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Facile synthesis of 5-substituted-1*H*-tetrazoles catalyzed by reusable nickel zirconium phosphate nanocatalyst

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ABSTRACT

5-Substituted-1*H*-tetrazoles were synthesized by the [3 + 2] cycloaddition of sodium azide with various nitriles in the presence of nickel zirconium phosphate (NiZrP) as an effective heterogeneous catalyst in dimethylsulfoxide at 120°C. This method has the advantages of good to high yields, simple methodology and easy work-up. The catalyst can be recovered by centrifuging and reused with good yields. There is no appreciable loss of catalytic activity up to five cycles. All aromatic nitriles with electron-donating group could be accomplished as well as that with electron-withdrawing groups. The structural characteristics of the catalyst are identified by scanning electron microscopy (SEM) and XRD instruments.

Keywords: *Heterogeneous catalyst, Nickel zirconium phosphate, Cycloaddition, Reusable, 5-Substituted-1H-tetrazoles.*

1. Introduction

Tetrazoles have attracted considerable interest in recent years because of their wide range of applications. In particular, they have shown strong activities in biomedical applications [1-3]. These nitrogen-rich rings have also been applied in coordination chemistry as ligands [4,5], and a metabolically stable surrogate for carboxylic acid functionalities [6]. In addition, tetrazoles have successfully served as valuable synthetic intermediates in making a variety of nitrogen containing heterocyclic compounds like imidoyl azides [7], thiazoles, oxazolidones, and triazoles [8,9]. Also, they have been studied as lipophilic spacers [10], and catalysts in asymmetric synthesis [11].

The most convenient method for the preparation of 5-substituted-1*H*-tetrazoles, which was first reported by Hantzsch and Vagt in 1901, typically involves the [3+2] cycloaddition of an azide and a nitrile in suitable solvent or solvent free conditions in the presence of a catalyst [12]. This method suffers from drawbacks such as long reaction times, high temperatures, the use of strong Lewis acids, or expensive and toxic metals, and the *in situ* generated hydrazoic acid, which is highly volatile, toxic and explosive [13,14].

In 2001, Sharpless and co-workers reported an innovative, safe, convenient, and environmentally friendly procedure for the preparation of 5-substituted-1*H*-tetrazoles in aqueous solution with zinc salts as catalysts in water or a water/isopropanol mixture [15]. The different homogeneous and heterogeneous catalyst systems have been expanded to generate 5-substituted-1*H*-tetrazoles including $ZrOCl_2$ [16], $BF_3.OEt_2$ [17], $Pd(OAc)_2/ZnBr_2$ [18], ZnO [19], Zn/Al hydrotalcite [20], $Zn(OTf)_2$ [21], mesoporous ZnS nanospheres [22], natural natrolite zeolite [23], $FeCl_3{\cdot}SiO_2$ [24], I_2 [25], $(CH_3)_2SnO$ [14], TBAF [26], copper triflates [27], nano $NiFe_2O_4$ [28], and COY zeolites [29]. Among them, heterogeneous nano-catalysts have many advantages such as higher surface area, easy-to-access active sites and the ease in separation from the product compared to homogeneous catalysts.

Our continued effort to explore and develop synthetic protocols involving reusable heterogeneous catalysts, we report herein the successful synthesis of 5-substituted-1*H*-tetrazoles using the nickel zirconium phosphate nano particles in high yields. The structure and morphology of the catalyst was established on the

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basis of powder X-ray diffraction (XRD), and scanning electron microscopy (SEM).

2. Experimental

All melting points were determined on a Gallenkamp apparatus and were uncorrected. The FT-IR adsorption spectra were run on a spectrophotometer (Nicolet 800) as KBr disks. Vibrational transition frequencies were reported in wave number (cm^{-1}). ^1H and $^{13}CNMR$ spectra were recorded on a Bruker (Avance DRX-500) spectrometer at 500, 400 and 125 MHz, respectively. Chemical shifts (δ) are given in ppm from tetramethylsilane as an internal standard, and the spectra were recorded in DMSO-d_6 as solvent at room temperature. X-ray diffraction (XRD) patterns of the catalyst were recorded with a PW 3710 Philips X-ray diffractometer at room temperature using monochromatic Cu Kα radiation with wavelength of $\lambda = 0.15418$ nm. The peak position and intensity were obtained between 0° and 50° with a rate of $0.04°s^{-1}$. The morphology of the catalyst was observed using a TSCAN scanning electron microscope (SEM). All reagents and solvents used in this study are commercially available and were purchased from commercial suppliers (Acros, Merck and Aldrich) and used without further purification.

