

An efficient synthesis of 5-alkylthio and 5-arylthiotetrazoles using Fe₃O₄ nanoparticles as a magnetically recoverable and reusable catalyst

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Abstract: The 5-alkylthio and 5-arylthiotetrazoles were efficiently synthesized from thiocyanates using Fe₃O₄ nanoparticles as a magnetically recoverable and reusable catalyst. The main advantages allocated to this method are elimination of hydrazoic acid as a dangerous and harmful reagent, high yields and ease of product isolation. The catalyst can be simply recovered by an external magnet and reused with no significant loss in its reactivity.

Keywords: Fe₃O₄ Nanoparticles, thiocyanate, sodium azide, thiotetrazole, heterogeneous catalyst

INTRODUCTION

In the last few years, tetrazoles have been the focus of much research interest owing to their important role as lipophilic spacers and carboxylic acid surrogates in pharmaceuticals. Moreover, tetrazoles have been employed as ligands in coordination chemistry, as special explosives and as precursors to a variety of nitrogen-containing molecules [1-5].

Several methods have been reviewed in the literature for the synthesis of tetrazoles by the reaction between sodium azide and nitrile or cyanamide derivatives [6]. Among tetrazole derivatives, thiotetrazoles, specifically 5-alkylthiotetrazoles have received considerable attention because of their wide application in the synthesis of DNA and RNA [7]. However, the lack of convenient methods for preparation of these compounds strongly restricts their potential application in the synthetic organic chemistry. One of the most promising methods of synthesis of the 5-alkylthio or 5-arylthiotetrazoles involves the reaction between thiocyanates and sodium azide using dangerous and harmful hydrazoic acid in high polar solvents [8].

However, some of these procedures suffer from certain disadvantages such as environmentally unpleasant use of hydrazoic acid, harsh reaction conditions, long reaction times and low yields of the products. A substitute for hydrazoic acid is a mixture of sodium azide and ammonium chloride [9]. However, combining sodium azide with ammonium chloride as an acid may yield gaseous HN₃, which is toxic and flammable.

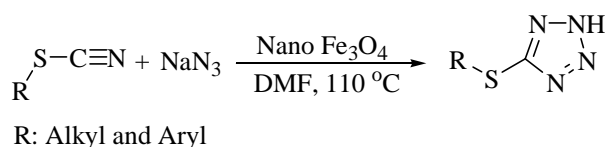
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Among various catalysts for the synthesis of thiotetrazoles, homogeneous catalysts such as Zn(II) salts [10] have been widely investigated, while less expensive heterogeneous catalysts

received scant attention. Therefore, development of more convenient synthetic approaches to 5-alkylthio or 5-arylthiotetrazoles still appears as challenging in research.

In recent years, there has been a tremendous upsurge of interest in various chemical transformations performed under heterogeneous catalysis. Moreover, with using inexpensive and non corrosive heterogeneous catalysts, chemical transformations occur, especially for industrial processes, with higher efficiency and purity of the products, and easier work-up, that create economical and ecological advantages [11]. Among the heterogeneous catalysts, magnetic nanoparticles have attracted much attention due to their unusual magnetic, physical and surface chemical and catalytic properties, high stability and ease of recovery with external magnetic field [12]. Among various magnetic catalysts, Fe₃O₄ nanoparticles have been reported to be an efficient catalyst in a number of chemical transformations [12].

In continuation of our recent work on the heterogeneous catalysts [13], we herein describe an effective and simple procedure for the synthesis of 5-alkylthio or 5-arylthiotetrazoles using magnetically separable Fe₃O₄ nanoparticles as novel heterogeneous catalyst (Eco-friendly, Efficient and Economical) [12c] (Scheme 1). Throughout our search in the literature, no reports were found concerning the synthesis of thiotetrazoles using Fe₃O₄ nanoparticles.



Scheme 1. Synthesis of thiotetrazoles using magnetically separable Fe₃O₄ nanoparticles.

RESULTS AND DISCUSSION

To further understanding of the roles of Fe₃O₄ magnetic nanocatalyst, a comprehensive study of the synthesis of thiotetrazoles was carried out. Initially, to determine the optimum reaction conditions, a reaction between phenylthiocyanate (2.0 mmol) and sodium azide (3.0 mmol) in the presence of Fe₃O₄ magnetic nanocatalyst was carried out in different solvents under thermal conditions at 110 °C for 20 h which 5-phenylthiotetrazole was obtained (Table 1). As proved by control experiments, no reaction occurs in the absence of Fe₃O₄ magnetic nanocatalyst. However, addition of Fe₃O₄ magnetic nanocatalyst to the mixture caused rapid enhancement of the synthesis of thiotetrazoles with high yields. The best result in terms of the reaction yield was obtained when the reaction was conducted in DMF as the solvent of choice at 110 °C with using 0.05 g of Fe₃O₄ magnetic nanocatalyst (Table 1, entry 4). No significant improvement on the yield was observed with using higher amounts of the catalyst (Table 1, entries 7-9).

