



# Tungstates: Novel heterogeneous catalysts for the synthesis of 5-substituted 1H-tetrazoles

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## ARTICLE INFO

### Article history:

Received 2 December 2008  
Received in revised form 30 January 2009  
Accepted 31 January 2009  
Available online 10 February 2009

### Keywords:

Tetrazoles  
Tungstate  
BaWO<sub>4</sub>  
[2+3]-Cycloaddition  
Heterogeneous catalyst

## ABSTRACT

Most heterogeneous catalysts utilized for the formation of 5-substituted 1H-tetrazoles contain zinc as the metal core at the catalytically active site. In this paper, we report that the tungstate MWO<sub>4</sub> (M = Ba, Ca, Zn, Cd, Cu, Na, H) can catalyze the [2+3] cycloaddition reaction of nitriles with sodium azide to produce 5-substituted 1H-tetrazoles in DMF. The catalyst is very efficient, affording good yield of aromatic nitriles and can be reused for several cycles. The mono- and di-addition products from dicyanobenzene can be selectively synthesized, which is a development being reported for the first time. The mechanism of the catalysis may originate from the nitrile group coordinating with the unsaturated W atoms, formed by oxygen vacancies on the surface of solid tungstates.

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## 1. Introduction

Tetrazoles are a class of heterocyclic compounds that contain nitrogen and are currently under intensive focus due to their wide range of applications [1]. For example, they can function as lipophilic spacers and carbonylic acid surrogates [2] in pharmaceuticals, specialty explosives [3,4] and information recording systems in materials [5], ligands, and precursors of a variety of nitrogen-containing heterocycles in coordination chemistry [6,7].

The conventional method of synthesizing tetrazoles is by addition of azide ions to organic nitriles. Several methods of synthesis are in use [8–14] but each has its own disadvantage, such as the use of toxic metals, expensive reagents, explosive hydrazoic acid, or severe reaction conditions. Recently, Sharpless and co-workers have reported a method of synthesizing tetrazoles from nitriles and sodium azide instead of using hydrozoic acid with stoichiometric amounts of zinc bromide in water [15,16]. As the catalytic load on these homogeneous catalysts is high, the separation of the products and recycling of catalyst becomes difficult, shifting our preference in favor of high efficient heterogeneous catalysts. Since then there have been reports of the use of various heterogeneous catalysts [17–21], but most of these catalysts contain zinc. Beside the innovation of synthetic methods concentrating on zinc salt, theoretical calculations also indicate that the catalytic activity originates from activation of the CN triple bond of the nitrile by the coordination

of the nitrogen atom with the Lewis acidic zinc ions [22–24]. However, it has been reported that most of other metallic ions showed no catalytic activity in water [15,16]. The heterogeneous catalysts effective in the synthesis of tetrazoles were believed to be limited to the compounds containing zinc. In this paper, to extend the range of high efficient heterogeneous catalyst for synthesis of tetrazoles, we report that a new family of salts without zinc: BaWO<sub>4</sub> and other tungstates MWO<sub>4</sub> (M = Cu, Zn, Cd, Ca, Na, H) can be efficient catalytic systems for the synthesis of tetrazoles with good yields being obtained [25].

## 2. Experimental

### 2.1. Preparation of catalysts

Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O (99.55%), CaWO<sub>4</sub> (99%) and H<sub>2</sub>WO<sub>4</sub> (99%) were purchased and used without further purification. By heating H<sub>2</sub>WO<sub>4</sub> at 400 °C and 700 °C for 2 h, WO<sub>3</sub>·xH<sub>2</sub>O and monoclinic WO<sub>3</sub> were produced and were characterized by X-ray diffraction. The white precipitate of BaWO<sub>4</sub> was synthesized by mixing 100 mL of 0.1 mol/L sodium tungstate (AR, Aldrich) with 100 mL of 0.1 M BaCl<sub>2</sub> (AR, Aldrich) in 100 mL of ethanol with vigorous stirring. The product was separated by centrifugation and washed several times with deionized water until no chloride ions were detected in the centrifugate solution. After drying at 50 °C for 5 h the sample was denoted as BaWO<sub>4</sub>. The remaining tungstates were synthesized by the same method by changing the chloride solution accordingly. Another BaWO<sub>4</sub> sample with larger surface area was prepared in an aqueous medium and was noted as BaWO<sub>4</sub>-water. All the

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catalysts used in the reaction contained an identical amount of  $\text{WO}_4^{2-}$ . The BET surface area was measured on ASAP2020 equipment (Micromeritics, USA).

