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ORIGINAL PAPER

# Heteropolyacid catalyzed click synthesis of 5-substituted 1*H*-tetrazoles from [bmim]$N_3$ and nitriles under solvent-free conditions

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**Abstract** A simple and solvent-free route for the synthesis of 5-substituted 1*H*-tetrazoles is reported. In this method, 5-substituted 1*H*-tetrazoles are synthesized from nitriles and [bmim]$N_3$ with heteropolyacid ($H_3PW_{12}O_{40}$) as a catalyst under solvent-free conditions.

**Keywords** Nitriles · 1-Butyl-3-methylimidazolium azide · Cycloadditions · Heteropolyacid · 5-Substituted 1*H*-tetrazoles · Solvent-free

## Introduction

Tetrazoles are an important group of heterocycles and it has been recognized that tetrazoles can use as substitutes of carboxylic acids. This functional group is important in coordination chemistry and found widespread application in pharmaceutical and material science [1]. 5-Substituted 1*H*-tetrazoles are usually obtained by the cycloadditions of azide ion with organic nitriles. The first reported method for synthesis of tetrazoles was the reaction of hydrazoic acid ($HN_3$) with nitriles in 1932 [2]. This procedure had some disadvantages, such as high toxicity, explosive nature, and low boiling point (37 °C) of hydrazoic acid [2]. [3 + 2] Cycloadditions between nitriles and azide anion constitute an efficient method for the synthesis of 5-substituted 1*H*-tetrazoles. In 2001, Demko and Sharpless [3] reported cycloaddition reactions between nitriles and sodium azide in water with $ZnBr_2$ as a catalyst. Currently, several methods have been reported for the synthesis of 5-substituted 1*H*-tetrazoles. These include $NaN_3$/HOAc/ionic liquids/microwave heating [4], $TMSN_3$/TBAF·$3H_2O$/solvent-less/50–120 °C [5], $TMSN_3$/$Fe(OAc)_2$/DMF-$H_2O$/80 °C [6], $NaN_3$/Cu–Zn alloy nanopowder/DMF/90–135 °C [7], $R_2AlN_3$/toluene/−40 to 120 °C [8], $NaN_3$/$InCl_3$/DMF/microwave heating [9], $NaN_3$/CoY/DMF/120 °C [10], $NaN_3$/$Cu_2O$/DMF-MeOH/80 °C [11], $NaN_3$/$CuFe_2O_4$/DMF/120 °C [12], $NaN_3$/zeolite and zirconia/DMF and $H_2O$/reflux [13], $NaN_3$/ionic liquids/100 °C [14], $NaN_3$/MBA-ZnO/DMSO/120–130 °C [15], $NaN_3$/AcOH/NMP-$H_2O$/microwave [16], $NaN_3$/montmorillonite K10-M (M = Fe, Zn, Cu, Ni)/DMF/reflux [17], $NaN_3$/montmorillonite K10/microwave [18], $NaN_3$/$Et_3N$·HCl/$PhNO_2$/microwave [19], $NaN_3$/TMSCl-NMP/microwave [20] systems.

In this letter we wish to report a simple method for the synthesis of 5-substituted-1*H*-tetrazoles using click reaction conditions (Scheme 1).

## Results and discussion

In recent years, considerable attention has been paid to the use of green methods in the synthesis of organic compounds. To improve the ecocompatibility of organic processes, we have tried to develop to use of environmentally friendly and non-toxic reactants and catalysts in the cycloaddition reactions.

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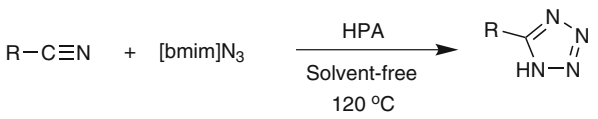
**Scheme 1**



