Magnetite (Fe_3O_4) nanoparticles: an efficient and reusable catalyst for the synthesis of thioethers, vinyl thioethers, thiol esters, and thia-Michael adducts under solvent-free condition

Barahman Movassagh* and Ali Yousefi

Department of Chemistry, K. N. Toosi University of Technology, P. O. Box 16315-1618, Tehran, Iran; E-mail address: bmovass1178@yahoo.com

Abstract:

Magnetic iron(III) oxide nanoparticles (Fe_3O_4 MNPs) were used as a readily available, highly efficient and recyclable catalyst for the anti-Markovnikov 1,2-addition of thiols to alkenes and alkynes, affording thioethers and vinyl thioethers in excellent yields in short reaction times under mild and solvent-free conditions. This catalyst was also utilized for thia-Michael addition, substitution reaction, and the synthesis of thiol esters.

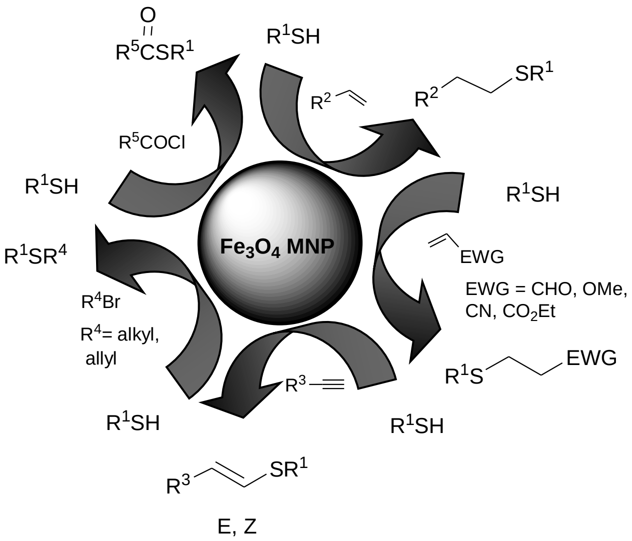
Keywords: Magentite; thiols; thiol esters; thioethers

1. Introduction

Magnetically recoverable nanoparticles (MNPs) represent an economical, practical and environmentally benign means for catalyst recovery [1], providing catalytic properties intermediate between homogeneous [2] and bulk heterogeneous materials [3,4]. Magnetic separation of the magnetic nanoparticles is simple, economical and promising for industrial applications [5]. Many schemes exist for using magnetically recoverable catalysts: anchoring homogeneous metal complexes [6], or organocatalysts [7] to a magnetic core, plating a catalytically-active metal [8], or, more simply, direct use of bare Fe(0) [9] or iron oxide NPs [10]. In recent years, nano Fe_3O_4 (magnetite) has attracted a great attention as heterogeneous catalyst due to its simple handling, ease of recovery with an external magnetic field, oxidative stability, biological compatibility, and high catalytic activities in various organic transformations [10a,11].

The construction of carbon–sulfur bond, especially under a green and safe condition, is an important transformation in organic synthesis. Sulfur containing compounds are found in many products of biological [12] and medical [13] relevance as well as in commercial drugs [14]. Among them, thioethers (sulfides) and thiol esters are two important classes of organosulfur compounds. Thioethers are the starting compounds for the preparation of other sulfur compounds, such as sulfoxides, sulfanes, and sulfonium compounds, etc [15]. They also act as synthetic reagents and intermediates in organic, medicinal, bio-organic, and heterocyclic chemistry [16]. Thiol esters are used as mild acyl transfer reagents [17], as intermediates in the synthesis of ketones [18], and macrocyclic lactones [19].

The addition of thiols on to carbon-carbon double bond is either catalyzed by protic [20] as well as Lewis acids [21] to give Markovnikov products, or takes place through a free-radical mechanism leading, usually, to anti-Markovnikov addition [22]. Very few catalysts, such as $CeCl_3$ [23], InI [24], H-Rh-zeolite [25], silica NPs [26], Brønsted acidic ionic liquid $[NMP]^+$ HSO^{4-} [27], and reaction in aqueous media [28], are reported for the electrophilic anti-Markovnikov addition of thiol to an alkene.



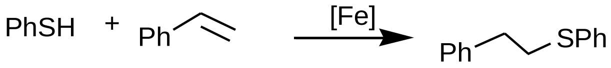
Scheme 1 Fe_3O_4 MNPs-Catalyzed reactions of thiols with various substrates.

