Received: 15 June 2016 | Revised: 28 July 2016 | Accepted: 7 August 2016

DOI 10.1002/aoc.3602

WILEY Applied Organometallic Chemistry

FULL PAPER

Efficient synthesis of 5-substituted tetrazoles catalysed by palladium–*S*-methylisothiourea complex supported on boehmite nanoparticles

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An efficient and general method is reported for the synthesis of 5-substituted 1*H*-tetrazole derivatives in the presence of *S*-methylisothiourea complex of palladium immobilized on boehmite nanoparticles (Pd-SMTU@boehmite) as an efficient and recyclable nanocatalyst. Boehmite nanoparticles were not sensitive to air or moisture and were prepared without inert atmosphere in water at room temperature. Then a novel type of phosphine-free palladium complex was immobilized on these nanoparticles. This catalyst was characterized using Fourier transform infrared, thermogravimetric, Brunauer–Emmett–Teller, transmission and scanning electron microscopic, energy-dispersive X-ray spectroscopic, X-ray diffraction and inductively coupled plasma optical emission spectroscopic techniques. The catalyst was reused several times without palladium leaching or change in its structure.

KEYWORDS

5-substituted 1*H*-tetrazole, boehmite nanoparticles, organometallic catalyst, palladium, *S*-methylisothiourea

1 | INTRODUCTION

In the last few decades, supporting of homogeneous catalysts on various heterogeneous solids has been studied as a means to realize recyclable catalysts.[1] Many supports such as TiO_2 nanoparticles,[2] MCM-41,[3] SBA-15,[4] iron oxide,[5] carbon nanotubes,[6] heteropolyacids,[7] graphene oxide,[8] ionic liquids,[9] molecular sieves[10] and various polymers[11] have been used as heterogeneous catalysts or as supports for homogeneous catalysts. However, most of them are expensive, require inert atmosphere or high temperature for calcination and involve a lot of time and tedious conditions to prepare. In contrast, the synthesis of boehmite nanoparticles is not moisture or air sensitive, and also can be synthesized in water at room temperature using available materials.[12] Nanoboehmite has several attractive features such as stability, non-toxicity, high dispersion of the active phases, high specific surface area, ease of surface modification, readily and easily available and favourable biocompatibility.[13,14] However, boehmite nanoparticles have rarely been employed as a heterogeneous support.[15] Therefore herein a moisture- and air-stable *S*-methylisothiourea complex of palladium immobilized on boehmite nanoparticles (Pd-SMTU@boehmite) is reported as new organometallic catalyst for the synthesis of tetrazole derivatives.

Tetrazoles are important heterocyclic compounds, having several applications in organic synthesis, material science, coordination chemistry, in organometallic chemistry as effective stabilizers of metallopeptide structures, stable surrogates for carboxylic acids and medicinal chemistry.[16–18] For example, valsartan and losartan are two typical examples of the extensive application of these compounds in drugs.[19] Also, recently tetrazole derivatives were used for binding aryl thiotetrazolylacetanilides with HIV-1 reverse transcriptase.[20] Tetrazoles and their derivatives have been reported as anti-viral, anti-bacterial, anti-inflammatory and herbicidal agents, potential anti-HIV drug candidates and anti-proliferative, analgesic and anti-tumour agents.[21–23] Tetrazoles can be used as isosteric replacements for carboxylic acids in drug design[24] and have found use in information recording systems.[25]

Conventional synthesis of 5-substituted 1*H*-tetrazoles is via [3 + 2] cycloaddition of azides to nitriles. Based on this method, several procedures have been reported. Unfortunately, most of them suffer from some disadvantages such as: the use of organic solvents, harsh reaction conditions, water sensitivity, long reaction time and difficulty in separation and recovery of the catalysts.[26–28] Thus, the synthesis of these heterocycles has become an area of great interest.

