmission electron microscopy (TEM) images of the Fe_3O_4

MNPs. We can clearly see that the Fe_3O_4 MNPs are composed of small particles. The average particle size is about 20-80 nm.

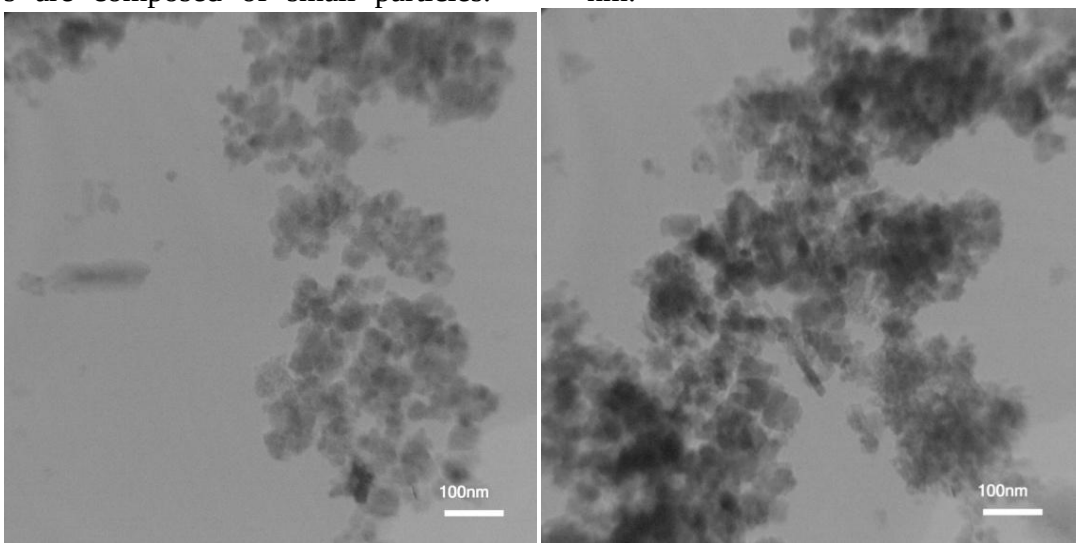


Figure 2. *TEM images of Fe_3O_4 MNPs.*

The FT-IR spectra of prepared Fe_3O_4@SiO_2 nanoparticles are shown in Figure 3. The FT-IR spectrum of Fe_3O_4@SiO_2 was clearly different from Fe_3O_4. The broad band at around 3000–3600 and 1633 cm^{-1} corresponds to adsorbed water. The band at 457 cm^{-1} was assigned to the Si-O symmetric stretching. The strong absorption at 595 cm^{-1} was characteristic of the Fe–O-Si stretching vibration. Bands corresponding to Si–O–Si stretching appeared at 1081 cm^{-1} (Figure 3).