Table 1. Optimization of conditions in the preparation of 5-phenylthiotetrazole^a

Entry	Fe ₃ O ₄ magnetic nanocatalyst (g)	Solvent	Yield % ^b
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1	0	DMF	0 ^c
2	0.03	DMF	56
3	0.05	DMF	84
4	0.07	DMF	83
5	0.07	H ₂ O	10
6	0.07	DMSO	82
7	0.10	DMF	83
8	0.11	DMF	83
9	0.15	DMF	84
10	0.05	CH ₃ CN	70
11	0.05	Toluene	72
12	0.05	NMP	80

^a Conditions: phenylthiocyanate (2.0 mmol), sodium azide (3.0 mmol), DMF (6.0 mL) at 110 °C for 20 hours.

^b Yield refers to pure isolated product.

^c In the absence of catalyst at 110 °C, no reaction occurred after 30 h.

Then, the catalytic potential of some magnetic nanoparticles with different sizes were investigated for the reaction between phenylthiocyanate and sodium azide at 110 °C (Table 2). As shown in Table 2, the best result was obtained with 0.05 g of Fe₃O₄ at 110 °C which gave product in higher yield.

Table 2. Comparison of some magnetic nanoparticles with different sizes in the preparation of 5-phenylthiotetrazole^a

Entry	Magnetic nanocatalyst (0.05 g)	Solvent	Yield % ^b
1	Fe ₃ O ₄	DMF	84
2	MgFe ₂ O ₄ ^c	DMF	79
3	CuFe ₂ O ₄ ^d	DMF	80
4	CoFe ₂ O ₄ ^e	DMF	82

^a Conditions: phenylthiocyanate (2.0 mmol), catalyst (0.05 g), sodium azide (3.0 mmol), DMF (6.0 mL) at 110 °C for 20 hours.

^b Yield refers to pure isolated product.

^c See reference 14.

^d See reference 15.

^e See reference 16.

Various thiotetrazoles were synthesized from different aromatic and aliphatic thiocyanates with sodium azide in DMF in excellent yields under thermal conditions (Table 3).

Table 3. Synthesis of various thiotetrazoles in the presence of Fe₃O₄ nanoparticles at 110 °C

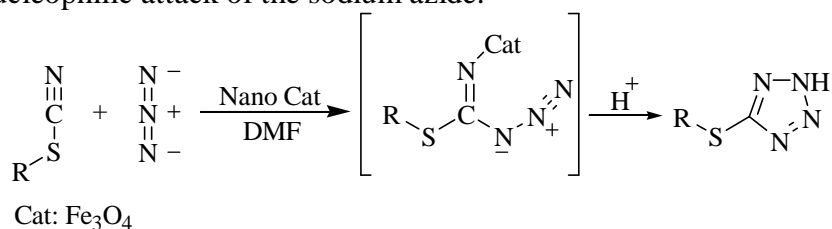
Entry	Substrate	Product	Time (h)	Yield [%] ^a
1			24	90
2			24	88
3			24	92
4			24	91
5			24	88

6			20	94
7			20	94

^aYield refer to the pure isolated product.

^bYield after the third cycle.

The nano Fe₃O₄ probably has an important role in promotion of the synthesis of thiotetrazoles as a Lewis acid and the plausible mechanism is shown in Scheme 2. The catalyst may show complexation towards nitrile group of thiocyanate and thus may enhance the electrophilic character. It involves activation of the nitrile group over surface of the catalyst and subsequent nucleophilic attack of the sodium azide.



Scheme 2. Proposed mechanism for the formation of thiotetrazoles using Fe₃O₄ magnetic nanocatalyst.

Moreover, the recyclability of nano Fe₃O₄ catalyst was examined using the reaction of n-butyl thiocyanate with sodium azide (Table 3, entry 2). It was noticed that, this catalyst could be easily recovered simply by an external magnet and reused for three consecutive fresh runs without pre-activation and with no significant drop in its catalytic activity. The recovered catalyst was purified by washing with ethyl acetate and drying in oven. In each experiment, more than 98% of the catalyst was easily recovered from the reaction mixture (Table 4). The catalyst was separated and reused for subsequent experiments under similar reaction conditions. Yields of the product only slightly decreased after three times of reusing of catalyst.

