

## **Bis( $\mu$ -5-diisopropylamino-1,2,3,4-tetrazolido- $\kappa^2\text{N}^2:\text{N}^3$ )bis[(triisopropylphosphane)copper(I)]: an Efficient Catalyst for Interfacial Cycloaddition of Nitriles to Sodium Azide**

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**Abstract:** *Equimolar amounts of sodium azide dissolved in water were reacted with organic nitriles dissolved in an organic solvent and loaded with 10 mol% of the title complex. Efficient production of the tetrazolate anion was observed in the aqueous phase especially for nitriles that are insoluble in water.*

**Keywords:** *Copper; tetrazole; click; chemistry; interfacial.*

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### **1. INTRODUCTION**

Tetrazoles are a class of 5-membered heterocyclic compounds comprising four nitrogen atoms and one carbon atom in the ring. Tetrazoles are not found in nature [1]. One widely used method to prepare tetrazoles is the reaction of an organic nitrile with an azide (click-chemistry). This is a very useful method due to the availability of the nitrile functionality [2]. Tetrazoles have found a plethora of applications in synthetic, medicinal, and pharmaceutical applications [3]-[5]. In addition, tetrazoles are also used as propellants, explosives [6]-[7], and in photography [6]-[8].

Much interest lies specifically in the synthesis of a tetrazole from sodium azide to produce the 5-substituted-1*H*-tetrazole [9]. The majority of reported procedures involve the click-chemistry approach of reacting sodium azide with the nitrile in the presence of an efficient catalyst, such as copper triflates [10]-[11], Fe(OAc)<sub>2</sub> [12], zinc(II) salts [13], Lewis acids such as AlCl<sub>3</sub> [14], BF<sub>3</sub>-OEt<sub>2</sub> [15], FeCl<sub>3</sub> [16], TBAF [17], heterogeneous catalysis COY zeolites [18], mesoporous ZnS nanospheres [19], Cu<sub>2</sub>O [20], and CuFe<sub>2</sub>O<sub>4</sub> nanoparticles [21].

There has been several recent publications reporting novel synthetic pathways for tetrazoles. A metal free synthetic method has been developed based on using 20 mol % of cyanuric chloride or 2,4,6-trichloro-1,3,5-triazine (TCT) as a catalyst to react sodium azide with wide variety of nitriles and obtain the 5-substituted-1*H*-tetrazoles. This available and inexpensive catalyst, has high efficiency to obtain high product yields via clean reaction in relatively short time [22].

Another metal free methodology has been developed to obtain excellent yields of tetrazole through the rapid and green reaction of nitriles with sodium azide. The reaction was catalyzed with a heterogeneous catalyst composed of cuttlebone in dimethyl sulfoxide (DMSO). The mesoporous cuttlebone forms hydrogen bonding with nitriles leading to electrophilic activation of the nitrile, which in turn leads to cycloaddition with sodium azide. With a yield of 87-98%, this new method has been shown to be very promising. Moreover, this method is efficient in converting several types of nitriles to corresponding 5-substituted-1*H*-tetrazoles including alkyl, aryl, and heteroaryl nitriles, in addition to sterically hindered *ortho*-substituted aryl nitriles, and organic nitriles with bulky aryl and halo aryl groups [23].

Mesoporous silica was also examined as a heterogeneous catalyst by benzylating Mobile Composition of Matter No. 41 (MCM-41), followed by sulfonation through chlorosulfonic acid, to produce the functionalized catalyst (MCMBSA), which was used to catalyze the synthesis of 5-Aryl-1*H*-tetrazoles via the reaction of aryl nitriles with sodium azide. The results showed that the optimum reaction conditions for tetrazole derivatives formation were obtained for 1:3 ratio of benzonitrile: sodium azide with 5 mg MCMBSA catalyst. The effect of the solvent on the reaction time was tested and the best performance was obtained by using DMF as aprotic polar solvent [24].

One very simple and effective method for the synthesis of 5-substituted-1*H*-tetrazoles is the use of nanosized Cu(II) immobilized on aminated epichlorohydrin activated silica (CAES) as catalyst for the [3+2] cycloaddition reactions of nitriles and sodium azide [25].

Another efficient method uses 4-(*N,N*-dimethylamino)pyridinium acetate as a recyclable nucleophilic basic catalyst with ionic liquid character. The reaction proceeds at 100 °C with good to excellent yields. The catalyst was prepared by reacting acetic acid with 4-(*N,N*-dimethylamino)pyridine in CH<sub>2</sub>Cl<sub>2</sub>. It was then used to catalyze the reaction of equimolar amounts of substituted benzonitriles and sodium azide [26].

A very elegant method for the synthesis of tetrazoles involves the reaction of sodium azide with organic nitrile with one equivalent of ZnBr<sub>2</sub>, with the only solvent used being water [27]. This green method was tremendous with its reduction of organic waste. However, a major shortcoming of this method was the poor solubility of organic nitriles in water. To overcome the poor solubility, isopropyl alcohol was added to the water to increase the solubility and/or dispersibility of the organic nitrile. This causes loss of the isopropyl alcohol and reduces the usefulness of the procedure.

