



ORIGINAL ARTICLE

Highly efficient three-component synthesis of 5-substituted-1*H*-tetrazoles from aldehydes, hydroxylamine, and tetrabutylammonium azide using doped nano-sized copper(I) oxide (Cu₂O) on melamine–formaldehyde resin



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Three-component reaction

Abstract A simple and facile one-pot three-component synthesis of 5-substituted 1*H*-tetrazole derivatives from aldehydes catalyzed by doped nano-sized Cu₂O on melamine–formaldehyde resin (nano-Cu₂O–MFR) is described. In this protocol, treatment of structurally diverse aldehydes, hydroxylamine hydrochloride and tetrabutylammonium azide (TBAA) as an azide source in the presence of nano-Cu₂O–MFR as an efficient heterogeneous nano-catalyst affords the corresponding 5-substituted 1*H*-tetrazoles in good to excellent yields. The influence of different parameters on the progress of reaction was studied. The nano-Cu₂O–MFR is a cheap and stable nano-catalyst that could be easily prepared, recycled and reused for many consecutive reaction runs without significant decrease in its activity.

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1. Introduction

Tetrazoles as one of the most important synthetic heterocyclic compounds exhibit numerous applications in different areas of

sciences especially in chemistry, material, and medicinal sciences [1]. These nitrogen-rich heterocycles have important roles as ligands [2], information-recording systems [3], explosives [4], propellants [5], stabilizers in photography [6], and anti-wears [7]. The tetrazole functionality can be served as bioisosteric replacement of carboxylic acid moiety [8,9]. The presence of tetrazolyl moiety was found to improve the cell permeability, *in vivo* half-life, and bioavailability of a drug molecule since tetrazoles exhibit higher lipophilicity than their corresponding isosters (i.e.: carboxylic acids) and also good metabolic stability [10,11]. Tetrazoles have displayed important pharmacological and biological properties such as

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anticancer [12], antiviral [13], anti-HIV [14], anti-inflammatory [15], antifungal [16], and antibacterial [17] activities. In addition, tetrazolyl moieties are present in the structures of several famous drugs such as candesartan, losartan, valsartan, and zolarsartan [18,19].

Due to the widespread applications of tetrazole derivatives, a great deal of efforts have been devoted toward the development of various preparative methods for establishing numerous tetrazole derivatives [20,21]. Among them, [3+2]-cycloaddition reaction between nitriles and an azide source is the most extensively used procedure to access 5-substituted 1*H*-tetrazoles. In 2001, Demko and Sharpless developed a cycloaddition reaction between organic nitriles and sodium azide catalyzed by ZnBr₂ [21]. Since then, many homogeneous and heterogeneous catalysts were developed to promote [3+2]-cycloaddition of nitriles with an azide source [22]. Although a plenty of these methods are efficient and effective for synthesis of 5-substituted 1*H*-tetrazole derivatives, some nitriles as the key starting materials are fairly expensive, toxic and not readily available which in turn restricts the applicability of these methods. Therefore, the use of more available, less toxic, and cheap starting materials for efficient synthesis of 5-substituted 1*H*-tetrazoles is of great significance.

In view of the availability, wide diversity, lower toxicity, and ease of handling of aldehydes compared with nitriles, the direct application of aldehydes for synthesis of 5-substituted 1*H*-tetrazole derivatives would be a highly attractive and advantageous strategy. In this connection, the direct conversion of aldehydes to the corresponding tetrazoles via [3+2]-cycloaddition reaction has been reported by the use of aqueous ammonia [23] or acetohydroxamic acid [24] for the *in situ* generation of the prerequisite nitriles and/or oximes. Heravi and co-workers have reported the click synthesis of 5-substituted 1*H*-tetrazoles via three-component reaction of aldehydes, hydroxylamine hydrochloride, and [bmim]N₃ in the presence of Cu(OAc)₂ [25]. Recently, Abdollahi-Alibeik and Moaddeli reported the use of Cu-MCM-41 nanoparticles for three-component reaction of various aldehydes, hydroxylamine hydrochloride, and NaN₃ to afford the corresponding 5-substituted 1*H*-tetrazoles [26]. The utilization of aldehydes in synthesis of 5-substituted 1*H*-tetrazoles through a multi-component process, not only provides the advantageous mentioned above, but also affords various attractive features such as atom economy, ease of operation, lower environmental costs, and quantitative yields [27].

