CHAPTER - III

Synthesis and characterization of certain new Tetrazole compounds
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3.1. Introduction

The development of tetrazoles chemistry has been largely associated with their broad spectrum of applications in pharmaceuticals, medicine, biochemistry, agriculture, and photography. Tetrazoles are used as lipophilic spacers and carboxylic acid surrogates, as well as corrosion inhibitors, components of gas generating compositions, in specialty explosives, photography, and information recording systems [1]. They are known to serve as effective ligands for a number of useful biochemical transformations and also as precursors for a variety of N-containing heterocycles [2]. Several tetrazoles are pharmaceutical agents, which act as pharmacophores for the carboxylate group, increasing their utility. Angiotensin II receptor blockers, in particular, often contain tetrazoles, such as Losartan and Candesartan. Although tetrazoles were discovered more than one hundred years ago, a systematic examination of these compounds was initiated in the latter half of the twentieth century.

Tetrazole was first prepared by the reaction of anhydrous hydrazoic acid and hydrogen cyanide under pressure. The reagents used in the basic method are highly toxic and expensive and are also water sensitive. In addition, hydrazoic acid is not only highly toxic, but also explosive and volatile. In view of these drawbacks, there has been an upsurge in the direction of modifying the method of preparation of tetrazoles [3-6]. Su et al [7] reported a series of 1-substituted 1H-1,2,3,4-tetrazoles that have been synthesized in good yields from amines, triethylorthoformate, and NaN\textsubscript{3} through the catalyzed reaction with Yb(OTf)\textsubscript{3}. A series of primary alcohols and aldehydes were treated with I\textsubscript{2} in NH\textsubscript{3}/H\textsubscript{2}O under microwave irradiation to give the intermediate nitriles, which, without isolation, underwent [2 + 3] cycloaddition with dicyandiamide and NaN\textsubscript{3} to afford the corresponding triazines and tetrazoles in high yields [8].Katritzky and co-workers [9] suggested a general method for the synthesis of 1, 5-disubstituted tetrazoles from imidoylbenzotriazoles under mild reaction conditions and shorter reaction times. A versatile and highly efficient Zn(OTf)\textsubscript{2}-mediated one-pot synthesis of 1,5-disubstituted tetrazoles derivatives has been achieved by Bhowmick et al [10] from alkenes, NBS, nitriles, and TMSN\textsubscript{3}. Sharpless and coworkers reported an innovative and safe procedure
for the synthesis of tetrazoles by the addition of sodium azide to nitriles using stoichiometric amounts of Zn (II) salts in H₂O [5]. Pizzo et al efficiently synthesized tetrazoles by the addition of TMSN₃ (trimethyl silyl azide) to organic nitriles using 10 mol% Bu₄NF as catalyst [6]. Recently Lakshmikantham et al [11] have developed a simple and efficient method for the preparation of 5-substituted 1H-tetrazoles via [2+3]-cycloaddition using nanoZnO as a heterogeneous catalyst. Various nitriles reacted with NaN₃ at 120–130°C to yield the corresponding 5-substituted 1H-tetrazoles with moderate to good yields. The catalyst could also be readily recovered and reused.

Treatment of organic nitriles with NaN₃ in the presence of varieties of catalysts enabled synthesis of 5-substituted 1H-tetrazoles, which found advantageous in the filled of C-N bond formation reactions [12–15]. Heravi et al [16] developed an easy and efficient one-pot, three-component Cu(OAc)₂ catalyzed reaction of aldehydes, hydroxylamine, and [bmim]N₃, which enabled the synthesis of 5-substituted 1H-tetrazole derivatives.

\[
\text{R} - \text{N} = \text{N} \quad \text{O} + 1.2 \text{eq.} \quad \text{NH}_2 \text{OH} + 1.5 \text{eq.} \quad [\text{bmim}]\text{N}_3 \quad \frac{0.2 \text{eq. Cu(OAc)}_2}{\text{DMF}} \quad 120°C, 12 \text{h}
\]