## 2.2. Typical procedure for preparation of 5-substituted 1H-tetrazole

All nitriles were purchased from Aldrich. Barium tungstate (0.1 g, 0.26 mmol) was added to a mixture of benzonitrile (0.257 g, 2.5 mmol) and sodium azide (0.350 g, 5.4 mmol) in DMF (5 mL) and the resulting composition stirred constantly for 24 h at 120 °C. After the completion of the reaction, the catalyst was separated by centrifugation, washed with 4 mL water twice, and the centrifugate was treated with 6 M HCl (20 mL) and while being stirred vigorously. The aqueous solution finally obtained was extracted twice with ethyl acetate; the combined organic phase was washed with water and concentrated to precipitate the crude solid crystalline 5-phenyltetrazole. To obtain pure 5-phenyltetrazole from it, column chromatography was performed using silica gel (100–200 mesh) (0.28 g, 75%),  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.00 (m, 2H), 7.59 (m, 3H), MS (70 eV):  $m/z$  (%) = 146.1 ( $\text{M}^+$ , 6.87%), 118.1 (M-N<sub>2</sub>, 100.0%), 103.1 (M-HN<sub>3</sub>, 10.3%), 91.1 (M-HCN<sub>3</sub>, 30.35%), 77.1 (M-HCN<sub>4</sub>, 14.93%), 63.0 (M-H<sub>3</sub>C<sub>2</sub>N<sub>4</sub>, 9.72%), and 51.0 (M-H<sub>3</sub>C<sub>3</sub>N<sub>4</sub>, 5.73%).

## 3. Results and discussion

As a part of the effort to develop a new catalytic system,  $\text{BaWO}_4$  was first evaluated as the catalyst for the preparation of 5-phenyltetrazole using various reaction parameters. The results are summarized in Table 1. Generally, with the catalysis of  $\text{BaWO}_4$  in DMF (Table 1, entries 4–7), the reaction gave moderate to good yields, whereas no products were obtained without catalytic loading (Table 1, entry 8). The solvent had significant effect on the catalytic performance of the  $\text{BaWO}_4$  catalyst in the reaction (Table 1, entries 1–3 and 6), in which DMF afforded good yield (75%) (Table 1, entry 6), and dimethyl sulfoxide (DMSO) moderate yield (55%) (Table 1, entry 2). Water and tetrahydrofuran (THF) are not suitable solvents for the reaction. The quantities of  $\text{NaN}_3$  and catalyst used also affect the yield significantly. On using twice the amount of  $\text{NaN}_3$ , the yield increased from 27% (Table 1, entry 4) to 75% (Table 1, entries 4 and 5; entries 6 and 7). An abnormal phenomenon can be observed from Table 1, which is, keeping the amount of  $\text{NaN}_3$  used constant, the yields decreased with increasing amounts of the catalyst (Table 1, entries 4 and 5, 6 and 7). The possible reason for this occurrence might be the adsorption of the product occasioned by the increased loading of the catalyst. By simple centrifugation,

**Table 1**  
Formation of 5-phenyltetrazole using various reaction parameters<sup>a</sup>.

Entry	Solvent	$\text{NaN}_3$ (mmol)	$\text{BaWO}_4$ (mmol)	Yield <sup>b</sup> (%)	TOF <sup>c</sup> ( $10^{-1} \text{ h}^{-1}$ )
1	Water	5.3	0.26	0 <sup>d</sup>	0
2	DMSO	5.3	0.26	55	2.20
3	THF	5.3	0.26	0 <sup>e</sup>	0
4	DMF	2.6	0.26	27	1.08
5	DMF	2.6	0.78	17	0.23
6	DMF	5.3	0.26	75 <sup>f</sup> , 73 <sup>g</sup>	3.00, 2.92
7	DMF	5.3	0.78	68	0.91
8	DMF	5.3	0	0	0