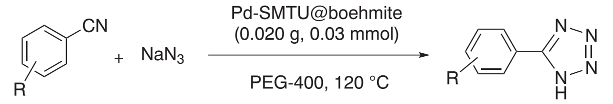
2 | EXPERIMENTAL

2.1 | Preparation of catalyst

The catalyst was prepared via the following procedure. A solution of NaOH (6.490 g) in 50 ml of distilled water was added dropwise to a solution of $Al(NO_3)_3{\cdot}9H_2O$ (20 g) in 30 ml of distilled water under vigorous stirring. The resulting milky mixture was subjected to mixing in an ultrasonic bath for 3 h at 25°C. The resulting nanoboehmite was filtered and washed with distilled water and kept in an oven at 220°C for 4 h. The obtained boehmite nanoparticles (1.5 g) were dispersed in 50 ml of toluene by sonication for 30 min, and then 2.5 ml of (3-chloropropyl)triethoxysilane was added. The reaction mixture was stirred at 40°C for 8 h. Then, the prepared nanoparticles (nPr-Cl-boehmite) were filtered, washed with ethanol and dried at room temperature. The obtained Cl-boehmite (1 g) was dispersed in 50 ml of ethanol for 20 min, and then *S*-methylisothiourea hemisulfate salt (2.5 mmol) and potassium carbonate (2.5 mmol) were added to the reaction mixture and stirred for 18 h at 80°C. The resulting nanoparticles (SMTU@boehmite) were filtered, washed with ethanol and dried at room temperature. Thermogravimetric analysis (TGA) was used to determine the percentage of organic functional groups chemisorbed onto the boehmite nanoparticles. The obtained SMTU@boehmite (0.5 g) was dispersed in 25 ml of ethanol by sonication for 20 min, and then palladium acetate (0.25 g) was added to the reaction mixture. The reaction mixture was stirred at 80°C for 20 h. Then, $NaBH_4$ (0.3 mmol) was added to the reaction mixture and stirred for 2 h. The final product (Pd-SMTU@boehmite) was filtered, washed with ethanol and dried at room temperature. The amount of palladium was determined using energy-dispersive X-ray spectroscopy (EDS) and inductively coupled plasma optical emission spectroscopy (ICP-OES).

2.2 | General procedure for synthesis of 5-substituted 1*H*-tetrazoles

A mixture of nitrile (1 mmol) and sodium azide (1.4 mmol) in the presence of 0.020 g (0.03 mmol) of Pd-SMTU@boehmite was stirred at 120°C in poly(ethylene glycol) (PEG) (Scheme 1). After completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature. The catalyst was removed by simple filtration and HCl (4 N, 10 ml) was added to the filtered solution and the corresponding tetrazole extracted with ethyl acetate (2 × 10 ml). The resulting organic layer was washed with distilled water, dried over anhydrous sodium sulfate and concentrated to afford the crude solid product.



SCHEME 1 Synthesis of 5-substituted 1H-tetrazole derivatives in the presence of Pd-SMTU@boehmite as catalyst.

3 | RESULTS AND DISCUSSION

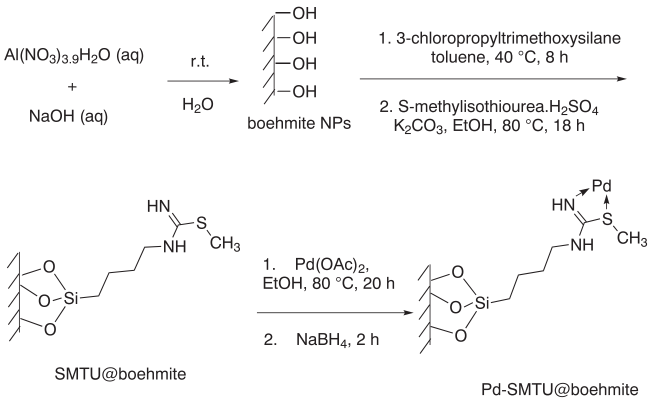
3.1 | Catalyst preparation

Herein report the preparation and characterization of moisture- and air-stable Pd-SMTU@boehmite. Initially, the boehmite nanoparticles were prepared, and subsequently were modified with (3-chloropropyl)triethoxysilane. Then, in order to prepare SMTU@boehmite, *S*-methylisothiourea was grafted on the surface of nPr-Cl@boehmite and finally Pd nanoparticles were immobilized on SMTU@boehmite by a concise route (Scheme 2).