2.1. Synthesis of α-zirconium phosphate, $Zr(HPO_4)_2\cdot H_2O$ (referred to as α-ZrP)

A sample of 5 g $ZrOCl_2\cdot 8H_2O$ was refluxed with 50 mL 12.0 M H_3PO_4 for 24 h. After cooling, the obtained precipitate was filtered off and washed with 0.1 M H_3PO_4 until the filtrate was free of chloride ion. Then, the solid was washed with distilled water several times until the pH of the filtrate was neutral and dried in an oven at 110 °C for 24 h [30,31].

2.2 *Synthesis of nickel zirconium phosphate nanoparticles, $NiZr(PO_4)_2$ (referred to as NiZrP NPs)*

The suspension of zirconium phosphate (3 g) in deionized water (50 mL) at 50°C was treated with a solution of $Ni(OAc)_2$ (100 mL, 0.1 mol/L). This mixture was refluxed for 4 d. The resulting slurry was cooled and filtered to give a light green solid, which was washed with distilled water several times. The solid product was then dried at 100°C for 24 h [31].

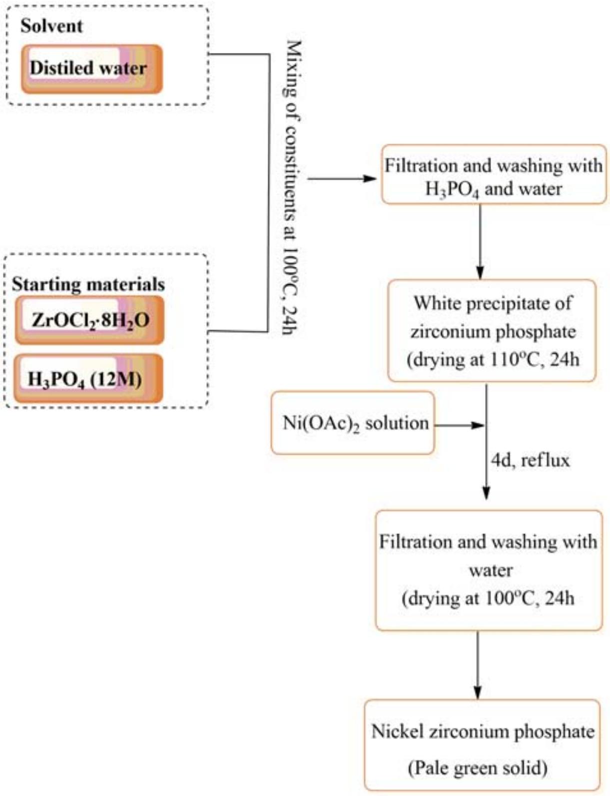
2.3 *General procedure for the preparation of 5-substituted 1H-tetrazole*

A mixture of nitrile (1 mmol), sodium azide (2 mmol), ammonium acetate (1 mmol), nickel zirconium phosphate nanoparticles (0.017 g, 5mol%) and DMSO (1 mL) was taken in a round-bottomed flask and stirred at 120°C under air atmosphere. After completion of the reaction, as indicated by TLC (EtOAc:*n*-hexane, 75:25), the reaction mixture was treated with ethyl acetate (10 mL), the catalyst was filtered, and the filtrate was washed with distilled water. The organic layer was treated with HCl (10 mL, 5N) and stirred vigorously. The resultant organic layer was separated, and the aqueous layer was again extracted with ethyl acetate (10 mL). The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure using a rotary evaporator to give the crude solid crystalline 5-substituted-1*H*-tetrazole. The crude solid product was chromatographed on silica gel (EtOAc:*n*-hexane, 75:25) to afford the pure product. The products were characterized by comparing their m.p., IR, ^1H and $^{13}CNMR$ spectra with those found in the literature [26,29,32-36].

3. Results and Discussion

The nickel zirconium phosphate nanoparticles were prepared through an ion exchange reaction (scheme 1) [31].

Scanning electron microscopy (FE-SEM) was used for the characterization of fabricated nanostructures. The FE-SEM images of ZP (Fig. 1 (a, b)) showed that the product is composed of agglomerated nanosheets. Fig. 1 (c, d) reveals that the synthesized NiZrP is composed of nanostructures and has no special shape. The mean particles size of ZP and NiZrP are 205 and 281 nm, respectively. In Fig. 2, particles size distribution is discernible.