Table 4. Reusability of nano Fe₃O₄ catalyst.^a

Entry	Yield ^b (%)	Recovery of nano Fe ₃ O ₄ (%)
Refresh	88	99
1	88	99
2	87	99
3	86	98
4	82	94

^aReaction conditions: n-butyl thiocyanate (2.0 mmol), sodium azide (3.0 mmol), catalyst (0.05 g) and DMF (6 mL), 110 °C.

^bYield refers to pure isolated product.

The products were characterized on the basis of their spectral (IR, NMR) and melting points and compared with the literature [8,10]. The structure of the thiotetrazoles was in

agreement with their spectra data. The carbon of the tetrazole ring can be seen at about $\delta = 150\text{-}155$ ppm in the ^{13}C NMR.

CONCLUSION

We were able to do the simple synthesis of 5-alkylthio and 5-arylthiotetrazoles from thiocyanates using Fe_3O_4 nanoparticles as a magnetically recoverable and reusable catalyst in dimethylformamide under thermal conditions in excellent yields without the application of dangerous and harmful hydrazoic acid.

EXPERIMENTAL

Preparation of Fe_3O_4 nanoparticles

The catalyst was prepared according to the literature [12c].

Characterization of Fe_3O_4 nanoparticles

The catalyst was characterized by using powder SEM, SAED and TEM [12c].

General experimental procedure for the preparation of thiotetrazoles

To a mixture of thiocyanates (2.0 mmol) and sodium azide (3.0 mmol) in distilled dimethylformamide (6 mL) was added Fe_3O_4 nanoparticles (0.05 g). Then, the resulting mixture was heated at $110\text{ }^\circ\text{C}$ for the appropriate time (Table 2). Upon completion of the reaction, as monitored by TLC analysis, the mixture was cooled to room temperature, the catalyst was separated through the magnetic absorption by a magnet and the residue was diluted with ethyl acetate (35 mL) and 5 N HCl (20 mL). Organic layer was separated and evaporated under reduced pressure using rotary evaporator to give the crude product. The residue was purified by recrystallization using ethanol. All the products are known compounds and the spectral data and melting points were consistent with those reported in the literature [8,10].

5-(Butylthio)tetrazole (Table 2, entry 2): M.p. $95\text{-}97\text{ }^\circ\text{C}$ (lit. [9] $96.4\text{-}96.8\text{ }^\circ\text{C}$); ^1H NMR ($\text{DMSO-}d_6$, 300 MHz): δ 0.87 (t, $J = 7.8$ Hz, 3H), 1.39 (m, $J = 7.8$ Hz, 2H), 1.8 (m, $J = 7.2$ Hz, 2H), 3.31 (t, $J = 6.8$ Hz, 2H).

5-(Butylthio)tetrazole (Table 2, entry 2): M.p. $95\text{-}97\text{ }^\circ\text{C}$ (lit. [9] $96.4\text{-}96.8\text{ }^\circ\text{C}$); ^1H NMR ($\text{DMSO-}d_6$, 300 MHz): δ 0.87 (t, $J = 7.8$ Hz, 3H), 1.39 (m, $J = 7.8$ Hz, 2H), 1.8 (m, $J = 7.2$ Hz, 2H), 3.31 (t, $J = 6.8$ Hz, 2H).

5-Benzylthiotetrazole (Table 2, entry 5): M.p. $132\text{-}133\text{ }^\circ\text{C}$ (lit. [9] $133.0\text{-}133.1\text{ }^\circ\text{C}$); ^1H NMR ($\text{DMSO-}d_6$, 300 MHz): δ 4.50 (s, 2H), 7.28 (t, $J = 7.3$ Hz, 1H), 7.32 (d, $J = 7.2$ Hz, 2H), 7.40 (d, $J = 7.2$ Hz, 2H).

5-(4'-hydroxy-2'-methyl-5'-isopropylphenylthio)tetrazole (Table 2, entry 7): M.p. $165\text{-}166\text{ }^\circ\text{C}$ (lit. [9] $165.1\text{-}165.6\text{ }^\circ\text{C}$); ^1H NMR ($\text{DMSO-}d_6$, 300 MHz): δ 1.12 (d, $J = 6.9$ Hz, 6H), 2.21 (s, 3H), 3.11 (m, $J = 7.3$ Hz, 1H), 6.80 (s, 1H), 7.31 (s, 1H), 9.86 (s, 1H).

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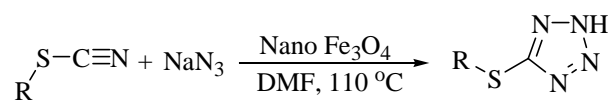
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Synthesis of thiotetrazoles