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$Zn(OAc)_2•2H_2O$-catalyzed efficient synthesis of 5-Substituted 1*H*-tetrazoles

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In this communication, condensation from different aromatic, aliphatic and heteroaromatic aldehydes, hydroxyl amine, and sodium azide in toluene reflux was used to produce electronically and structurally distinct tetrazoles with a range of yields 5-94%. $Zn(OAc)_2•2H_2O$ (10 mol%) was used as a catalyst in the synthesis, which was eco-friendly, readily available, and affordable. The IR, NMR, and mass spectral studies were utilized in order to carry out a comprehensive characterization for all the 5-aryl tetrazole derivatives. This approach contributes to the current chemical synthesis of 5-substituted-1*H*-tetrazoles in an appealing and convenient manner thanks to its quick reaction times, good to exceptional yields, safe process, and straightforward workup.

1. Introduction

Since they perform many reactions in a single reaction step, multi-component reactions (MCRs) offer a tremendous potential for creating a variety of tiny bioactive frameworks with exceptional structural/atom economy. In addition, they are considered helpful tools for the creation of heterocyclic motifs that are active in biological and pharmacological processes.[1-3] Heterocyclic compounds make up the biggest diversity of chemical compounds and have a significant impact on industry. As a result, they are regarded as some of the most essential organic molecules.[4-8]

Tetrazoles, which are among the most significant synthetic heterocyclic compounds, have a wide range of applications across a variety of scientific disciplines, particularly in the fields of chemistry, materials science, and the medical sciences.[9-11] Tetrazoles have been shown to have higher lipophilicity than their comparable isosters (carboxylic acids), which increase their capacity to penetrate cells and increase their *in vivo* half-life and bioavailability. This is due to the fact that tetrazoles also have good metabolic stability. Tetrazoles have been shown to have significant pharmacological and biological effects, including anticancer, antiviral, and anti-HIV activity, as well as anti-inflammatory, antifungal, and antibacterial capabilities (**Fig. 1**).[12-15]

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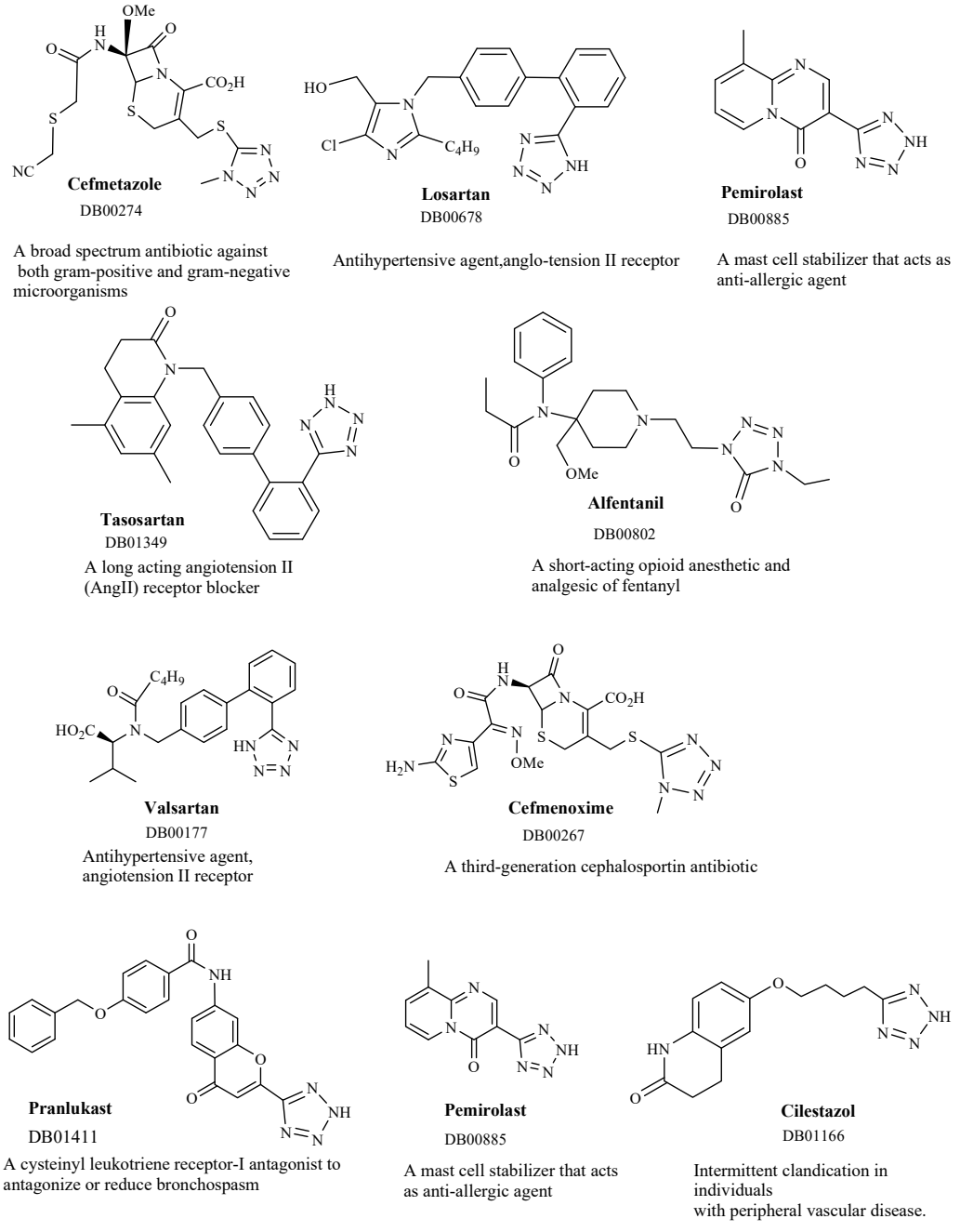


