Chapter II

One-pot three-component synthesis of 5-substituted 1*H*-tetrazoles from aldehydes

II.1. Introduction

Tetrazoles are five-member heterocyclic compound with one carbon atom and four nitrogen atoms. They are considered to have highest number of nitrogen atoms among all the heterocyclic compounds reported in literature. There are three possible canonical forms of tetrazole (Figure II.1).

Figure II.1. Tautomers of tetrazole

Nowadays, multi-component reactions have been focused on exploring the synthesis of most profuse and integral scaffold, *N*-heterocyclic compounds which are found in large number of bioactive natural products, synthetic drugs and pharmaceuticals. Recently, among the *N*-heterocycles, tetrazole has received much attention due to its diverse applicability (Figure II.2) which are ubiquitous such as in drugs and pharmaceuticals due to its low toxicity and high lipophilicity, in coordination chemistry as ligands due to its ability of formation of stable complexes with various metal, in catalysis technology, in medicinal chemistry as stable surrogates for carboxylic acids, in the photographic industry, in organometallic chemistry as effective stabilizers of metallopeptide structures, in various materials science applications and

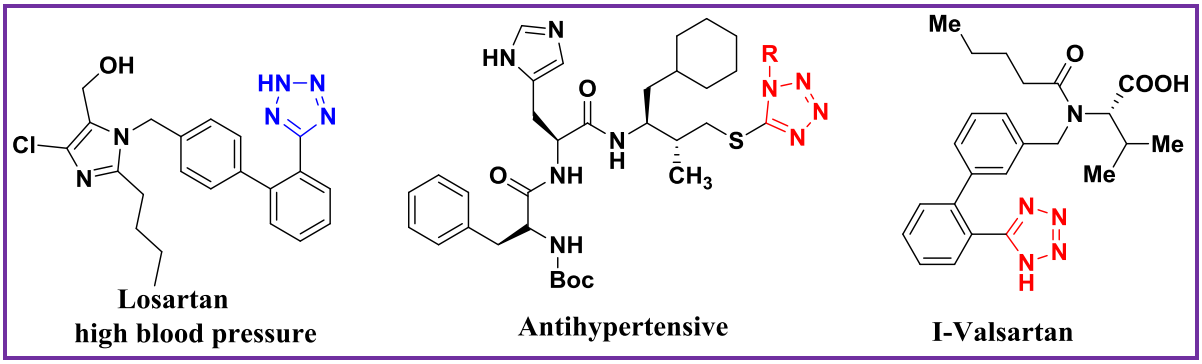


Figure II.2. Biologically active compounds containing tetrazole moiety

also broadly used as herbicides and fungicides in agriculture.[1–9] Owing to its stability over broad pH range, good tolerance of oxidizing and reducing agent, it is considered as a versatile moiety in organic synthesis.[10] Tetrazole based drugs are explored in pharmaceutical and medicinal industry due to its vast array of activities like antihypertensive, anti-allergic, antibiotic[11-13] and anticonvulsants[14] which are found well documented in literature.[15] Besides,

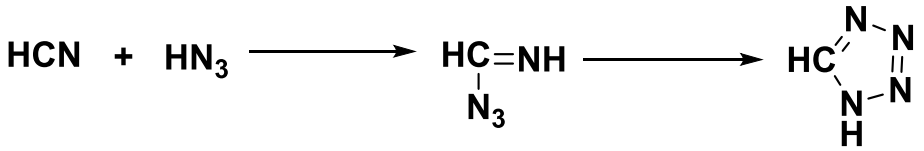
in treatment of dreaded diseases, such as cancer and AIDS tetrazole based drugs are very effective.[17]

II.2. Background and Objectives

II.2.1. Classical method for synthesis of tetrazole

Tetrazole was first prepared by J. A. Bladin, a Swedish chemist, in the year of 1885 at the University of Upsala while he was investigation reactions of dicyanophenylhydrazine.[18]

Later simplest synthesis of tetrazole was reported by Dimroth and Fester [19] in 1910 by direct combination of hydrazoic acid and hydrogen cyanide (Scheme II.1). They suggested the formation of formimidazide followed by rearrangement to give tetrazole although no experimental evidence was presented then to support the mechanism.