3.2 | Catalyst characterization

Pd-SMTU@boehmite was characterized using Fourier transform infrared (FT-IR) spectroscopy, TGA, Brunauer–Emmett–Teller (BET) measurements, transmission electron microscopy (TEM), scanning electron microscopy (SEM), EDS, X-ray diffraction (XRD) and ICP-OES.

The XRD patterns of nanoboehmite and Pd-SMTU@boehmite are presented in Figure 1. The boehmite phase is identified by the peaks at 2*θ* values of 14.40°, 28.41°, 38.55°, 46.45°, 49.55°, 51.94°, 56.02°, 59.35°,



SCHEME 2 Synthesis of Pd-SMTU@boehmite.

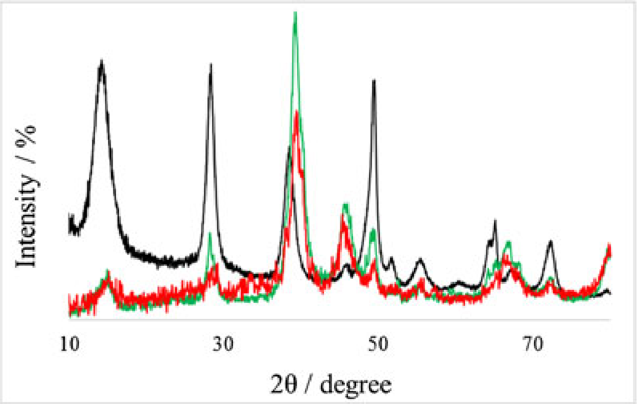


FIGURE 1 XRD patterns of boehmite nanoparticles (black), Pd-SMTU@boehmite (green) and recovered Pd-SMTU@boehmite (red).

65.04°, 65.56°, 68.09° and 72.38° in the XRD patterns.[12,13] Also, the recovered catalyst was investigated using XRD (Figure 1, red curve). This indicates that the catalyst can be recycled without any change in its structure.

The sizes of boehmite nanoparticles and catalyst were confirmed using SEM and TEM (Figure 2a–c) techniques. TEM and SEM images reveal most of the particles are prepared at the nanoscale with an average diameter of about 5–15 nm.

In order to show the presence of Pd metal in Pd-SMTU@boehmite, EDS (Figure 2d) and ICP-OES analyses were conducted. The EDS spectrum of Pd-SMTU@boehmite shows the presence of Al, O, Si, C, N, S and Pd species in this catalyst. In order to determine the exact amount of Pd, ICP-OES was applied. According to the ICP-OES results, the exact amount of Pd in this catalyst is 1.64 mmol g^{-1}.

The nitrogen adsorption–desorption isotherms were obtained at 120°C (Figure 3I), from which the pore volume and average pore diameter of Pd-SMTU@boehmite (0.19 cm^3 g^{-1} and 1.64 nm) are lower than those of nanoboehmite (0.22 cm^3 g^{-1} and 1.21 nm). Also, when the Pd complex is grafted on boehmite nanoparticles, the BET specific surface area decreases from 122.8 to 82.90 m^2 g^{-1}. The decrease in average pore diameter, surface area and pore volume of the modified boehmite nanoparticles is related to the grafting of organic layers and Pd complex on the surface of nanoboehmite.