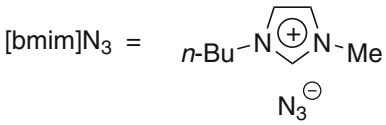



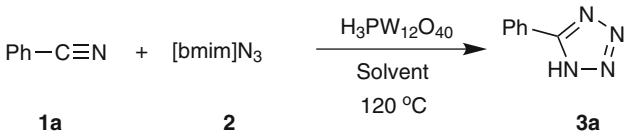

**Fig. 1** Structure of 1-butyl-3-methylimidazolium azide

In cycloaddition reactions between nitriles and azide, we have used ionic liquid [bmim]$N_3$ as a reactant instead of $NaN_3$ or $TMSN_3$. In the structure of this ionic liquid, azide is a counter ion and it could be used as a nucleophile in the reactions (Fig. 1). [Bmim]$N_3$ has been already used as an azide source for synthesis of 1,2,3-triazoles [21]. Along this line, using heteropolyacids (HPAs) has many advantages finding economically and environmentally attractive in both academic and industrial significance [22]. HPAs are strong bronsted acids composed of heteropoly anions and protons as the counter cations. They are low in toxicity, highly stable to humidity, and air-stable [23]. We have found that the tungstophosphoric acid ($H_3PW_{12}O_{40}$) as a Keggin type heteropolyacid could be an efficient nontoxic catalyst for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles and [bmim]$N_3$.

The reaction of benzonitrile (**1a**) with [bmim]$N_3$ as an azide source was used as a model reaction. We examined the effects of various solvents such as DMF, $H_2O$, and PEG. Reaction under solvent-free conditions was chosen as an effective medium for this reaction (Table 1).

Under the optimized reaction conditions, we chose several substituted nitriles to react with [bmim]$N_3$ (Table 2). All reactions proceeded to completion within 5–12 h, and tetrazoles were isolated in excellent yields. The nature of the substituents on the nitriles had a significant effect on the yields and reaction times. Reactions of benzonitrile and nitriles with electron withdrawing substituents, such as 4-nitrobenzonitrile (**1c**), 4-chlorobenzonitrile (**1d**), 3-cyanobenzonitrile (**1e**), and 2-nitrobenzonitrile (**1i**) were completed in the shorter reaction times and higher yields than other derivatives of nitriles (Table 2, entries 1, 3–5, 9), whereas the reactions of nitriles with electron donating substituents such as 4-methylbenzonitrile (**1b**) and 3-methoxybenzonitrile (**1h**) required the more reaction time than nitriles with electron withdrawing substituents (Table 2, entries 2, 8). Among of nitriles with electron withdrawing substituents, 3-cyanobenzonitrile was reacted

**Table 1** HPA-catalyzed 1,3-dipolar cycloaddition of benzonitrile with [bmim]$N_3$[a]




**1a** **2** **3a**

| Entry | Solvent | Time/h | Yield/%[c] |
|---|---|---|---|
| 1 | DMF | 12 | 46 |
| 2[b] | $H_2O$ | 24 | Trace |
| 3 | PEG | 8 | 70 |
| 4 | Solvent less | 6 | 93 |

[a] All reactions were performed on a 0.5 mmol scale, 0.7 mol% of HPA in 1.5 $cm^3$ of solvent

[b] Reaction temperature = 100 °C

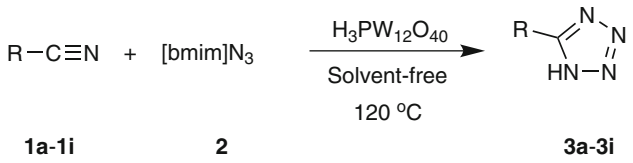
[c] Yields are given for isolated products

with 1.5 mmol of [bmim]$N_3$ in order to produce monotetrazole and it was also reacted with 3 mmol of [bmim]$N_3$ in order to obtain bis-tetrazole, but we could isolate monotetrazole (**3e**) in these two reactions as a final product. Thus the best results are obtained with nitriles containing an electron withdrawing substituent (Table 2, entries 3–5, 9). Among of other nitriles, 2,2-diphenyl acetonitrile (**1f**) provided moderate yield (89 %) of product in 12 h (Table 2, entry 6) and ethyl cyanoacetate (**1g**) in this reaction with [bmim]$N_3$ produced the corresponding tetrazole (**3g**) in 92 % yield (Table 2, entry 7).

In summary, we have developed a new and efficient route for the synthesis of 5-substituted 1*H*-tetrazoles. In this method, the reaction of nitriles with [bmim]$N_3$ as an azide source is catalyzed by HPA as an efficient catalyst under solvent-free conditions. In this reaction, the use of [bmim]$N_3$ as an ionic liquid and green source of azide, and the use of HPA as an economically and environmentally friendly bronsted acid in solvent-free conditions for this method, defines it as a green and non-toxic reaction for the synthesis of 5-substituted 1*H*-tetrazoles.