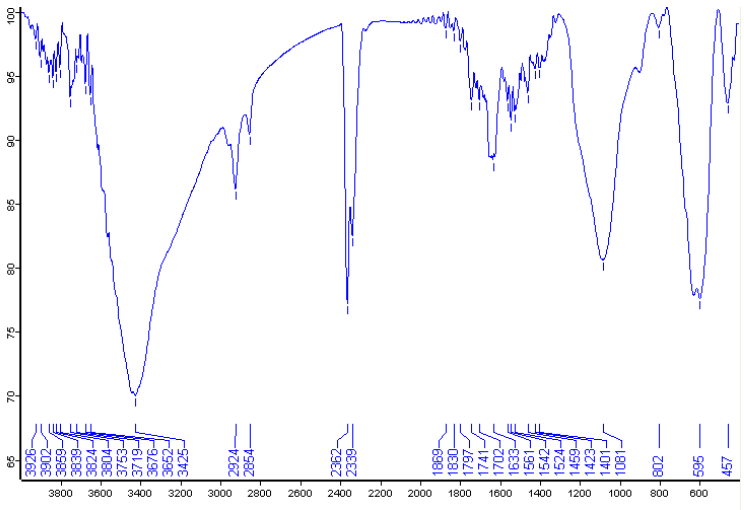


Figure 3. *FT-IR spectra of Fe_3O_4@SiO_2 Magnetic Nanoparticles.*

In the preliminary stage of investigation, the model reaction of cinnamaldehyde and thiosemicarbazide was carried out by using various amounts of Fe_3O_4 nanoparticles in the presence of $NaBH_4$ in various solvents and solvent-free conditions. The optimum amount of nano-Fe_3O_4 was 5 mol% as shown in Table1. It was found that in the absence of Fe_3O_4 magnetic nanoparticles, only trace of the desired product was observed on TLC plate even after 2h of reaction. When the reaction was performed in the presence of Fe_3O_4 magnetic nanoparticles, it proceeded to give the

desired product. The best results were obtained with 5 mol% of Fe_3O_4 magnetic nanoparticles in ethanol under reflux conditions (Table 1, entry 25). Increasing the amount of catalyst does not improve the yield of the product any further, whereas decreasing the amount of catalyst leads to decrease in the product (Table 1, entry 22-26). There is a decrease in the catalytic activity when the reaction was catalyzed by silica coated Fe_3O_4 MNPs because the silica shells decrease the catalytic activity of Fe^{3+} (Table 1, entry 6, 28-30).

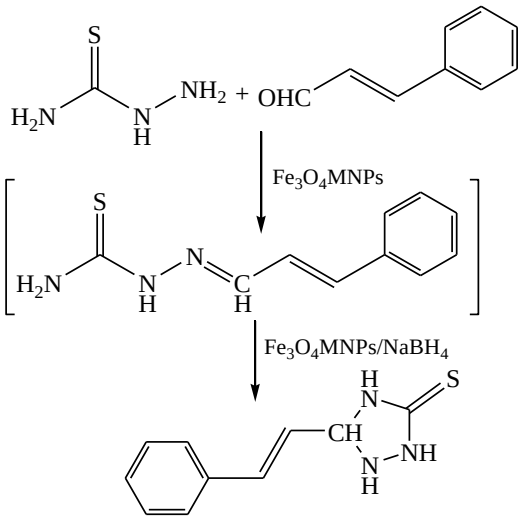
Table 1. *Reaction of cinnamaldehyde (1mmol), thiosemicarbazide (1 mmol) and $NaBH_4$ (1 mmol) under different conditions at R.T.*

Entry	Solvent	Catalyst	Catalyst (%)	Time (Befor $NaBH_4$+ After $NaBH_4$)	Yield[a] (%)
1	THF	-	-	2h	trace
2	THF	Fe_3O_4 MNPs	3	1h+1h	60
3	THF	Fe_3O_4 MNPs	4	1h+40min	76
4	THF	Fe_3O_4 MNPs	5	20min+ 20min	92
5	THF	Fe_3O_4 MNPs	7	20min+ 20min	92
6	THF	Fe_3O_4@SiO_2 MNPs	5	1h+ 1h	78
7	CH_3CN	-	-	2h	trace
8	CH_3CN	Fe_3O_4 MNPs	3	1h+1h	38
9	CH_3CN	Fe_3O_4 MNPs	4	1h+1h	62
10	CH_3CN	Fe_3O_4 MNPs	5	1h+1h	79
11	CH_3CN	Fe_3O_4 MNPs	7	1h+1h	79
12	*n*-Hexaneee	-	-	2h	trace
13	*n*-Hexaneee	Fe_3O_4 MNPs	3	1h+1h	25
14	*n*-Hexaneee	Fe_3O_4 MNPs	4	1h+1h	43
15	*n*-Hexaneee	Fe_3O_4 MNPs	5	1h+1h	57
16	*n*-Hexaneee	Fe_3O_4 MNPs	7	1h+1h	58
17	EtOEt	-	-	2h	trace
18	EtOEt	Fe_3O_4 MNPs	3	1h+1h	40
19	EtOEt	Fe_3O_4 MNPs	4	1h+1h	52
20	EtOEt	Fe_3O_4 MNPs	5	1h+1h	64
21	EtOEt	Fe_3O_4 MNPs	7	1h+1h	65
22	EtOH	Fe_3O_4 MNPs	-	2h	trace
23	EtOH	Fe_3O_4 MNPs	3	1h+40min	68
24	EtOH	Fe_3O_4 MNPs	4	40min+40min	85
25	EtOH	Fe_3O_4 MNPs	5	20min+ 20min	96
26	EtOH	Fe_3O_4 MNPs	7	20min+ 20min	96
27	Solvent-free	Fe_3O_4 MNPs	7	1h+ 1h	67
28	EtOH	Fe_3O_4@SiO_2 MNPs	5	1h+ 1h	68
29	EtOH	Fe_3O_4@SiO_2 MNPs	7	1h+ 1h	68
30	Solvent-free	Fe_3O_4@SiO_2 MNPs	7	1h+ 1h	60