Successful functionalization of the boehmite nanoparticles can be confirmed from FT-IR spectra (Figure 3II). In Figure 3(IIa), two bands at 3086 and 3308 cm^{-1} are indicative of the OH surface[13] and several peaks at 480, 605 and 735 cm^{-1} can be attributed to Al—O bonds.[15] Also, the vibrations of hydrogen bonds appear at 1164 and 1069 cm^{-1}.[13] In Figure 3(IIb), the anchored (3-chloropropyl)triethoxysilane is confirmed by C—H and O—Si stretching vibrations that appear at 2955 and 1073 cm^{-1}, respectively.[3,5] In Figure 3(IIc), the existence of the grafted *S*-methylisothiourea is characterized by C═N vibrations that appear at 1638 cm^{-1}, this band being shifted to lower frequency (1631 cm^{-1}) in the spectrum of the catalyst (Figure 3IId), which indicates the formation of Pd complex on surface of boehmite nanoparticles.[29]

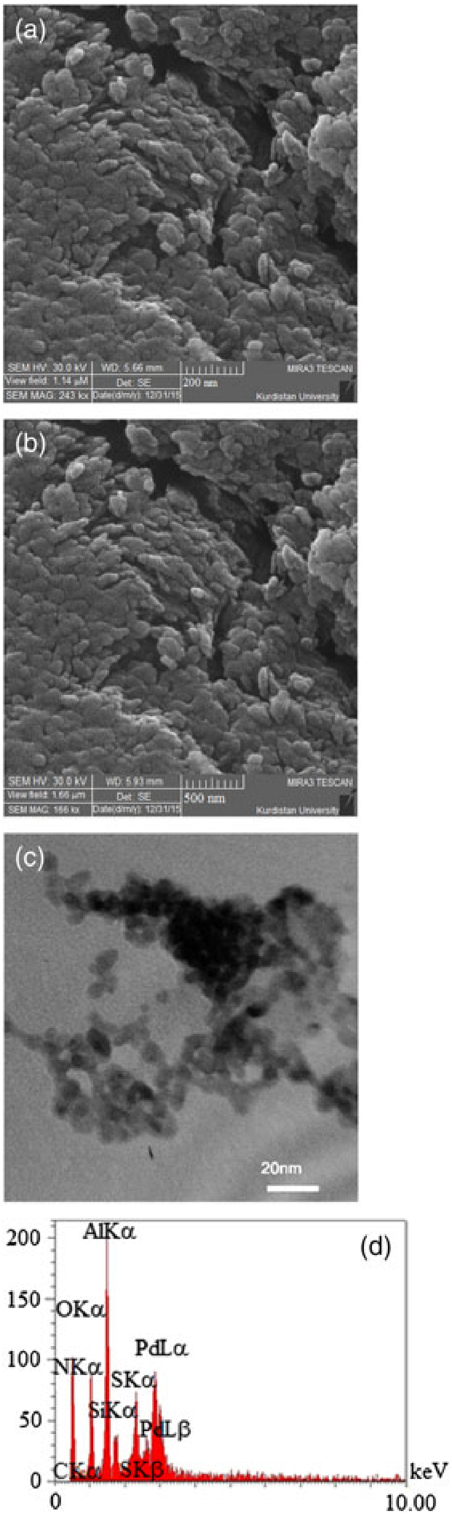


FIGURE 2 SEM images of (a) boehmite nanoparticles and (b) Pd-SMTU@boehmite. (c) TEM image of Pd-SMTU@boehmite. (d) EDS spectrum of Pd-SMTU@boehmite.

Also the FT-IR spectrum of recovered Pd-SMTU@boehmite (Fig. 3IIe) indicates that this catalyst is stable after recovery and can be reused without any change in its structure.