Scheme II.1. Synthesis of tetrazole as proposed by Dimroth and Fester

II.2.2. Modern methods of synthesis of 5-substituted 1*H*-tetrazole

Many different protocols (Figure II.3) have been reported for synthesis of 5-substituted-1*H*-tetrazole but the most extensively used methods involve [3+2] cycloadition of organic nitrile and azide anion in presence of homogenous[20-24] and heterogeneous catalyst[25-34] where the source of azide may be metal azide or hydrazoic acid. Some of these methods are not promising and limited due to use of toxic solvents, expensive reagents, formation of side products, use of strong Lewis gastric acid or organic azide complexes such as tin or silicon organic azide which leads to metal contamination and in some processes, the reaction proceeds *via* producing *in situ* toxic and water sensitive low boiling hydrazoic acid (b.p.-37 ^{o}C). Some of the reported protocols from literature using various substrates are briefly discussed below.

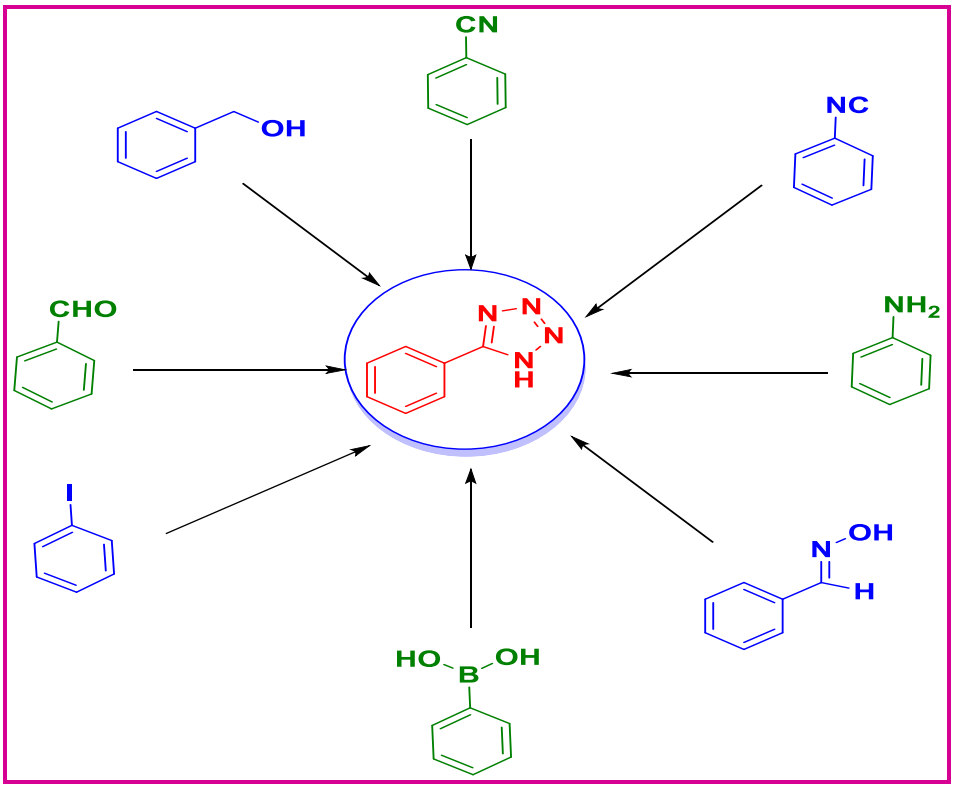
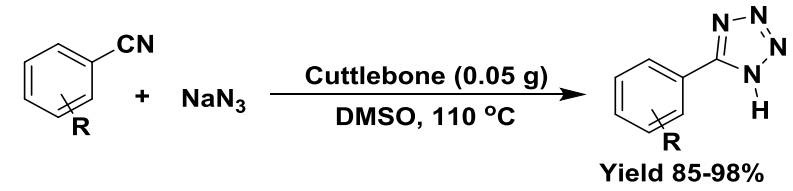


Figure II.3. Schematic approaches for synthesis of tetrazole derivatives from various synthons

II.2.2.1. Synthesis of tetrazole derivatives from nitriles

As I previously mentioned that the broadly used methods for synthesis of tetrazole involves [3+2] cycloadition of organic nitrile and azide anion in presence of various catalysts. Some of the examples are discussed below.