[a] *Isolate Yield.*

To evaluate the scope and limitations of this methodology, we extended our studies to include a variety of structurally different carbonyl compounds carrying both electron-donating and electron-withdrawing substituent produced the corresponding 1,2,4-triazolidine.

In almost all cases, the reactions proceeded smoothly within 40 min in ethanol to give 1,2,4-triazolidines, providing the corresponding products in good isolated yields without formation of any side products. The structures of compounds **3a-f** were determined by NMR, IR, mass spectrometry and Microanalysis. They were in full agreement with the proposed structures.



Scheme 2. *Synthesis of 5-Styryl-[1,2,4]triazoline-3-thione.*

The FT-IR spectra of prepared 5-Styryl-[1,2,4]triazoline-3-thione are shown in Figure 4. The infrared spectrum of compound **3a** showed broad absorption for NH stretching vibrations in 3155, 3260 and 3416 cm^{-1}, C=S vibrations in 1622 cm^{-1}, and C=C vibration in 1538 and 1591 cm^{-1}.

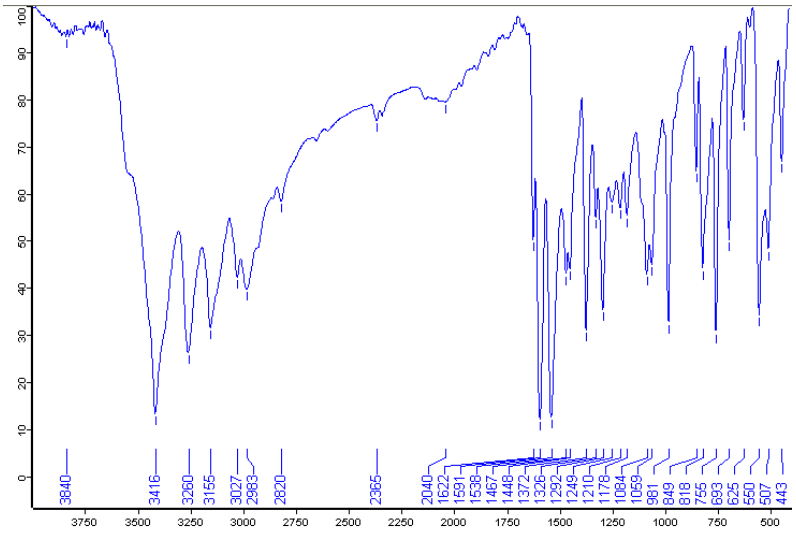


Figure 4. *FT-IR spectra of 5-Styryl-[1,2,4]triazoline-3-thione.*

The ^{1}H-NMR spectra of **3a** exhibited three broad signals for NH protons at 7.62, 8.12 and 11.40 ppm. A doublet signal of 8.8 Hz at 7.90 ppm for CH proton of triazolidine, a doublet signal of 16 Hz at 7.02 ppm for Ph-CH= and a doublet doublet signal of 16 and 8.8 Hz at 6.87 ppm due to a =CH- proton were presented. Five aromatic protons exhibited as doublet doublet and two multiplet protons at 7.55-7.31 ppm (Figure 5). ^{13}C-NMR of compound **3a** indicates sharp signal for C=S carbon at 178.11 ppm and CH carbon of triazolidine at 125.53 ppm. The signal attributed to an unsaturated carbon double bond (-CH=CH-) appears at 127.38 and 129.30 ppm (Figure 6).