Scheme 1. Schematic representation of the synthesis of nickel zirconium phosphate catalyst.

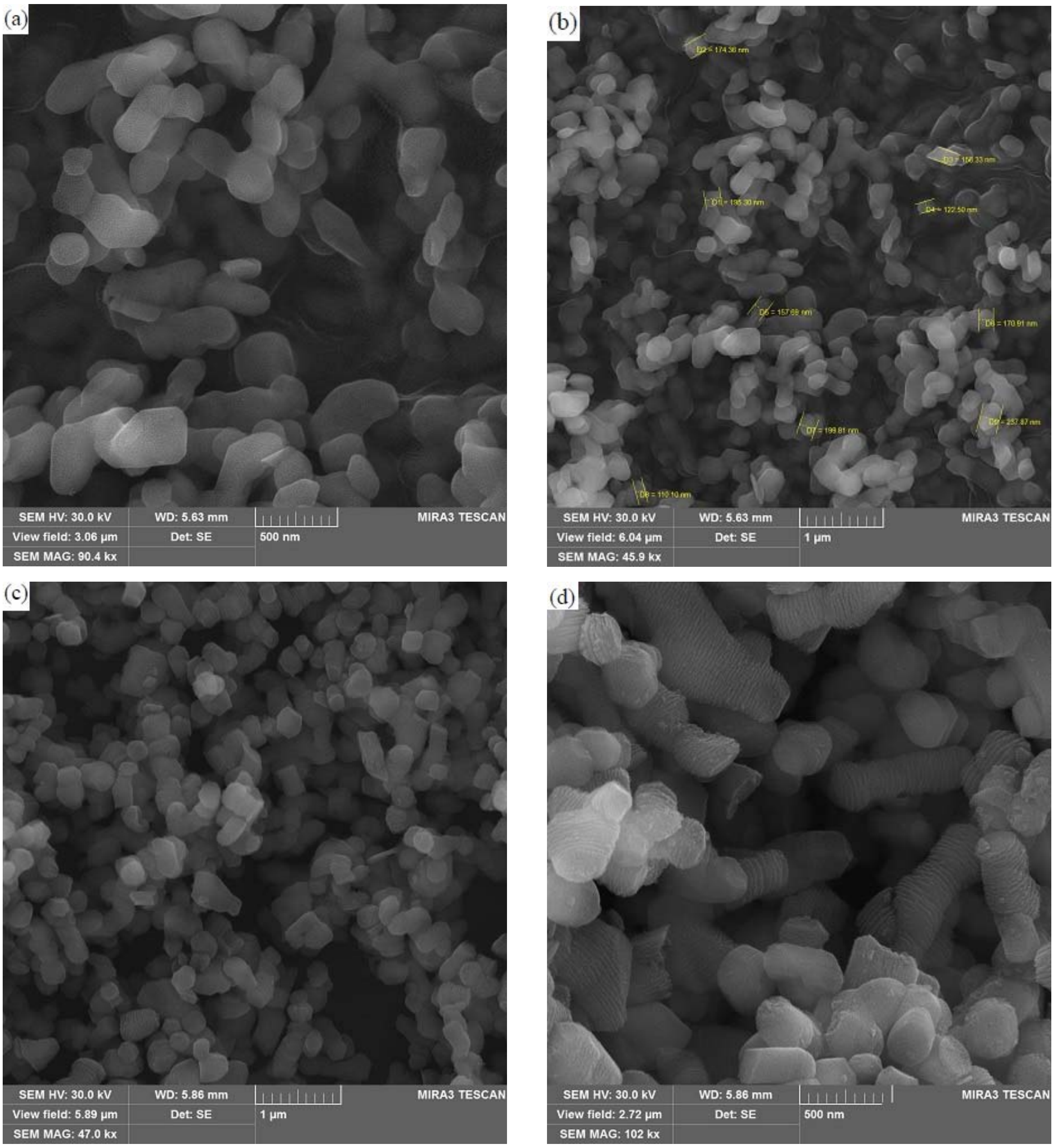


Fig. 1. SEM images of ZrP (a, b) and NiZrP (c, d).

Fig. 3 shows the powder XRD patterns of the ZrP (a) and NiZrP (b) materials. The results show some characteristic reflections in the 2θ range of 0°–40°. All of the characteristic peaks of zirconium phosphate are present in the diffraction pattern that was previously reported [37]. The characterization of nickel zirconium phosphate was shown the XRD pattern of formerly synthesized catalyst [31].