In another reaction scheme, Su and co-workers [17] synthesized. A series of 1-substituted 1H-1,2,3,4-tetrazole compounds have been synthesized in good yields from amines, triethylorthofomrate, and sodium azide through the catalyzed reaction with Yb(OTf)₃.

\[
\text{R} - \text{NH}_2 + \text{HIO} \quad \text{CET} + \text{NaN}_3 \quad \frac{0.2 \text{eq. (Yb(OTf))}}{\text{MeOCH}_2\text{CHCH}} \quad 100°C, 69 \text{h}
\]

The work of Shie and Fang [18] a series of primary alcohols and aldehydes were treated with iodine in ammonia water under microwave irradiation to give the intermediate nitriles, which without isolation underwent [2 + 3] cycloadditions with dicyandiamide and sodium azide to afford the corresponding triazines and tetrazoles in high yields.

\[
\text{R} - \text{H} \quad 1.1 \text{eq. I₂} \quad \text{NH}_3(28\% \text{aq.}) \quad \text{r.t., 1-2 h} \quad \left[\text{R-CN}\right] \quad \frac{4 \text{eq. NaN}_3 \quad 2 \text{eq. ZnBr}_2}{\text{MW (80 W)}} \quad 80°C \quad 10-15 \text{min}
\]
Cascade reactions starting from isocyanides allowed El Kaim and others [19] a straightforward synthesis of five-membered ring heterocycles. Addition of sodium azide on isocyanide dibromides followed by electrocyclization and a Suzuki coupling affords tetrazoles scaffolds, whereas addition of tetrazoles on isocyanide dibromides followed by Huisgen rearrangement and a Suzuki coupling gives triazoles scaffolds.

Katritzky’s research group [20] developed a general method for the synthesis of 1,5-disubstituted tetrazoles from imidoyl benzotriazoles involves mild reaction conditions and short reaction times.

Joo and Shreeve [21] examined a reaction of cyanogen azide and primary amines, which generated imidoyl azides as intermediates in acetonitrile/water. After cyclization, these intermediates gave 1-substituted amino tetrazoles in good yield.

Hajra, Sinha and Bhowmick [22] conducted a versatile and highly efficient Zn (OTf)2-catalyzed one-pot reaction of alkenes, NBS, nitriles, and TMSN3 gives various 1,5-disubstituted tetrazoles containing an additional α-bromo functionality of the N1-alkyl substituent.

Laha and Cuny [23] successfully performed a reaction of 2-halopyridines with trimethylsilyl azide in the presence of tetrabutylammonium fluoride hydrate gives
tetrazolo[1,5-a]pyridines. 8-bromotetrazolo [1, 5-a] pyridine is further transformed into a variety of novel tetrazolo[1,5-a]pyridine derivatives.

Keith’s work on tetrazoles [24] revealed that Pyridine N-oxides were converted to tetrazolo[1,5-a]pyridines in good yield in the presence of sulfonyl or phosphoryl azides and pyridine by heating in the absence of solvent. Diphenyl phosphorazidate (DPPA) was the most convenient reagent for this protocol.

The best known and most successful example of such use of tetrazole is the series of antihypertensive preparations. Losartan 1, irbesartan 2, candesartan 3 and valsartan 4 are famous anti-hypertensive drugs belong to the class of non-peptide angiotensin-II inhibitors, which prevents the increase in blood pressure have biphenyl tetrazolyl moiety in their structure. Losartan belongs to the class of angiotensin II receptor antagonists, and a large number of papers have been dedicated to it.
In spite of a significant work on the synthesis on a broad spectrum of tetrazole synthesis continuous efforts are still diverted on the development of new eco-friendly catalysts for the synthesis of tetrazoles as part of author’s efforts on the formation of C-N bonds. The findings are compiled Chapter-III, depicts Cadmium Chloride as an efficient catalyst for a neat synthesis of 5-substituted 1H-tetrazoles.