The elemental analysis result of compounds **3a** was satisfactory. The mass spectra of this compound displayed a molecular ion peak at *m*/*z* 205. Any initial fragmentation involves loss from or complete loss of the side chain and part of the triazolidine system.

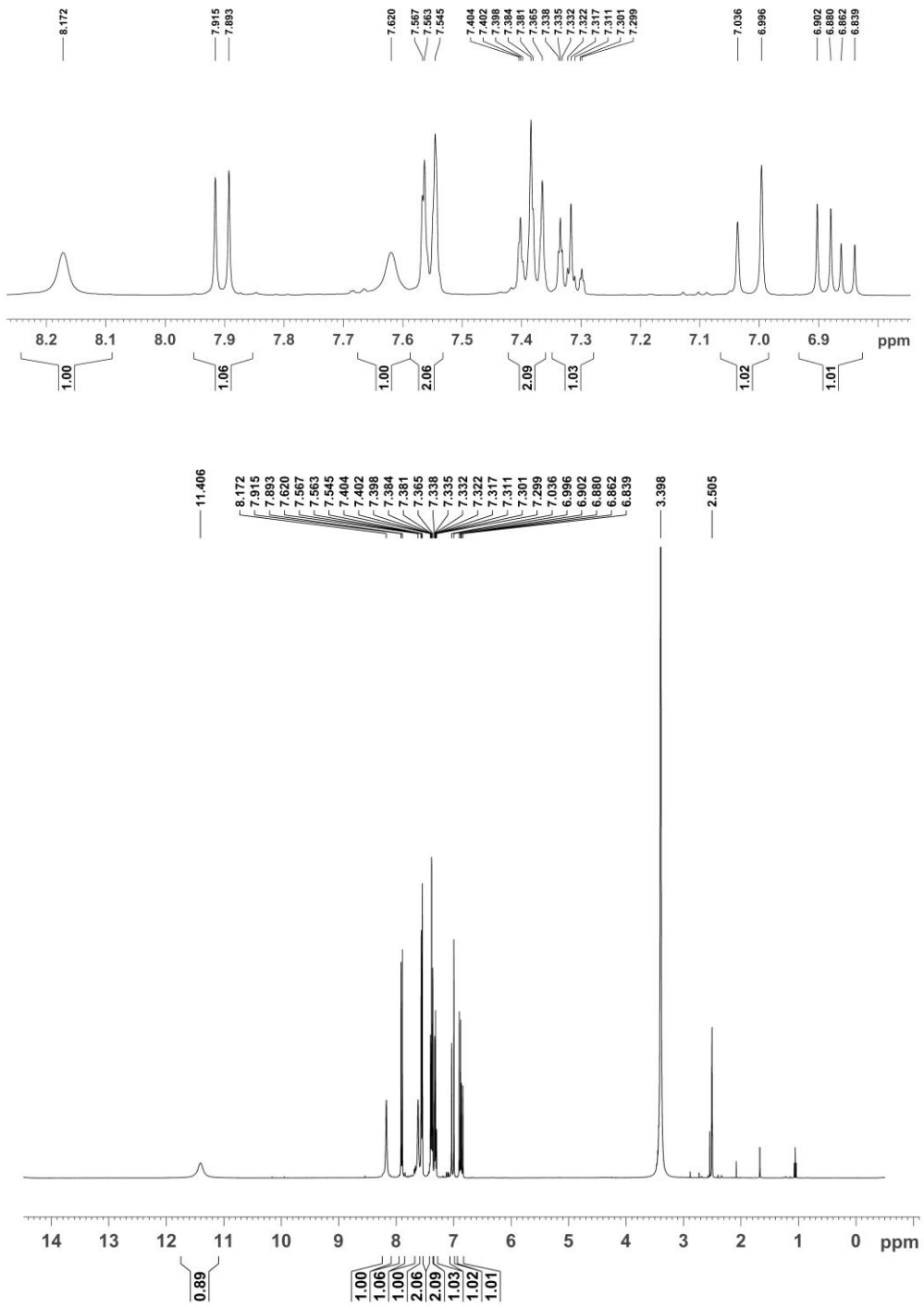


Figure 5. *^{1}H-NMR spectra of 5-Styryl-[1,2,4]triazoline-3-thione.*

A plausible mechanism for the reaction is envisaged in (scheme 3). Carbonyl group is first activated by MNPs (Fe^{3+}), then the nitrogem of thiosemicarbazide attacks to positive center to afford thiosemicarbazone