After confirming the characteristics of the catalyst, the catalytic activity of these nanoparticles was examined in the synthesis of 5-substituted-1*H*-tetrazoles of various cyanides. To optimize the reaction conditions, 4-chlorobenzonitrile and sodium azide were used as test substrates to yield 5-(4-chlorophenyl)-1*H*-tetrazole and the results are summarized in Table 1. The influence of experimental parameters such as solvent, temperature, and amount of catalyst were investigated. The reaction was carried out in toluene, tetrahydrofuran (THF), H_2O, dimethylsulfoxide (DMSO), *N,N'*-dimethylformamide (DMF) and isopropanol/H_2O as solvent (Table 1, entries 1-6).

When the reaction was performed in DMSO, the progress of the reaction was higher in comparison with other solvents. In order to improve the efficiency of the reaction, the effect of temperature was studied by carrying out the model reaction at different

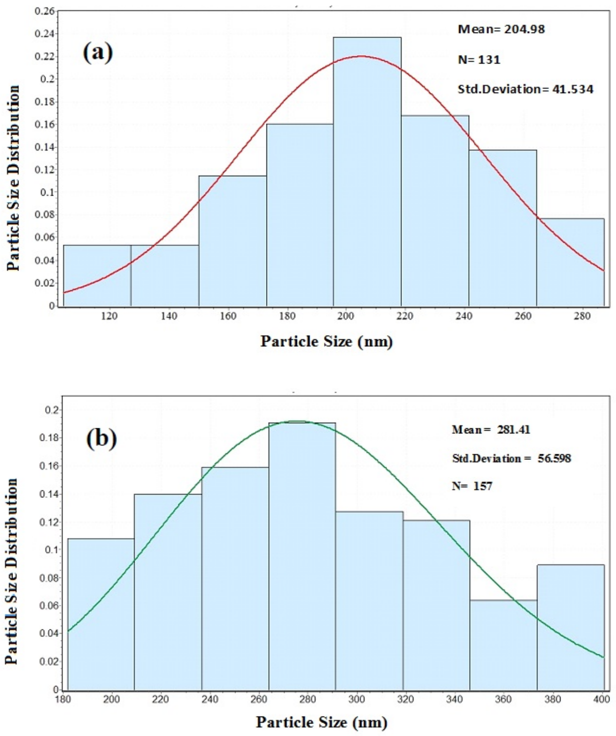


Fig. 2 Particle size distributions of (a) ZrP and (b) NiZrP.

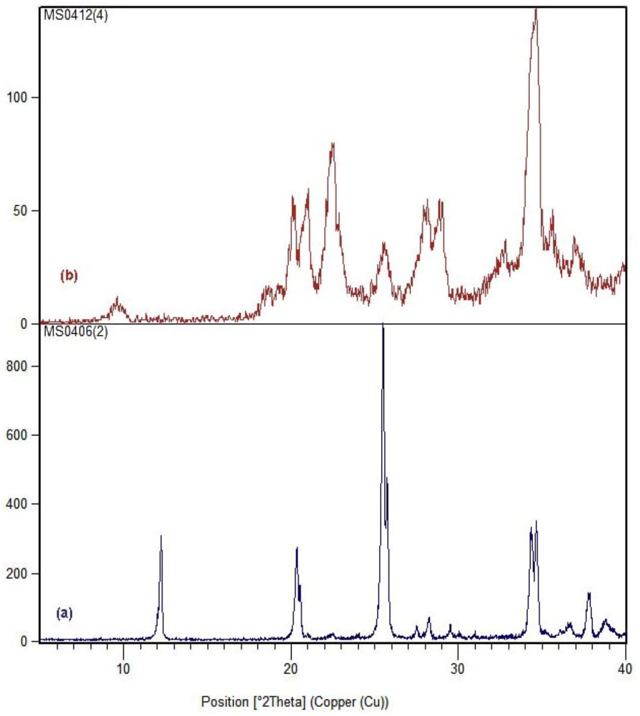


Fig. 3. XRD patterns of (a) ZrP and (b) NiZrP based on the refluxing method.