Unfortunately, various disadvantages such as long reaction times, unsatisfactory yield, use of toxic solvents, and use of costly and/or difficultly available catalysts encountered in some of the reported procedures. In a recent report, bis(triflimide)iron(III) salt was introduced as a potential catalyst for the hydrothiolation of styrene derivatives in a Markovnikov fashion [29]. The growing importance of thioethers and thiol esters in organic synthesis has stimulated recent extensive research towards improved methods for their preparations [26-28,30,31]. In continuation of our interest in applications of Fe_3O_4 MNPs for organic transformations [11d-e], herein we report a simple and highly efficient protocol for the preparation of thioethers, vinyl thioethers, thiol esters and thia-Michael adducts under neat and neutral reaction conditions (Scheme 1).

2. Results and discussion

For optimization of the reaction conditions, we chose the reaction of thiophenol with styrene under neat condition at room temperature. As shown in Table 1, we screened a wide range of iron sources as catalyst and found that the addition reaction proceeded smoothly and generated the anti-Markovnikov product in 80% yield,

Table 1 Effect of iron sources on the anti-Markovnikov addition of thiophenol to styrene[a]



Entry	Iron Source	mol%	Yield[b] (%)
1	Fe (powder)	4	64
2	FeS	4	67
3	$FeSO_4.7H_2O$	4	21
4	$FeCl_2$	4	42
5	$FeCl_2.4H_2O$	4	53
6	$FeCl_3.6H_2O$	4	57
7	$Fe_2(SO_4)_3$	4	80
8	$Fe(NO_3)_3.9H_2O$	4	24
9	Fe_3O_4 (Bulk)	4	81
10	**Fe_3O_4 (MNPs)**	**4**	**97**
11	Fe_3O_4 (MNPs)	5	94
12	Fe_3O_4 (MNPs)	3	89
13	Fe_3O_4 (MNPs)	2	71

[a] Reaction conditions: thiophenol (1.0 equiv.), styrene (1.0 equiv.), Fe source, neat, room temperature, 3 min. [b] Isolated yields.

representing one of the best results when 4 mol% of bulk Fe_3O_4 was used as catalyst (Table 1, entry 9). Other iron sources, such as Fe(II) and Fe(III) salts, as well as Fe(0) powder gave inferiors results (Table 1, entries 1-8). To our delight 97% yield of the desired product was obtained when 4 mol% of Fe_3O_4 MNPs was used (Table 1, entry 10). Lower product yields were obtained when higher or lower loading of Fe_3O_4 MNPs catalyst were used (Table 1, entries 11-13). Therefore, the condition of entry 10 of Table 1 was regarded as optimal.

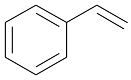
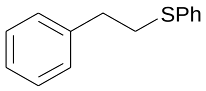
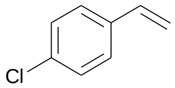
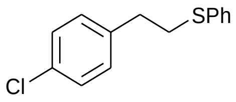
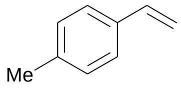
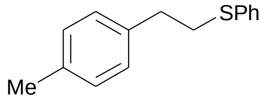
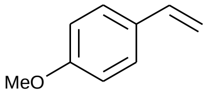
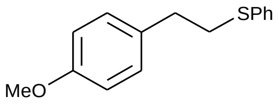
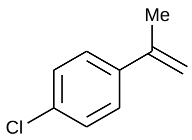
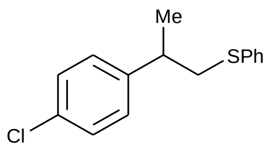
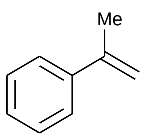
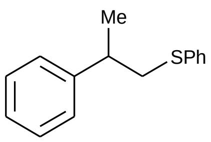
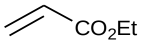
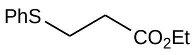
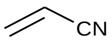
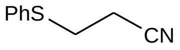
To survey the generality of the catalytic protocol, various olefins were treated with a range of thiols under the optimized conditions. Table 2 shows the results of the regioselective addition of thiols to various olefins and alkynes at room temperature under neat and aerial conditions. We noticed that all the additions were in an anti-Markovnikov fashion and no Markovnikov adducts were isolated in any case studied herein, hence highlighting the unique catalytic nature of Fe_3O_4 MNPs. We found that this method was applicable for the preparation of thioethers from the reaction of aromatic thiols, bearing electron-withdrawing and electron-donating groups, with styrenes of the types $ArCH=CH_2$ and $ArC(CH_3)=CH_2$ (Table 2, entries 1-6 and 12-18); these reactions are in general very fast (3-10 min) and clean, affording the anti-Markovnikov products in excellent yields (86-97%). To our surprise, 1,1-diphenylethylene, styrene of type $Ph_2C=CH_2$ (Table 2, entry 10) appears to be less reactive than the previously mentioned ones. In the latter case, longer reaction time (2 h) had to be employed in order to obtain the corresponding thioether in high yield. Also, thia-Michael addition of aromatic thiols to activated olefins gave excellent yields of the expected products (Table 2, entries 7-9 and 11). The addition reaction of aliphatic thiols to styrene were slow giving very low yields of the corresponding sulfides (Table 2, entries 19, 20). However, under the same reaction conditions, the addition of thiophenol to inactivated olefins such as cyclohexene and 1-octene were not successful, even after 24 h (Table 2, entries 21, 22); but, moderate yield was obtained, in 4 h, when thiophenol was added to 3,4-dihydro-2H-pyran (Table 2, entry 23).