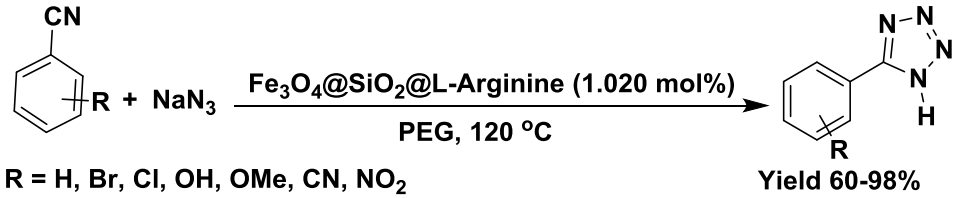
In 2015, S. S. E. Ghodsinia *et al*. reported a [3+2] cyclo-addition for synthesis of 5-substituted-1*H*-tetrazoles from nitriles with sodium azide in absence of any metal catalyst (Scheme II.2).[35] This reaction was catalyzed by mesoporous cuttlebone, a natural low cost heterogeneous catalyst in DMSO through "electrophilic activation" of nitriles *via* hydrogen bond formation between cuttlebone and nitrile.



R = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 9-phenanthrene, 2-thiophene, 4-pyridine, 2-pyridine

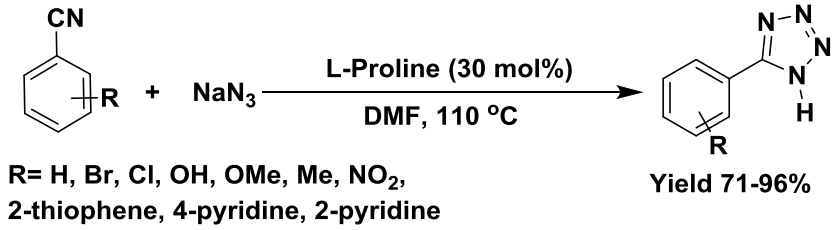
Scheme II.2. Synthesis of tetrazoles from nitrile using cuttlebone

In 2016, A. Ghorbani-Choghamarani *et al*. synthesized a non-corrosive heterogeneous nano structural compound (Scheme II.3).[36] The synthesized catalyst was then used to perform the [3+2] cyclo-addition of nitriles with sodium azide for synthesis of 5-substituted-1*H*-tetrazole very nicely with reusability of the catalyst for four continuous cycles.



Scheme II.3. Cu(II) immobilized on Fe_3O_4@SiO_2@L-Arginine catalyst in the preparation of tetrazole

In 2018, S. B. Bhagat *et al*. demonstrated the same protocol with the greener catalyst L-proline which is safer and economical alternative to hazardous Lewis acid catalyzed methods (Scheme II.4).[37]

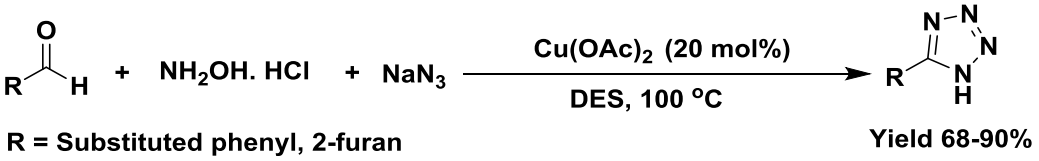


Scheme II.4. A simple synthesis of tetrazole using amino acid

II.2.2.2. Synthesis of tetrazole derivatives from aldehydes *via* one-pot three-component protocol

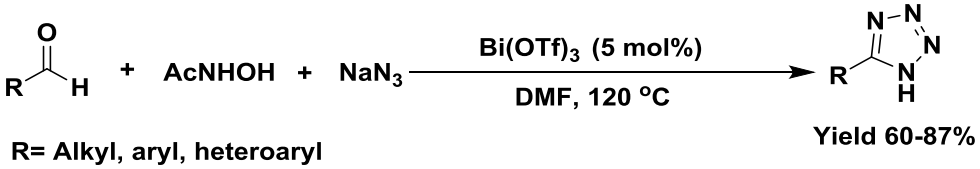
In past decade, one pot multi-component reactions (MCR) have received much attention for the synthesis of diverse heterocyclic molecules and contribute to sustainability by simplifying the synthetic route. MCRs combine three or more starting reagents at a time in the same pot to create the target molecule since there is no need of separating intermediate which help to reduce the energy consumption, solvent waste and reaction time and thus have the advantages of synthetic efficiency, simplicity and atom economy compared to the conventional multistep synthetic routes. MCRs are more powerful procedures in the diversity-oriented convergent synthesis of organic heterocycles from simple and easily available substrates.

X. Xiong *et al*. in 2019 synthesized tetrazole moiety in presence of catalytic amount of $Cu(OAc)_2$ in deep eutectic solvent (DES) as a greener solvent (Scheme II.5).[38] DES is a eutectic mixtures of quaternary ammonium salts and hydrogen bond donors with low melting points.