intermediate. Imine bond in thiosemicarbazone is activated by Fe_3O_4 MNPs to provide more positive center for intermolecular cyclization and production of 1,2,4-triazolidine. The catalyst was simply recovered by external magnetic field, washed with ethanol, and dried at 60 °C for 1 h. The recovered catalyst was then added to a fresh reaction mixture under the same conditions and reused 7 times without significant loss of activity (Table 2). Further recycling of the nanocatalyst led to gradual loss of the

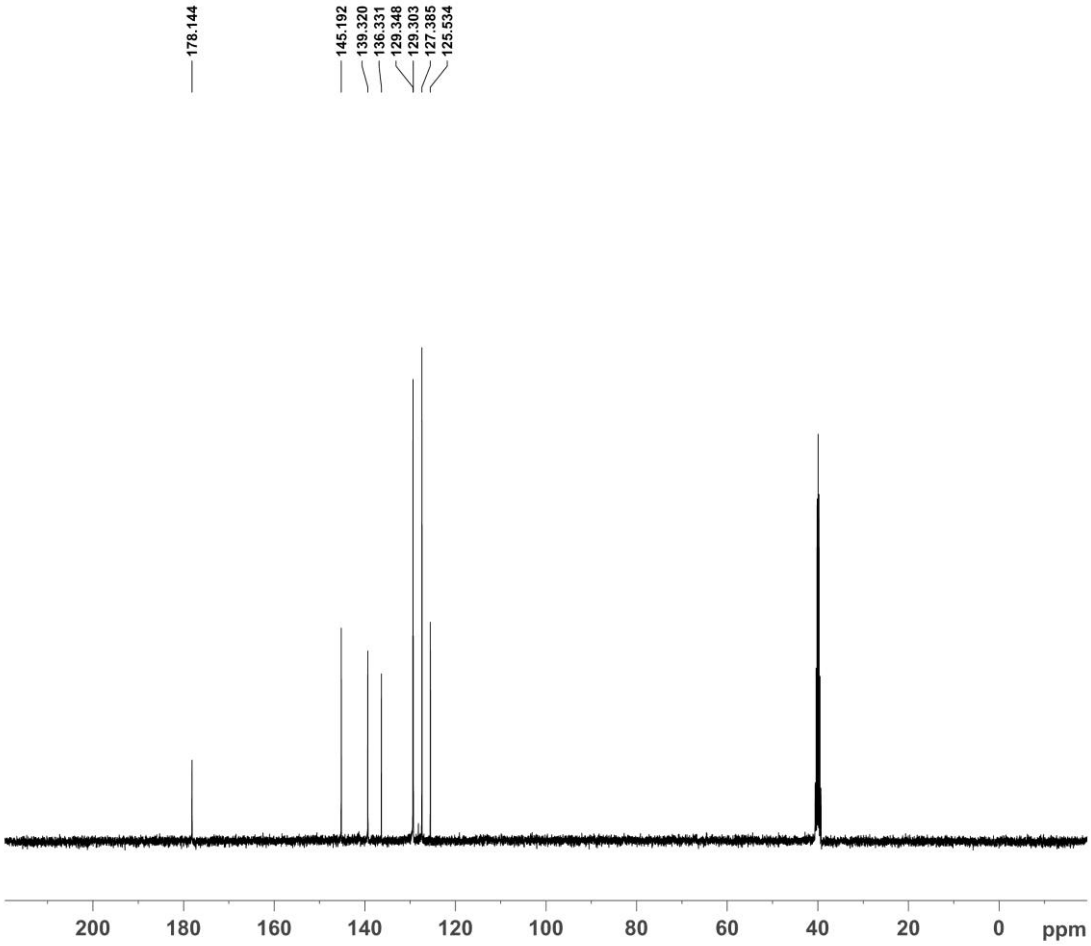
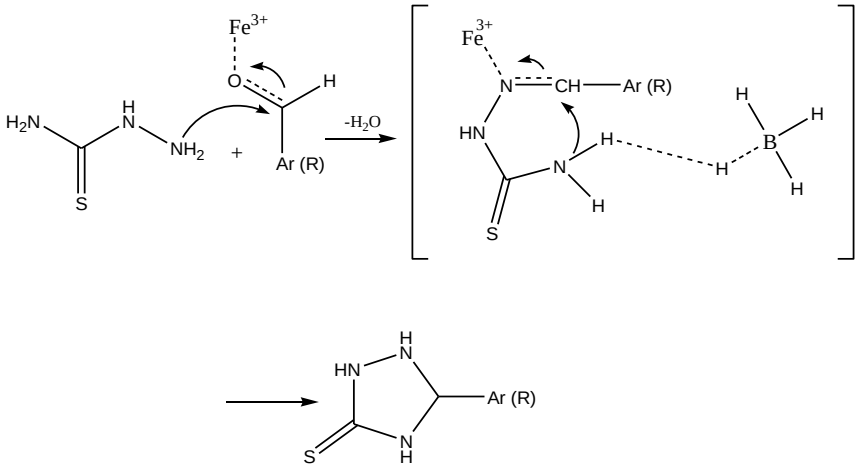