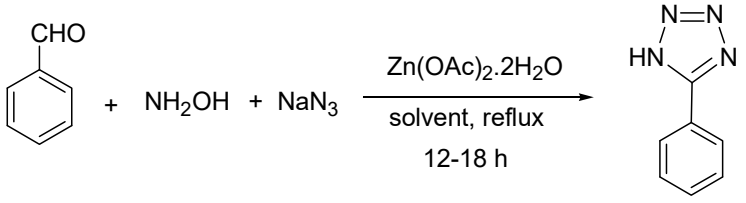
Fig. 1. Drugs containing 5-substituted 1*H*-tetrazole moiety commercially available.

The 5-substituted 1*H*-tetrazoles are the most fascinating heterocycles among the tetrazoles, and several different synthetic strategies have been established to construct such an important functionality. The fundamental step in the synthesis of 5-substituted 1*H*-tetrazole derivatives is the [2+3] cycloaddition of various nitriles with NaN_3 or $TMSN_3$ in polar aprotic solvents. It has been discovered that one can make tetrazoles by synthesizing them from nitriles, amides, thioamides, imidoyl chlorides, halides, ketones, amines, alkenes, or isocyanides using a variety of different methodologies. For this particular kind of reaction, a wide variety of catalysts have been tried and tested, including Bronsted or Lewis acids like $ZnBr_2$, $Fe(OAc)_2$, $FeCl_3$-SiO_2, $CdCl_2$, $B(C_6H_5)_3$, cyanuric chloride, CAN, TABF, $Ln(OTf)_3$-SiO_2, $NaHSO_4$-SiO_2, $InCl_3$, polymeric catalyst, ionic liquids, metal oxide nanoparticles, etc.[16-26] Low yields, creation of unwanted byproducts, exposure to dangerous or explosive chemicals, and high temperatures are common problems associated with the majority of these processes. Aluminum azide, tin azide, or silicon azide were typically used as the source of azide; however, each of these has a number of obvious disadvantages, including the fact that they are toxic organometallic reactants, that they are difficult to remove metal residuals, and that they are expensive substances. The discovery of Sharpless' click chemistry, which uses $ZnBr_2$ and sodium azide as a nitrogen source, represented a significant step forward in the process of synthesis for 5-substituted 1*H*-tetrazoles.[22]