<sup>a</sup> Reaction conditions: nitrile (2.5 mmol),  $\text{NaN}_3$  (2.6–5.3 mmol),  $\text{BaWO}_4$  (0.26–0.78 mmol), DMF (5 mL), reaction time (24 h) and 120 °C.

<sup>b</sup> Average of yields of two parallel experiments.

<sup>c</sup> Turnover frequency of nitrile.

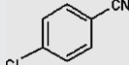


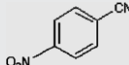

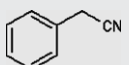
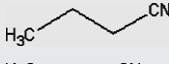
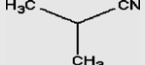
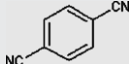
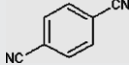
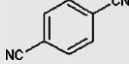
<sup>d</sup> Reaction using reflux of water (100 °C).

<sup>e</sup> Reaction using reflux of THF.

<sup>f</sup> Yield for first use.

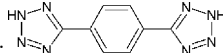
<sup>g</sup> Yield for the third cycle.

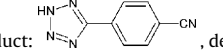
**Table 2**  
 $\text{BaWO}_4$  mediated preparation of 5-substituted 1H-tetrazoles<sup>a</sup>.

Entry	Substrate	$\text{NaN}_3$ (mmol)	Time (h)	Yield <sup>b</sup> (%)	TOF ( $10^{-1} \text{ h}^{-1}$ )
1		5.3	24	90	3.61
2		5.3	24	93	3.73
3		5.3	24	85	3.41
4		5.3	24	88	3.53
5		5.3	24	85	3.41
6		5.3	24	93	3.73
7		5.3	24	<5	<0.2
8		5.3	24	<5	<0.2
9		5.3	24	84 <sup>c</sup>	3.37
10		2.6	12	24 <sup>c</sup> + 61 <sup>d</sup>	–
11		2.6 <sup>e</sup>	6	6 <sup>c</sup> + 70 <sup>d</sup>	–

<sup>a</sup> Reaction conditions: nitrile (2.5 mmol),  $\text{NaN}_3$  (2.6 or 5.3 mmol),  $\text{BaWO}_4$  (0.26 mmol), DMF (5 mL), 120 °C.

<sup>b</sup> Average of yields of two parallel experiments.

<sup>c</sup> Di-addition product: , determined by H NMR.

<sup>d</sup> Mono-addition product: , determined by H NMR.

<sup>e</sup>  $\text{NaN}_3$  added gradually over 12 h period.

$\text{BaWO}_4$  can be quantitatively recovered and reused for three consecutive cycles (Table 1, entry 6).

A variety of organic nitriles was used as substrates to evaluate the catalytic performance of  $\text{BaWO}_4$ . The reactions proceeded under the optimum reaction conditions as shown above. The results show that aromatic nitriles give good yields (Table 2, entries 1–6). Among them, three nitrobenzolenitriles offered the yields higher than benzonitrile with no substitutions; furthermore, the yields for nitrobenzolenitrile with 2-substitutions or 4-substitutions were higher than for the isomer with 3-substitutions, indicating possible contributions from the electronic effects of the aromatic ring. This is also proved by the results obtained from the heteroaromatic nitriles such as 2-pyridinecarbonitrile whose yield was similar to that of nitrobenzolenitrile (Table 2, entry 5). However, in comparison with Zn-containing catalysts, tungstates catalysts exhibit negligible activity for alkyl nitriles (Table 2, entries 7 and 8) with the exception of phenylacetone nitrile (Table 2, entry 6).