Scheme II.5. $Cu(OAc)_2$ in deep eutectic solvent (DES) for synthesis of tetrazole

In 2013 M. Sridhar *et al*. demonstrated a methodology using acetohydroxamic acid as a best alternative of hydroxyl amine hydrochloride in presence of Lewis acid catalyst $Bi(OTf)_3$ furnishing good yield of the product (Scheme II.6).[39]

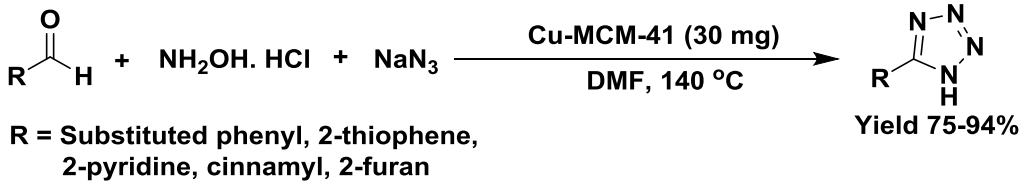


Scheme II.6. $Bi(OTf)_3$: A Lewis acid catalysed synthesis of tetrazole

In 2019, N. T. Hatvate *et al*. utilized zeolite-based heterogeneous catalyst (ZSM-5) in DMF at 100 ^oC (Scheme II.7).[40] The heterogeneous catalyst was recovered and recycled without noticeable loss of its catalytic activity.

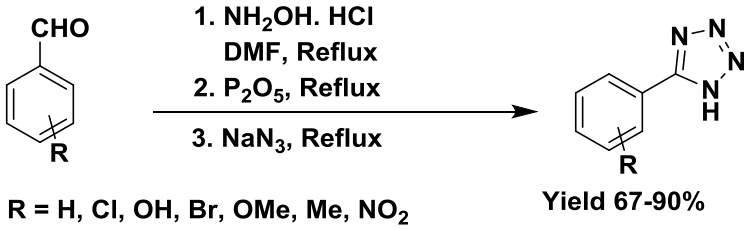
Scheme II.7. Synthesis of tetrazole derivatives using zeolite-based heterogeneous catalyst

The use of catalytic amount of Cu-MCM-41 as a nanostructured, heterogeneous and reusable catalyst was proposed by M. Abdollahi-Alibeik *et al*. for synthesis of tetrazole derivatives in 2015 (Scheme II.8).[41] In their research, Cu-MCM-41 nanoparticles with three Cu/Si molar ratios were prepared and characterized by various techniques. The characterization and optimization results show that the catalyst with Cu/Si molar ratio of 0.050 has the best catalytic activity.



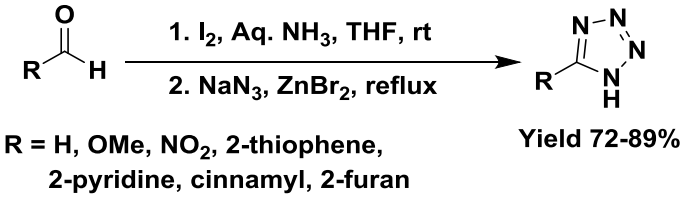
Scheme II.8. Cu-MCM-41 nanoparticles induced three-component synthesis of tetrazole

A simple protocol was described by K. M. Khan *et al*. in 2015 by using dehydrating agent P_2O_5 proceeding *via* non-isolated oxime and nitrile intermediates in absence of any additional catalyst (Scheme II.9).[42]



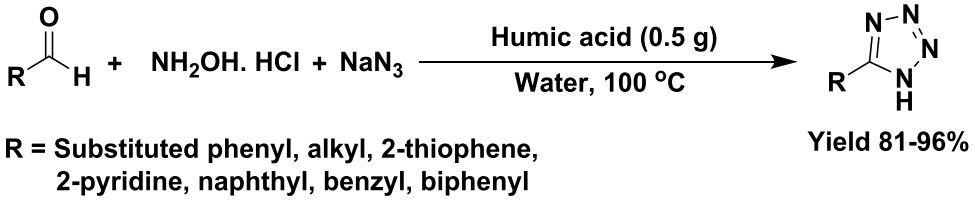
Scheme II.9. Utilisation of dehydrating agent P_2O_5 for development of tetrazole

The role of iodine as catalyst was demonstrated in the same methodology by J. -J. Shie *et al*. in 2003 (Scheme II.10).[43] This one-pot tandem reaction was performed in THF medium at room temperature and ammonia was used instead of hydroxyl amine as a source of nitrogen atom.