The practical use of aldehydes for the preparation of target compounds would be very appealing due to their accessibility, diversity, lack of toxicity, and ease of handling.[27-35] In the past, the compounds that are based on zinc have been exploited in a wide variety of various catalytic processes.[36] After doing a meticulous search of all of the pertinent published information, we arrived to the conclusion that the relevant reaction has not involved $Zn(OAc)_2•2H_2O$. Other zinc catalysts such as $ZnBr_2$, ZnO, $ZnCl_2$, mesoporous ZnS nanospheres, and zinc hydrotalcite were utilized for the purpose; however, their application was limited to the [2+3] cycloaddition of a variety of nitriles with sodium azide (NaN_3).[22, 37-40] Under the conditions that are typically found in laboratories, zinc acetate is not only affordable but also simple to acquire and resistant to change in the presence of moisture and air.[41-58] Enthaler and his group observed that in the presence of zinc acetate, aldehydes and hydroxyl amines react together to get corresponding aldoximes in the presence of toluene with a negligible synthesis of corresponding nitriles.[59] In light of our prior knowledge and experience with zinc catalysis,[19, 43-46] a thorough search of the relevant literature, and the outcomes of control experiments, we decided to carry out the reactions necessary to synthesize 5-substituted tetrazoles by one-pot condensation from aldehydes, hydroxyl amine, and sodium azide using $Zn(OAc)_2•2H_2O$ as a catalyst.

2. Results and Discussion

As a model reaction, benzaldehyde (1 mmol) reacted with hydroxylamine hydrochloride (1.2 mmol) and sodium azide (1 mmol) under reflux conditions and tested in different solvents using $Zn(OAc)_2•2H_2O$ (20 mol%) as catalyst (**Scheme 1**). According to the findings in **Table 1**, the kind of solvent has an indisputable function in determining how far the reaction gets. In this regard, the model reaction was carried out under clean conditions at room temperature. Despite the fact that the reaction period was increased all the way up to 48 hr, no product production was observed (Table 1, entry 1). When determining whether or not a chemical reaction is possible, one important consideration is the temperature at which the reaction takes place. It is crucial in the context of one-pot MCR reactions given that excessively high temperatures frequently cause the development of a variety of undesirable byproducts.



Scheme 1. $Zn(OAc)_2•2H_2O$-Catalyzed synthesis of 5-phenyl-1*H*-tetrazole.

As it can be seen in Table 1, the use of toluene at reflux temperature produced the best results out of all of the other solvents that were tested for this study. As a result, this method was chosen for all of the subsequent reactions (Table 1, entry 3). THF was utilized in the reaction, which resulted in a moderate yield of 5-phenyl-1*H*-tetrazole (Table 1, entry 2). Even when the reactions were allowed to take longer, it was discovered that other solvents such as CH_3CN, EtOAc, DMF, acetone, and $CHCl_3$ were inappropriate (Table 1, entries 4-8).

Table 1. Effect of solvent

Entry	Solvent	Time (h)	Reaction condition	Yield (%)[a]
1	Neat	48	RT	0
2	THF	18	reflux	48
3	toluene	12	reflux	94
4	acetone	18	reflux	17
5	$CHCl_3$	18	reflux	22
6	DMF	18	reflux	32[b]
7	CH_3CN	18	reflux	12
8	EtOAc	18	reflux	8

[a]Isoalted yields; [b]Complex reaction mixture; [c]$Zn(OAc)_2•2H_2O$ loading: (95%, 20 mol%); (94%, 10 mol%) and (28%, 5 mol%)

Disappearance of aldehydic proton (δ 10.01) in ^{1}H NMR, δ 192.38 in ^{13}C NMR and ν 1710 cm^{-1} based on IR studies (aliquots taken in regular intervals) and appearance of broad peak of 3449 cm^{-1} (NH), 1562 (C=N), 1164 (C-N) peaks in IR proved to be the formation of desired tetrazole product in initial screening. Peak value of δ 155.33 (NH-**C**-C=N) in ^{13}C NMR further confirmed the formation of tetrazole. In addition, melting point of the synthesized tetrazole (214-216 ^{0}C) derived from benzaldehyde (model reaction) matched with the reported data[31].