3.2. (Chapter –III): Cadmium Chloride as an efficient catalyst for a neat synthesis of 5-substituted 1H-tetrazoles

Catalysis plays an ever increasing role in pharmaceutical and industrial manufacturing because of process efficiency. CdCl₂ is an economically cheap Lewis acid that is used in a variety of reactions as an efficient catalyst [25-28]. Electron-deficient olefins undergo rapid Aza-Michael reaction with a wide range of amines catalyzed by CdCl₂ at room temperature[25]. CdCl₂ is described as an efficient catalyst for one-pot synthesis of 3,4-dihydropyrimidin-2-ones from a three-component Biginelli reaction of acetoacetate, aldehydes and urea [26], an improved safe method that does not contaminate the environment with cadmium chloride, a toxic heavy metal salt, was developed for the synthesis of phosphatidylcholine [27]. However, to the best of our knowledge CdCl₂ has not been employed as a catalyst for the synthesis of tetrazoles. In this communication we report the synthesis of 5-substituted 1H-tetrazoles from a wide variety of organic nitriles with NaN₃ using CdCl₂ as a Lewis acid catalyst for the first time (Scheme 3.1).

Scheme 3.1. Synthesis of 5-substituted 1H- tetrazoles catalyzed by CdCl₂
Table 3.1: Screening of reaction parameters for the formation phenyltetrazole\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Azide</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>NaN</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>NaN</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>NaN</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>NaN</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>TMSN\textsubscript{3}</td>
<td>62</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: Benzonitrile (1 mmol), NaN\textsubscript{3} (2 mmol), CdCl\textsubscript{2} (0.1 mmol), DMF (5 mL), reaction time (6 h), 80°C.; \textsuperscript{b}Yields of isolated products.

In an effort to develop a better catalytic system, various reaction parameters were screened for [2+3] cycloaddition of benzonitrile with NaN\textsubscript{3} to yield 5-phenyltetrazole and are presented in Table 3.1. The solvent has a pronounced effect in these reactions (Table 2.1, entries 1-4), in which DMF was proved to be the best solvent to give good yields of corresponding tetrazole, whereas DMSO and NMP provided moderate yields, and H\textsubscript{2}O gave poor yields of 5-phenyltetrazole. TMSN\textsubscript{3} is also used in the reaction with benzonitrile in DMF at about 80°C (Table 3.1).

In order to clarify the scope and limitations of the CdCl\textsubscript{2} mediated [2+3] cycloaddition reaction, various structurally divergent benzonitriles possessing a wide range of functional groups were reacted with NaN\textsubscript{3} to give the corresponding tetrazoles and the results are summarized in Table 3. The various nitriles tested are aromatic, heteroaromatic and benzylic, the aromatic benzonitrile gave moderate to good yields (Table 3.2, entries 1-11). 4-Chlorobenzonitrile provided the corresponding tetrazole with good yield whereas 2-chlorobenzonitrilene(not included in table) gave slightly less yield compared to its paracounter part this might be due to a more pronounced steric effect of chloro group at orthoposition. Compared with electron-withdrawing groups such as hydroxy, chloro, cyano, and formyl groups present on the aromatic ring (Table 2, entries 2-7). 4-formylbenzonitrile gave only 1\textit{H}-tetrazole with carbonyl (aldehyde) functionality untouched (Table 3, entry 3). 1,2-dicyanobenzene and 1, 4-dicyanobenzene afforded mono
addition product (Table 3.2, entry 2 and 5). Aliphatic nitriles such as 4-chlorophenyl acetonitrile, phenyl acetonitrile and (Phenylsulfonyl) acetonitrile provided moderate yields of corresponding tetrazoles with long duration of time (Table 2. entries 11 and 12). Heteroaromatic nitriles such and 2-pyridinecarbonitrile, cyanopyrazine gave the corresponding tetrazoles in shorter reaction times with excellent yields (Table 2.2, entries 9 and10).