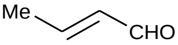
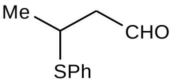
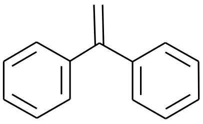
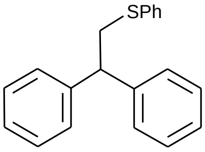
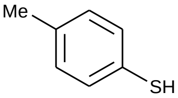
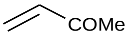
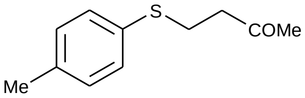
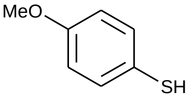
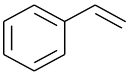
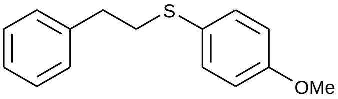
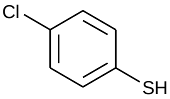
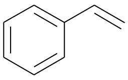
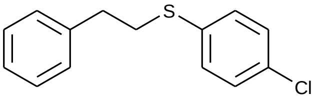
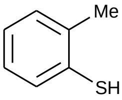
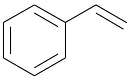
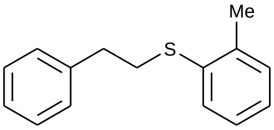
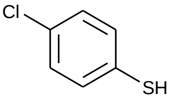
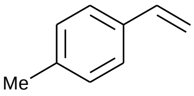
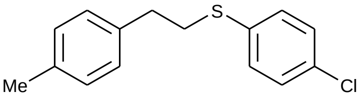
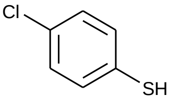
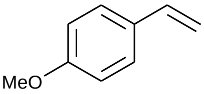
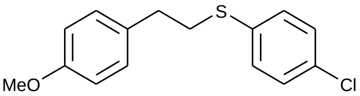
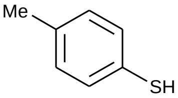
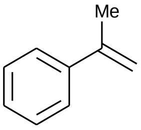
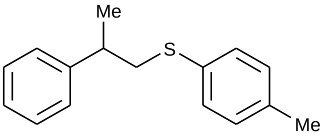
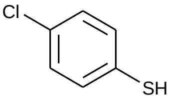
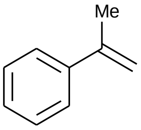
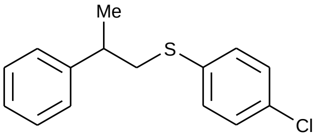
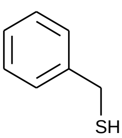
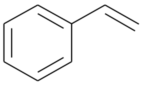
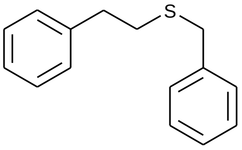
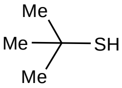
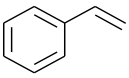
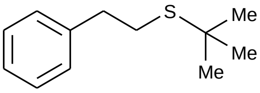
Fe_3O_4 MNPs also promoted the addition of thiophenol to alkynes such as phenylacetylene and propargyl alcohol, to afford a mixture of (*E*)- and (*Z*)-vinyl thioethers in 98 and 91% yields, respectively; detailed ^1H NMR analyses of the pure isolated products indicated the stereoselective formation of one stereoisomer for the above alkynes (*E*:*Z* ratio = 87:13 and 80:20, Table 2, entries 24 and 25 respectively).

