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Phosphomolybdic Acid ($\text{H}_3\text{Mo}_{12}\text{O}_{40}\text{P}$) as a Reusable Heterogeneous Catalyst for the Synthesis of 5-Substituted 1H-Tetrazoles via [2 + 3] Cycloaddition of Nitriles and Sodium Azide

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PHOSPHOMOLYBDIC ACID ($\text{H}_3\text{Mo}_{12}\text{O}_{40}\text{P}$) AS A REUSABLE HETEROGENEOUS CATALYST FOR THE SYNTHESIS OF 5-SUBSTITUTED 1H-TETRAZOLES VIA [2 + 3] CYCLOADDITION OF NITRILES AND SODIUM AZIDE

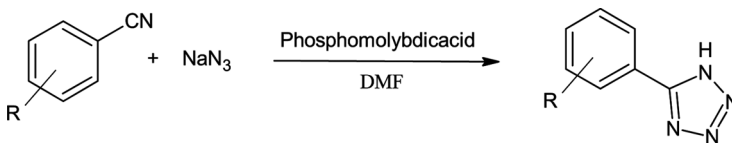
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GRAPHICAL ABSTRACT



Abstract An efficient and practical protocol for the preparation of 5-substituted 1H-tetrazole derivatives is reported using phosphomolybdic acid as an effective heterogeneous catalyst. Good yields, simple methodology, and easy workup make this protocol more attractive for the diversity-oriented synthesis of these heterocycle libraries. The catalyst can be recycled three times with good yields.

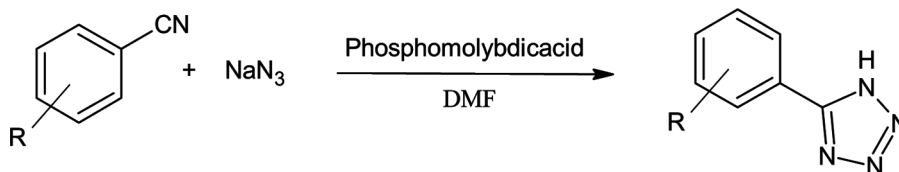
Keywords [2 + 3] Cycloaddition; heteropoly acid; nitriles; sodium azide; tetrazoles

INTRODUCTION

Tetrazoles, a group of heterocyclic compounds, have various advantages and play profound roles in coordination chemistry, medicinal chemistry, material chemistry, explosives, rocket propellants, and agriculture.^[1–8] Besides this tetrazoles are also being used in syntheses of diverse drug intermediates.^[6] In the literature a number of methods are cited to produce tetrazoles; the most convenient methods are addition of azide ions to either organic nitrites or cyanamides,^[9–12] and addition of sodium azide to nitriles with stoichiometric amount of Zn(II) salts.^[13–15] Though these are the convenient methods,^[16–23] they have their own limitations, including

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Scheme 1. Synthesis of 5-substituted 1*H*-tetrazole.

use of harsh reaction conditions and expensive reagents, generation of highly toxic by-products, and poor yield of product^[24–27].

Adhering to our objective of developing a protocol that could fulfill the necessity for mild, environmentally compatible, less expensive, and safe synthetic methods^[28–30], we have developed a new protocol for the preparation of 5-substituted 1*H*-tetrazoles from a wide variety of nitriles using phosphomolybdic acid as a heterogeneous solid acid catalyst (Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of benzonitrile with sodium azide was carried out in dimethylformamide (DMF) at 80 °C as a model reaction to examine the effect of various catalysts on the yield and rate of reaction for the preparation of 5-substituted 1*H*-tetrazoles, in comparison with phosphomolybdic acid. We found that the yield and the rate of reaction were quite good when phosphomolybdic acid was used as catalyst (Table 1).

To identify optimum reaction conditions for preparation of 5-substituted 1*H*-tetrazoles, various solvents were studied (Table 2) at different temperatures by reacting benzonitrile with sodium azide in the presence of phosphomolybdic acid.

Encouragingly, we noticed that when DMF was used as a solvent, the product was obtained with complete conversion, as indicated by thin-layer chromatography (TLC). The conditions identified were used further to study the scope of the transformation of other nitriles to 5-substituted 1*H*-tetrazole derivatives. Keeping all

Table 1. Influence of various catalysts on the preparation of 5-substituted 1*H*-tetrazoles^a

Entry	Catalyst	Time (h)	Yield ^b (%)
1	BiCl ₃	09	65
2	CdCl ₂	14	53
3	InCl ₃	12	40
4	CeCl ₃	12	52
5	AlCl ₃	9.5	73
6	Bi(NO ₃) ₃	08	65
7	CuCl ₂	14	42
8	FeCl ₃	10	61
9	Phosphomolybdic acid	04	89

^aReaction conditions: benzonitrile (1 mol), sodium azide (1.5 mol), catalyst (2 mol %).

^bIsolated yield.

Table 2. Optimization of reaction conditions for the preparation of 5-substituted 1*H*-tetrazoles^a

Entry	Solvent	Time (h)	Temp. (°C)	Yield ^b (%)
1	CH ₃ CN	5	75	59
2	THF	8	70	70
3	CH ₂ Cl ₂	7.5	38	34
4	CCl ₄	7	55	54
5	MeOH	7	55	63
6	DMF	4	80	89
7	DMSO	8	100	60

^aReaction conditions: benzonitrile (1 mol), sodium azide (1.5 mol), catalyst (2 mol %).^bIsolated yield.

these results in view, we decided to generalize the protocol by carrying out the reaction of various aryl nitriles with sodium azide in the presence of phosphomolybdic acid in DMF. All the products were obtained with 63 to 96% yields (Table 3). Physical and spectral data of known compounds are in agreement with the literature.