Scheme II.10. One-pot tandem reaction for synthesis of tetrazole moiety

Development of an one-pot three-component protocol using a non-toxic high molecular weight polymer, humic acid was done by H. Wang *et al*. in 2020 (Scheme II.11).[44] Humic acid is a reusable catalyst and good alternative to any hazardous acid catalyst.

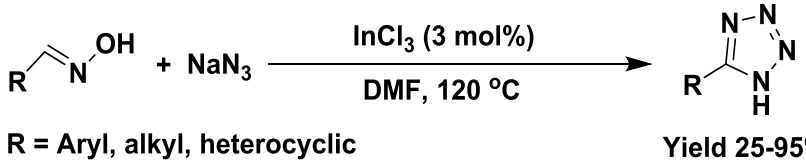


Scheme II.11. Synthesis of tetrazole by high molecular weight polymer

II.2.2.3. Synthesis of tetrazole moiety from various synthons

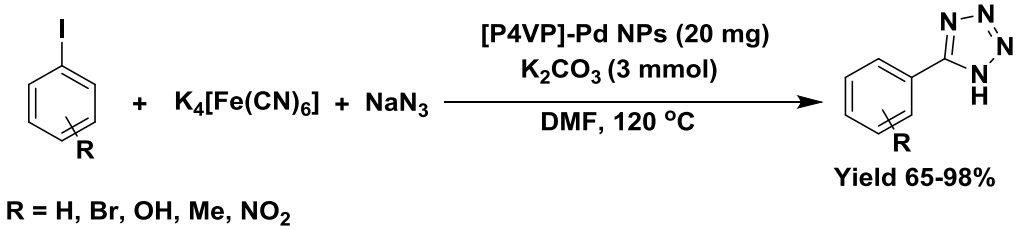
Tetrazole can be synthesized from various starting materials. Few reactions are depicted below.

S. D. Guggilapu *et al*. in 2016 demonstrated the synthesis of tetrazoles from oxime utilizing $InCl_3$ as a Lewis acid catalyst (Scheme II.12).[45] Here, they used oxime, the intermediate formed during the synthesis of tetrazoles from aldehydes for this reaction.



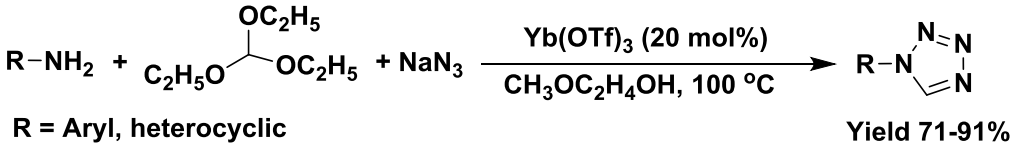
Scheme II.12. Synthesis of tetrazole from oxime using Lewis acid catalyst

In 2017, S. S. A. D. M. Abadi *et al*. described a one-pot tandem method for synthesis of tetrazole moiety from iodobenzene using heterogeneous Pd-nanoparticle as catalyst. In this protocol, $K_4[Fe(CN)_6]$ was used as a source of cyanide (Scheme II.13).[46]



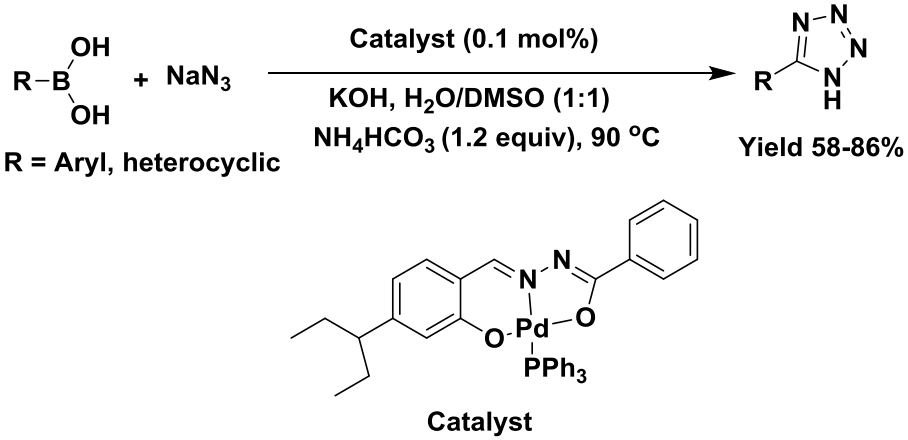
Scheme II.13. A heterogeneous Pd-nanoparticle for synthesis of tetrazole from iodobenzene in presence of $K_4[Fe(CN)_6]$

A series of tetrazole compounds have been synthesized from amines, triethyl orthoformate and sodium azide through a Lewis acid catalyst $Yb(OTf)_3$ by W. –K. Su *et al*. in 2006 (Scheme II.14).[47] Some of the 1-susbstituted 1*H*-1,2,3,4-tetrazole compounds showed strong phytocidal activity.