Another significant component in the current procedure that must be considered in order to obtain 5-substituted 1*H*-tetrazole derivatives is the catalyst loading. When the model reaction was carried out without the presence of a catalyst, there was no increase in the yield of 5-phenyl-1*H*-tetrazole. In addition, it was discovered that a catalyst concentration of 10 mol% was adequate to keep the reaction going and produce a maximum isolated yield of 94%. Because of this, it was

decided that a 10 mol% concentration of $Zn(OAc)_2•2H_2O$ would be used in each of the succeeding processes. The following step was to analyze the effectiveness of the control reaction using a number of different zinc salts that were available (**Table 2**). The use of alternative zinc catalysts also resulted in the production of 5-phenyl-1*H*-tetrazole in yields that were either nil, very low, or moderate; however, the reaction durations needed to be lengthened (Table 2, entries 1-5). Therefore, the following reaction conditions have been determined to be optimal for the newly discovered method: $Zn(OAc)_2•2H_2O$ (10 mol%) in toluene with a reflux (Table 2, entry 6).

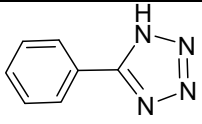
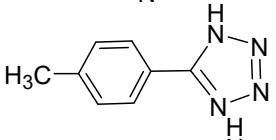
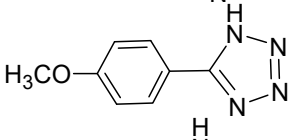
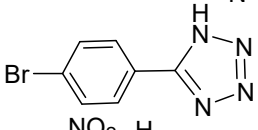
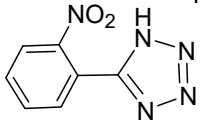
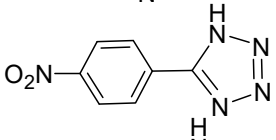
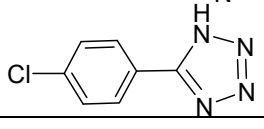
Table 2. Effect of zinc salts

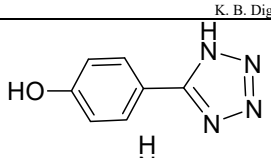
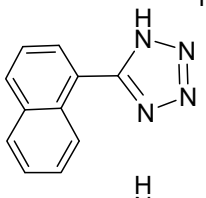
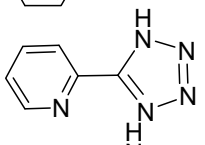
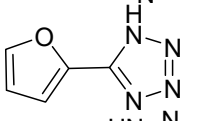
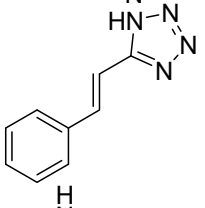
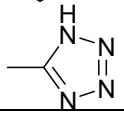
Entry[b]	Zinc salt	Reaction Time (h)	Yield[a] (%)
1	Zinc granules (crystalline)	20	-
2	$Zn(NO_3)_2$	48	11
3	$ZnCl_2$	12	48
4	$ZnSO_4$	48	07
5	$Zn_3(PO_4)_2$	48	15
6	$Zn(OAc)_2•2H_2O$	12	94

[a]Isolated yields. [b]reactions performed in toluene reflux for the specified time

In order to evaluate the effectiveness of this MCR, a number of 5-substituted-1*H*-tetrazoles were prepared by reacting a variety of aromatic, heteroaromatic and aliphatic aldehydes with sodium azide and hydroxyl amine under the optimized conditions. The results of this evaluation will be presented in the following excerpts (**Table 3**). It was revealed that the electron-donating groups and the electron-drawing groups that are present in aromatic aldehydes were able to interact with one another without any difficulty whatsoever (Table 3, entries 2-9). It was noteworthy to observe that the reaction involving heteroaromatic aldehydes, resulted in the creation of corresponding tetrazoles in high yields (Table 3, entries 10-11). Cinnamaldehyde, which is α,β-unsaturated compound, likewise responded favourably for the creation of the corresponding tetrazole (Table 3, entry 12). Alkyl aldehyde, such as acetaldehyde, was also put through the reaction, which led to the creation of the corresponding compounds in virtually insignificant amounts (Table 3, entry 13). IR, NMR, and mass spectrometry analyses were used to adequately characterize all of the known compounds, and these analyses revealed that the melting points of these compounds were in agreement with the data that was obtained in the published research.