Therefore, this method appears attractive for industrial and pharmaceutical applications. In comparison with other methods which needed long reaction times (14, 24 h) [6, 10] and the crude products were purified by column chromatography on silica gel [7, 10], this method is completed in 5–12 h giving excellent yields of products (89–97 %) and the pure products are obtained after simple extraction. The most advantages of this method compared to previously published procedures is in using 1-butyl-3-methylimidazolium azide as an ionic liquid azide source in place of the highly toxic reagents $NaN_3$ or $TMSN_3$ [4–7, 9–20], and using of heteropolyacid ($H_3PW_{12}O_{40}$) as a low toxic catalyst in solvent-free conditions instead of toxic

**Table 2** Synthesis of 5-substituted 1*H*-tetrazoles[a]




**1a-1i** **2** **3a-3i**

| Entry | Prod. | *R* | Time/h | Yield/%[b] | M.p./°C | Lit. m.p./°C |
|---|---|---|---|---|---|---|
| 1 | **3a** | $C_6H_5$– | 6 | 93 | 214–215 | 215–216 [3, 7] |
| 2 | **3b** | 4-Me–$C_6H_4$– | 7 | 90 | 250–252 | 251–252 [20] |
| 3 | **3c** | 4-$NO_2$–$C_6H_4$– | 5 | 97 | 218–221 | 219–221 [10] |
| 4 | **3d** | 4-Cl–$C_6H_4$– | 6 | 92 | 255–256 | 250–252 [12] |
| 5 | **3e** | 3-CN–$C_6H_4$– | 5 | 91 | 211–214 | 214–216 [13] |
| 6 | **3f** | $(C_6H_5)_2CH$– | 12 | 89 | 162–165 | 165–166 [16] |
| 7 | **3g** | –$CH_2COOEt$ | 8 | 92 | 128–131 | 126–128 [24] |
| 8 | **3h** | 3-MeO–$C_6H_4$– | 7 | 91 | 160 | 157–159 [12] |
| 9 | **3i** | 2-$NO_2$–$C_6H_4$– | 5 | 89 | 155–156 | 158–161 [6] |

[a] Reaction conditions nitriles (1 mmol), $[bmim]N_3$ (1.5 mmol), HPA ($H_3PW_{12}O_{40}$, 0.02 g, 0.7 mol%), 120 °C

[b] Yields of pure products

solvents such as DMF, DMSO, and toluene [6–13, 15, 17]. High yields, short reaction times and green reaction conditions make this method very simple and efficient for the preparation of 5-substituted 1*H*-tetrazoles.

## Experimental

Melting points were measured using a capillary tube method with a Barnstead Electrothermal 9200 apparatus. FTIR spectra were recorded using KBr discs on a FTIR Bruker Tensor 27 instrument. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AQS-AVANCE spectrometer at 500 and 125 MHz, using TMS as an internal standard. All reagents were purchased from Aldrich and Merck with high-grade quality, and used without any purification.

*Synthesis of 1-butyl-3-methylimidazolium azide [21]*

Freshly prepared 1-butyl-3-methylimidazolium chloride (20 mmol) and $NaN_3$ (20 mmol) were added into 25 $cm^3$ deionized water, and the mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure at 50 °C to obtain the crude product containing azide ionic liquid and NaCl, which was washed with acetonitrile (3 × 10 $cm^3$). The remaining acetonitrile was removed under high vacuum to yield yellow transparent liquid that became more viscous upon extensive drying. Isolated yield was 92 %. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (t, 3H, $CH_3$), 1.48 (m, 2H, $CH_2$), 1.80 (m, 2H, $CH_2$), 3.85 (s, 3H, $NCH_3$), 4.01 (t, 2H, $NCH_2$), 7.24 (d, 1H, ArH), 7.45 (d, 1H, ArH), 9.21 (brs, 1H, ArH) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 12.3, 19.1, 24.4, 36.4, 38.7, 124.1, 127.0, 142.8$ ppm; IR (KBr): $\bar{\nu} = 2{,}019$, 1,636, 1,571, 1,465, 1,337, 1,168 $cm^{-1}$.

*General procedure*

HPA ($H_3PW_{12}O_{40}$, 0.02 g, 0.7 mol%) was added to a mixture of nitriles (1 mmol) and $[bmim]N_3$ (1.5 mmol) and stirred at 120 °C. After completion of reaction (monitored by thin-layer chromatography), the reaction mixture was treated with 10 $cm^3$ water and extracted with ethyl acetate (2 × 15 $cm^3$). The aqueous layer was treated with 3 N HCl and extracted with ethyl acetate (2 × 15 $cm^3$). The organic layers were dried over anhydrous sodium sulfate and concentrated to give the 5-substituted 1*H*-tetrazoles (Table 2).

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