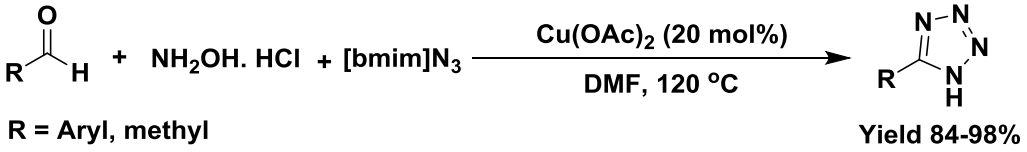
Scheme II.14. Synthesis of 1-susbstituted 1*H*-1,2,3,4-tetrazole from amine and orthoformate

A. Vignesh *et al*. in 2019 reported the direct conversion of arylboronic acids into tetrazole derivatives catalyzed by a new ONO pincer type Pd(II) complex (Scheme II.15).[48]



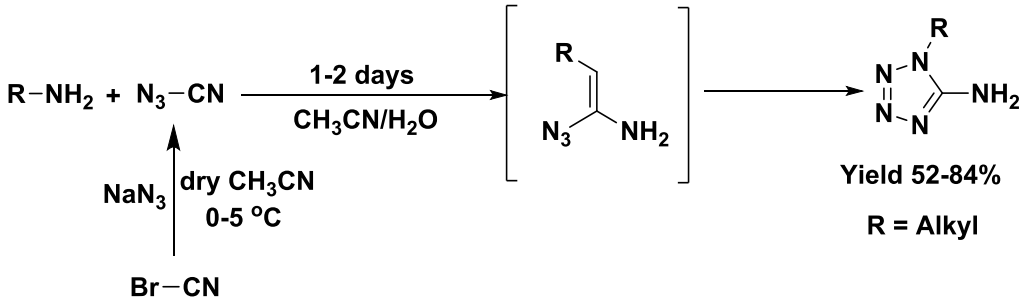
Scheme II.15. ONO pincer type Pd(II) complex: A heterogenous catalyst for synthesis of tetrazole from phenyl boronic acid

M. M. Hevari *et al*. in 2012 developed a protocol using ionic liquid as a source of azide ion instead of classical NaN_3 (Scheme II.16).[49] In the structure of this ionic liquid, azide is a counter ion and it was used as nucleophile in the reaction.



Scheme II.16. Synthesis of tetrazole derivative using ionic liquid azide

In 2008, J. M. Shreeve *et al.* synthesized 1-substituted-5-aminotetrazoles from primary amines using cyanogen azide and the reaction was proposed to take place through imidoyl azide as an intermediate (Scheme II.17).[50]