3.2 (a) **Experimental:** To a mixture of benzonitrile (1mmol), sodium azide (2 mmol) in DMF (5 mL) CdCl$_2$ was added (0.1 mmol) and stirred at 80 °C for 6 h. After completion of reaction (as monitored by TLC), the reaction mixture is treated with ethyl acetate (30 mL) and washed with distilled water, and then the organic layer is treated with 5N HCl (20 mL) and stirred vigorously. The resultant organic layer is separated and the aqueous layer is again extracted with ethyl acetate (20 mL). The combined organic layers are washed with water and concentrated to give the crude solid crystalline 5-phenyltetrazole. Column chromatography is performed using silica gel (100-200 mesh) to afford pure 5-phenyltetrazole, which was characterized by NMR, and mass spectroscopic studies:

\[ ^1H \text{NMR} \ (200 \text{ MHz, CDCl}_3+\text{DMSO}) \delta 8.04 \ (m, 2H), \ 7.61 \ (m, 3H) ; \ MS \ (70 \text{ eV}) \ m/z (\%) \]

1460

Othersynthesized compounds were characterized similarly.
Table 3.2. CdCl\(_2\) mediated preparation of 5-substituted 1\(H\)-tetrazoles\(^a\)

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{Time (h)} & \text{Yield (\%)} \\
1 & \begin{array}{c}
\text{CN}
\end{array} & 5 & 91 \\
2 & \begin{array}{c}
\text{CN}
\end{array} & 5 & 82 \\
3 & \begin{array}{c}
\text{OH}
\end{array} & 5 & 80 \\
4 & \begin{array}{c}
\text{Cl}
\end{array} & 4 & 95 \\
5 & \begin{array}{c}
\text{CN}
\end{array} & 6 & 75 \\
6 & \begin{array}{c}
\text{HO}
\end{array} & 6 & 90 \\
7 & \begin{array}{c}
\text{CN}
\end{array} & 8 & 76 \\
8 & \begin{array}{c}
\text{HO}
\end{array} & 5 & 72 \\
9 & \begin{array}{c}
\text{CN}
\end{array} & 3 & 85 \\
10 & \begin{array}{c}
\text{CN}
\end{array} & 4 & 72 \\
11 & \begin{array}{c}
\text{SO}_2
\end{array} & 12 & 65 \\
12 & \begin{array}{c}
\text{CN}
\end{array} & 12 & 62 \\
\end{array}
\]

\(^a\) Reaction conditions: Benzo Nitrile (1 mmol), NaN\(_3\) (2 mmol), CdCl\(_2\) (0.1 mmol), DMF (5 mL), 80-90\(^\circ\)C.; \(^b\) yields of Isolated yields.
Conclusions:

In conclusion, efficient and clean methods have been developed for the synthesis of 5-substituted 1H-tetrazoles via [2+3] cycloaddition using an economically cheap CdCl$_2$ catalyst. In CdCl$_2$ catalysed protocol, a number of structurally divergent nitriles were used with NaN$_3$ in the reactions at 80°C temperatures to yield the corresponding 5-substituted 1H-tetrazoles with moderate to good yields. The methodology developed in this work may find widespread use for the preparation of 5-substituted 1H-tetrazoles in the field of organic synthesis.

References


$^1$H NMR spectrum of 5-Phenyltetrazole
Mass spectrum of 5-Phenyltetrazole

m/Z = 146
$^1$H NMR spectrum of 5-(4-Chlorophenyl) tetrazole
Mass spectrum of 5-(4-Chlorophenyl) tetrazole
$^1$H NMR spectrum of 5-Benzensulfonylmethyl-1H-tetrazole
Mass spectrum of 5-Benzensulfonylmethyl-1H-tetrazole