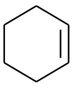
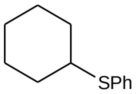
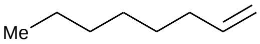
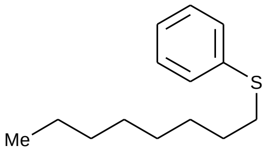
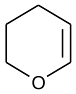
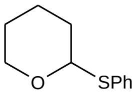
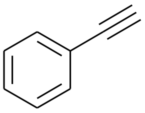
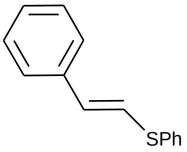
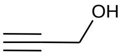
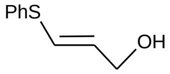
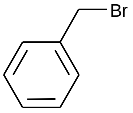
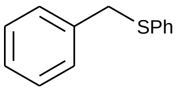
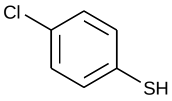
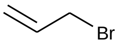
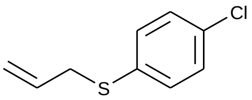
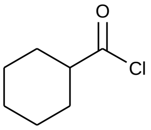
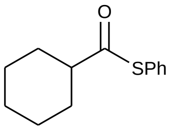
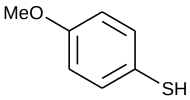
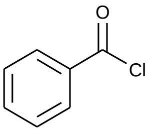
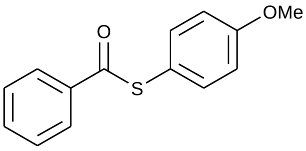
Thiolation of alkyl-, allyl- and acyl halides were also investigated by this catalyst at room temperature to afford thioethers and thiol esters, respectively (Table 2, entries 26-29) in high to excellent yields.

The reusability is one of the important properties of this catalyst. In this work, the possibility of recovery and reuse of Fe_3O_4 MNPs was tested upon the anti-Markovnikov addition of thiophenol to styrene under the same reaction conditions. The magnetic Fe_3O_4 nanoparticles were adsorbed onto the magnetic stirring bar when the magnetic stirring was stopped. The nanoparticles were then washed with ethanol, air-dried and used directly for the next run of the reaction without further purification. We observed that the catalytic activity of the catalyst was restored within the

Table 2 The Fe_3O_4 MNP-catalyzed reaction of thiols with alkenes, alkynes, alkyl-, allyl- and acyl-halides.

Entry	Thiol	Alkene / RX	Product[a]	Time	Yield (%)[b, c, d]
1	PhSH			3 min	97[28a]
2	PhSH			3 min	94[28a]
3	PhSH			3 min	90[28a]
4	PhSH			3 min	92[28a]
5	PhSH			10 min	86[28a]
6	PhSH			3 min	91[28a]
7	PhSH			1 min	98[26]
8	PhSH			1 min	91[26]

9	PhSH			1 min	98[32]
10	PhSH			2 h	87[28a]
11				3 min	94[26]
12				3 min	97[28a]
13				4 min	93[28a]
14				5 min	92[28a]
15				3 min	90[28a]
16				5 min	91[28a]
17				3 min	93[28a]
18				3 min	87[28a]
19				5 h (24 h)	25[28a] (22)
20				5 h (3 h)	21[28a] (20)

21	PhSH			24 h (24 h)	Trace (trace)
22	PhSH			24 h (24 h)	N.R. (N.R.)
23	PhSH			4 h (24 h)	45[28a] (43)
24	PhSH		 (*E*:*Z* = 87:13)	Immediately	98[26]
25	PhSH		 (*E*:*Z*= 80:20)	5 min	91[33]
26	PhSH			4 h	84[26]
27				5 min	94[26]
28	PhSH			Immediately	90[31]
29				3 min	92[31]

[a] Reaction conditions: thiol (1.0 mmol), olefin/alkyne/alkyl or acyl halide (1.0 mmol), Fe_3O_4 MNPs (0.04 mmol, 4 mol%), neat, room temperature. [b] Isolated yield. [c]References for known compounds. [d] In paranthesis yields obtained at 50 °C in the specified reaction times.

limits of the experimental errors for eight successive runs as presented in Fig.1.

On the basis of these results and on previous report [26], a plausible mechanism for the anti-Markovnikov 1,2-addition of thiols to alkenes can be proposed (Scheme 2). A Fe_3O_4 MNP’s surface consists of hydroxyl groups (**a**) [34a]. Reaction conditions: thiol

(1.0 mmol), olefin/alkyne/alkyl or acyl halide (1.0 mmol), Fe_3O_4 MNPs (0.04 mmol, 4 mol%), neat, room temperature. [b] Isolated yield. [c]References for known compounds. [d] In paranthesis yields obtained at 50 °C in the specified reaction times.