Dicyanobenzene is an interesting substrate for study of mono-addition reactions or di-addition reactions. It was reported that the di-addition product was obtained using soluble Zn(II) salts [15,16],

**Table 3**  
Preparation of 5-substituted 1H-tetrazoles with various catalysts<sup>a</sup>.

Entry	Catalyst <sup>b</sup>	BET surface Area (m <sup>2</sup> /g)	Yields <sup>c</sup> (%)	TOF (10 <sup>-1</sup> h <sup>-1</sup> )
1	BaCl <sub>2</sub>	Dissolving	0	0
2	Ba(NO <sub>3</sub> ) <sub>2</sub>	Dissolving	0	0
3	Na <sub>2</sub> WO <sub>4</sub> ·2H <sub>2</sub> O	Partly dissolving	36	1.44
4	H <sub>2</sub> WO <sub>4</sub>	38	89	3.57
5	WO <sub>3</sub> ·xH <sub>2</sub> O	12	95	3.81
6	WO <sub>3</sub>	0.88	47	1.88
7	BaWO <sub>4</sub>	17.0	75	3.00
8	BaWO <sub>4</sub> -water	5.7	52	2.08
9	CaWO <sub>4</sub>	1.4	74	2.96
10	ZnWO <sub>4</sub>	14.0	75	3.00
11	CdWO <sub>4</sub>	57.4	88	3.53
12	CuWO <sub>4</sub> ·2H <sub>2</sub> O	109.2	93	3.73

<sup>a</sup> Reaction conditions: nitrile (2.5 mmol), NaN<sub>3</sub> (5.3 mmol), catalyst (0.26 mmol), DMF (5 mL), 120 °C, 24 h.

<sup>b</sup> Amount of Ba<sup>2+</sup> or WO<sub>4</sub><sup>2-</sup> catalyst used is equivalent to that of 0.1 g BaWO<sub>4</sub> (0.26 mmol).

<sup>c</sup> Average value of two parallel experiments.

whereas the mono-addition product was achieved with the use of solid zinc oxide catalyst [8]. We found that mono- and di-addition products could be selectively synthesized by simply adjusting the molar ratio of NaN<sub>3</sub> to nitriles and the rate of addition of NaN<sub>3</sub> to the reaction solution. The di-addition product was obtained when the molar ratio of NaN<sub>3</sub> to nitrile was about 2 (molar ratio: 5.3:2.5) (Table 2, entry 9); whereas when the molar rate was about 1 (2.6:2.5), the methodology of adding NaN<sub>3</sub> to the reaction solution had a crucial influence on the formation of mono- and di-addition products. If NaN<sub>3</sub> is entirely added into the reaction solution before the reaction, both adducts are formed with similar yields (61:24, Table 2, entry 10). This indicates that the substrate and mono-addition products show similar reaction activity with NaN<sub>3</sub>. On the other hand, if NaN<sub>3</sub> was added gradually over a period of 6 h, the dominant product was mono-addition (Table 2, entry 11). The above results reveal that the dicyanobenzene is highly reactive, which is related to the withdrawal of the two electron groups (-CN) attached to the aromatic ring. In short, using tungstates for catalysis the yield of the mono- or di-addition products can be fine-tuned by adjusting the molar ratio of NaN<sub>3</sub> to the nitriles, the rate of addition of NaN<sub>3</sub>, and the reaction time.

In order to probe into the reactive sites of barium tungstate, several inorganic salts were used as catalysts in control experiments (Table 3). First, both barium nitrate (0.26 mmol) and barium chloride (0.28 mmol) with similar Ba<sup>2+</sup> contents as 0.1 g BaWO<sub>4</sub> (0.26 mmol) were selected as the catalysts to investigate if Ba<sup>2+</sup> is the active site. The results showed that they cannot catalyze the formation of tetrazoles; but all the tungstates exhibited moderate to good catalytic activity, regardless of whether the cations were transition metal ions (Zn<sup>2+</sup>, Cd<sup>2+</sup>, Cu<sup>2+</sup>, entries 10–12) or not (Na<sup>+</sup>, Ba<sup>2+</sup>, Ca<sup>2+</sup>, H<sup>+</sup>, entries 3–9), regardless of whether the tungstate was of scheelite type (CaWO<sub>4</sub>, BaWO<sub>4</sub>) or of wolfram type (ZnWO<sub>4</sub>, CdWO<sub>4</sub>, CuWO<sub>4</sub>), or even tungsten oxide. It is evident that the origins of catalytic activity whether from WO<sub>x</sub> polyhedrons (x = 4 or 6) or the counter ion seem to play no part in the catalytic activity.