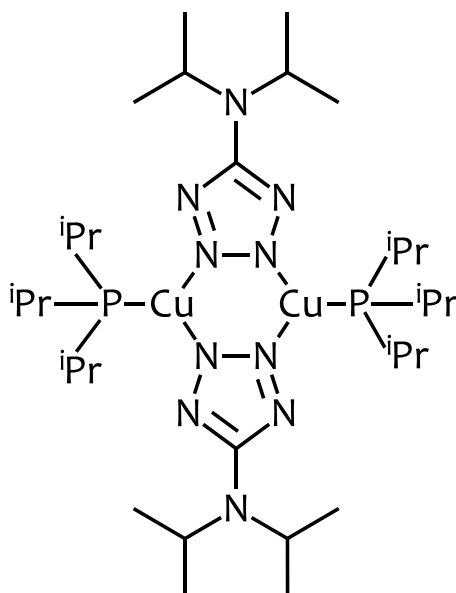
We have previously reported a copper(I) tetrazolate complex bearing a phosphine ligand [28]. It was envisioned that this complex could serve as an interfacial catalyst for tetrazole synthesis from a THF solution of the nitrile and an aqueous solution of sodium azide, thus resolving the issue of solubility of the nitrile.

## 2. METHODS

Bis( $\mu$ -5-diisopropylamino-1,2,3,4-tetrazolido- $\kappa$ 2N2:N3)bis[(triisopropylphosphane)copper(I)] (Cat, Fig. 1) was prepared according to the published procedure [23]. THF was distilled from Na/benzophenone. The nitriles and sodium azide were purchased from Aldrich and used as is.

50 mL of deionized water was charged with NaN<sub>3</sub> (0.500 g, 7.69 mmol) and layered with 50 mL of THF charged with an equimolar amount of the nitrile and 10 mol% Cat (0.603 g, 0.769 mmol). The mixture was stirred under reflux for 18h.

The aqueous layer was separated and acidified to neutral pH using 2.0 M HCl. Caution must be taken as the residual sodium azide produces HN<sub>3</sub> when acidified. The neutral tetrazole was filtered, washed with cold water, dried, and its identity checked by <sup>1</sup>H-NMR against literature values [17].



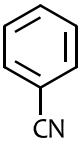
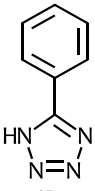
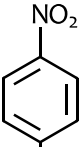
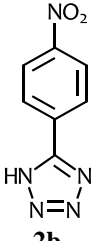
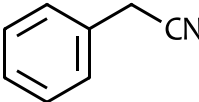
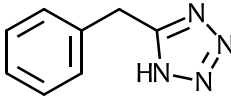
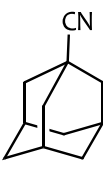
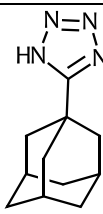
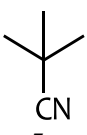
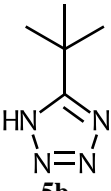
**Figure1.** The structure of Cat.

## 3. RESULTS AND DISCUSSION

Table 1 summarizes the results of the synthesis. While the yields are not optimal, they are exceptionally high in view of THF being the solvent. Tetrazole synthesis via click chemistry in THF generally proceeds with poor yields [20]. This is especially true for **5b**, which is generally very difficult to synthesize due to the bulkiness of the *tert*-butyl group [17].

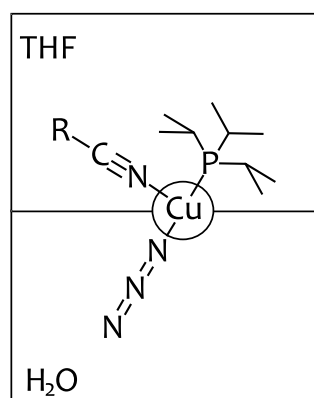
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**Table1.** Results of tetrazole synthesis including yield.

| Nitrile used   | Tetrazole  | % Yield | Yield without Cat |
|--|--|---------|-------------------|
|  <p><b>1a</b></p>   |  <p><b>1b</b></p>   | 43      | Trace             |
|  <p><b>2a</b></p>   |  <p><b>2b</b></p>   | 48      | Trace             |
|  <p><b>3a</b></p>   |  <p><b>3b</b></p>   | 42      | Trace             |
|  <p><b>4a</b></p>  |  <p><b>4b</b></p>  | 34      | Trace             |
|  <p><b>5a</b></p> |  <p><b>5b</b></p> | 12      | Trace             |

In the absence of Cat, none of the tetrazoles formed appreciably, and thus it can be concluded that Cat was effective at interfacially catalyzing the reaction of the nitrile with the azide anion.

It is well established that the intermediate in such reactions is copper azide [29], and thus a mechanism can be envisioned for this reaction comprising a step as shown in Fig. 2. In this step, the copper coordinates to the nitrile in the organic phase and the azide in the aqueous phase to facilitate their cycloaddition.



**Figure2.** Cat acting interfacially.

#### 4. CONCLUSION

While the yields may not be optimal, this study demonstrates that Cat can facilitate the cycloaddition of an organic nitrile in an organic phase with the azide anion in an aqueous phase, even using solvents that are generally poor for polar cycloaddition reactions.

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