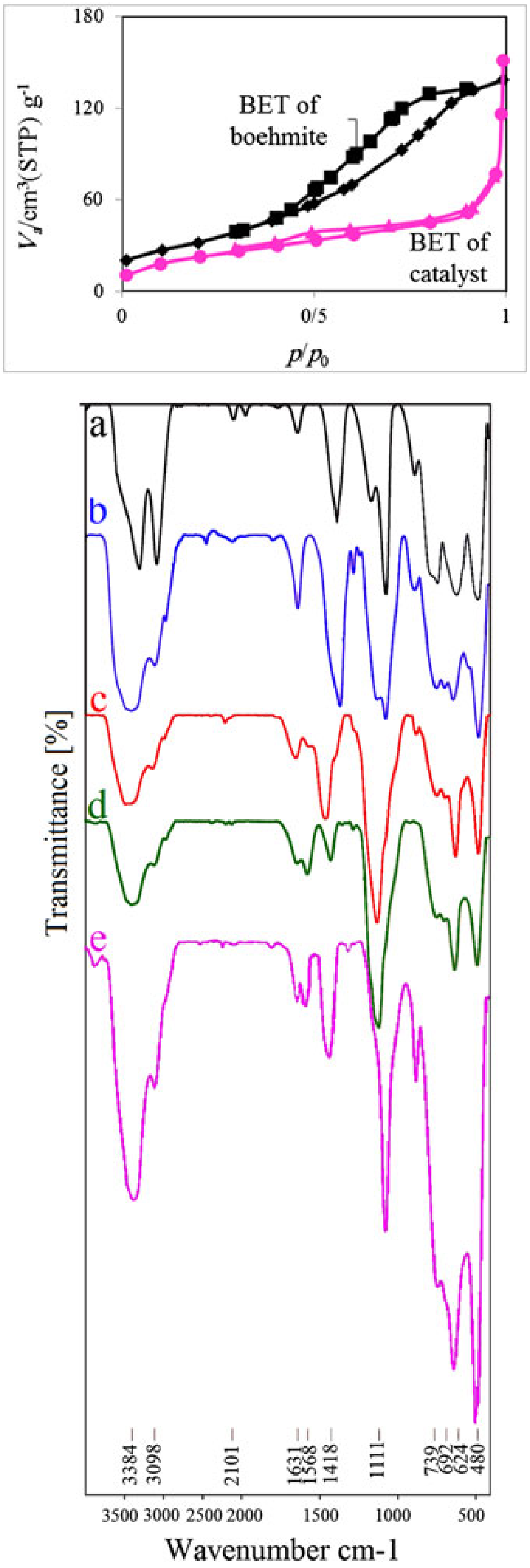


FIGURE 3 (I) Nitrogen adsorption–desorption isotherms of boehmite nanoparticles and Pd-SMTU@boehmite. (II) FT-IR spectra of (a) boehmite, (b) nPr-Cl@boehmite, (c) SMTU@boehmite, (d) Pd-SMTU@boehmite and (e) recovered Pd-SMTU@boehmite.

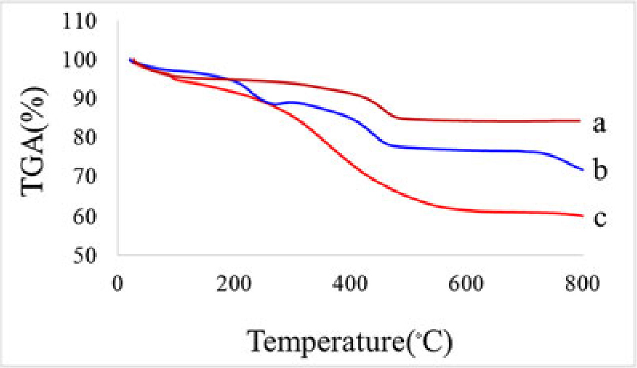


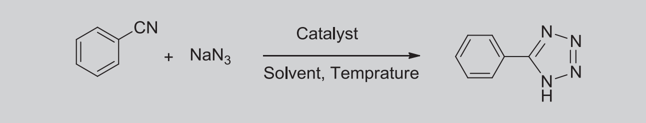
FIGURE 4 TGA curves of (a) boehmite, (b) SMTU@boehmite and (c) Pd-SMTU@boehmite.

TGA was used to determine the amount of functional groups chemisorbed onto the surface of boehmite nanoparticles (Fig. 4). The TGA curves of the samples show a small weight loss below 200°C due to desorption of physically adsorbed solvents and surface hydroxyl groups.[5] In the TGA curve of the boehmite nanoparticles, a weight loss of about of 16% from 25 to 200°C is observed. Meanwhile, weight losses of about 29 and 40% from 200 to 800°C are observed for SMTU@boehmite and Pd-SMTU@boehmite, respectively. These results indicate that organic layers and Pd complex have been grafted on the surface of boehmite nanoparticles.