Secondly, two catalysts, ZnWO<sub>4</sub> (Table 3, entry 10) and BaWO<sub>4</sub> (Table 3, entry 7), which have similar BET surface areas afforded similar yields. It is notable to mention that Zn<sup>2+</sup> (such as ZnBr<sub>2</sub> in aqueous solution [15,16]) and solid ZnO in DMF [17] can catalyze [2+3] cycloaddition reactions independently, but ZnWO<sub>4</sub> does not exhibit an extra catalytic activity compared with BaWO<sub>4</sub> (Table 3, entry 7). It further confirms that WO<sub>x</sub> polyhedrons are the catalytic active sites.

The high levels of catalytic activity of tungsten oxide and its hydrate also indicate that WO<sub>x</sub> polyhedrons are the reactive sites, as there are no metal cations in these species (Table 3, entries 4–6).

The non-stoichiometric hydrate of tungsten oxide shows the highest reactivity (Table 3, entry 5). There are two possibilities that could serve as the catalytically active sites: (1) the free WO<sub>4</sub><sup>2-</sup> ions or (2) the solid-state WO<sub>x</sub> polyhedron. Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O was selected as a catalyst because it has moderate solubility in DMF. If the free WO<sub>4</sub><sup>2-</sup> ions are the reactive sites, then Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O should display much higher activity than the solid tungstate catalyst due to its higher concentration of WO<sub>4</sub><sup>2-</sup>. In fact, its catalytic activity is remarkably lower (36%, Table 3, entry 3) than that of the other solid tungstates (Table 3, entries 7–11). Although the reason for low activity of Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O is unclear, it nevertheless proves that WO<sub>x</sub> polyhedrons in solid tungstate are the catalytically reactive sites.

The specific surface area of the solid catalyst usually plays an important role in catalytic activity. However, this correlation was not observed in our study. For example, both WO<sub>3</sub>·xH<sub>2</sub>O (12 m<sup>2</sup>/g, Table 3, entry 5) and CuWO<sub>4</sub>·2H<sub>2</sub>O (109.2 m<sup>2</sup>/g, Table 3, entry 12) afforded excellent yields, although their surface areas differ by the order of 10, which suggests that oxygen vacancies in solid tungstate may play a key role in catalytic activity [26–28].

Based on a previous report on the role of surface oxygen vacancies in many chemical catalytic reactions [29,30], we could conclude that the unsaturated coordination sites on the surface of the solid tungstates form WO<sub>3</sub>-like structures via oxygen vacancies. The unsaturated W atoms are supposed to activate the nitriles and enhance their reactivity with azides. However, further experiments are necessary to gain a clearer insight into these reactions.

#### 4. Conclusions

In summary, we report that tungstates are effective heterogeneous catalysts for the [2+3] cycloaddition of azides with a wide variety of nitriles to form 5-substituted 1H-tetrazoles with good yields. The selective synthesis of mono- or di-addition product is achieved by adjusting the adding rate and amounts of NaN<sub>3</sub> as well as the reaction time. This methodology may find widespread use in organic synthesis involving tetrazoles and inspire the exploring of new heterogeneous catalyst for synthesis of tetrazole.

#### Acknowledgements

We thank Tan Wee Boon for assistance rendered in language editing. This work was supported by NNSFC under major project of nanoscience and nanotechnology No. 90606005; major project No. 20490210, and surface program No. 20571040.

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