Figure 6. *^{13}C-NMR spectra of 5-Styryl-[1,2,4]triazoline-3-thione.*



Scheme 3. *Plausible mechanism for synthesis of 1,2,4-triazolidine using $NaBH_4$ and Fe_3O_4 MNPs.*

catalyst during the recovering and washing stages. The catalyst was simply recovered by external magnetic field, washed with ethanol, and dried at 60 °C for 1 h. The recovered catalyst was then added to a fresh reaction mixture under the same conditions and reused 7 times without significant loss of activity (Table 2). Further recycling of the nanocatalyst led to gradual loss of the catalyst during the recovering and washing stages.

Table 2. *Recycling of the Fe_3O_4 Magnetic Nanoparticles catalyst.*

Number of cycle	Yield[a] (%)
1	96
2	96
3	93
4	92
5	90
6	88
7	88

[a] *Isolated yield after chromatography*

3. EXPERIMENTAL

All solvents purified and dried using established procedures. FT-IR measurements were recorded on a Shimadzu 8400s spectrometer with KBr plates. The NMR spectra were recorded on Bruker XL 400 (400 MHz) instruments, Melting points were determined on an Electrothermal 9100 without further corrections. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The C, H, and N analyses were performed by the microanalytical service of the NIOC Research Institute of Petroleum Industry.

3.1. Preparation of Catalyst

MNPs (Fe_3O_4 and Fe_3O_4@SiO_2) were prepared according to previously reported procedures [32-34].

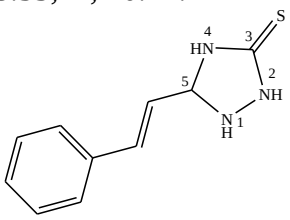
3.2. General Procedure for Synthesis of 1,2,4-triazolidine

Carbonyl compound (1mmol) and thiosemicarbazide (1mmol) were mixed in ethanol (5ml), and then Fe_3O_4 magnetic nanoparticles (5 mol%) was added. The mixture was vigorously stirred under reflux condition, after 20 min $NaBH_4$ (1mmol) was added. The precipitate appeared immediately, the mixture was refluxed with stirring for an additional 20 min. The progress of the reaction was monitored by TLC using *n*-hexane : ethyl acetate (4:1) and detected by UV lamp (254 & 366 nm). At the end of the reaction, the catalyst was recovered by an external magnet, washed with EtOH, dried at 60 °C for 1h and reused seven times for the same reaction. The residue of the reaction mixture was evaporated, and the crude product was purified by short-column chromatography on silica gel (eluent: *n*-hexane : EtOAc / 4:1). All products were identified by NMR, IR, mass spectrometry and microanalysis.