3.3 | Catalytic study

We examined the application of Pd-SMTU@boehmite as an efficient, stable, reusable and commercially available catalyst for the synthesis of tetrazole derivatives. In order to optimize the reaction conditions, the reaction of benzonitrile and sodium azide (NaN_3) was selected as a model reaction. The effects of various parameters such as temperature, solvent

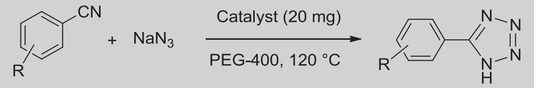
TABLE 1 Optimization of reaction conditions for synthesis of 5-substituted 1*H*-tetrazole derivatives



Entry	Catalyst (mg)	Solvent	NaN_3 (mmol)	Temperature (°C)	Time (min)	Yield (%)[a]
1	15	PEG	1.2	120	240	38
2	15	PEG	1.3	120	240	45
3	15	PEG	1.4	120	240	69
4	15	PEG	1.5	120	180	73
5	10	PEG	1.4	120	180	62
6	17	PEG	1.4	120	180	77
7	20	PEG	1.4	120	150	95
8	20	DMSO	1.4	120	150	77
9	20	DMF	1.4	120	150	83
10	20	EtOH	1.4	Reflux	150	Trace
11	20	PEG	1.4	100	150	64
12	20	PEG	1.4	120	150	39

[a] Isolated yield.

TABLE 2 Synthesis of 5-substituted 1*H*-tetrazole derivatives in presence of Pd-SMTU@boehmite



Entry	Nitrile	Time (h)	Yield (%)[a]	M.p. (°C)	Ref.
1	Benzonitrile	2.5	95	213–214	[17]
2	4-Nitrobenzonitrile	20	95	219–221	[17]
3	4-Acetylbenzonitrile	48	90	177–179	[31]
4	4-Bromobenzonitrile	8	89	265–268	[18]
5	3-Chlorobenzonitrile	4.5	91	128–130	[31]
6	2-Chlorobenzonitrile	4	89	181–182	[30]
7	2-Hydroxybenzonitrile	0.5	89	221–224	[31]
8	Terephthalonitrile	1.75	87	251–254	[16]
9	3-Nitrobenzonitrile	8	92	149–150	[31]
10	4-Methoxybenzonitrile	20	94	229–232	[16]

[a] Isolated yield.

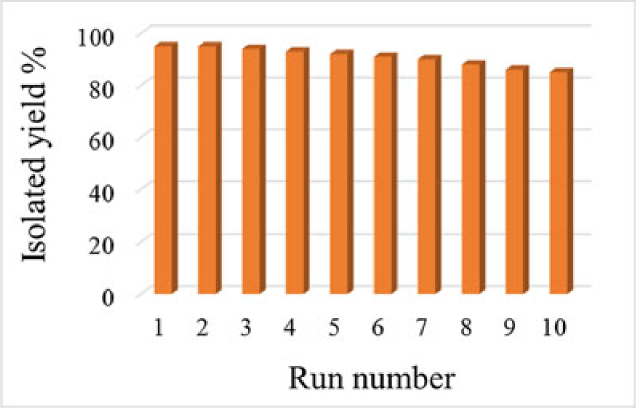


FIGURE 5 Recyclability of Pd-SMTU@boehmite in the synthesis of 2-(1H-tetrazol-5-yl)phenol.

(PEG-400, dimethylsulfoxide (DMSO), dimethylformamide (DMF) and ethanol), amount of catalyst and amount of NaN_3 were considered in the model reaction (Table 1). As evident from Table 1, 0.02 g of Pd-SMTU@boehmite in PEG-400 at 120°C using 1.4 mmol of NaN_3 are found to be ideal reaction conditions for the synthesis of 5-substituted 1*H*-tetrazole derivatives.