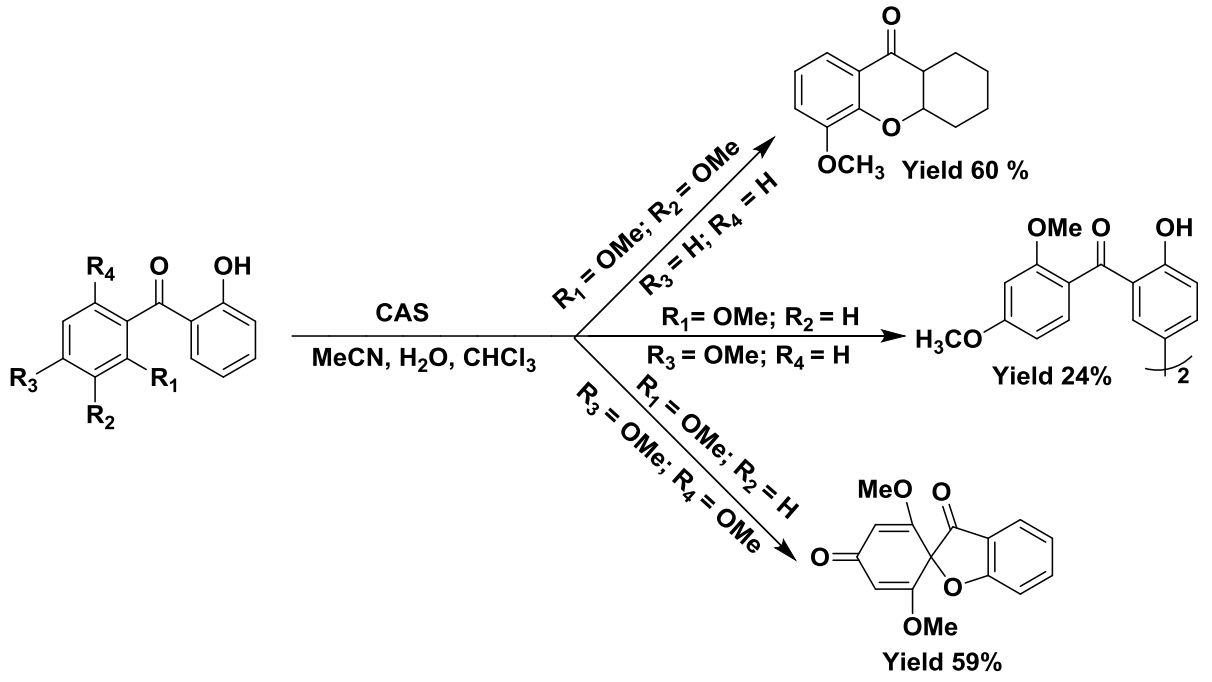
Scheme II.17. Cyanogens azide: A source of azide for synthesis of 5-aminotetrazoles

II.2.3. Role of various cerium components as catalyst in organic synthesis

Cerium has properties like non-toxic, eco-friendly[51] which is unique among the lanthanides. Further it is air stable, can be easily handled and has considerable degree of experimental simplicity. However, $(NH_4)_4Ce(SO_4)_4.2H_2O$, a commercially available, non-toxic and

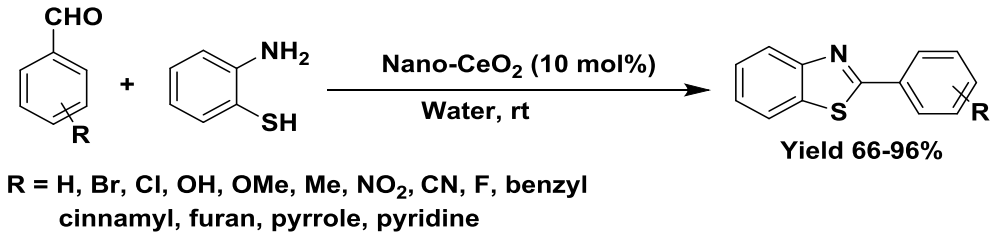
recyclable catalyst has not yet much explored to best of our knowledge. It has many remarkable features such as inexpensive, readily available, simple handling and environmentally friendly. Importantly, compared with other solid acid catalysts, it can be easily removed after completion of the reaction by simple filtration. So, keeping all these things in mind, we have chosen ceric ammonium sulphate [$(NH_4)_2Ce(SO_4)_4.2H_2O$] as a catalyst. From literature survey, we found only one article regarding the use of this catalyst which has been given below. Use of other salt of cerium metal as catalyst was observed in literatures which are also included here.

Exploration of reaction by subjecting an additional set of phenolic benzophenones to CAS to afford a range of compounds, including xanthones, 9*H*-xanthen-2,9(4a*H*)-diones, 3*H*-spiro[benzofuran-2,1-cyclohexa[2,5]-diene]-3,4-diones and biaryl compounds were depicted by J. Dam *et al*. in 2019 (Scheme II.18).[52] A comparison of these reactions with the more commonly used oxidant ceric ammonium nitrate (CAN) was also conducted. Based on these results, greater insight into the reaction mechanism has been gained. In addition, the conversion of the synthesized xanthen-2,9(4a*H*)-diones to xanthones by treatment with sodium dithionite was described.