Products were characterized by physical constant, IR and NMR. Because we used phosphomolybdic acid as a recyclable catalyst, after completion of reaction, the catalyst was recovered. The reaction mixture was poured into ice-cold water extracted with ethyl acetate, washed with water, and evaporated under reduced pressure to get the product. The aqueous layer was evaporated under reduced pressure to get phosphomolybdic acid and reused two more times (Table 4).

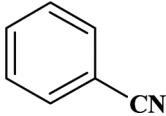
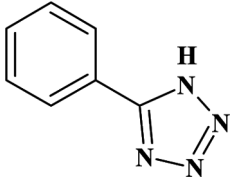
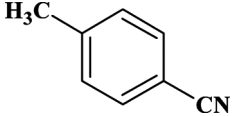
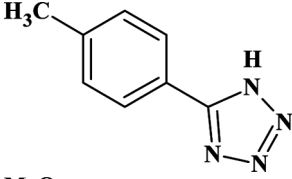
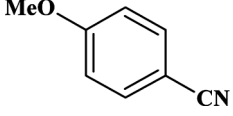
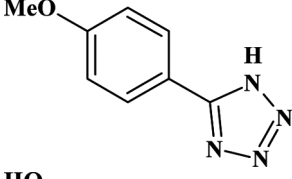
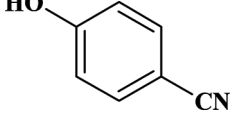
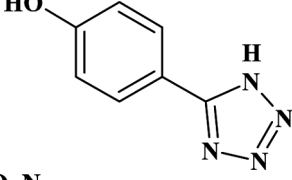
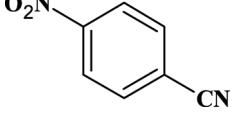
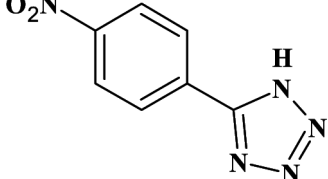
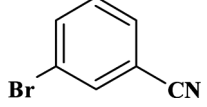
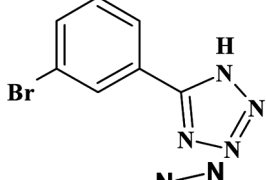
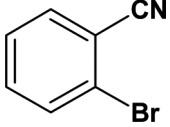
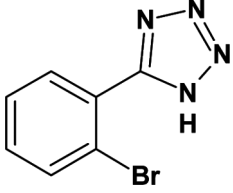
EXPERIMENTAL

All commercial reagents were used as received without purification, and solvents were of reagent grade. The reaction was monitored by TLC using 0.25-mm E-Merck silica-gel 60 F254 precoated plates and visualized under ultraviolet light. Melting points were taken in open capillaries and are uncorrected. The infrared (IR) spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs. ¹H NMR and ¹³C NMR spectra were recorded on a VXR300-MHz instrument using tetramethylsilane (TMS) as an internal standard.

A mixture of nitrile (1 mol), sodium azide (1.5 mol), and phosphomolybdic acid (2 mol %) was stirred at 80 °C in DMF for the appropriate time period, as indicated in Table 3. After completion of reaction, the reaction mixture was poured on to crushed ice, extracted with ethyl acetate, and washed with water. Ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product obtained was purified by column chromatography.

Representative spectral data for 5(4-methoxyphenyl)-1*H*-tetrazole are as follows: IR (KBr) cm⁻¹: 3250, 1296, 1186, 1035, 750. ¹H NMR (DMSO-*d*₆): δ = 3.79 (s, 3H), 7.11 (d, *J* = 7.5 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 2H), 11.0 (bs, 1H) ppm. ¹³C NMR (DMSO-*d*₆): δ = 56.10, 114.50, 116, 128, 155, 161 ppm. Elemental composition: Calc. C, 54.53%, H, 4.58%, N, 31.81%. Found: C, 54.61%, H, 4.82%, N, 32.07%.

Table 3. Preparation of 5-substituted 1*H*-tetrazoles in the presence of phosphomolybdic acid^a

Entry	Substrate	Product	Time (h)	Yield ^b	Mp (°C)	Ref.
1			4	89	215	10, 16
2			4.3	85	247	11, 22
3			4.5	81	233	22
4			4.5	83	234	22
5			3.4	96	219	22
6			4.0	79	150	15
7			5.0	81	182	15

(Continued)

Table 3. Continued

Entry	Substrate	Product	Time (h)	Yield ^b	Mp (°C)	Ref.
8			6.0	83	143	15
9			4.0	91	205	22
10			4.5	71	124	22
11			7.0	63	42	15
12			7.0	67	41	22
13			4.7	79	134	22

^aReaction conditions: nitriles (1 mol), sodium azide (1.5 mol), catalyst (2 mol %). Solvent: DMF. Temperature: 80 °C.

^bIsolated yield.

Table 4. Recyclability of the phosphomolybdic acid for preparation of 5-substituted 1H-tetrazoles

Run	Yield ^a (%)
1	89
2	84
3	80

^aIsolated yield.

CONCLUSION

In conclusion, we have developed a green and highly efficient method for the synthesis of 5-substituted 1*H*-tetrazoles by reacting nitriles with sodium azide in the presence of phosphomolybdic acid as a catalyst. Good yields of product, short reaction time, elimination of dangerous and harmful hydrazoic acid, a simple workup procedure, easy preparation, and easy handling of the catalyst are some of the advantages of this methodology.

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