After optimization of the reaction condition, the catalytic activity of Pd-SMTU@boehmite in the reaction of various benzonitriles including different functional groups was examined under optimized conditions (Table 2). As variety of benzonitriles bearing electron-donating and electron-withdrawing substituents were successfully employed and the corresponding 5-substituted 1*H*-tetrazole derivatives are obtained in good to excellent yields.

3.4 | Reusability of catalyst

The recyclability of the Pd-SMTU@boehmite catalyst was examined in the synthesis of 2-(1*H*-tetrazol-5-yl)phenol (Fig. 5). After the completion of the reaction, the catalyst was recovered by filtration and washed with ethyl acetate. Then, the reaction vessel was charged with fresh substrates and subjected to the next run. As shown, the Pd-SMTU@boehmite could be reused over 10 runs without any significant loss of its activity or palladium leaching, which clearly demonstrates the practical recyclability of this catalyst.

Metal leaching of the catalyst was studied using hot filtration test and ICP analysis. Based on the results from ICP-OES analysis, the amount of palladium in fresh catalyst and recovered catalyst after five runs is 1.64 and 1.62 mmol g^{-1}, respectively, which indicates that Pd leaching from the catalyst is very low. In order to examine the leaching of Pd in the reaction mixture and heterogeneity of this catalyst, we performed hot filtration in the reaction of 2-chlorobenzonitrile and NaN_3. In this study we found the yield of product in half the time of the reaction was 52%. Then the reaction was repeated and in half the time of the reaction, the catalyst was separated and the filtrate allowed to react further. The yield of the reaction in this stage was 53%, confirming that leaching of Pd does not occur.

3.5 | Comparison of catalyst

In order to show the efficiency of described catalytic system, the results obtained for the model compounds in this project were compared with previously reported procedures. Comparison of the results shows a better catalytic activity of Pd-SMTU@boehmite in the synthesis of 5-substituted 1*H*-tetrazoles (Table 3). Also, a comparison

TABLE 3 Comparison of results for Pd-SMTU@boehmite with other catalysts for synthesis of 5-phenyl-1*H*-tetrazole

Entry	Catalyst	Condition	Time (h)	Yield (%)[a]	TOF (h^{-1})	Ref.
1	Fe_3O_4@SiO_2/Salen Cu(II)	DMF, 120°C	7	90	—	[16]
2	$(NH_4)Ce(NO_3)_6$	DMF, 110°C	6	97	1.61	[19]
3	$AgNO_3$	DMF, 120°C	5	83	1.66	[30]
4	$Cu(OAc)_2$	DMF, 120°C	12	98	0.32	[31]
5	$FeCl_3$–SiO_2	DMF, 120°C	12	79	—	[32]
6	CAN-supported HY-zeolite	DMF, 110°C	4	93	0.77	[33]
7	Ammonium chloride and ammonium fluoride	DPOL/H_2O (6/4), 160°C	48	95	0.10	[34]
8	Pd-SMTU@boehmite	PEG, 120°C	2.5	95	12.66	This work

[a] Isolated yield.

of activity based on turnover frequency (TOF) shows excellent results for Pd-SMTU@boehmite in the synthesis of 5-substituted 1*H*-tetrazoles. As evident from Table 3, Pd-SMTU@boehmite shows a high TOF number in comparison with other catalysts. This result indicates that Pd-SMTU@boehmite is more effective and more efficient compared to other catalysts. This new catalyst is comparable in terms of price, non-toxicity, catalyst recycling, stability and ease of separation.

4 | CONCLUSIONS

In summary, a novel type of recoverable nanocatalyst was prepared via grafting of palladium on boehmite nanoparticles. This catalyst showed excellent catalytic activity, high reusability and stability to air and moisture for the synthesis of 5-substituted 1*H*-tetrazole derivatives in PEG-400. The advantages of this protocol are the use of eco-friendly, commercially available, chemically stable materials, operational simplicity and good to high yields, and, more importantly, the catalyst can be synthesized from inexpensive and commercially available starting materials. The catalyst can be reused ten times without Pd leaching or any significant loss of its activity or change in its structure.

ACKNOWLEDGMENTS

This work was supported by the research facilities of Ilam University, Ilam, Iran.

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