3.3. 5-Styryl-[1,2,4]triazoline-3-thione *3a*

Orange powder. Yield 96 %, m.p. 120 °C. FT-IR (KBr,ν_{max} cm^{-1}): 3416(N-H), 3260(N-H), 3155(N-H), 3020(CH_{Ar}), 2940(CH), 1622(C=S), 1538-1591 (C=C). ^{1}H-NMR (400 MHz, DMSO δ ppm): 11.40 (1H, s, NH-4$_{triazol}$), 8.12 (1H, br, NH-2 $_{triazol}$), 7.90 (1H, d, *J* = 8.8, $CH_{triazol}$), 7.62 (1H, br, NH-1 $_{triazol}$), 7.55 (2H, dd, *J* = 8, 1.6, H_{orto}), 7.39 (2H, m, H_{meta}), 7.31 (1H, m, H_{para}), 7.02 (1H, d, *J* = 16, Ph-CH=), 6.87 (1H, d d, *J* = 16Hz , 8.8 Hz, =CH-). ^{13}C NMR (100 MHz) δ: l78.11 (C=S), 145.19 (C_{Ar}-1), 139.32 (C_{Ar}-3,5), 136.33(C_{Ar}-3,5), 129.34 (Ph-C=), 129.30 (C_{Ar}-2,6), 127.38 (=CH-), 125.53 ($CH_{triazol}$). MS: *m/z*

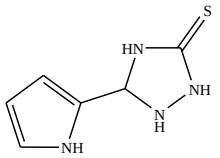
205 $[M]^+$. Anal Calcd. for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47 founded: C, 58.08; H, 5.35; N, 20.27.



3.4. 5-(1H-pyrrol-2-yl)-[1,2,4]triazoline-3-thione *3b*

Dark brown powder. Yield 98 %, m.p. 178 °C.

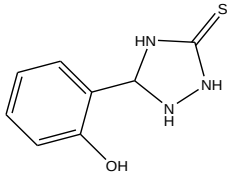
FT-IR (KBr,ν_{max} cm^{-1}): 3170-3417(N-H), 3013(CH_{Ar}), 2961(CH), 1625(C=S). ^{1}H-NMR (400 MHz, DMSO δ ppm): 11.37 (1H, s, NH-$4_{triazol}$), 11.25 (1H, br, NH $_{pyrrol}$), 8.05 (1H, s, H-5_{pyrrol}), 7.95 (1H, H-4_{pyrrol}), 7.76 (1H, s, NH), 7.83 (1H, H-3_{pyrrol}), 6.97 (1H, H-$5_{triazol}$), 6.39 (1H, s, NH). MS: *m/z* 168 $[M]^+$. Anal Calcd. for $C_6H_8N_4S$: C, 42.84; H, 4.79; N, 33.31 Founded: C, 43.54; H, 4.76; N, 33.91.



3.5. 5-(2-Hydroxyphenyl)-[1,2,4] triazolidine-3-thione *3c*

Yellow powder. Yield 94 %, m.p. 251°C.

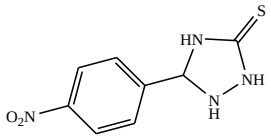
^{1}H-NMR (400 MHz, DMSO δ ppm): 11.140 (1H, s, $NH_{triazol}$), 8.57 (1H, s, $NH_{triazol}$), 7.62 (1H, d, *J* = 7.6Hz, CH_{Ar}), 7.29 (1H, t, *J* = 7.6 Hz, CH_{Ar}), 6.93 (2H, d, *J* = 6.8 Hz, CH_{Ar}), 6.67 (1H, br, $NH_{triazol}$), 6.45 (1H, s, $CH_{triazol}$), 5.80 (1H, br, OH). MS: *m/z* 195 $[M]^+$. Anal Calcd. for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52 founded: C, 49.78; H, 4.55; N, 21.38.