Nowadays, it is well established that heterogeneous catalysts offer many advantages from both economic and environmental points of view. The immobilization of the active species

on the heterogeneous supports often leads to thermal stability of the catalyst, ease of handling, mild reaction conditions, simple experimental procedures, minimization of the chemical wastes, recyclability and reusability of the catalyst [28]. Although heterogeneous catalysts effectively have been applied in a wide range of organic reactions, there are a few reports on the application of heterogeneous catalysts in direct synthesis of 5-substituted 1*H*-tetrazoles from aldehydes [26]. Hence, the development of efficient heterogeneous catalytic systems for promotion of such a three component reaction is highly demanded.

From the structural point of view, melamine–formaldehyde resin (MFR) contains the electron-deficient triazine cores. The presence of multi-coordinating nitrogen atoms as well as spaces between the triazine cores capable the MFR to form hydrogen bonds with substrates present in these cavities. Thus, the MFR can be applied as a valuable solid support for absorbing different metal salts. Moreover, the triazine cores in MFR potentially can generate π – π^* interaction between reactants and triazine cores. In general, these properties provide suitable binding sites for reactants in MFR which improved the performance of the MFR-based catalysts in comparison with other catalysts. The schematic view for potential hosting of cation and anion by MFR is shown in Fig. 1.

Previously, we have reported the synthesis and application of doped nano-sized Cu₂O on melamine–formaldehyde resin (nano-Cu₂O–MFR) as a novel and highly efficient heterogeneous catalyst in click synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles having antibacterial activity [29]. In an effort to discover the new applications for nano-Cu₂O–MFR in organic synthesis and also in continuation of our research interest in developing new synthetic methods for preparation of 5-substituted 1*H*-tetrazoles [22,30] as well as multi-component reactions [31–34], we now report a simple and convenient protocol for click synthesis of 5-substituted 1*H*-tetrazole derivatives from one-pot three-component reaction of structurally diverse aldehydes, hydroxylamine hydrochloride, and tetrabutylammonium azide (TBAA) as an azide source in the presence of nano-Cu₂O–MFR as a highly efficient heterogeneous catalyst at 100 °C in DMF (Scheme 1).

2. Experimental

2.1. General

All chemical reagents were purchased from Fluka, Merck or Sigma–Aldrich. nano-Cu₂O–MFR [29], Cu-MCM-41 [26],

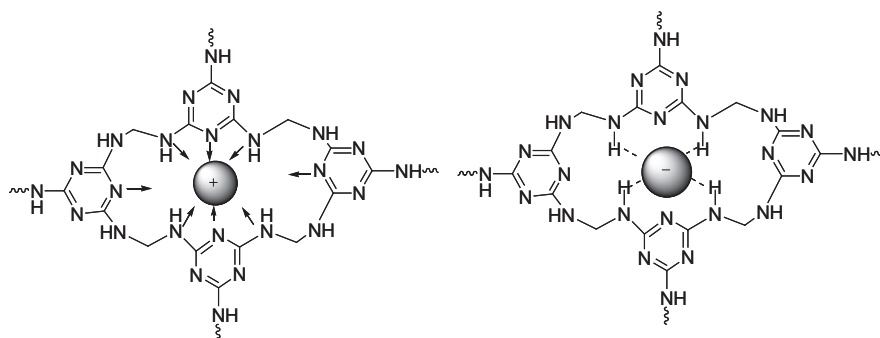


Figure 1 The schematic view for potential hosting of cation (left) and anion (right) by MFR.

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