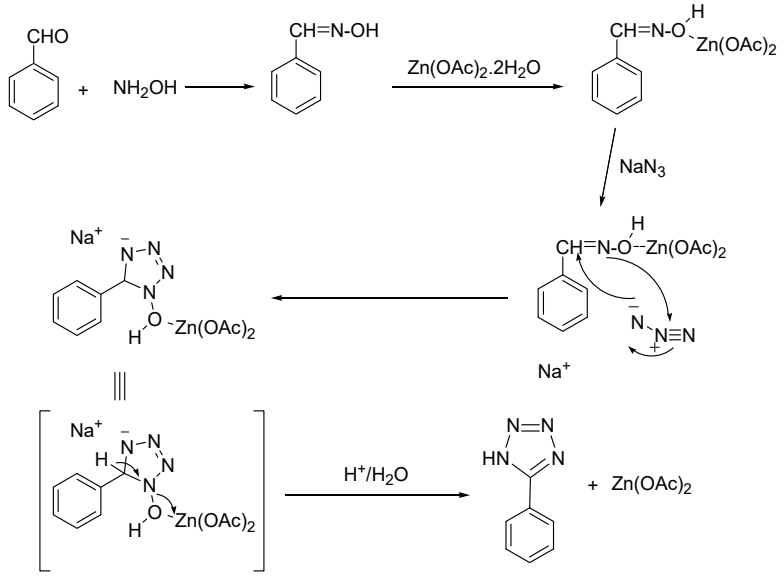
Table 3. $Zn(OAc)_2•2H_2O$-Catalyzed synthesis of 5-substituted 1*H*-tetrazoles

Entry	**Product**	**Time (h)**	**Yield[a] (%)**
1		12	94
2		12	89
3		12	92
4		12	85
5		18	78
6		12	81
7		12	80

8		12	68
9		12	90
10		12	85
11		12	88
12		12	82
13		24	5

[a]Isolated yields after column chromatography

There are excellent works reported on [3+2] cycloaddition reaction with the participation of azide moiety[59-60]. It should be noted that several mechanisms, such as polar or non-polar, might be possible for the transformation of azide to tetrazole [61-63]. Nitrile formation does not occur in the present work because of the azide ion's nucleophilic attack on the electron-deficient carbon atom[64]. Rather, cycloaddition occurs to create tetrazole. The activation of the C=N bond in this case is due to $Zn(OAc)_2$•$2H_2O$. By coordinating with the oxygen atom in the oxime, it does this. This might facilitate the [3+2] cycloaddition of NaN_3 over the C=N bond, leading to the formation of the substance known as 5-substituted 1*H*-tetrazole through the combination of acid hydrolysis and NaN_3 (**Scheme 2**).



Scheme 2. Plausible mechanism for $Zn(OAc)_2$•$2H_2O$-catalyzed 5-aryl-1*H*-tetrazole formation.

3. Conclusions

In conclusion, we have developed a novel method that is eco-friendly and atom inexpensive for the synthesis of 5-substituted 1*H*-tetrazoles in the presence of $Zn(OAc)_2$•$2H_2O$ as an effective catalyst. The addition of aldehyde and hydroxyl

amine as replacements for potentially hazardous nitrile precursors is the protocol's crowning achievement. The benefits of using this method include increased yields, a straightforward working-up approach, a catalyst that is not only readily available but also less expensive.

4. Experimental

For details, please see Supporting Information available.

This work confirms that heterocyclic compounds are very important in different fields due to the high variety of their applications.[65-72]

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