Table 1. Optimization of reaction conditions for the synthesis of 5-(4-chlorophenyl)-1*H*-tetrazole.[a]

Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)
1	Toluene	5	reflux	1	40
2	THF	5	reflux	1	50
3	DMSO	5	120	1	94
4	DMF	5	120	1	90
5	H_2O	5	reflux	1	70
6	Isopropanol/ H_2O	5	reflux	1	50
7[c]	DMSO	5	120	1	50
8	DMSO	5	RT	1	-
9	DMSO	5	50	1	30
10	DMSO	5	80	1	65
11	DMSO	5	100	1	80
12	DMSO	-	120	24	0
13	DMSO	2	120	1	70
14	DMSO	10	120	1	94
15[d]	DMSO	5	120	10	89

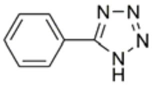
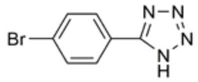
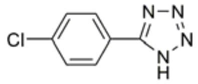
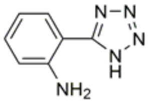
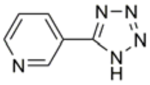
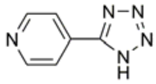
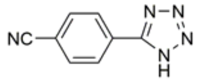
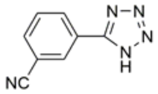
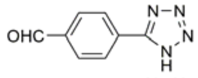
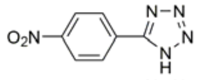
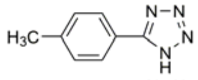
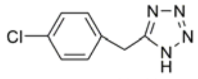
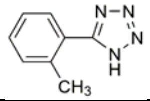
[a] Reactions conditions: 4-chlorobenzonitrile (1 mmol), NaN_3 (1.3 mmol), ammonium acetate (1 mmol), Solvent (1 mL).
[b] Yield of isolated product.
[c] In the absence of ammonium acetate.
[d] In the presence of ZP as a catalyst.

temperatures (room temperature, 50°C, 80°C, 100°C and 120°C) and the best results were obtained at 120°C (Table 1, entries 3, 8-11).

Then, in order to evaluate the optimum amount of catalyst for synthesis of 5-substituted-1*H*-tetrazoles, the reaction was accomplished in the presence of varying amounts of the catalyst under the obtained optimized reaction conditions and the results are presented in Table 1. The best result was achieved by carrying out the reaction with 5mol% of the catalyst (Table 1, entry 3). The results show clearly that the catalyst is effective for this transformation and in the absence of it; the reaction did not take place even after higher reaction times (Table 1, entry 12). Use of a higher amount of catalyst did not improve the yield (Table 1, entry14) while a decrease in the amount of catalyst decreases the yield (Table 1, entries 13).

The reaction was also carried out in the presence of ZrP as a catalyst. It took a longer time (10h) giving an 89% isolated yield (Table 1, entry 15). With these optimized reaction conditions in hand, the generality of this catalytic system for the synthesis of 5-substituted-1*H*-tetrazoles of various cyanides were examined. As shown in Table 2, under similar conditions a wide range of nitrile compounds with different functional groups gave the desired products in good to high yields. Nitrile compounds carrying electron-donating groups provided high yields of the desired products (Table 2, entry 11).

Table 2. Synthesis of 5-substituted-1*H*-tetrazoles catalyzed by NiZrP NPs.[a]

Entry	R	Product	Time (min)	Yield (%)[b]
1	C_6H_5-		60	94
2	*p*-BrC_6H_4-		70	99
3	*p*-ClC_6H_4-		60	98
4	*o*-$NH_2C_6H_4$-		60	79
5	3-pyridinyl-		30	85
6	4-pyridinyl-		25	90
7[c]	*p*-CNC_6H_4-		30	96
8[c]	*m*-CNC_6H_4-		40	87
9	*p*-$CHOC_6H_4$-		35	86
10	*p*-$NO_2C_6H_4$-		20	95
11	*p*-$CH_3C_6H_4$-		110	81
12	*p*-$ClC_6H_5CH_2$-		300	65
13	*o*-$CH_3C_6H_4$-		240	75

[a]Reactions conditions: nitrile (1 mmol), sodium azide (1.3 mmol), ammonium acetate (1 mmol), catalyst (5 mol%), DMSO (1 mL) at 120°C.
[b]Yield of isolated product.
[c]Reaction carried with 2.6 mmol of NaN_3.