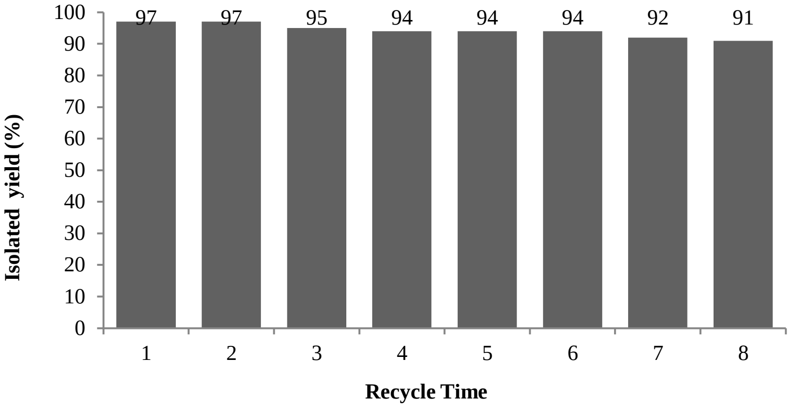
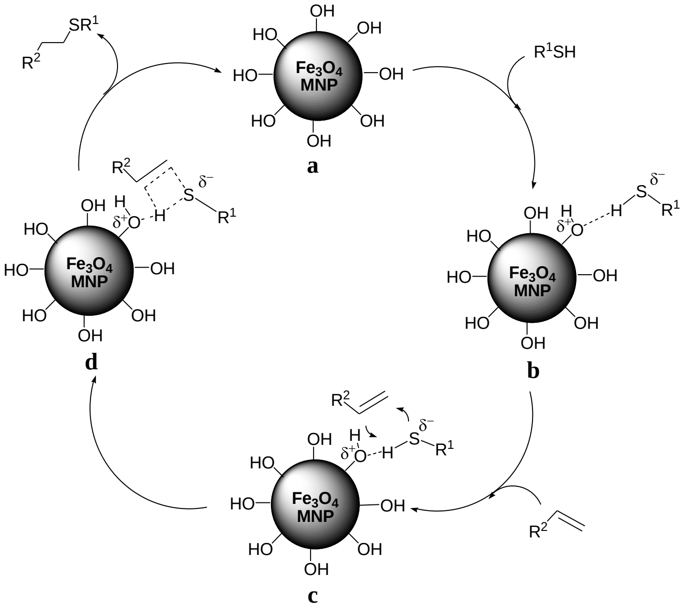


Fig. 1 Investigation of the reusability of Fe_3O_4 MNPs for catalyzing reaction between thiophenol and styrene.

We assumed that these groups polarize the SH hydrogen of thiols forming (**b**), which reacts with olefins leading to intermediate (**d**). Finally, the catalyst is regenerated, producing the 1,2-addition product (**e**).



Scheme 2 Plausible mechanism for the Fe_3O_4 MNPs-catalyzed anti-Markovnikov addition of thiols to alkenes.

3. Conclusion

In summary, we have established a robust and magnetically reusable Fe_3O_4 nanoparticle catalyzed reaction of thiols with alkenes, alkynes, alkyl- and acyl halides. A diverse range of thioethers, vinyl thioethers, and thiol esters were obtained in moderate to excellent yields under neat and aerial conditions at room temperature. The addition reaction of thiols to olefins and alkynes were highly regioselective leading to anti-Markovnikov products. The separation and recovery of the magnetic Fe_3O_4 MNPs were very simple, effective and economical. The catalyst was recycled and reused eight times with minor decrease in its catalytic activity. Moreover, the use of this catalyst is also safe and environmentally well-suited. The excellent catalytic performance, easy separation of the catalyst, and the ability to recycle and reuse, make it a good heterogeneous catalyst and a useful alternative to other catalytic systems.

4. Experimental

Representative experimental procedure for preparation of phenethyl(phenyl)sulfane (Table 1, entry 1)

In a typical experiment, a mixture of styrene (104 mg, 1 mmol), thiophenol (110 mg, 1 mmol), and Fe_3O_4 MNPs (9 mg, 4 mol%) was stirred at room temperature for 3 min. The course of the reaction was monitored by TLC until the starting materials had completely disappeared. Then, water (5 mL) was added to the reaction mixture, and extracted with ethyl acetate (3 × 3 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated under vacuum to afford 207 mg (97%) of pure phenethyl(phenyl)sulfane as yellow oil. In cases of other reaction products, further purification was performed by preparative TLC (silica gel, eluent n-hexane: ethyl acetate = 10: 1) to obtain pure products. All compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopy.

Acknowledgement

We gratefully acknowledge the funding support received for this project by the K. N. Toosi University of Technology Research Council.

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