3.6. 5-(4-nitrophenyl)-[1,2,4]triazolidine-3-thione *3d*

Yellow powder. Yield 92 %, m.p > 300 °C.

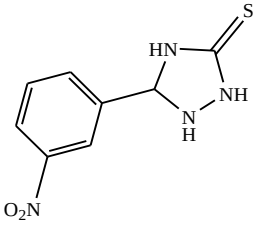
FT-IR (KBr,ν_{max} cm^{-1}): 3420(N-H), 3265(N-H), 3172(N-H), 3023(CH_{Ar}), 2940(CH), 1630(C=S), 1351-1556(NO_2). ^{1}H-NMR (400 MHz, DMSO δ ppm): 11.48 (1H, s, $NH_{triazol}$), 8.38 (٢H, d, *J* = ٨Hz, Ar-H), 8.25 (1H, br, $NH_{triazol}$), 8.09 (٢H, d, *J* = ٨Hz, Ar-H), 7.82 (1H, br, NH $_{triazol}$), 6.98 (1H, s, $H_{triazol}$). MS: *m/z* 224 $[M]^+$. Anal Calcd. for $C_8H_8N_4O_2S$: C, 42.85; H, 3.60; N, 24.99, founded: C, 42.88; H, 3.53; N, 24.90.



3.7. 5-(3-nitrophenyl)-[1,2,4]triazolidine-3-thione *3e*

Yellow powder. Yield 91 %, m.p. 280 °C.

FT-IR (KBr,ν_{max} cm^{-1}): 3411(N-H), 3120-3247(N-H), 3036(CH_{Ar}), 2952(CH), 1628(C=S), 1354-1546(NO_2). ^{1}H-NMR (400 MHz, DMSO δ ppm): 11.41 (1H, s, $NH_{triazol}$), 8.30 (2H, dd, *J*= 8, 2Hz, Ar-H), 8.23 (1H, br, $NH_{triazol}$), 8.21 (1H, s, Ar-H), 7.72 (1H, m, Ar-H), 6.89 (1H, s, $H_{triazol}$). MS: *m/z* 224 $[M]^+$. Anal Calcd. for $C_8H_8N_4O_2S$: C, 42.85; H, 3.60; N, 24.99, founded: C, 42.93; H, 3.64; N, 25.12.

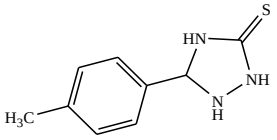


3.8. 5-(4-methylphenyl) -[1,2,4] triazolidine-3-thione *3f*

White powder. Yield 89 %, m.p. 205 °C.

FT-IR (KBr,ν_{max} cm^{-1}): 3415(N-H), 3028(CH_{Ar}), 2940(CH), 1608(C=S). ^{1}H-NMR (400 MHz, DMSO δ ppm): 11.23 (1H, s, $NH_{triazol}$), 7.85 (1H, br, $NH_{triazol}$), 7.56 (1H, br, $NH_{triazol}$), 7.٧٣ (2H, d, *J* = 7Hz, Ar-H), 7.31 (2H, d, *J* = 7Hz, Ar-H), 2.35 (3H, s, CH_3), 6.77 (1H, s, $H_{triazol}$). MS: *m/z* ١٩٣ $[M]^+$. Anal Calcd. for $C_٩H_{11}N_3S$:

C, ٥٥.٩٣; H, 5.٧٤; N, ٢١.٧٤ founded: C, 55.98; H, 5.68; N, 21.81.



4. CONCLUSION

In summary, an efficient protocol for synthesis of new 1,2,4-triazolidines was described. The reactions were carried out in *short reaction time* and mild reaction conditions and the corresponding products were obtained in good to excellent yields. In addition to having the general advantages attributed to the inherent magnetic property of nanocatalyst, Fe_3O_4 MNPs exhibited exceptionally *high* catalytic activity in green chemistry and increases reaction speed without air pollution. Fe_3O_4 MNPs could be successfully recovered and reuse. This method is easier and less expensive than the other methods.

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