It is noticeable that nitriles bearing electron withdrawing groups provided the corresponding products in shorter reaction times and comparatively higher reaction yields (Table 2, entries 2, 3, 7-10). The effect of steric hindrance was examined by the reaction of 2-methylbenzonitrile and the result showed an increase in reaction time and a decrease in the yield (Table 2, entry 13) with increase in steric crowding. The reactions of dicyanobenzene afforded mono addition products when the number of equivalents of sodium azide was doubled (Table 2, entries 7, 8).

The efficiency of this catalyst was determined by comparison with other heterogeneous catalytic systems and it gave a better yield in shorter time (Table 3).

Due to the environmental concerns, their costs and toxicities, recycling of the catalyst is of high importance. In order to recover the catalyst nanoparticles, after completion of the reaction of benzonitrile with sodium azide, the catalyst was separated from the reaction mixture through centrifuging the reaction mixture. The collected catalyst was washed with 5 mL of ethanol followed by doubly distilled water several times, and dried in an oven at 100°C for 2-3 h. The recovered catalyst can be reused over five consecutive runs. The yields of these five consecutive runs were 94, 91, 85, 79 and 73 % respectively.

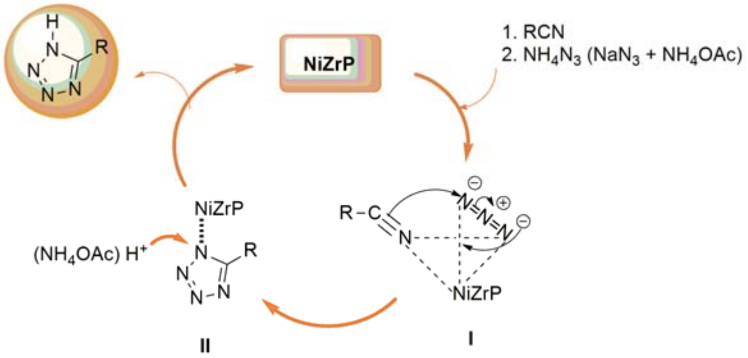
To prove the homogeneity of the catalyst, the reaction of benzonitrile with sodium azide was carried out in optimum conditions. After completion of the reaction, the catalyst was removed by filtration and the reaction solution was analyzed by ICP. The absence of nickel and zirconium in solution confirmed the heterogeneity of the catalyst.

A plausible reaction pathway for the formation of 5-substituted 1*H*-tetrazol by NiZrP nanoparticles as the catalyst is shown in Scheme 2. In the first step, the nitrogen atoms of nitrile and azide compounds are coordinated to Ni^{II} to form complex **I,** which can accelerate the cyclization step. To support this idea, the reaction was conducted in the absence of a catalyst. The result showed that the presence of the catalyst is essential for the completion of the reaction (Table 1, entry 12). Intermediate II is formed through a [3+2] cycloaddition reaction between the C≡N bond of nitrile compound and azide ion.

Protonolysis of the intermediate II could be done using H^+ of NH_4OAc or acidic extraction with HCl resulting in the formation of 5-substituted-1*H*-tetrazole over NiZrP catalyst.

Table 3. Comparison between NiZrP and some other catalysts for the synthesis of 5-phenyl-1*H*-tetrazole from the reaction of benzonitrile with sodium azide.

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]	Ref.
1	CoY Zeolite	DMF	120	14	90	[29]
2	Zn/Al hydrotalcite	DMF	120	12	84	[20]
3	Nano ZnO	DMF	120	14	72	[19]
4	Nickel zirconium phosphte	DMSO	120	1.2	94	This work
5	Sulfated zirconia	DMF	120	24	90	[32]
6	Mesoporous ZnS nanospheres	DMF	120	36	96	[22]
7	Graphene	DMF	120	36	63	[38]
8	$FeCl_3 \cdot SiO_2$	DMF	120	12	79	[24]



Scheme 2. A plausible mechanism for the formation of tetrazoles.

Ammonium acetate may produce ammonium azide *in situ* by reaction of ammonium acetate and sodium azide making availability of azide ion for [3+2] cycloaddition with nitrile easily and also ammonium acetate is used as the proton source to provide the desired tetrazoles [39,40].

4. Conclusions

A simple and efficient method for the synthesis of 5-substituted-1*H*-tetrazoles *via* the [3+2] cycloaddition reaction of nitriles with sodium azide in the presence of 5 mol % of nickel zirconium phosphate as a reusable catalyst was developed. The reaction with good to high yields and relatively short reaction time are the attractive advantages of this method. This methodology may find widespread use in organic synthesis for the preparation of 5-substituted-1*H*-tetrazoles.

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