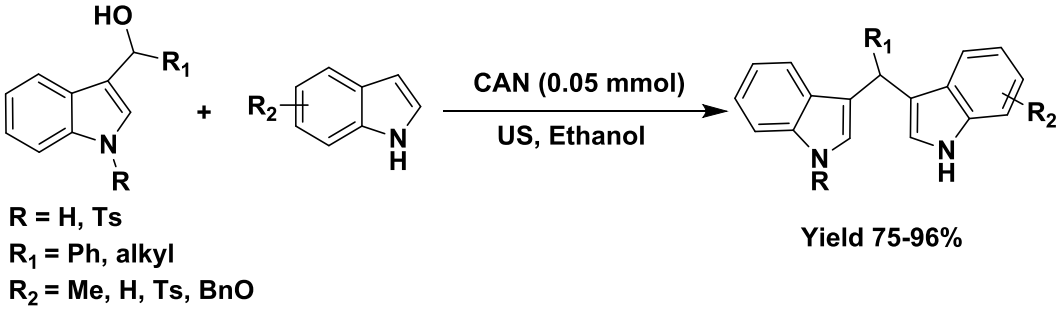
Scheme II.18. CAS as a catalyst in organic synthesis

In 2013, R. Shelkar *et al*. synthesized a series of substituted benzothiazoles by combining 2-aminothiophenol with a vast array of aldehydes in presence of nano-ceria (CeO_2) as an efficient heterogeneous catalyst (Scheme II.19).[53] Nano-ceria gave better yield for this reaction than other metal nano-particles. They reported that the used heterogeneous catalyst can be easily separable and recyclable up to three cycles.



Scheme II.19. Synthesis of substituted benzothiazoles by using nano-ceria

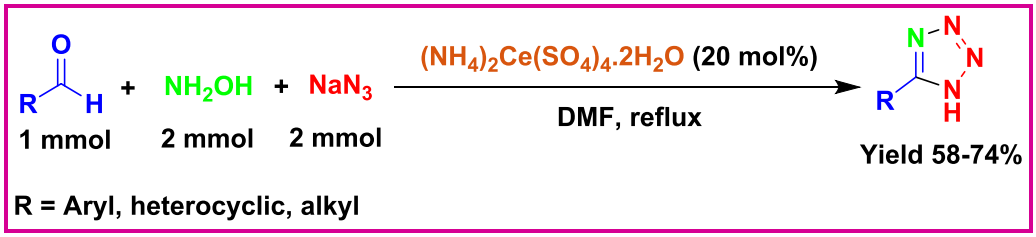
X. -F. Zeng *et al*. in 2005 reported a protocol in which the reaction of indole with (1*H*-indol-3-yl)(alkyl)methanol was catalyzed efficiently by inexpensive and easily accessible ceric ammonium nitrate under ultrasonic irradiation to afford the unsymmetrical bis(indolyl)alkane in good yields (Scheme II.20).[54]



Scheme II.20. CAN: A Lewis acid catalyst for synthesis of unsymmetrical bis(indolyl)alkane

II.3.Present work: Result and Discussion

Herein we report a simple, convenient and robust protocol for synthesis of 5-substituted 1*H*-tetrazole by the reaction of aldehyde, hydroxylamine hydrochloride ($NH_2OH.HCl$) with solid sodium azide (NaN_3) in presence of 20 mol% of $(NH_4)_4Ce(SO_4)_4.2H_2O$ as a catalyst in DMF solvent (Scheme II.21). Further recyclability of the solid catalyst has also been studied.

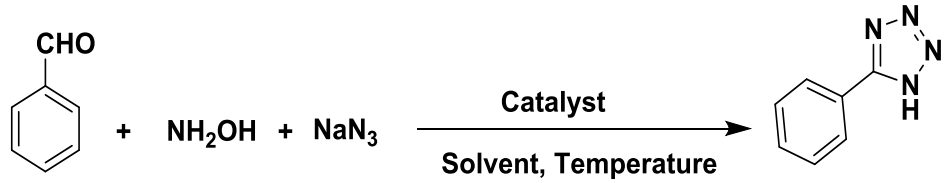


Scheme II.21. One-pot three-component synthesis of 5-substituted 1*H*- tetrazole from aldehyde

II.3.1. Optimization of the reaction conditions

A mixture of benzaldehyde, hydroxylamine hydrochloride and sodium azide was selected as a model reaction for screening the reaction condition. The reaction parameter such as solvent, temperature and amount of catalyst has profound effect in promoting the reaction. The reaction was carried out in presence of different amount of $(NH_4)_4Ce(SO_4)_4.2H_2O$ and different solvents like methanol, ethanol, water, acetonitrile, toluene and DMF (Table II.1, entry 1-6) which were monitored by TLC. For this investigation of the effect of solvent, loading of catalyst was 50 mol% per mmol of aldehyde. The result was shown in Table II.1. It was observed that only DMF afforded the desired product and it was the best solvent for this protocol in terms of time and yield (Table II.1, entry 7, 8). In other solvent, only oxime was formed which was monitored by TLC. In this regards, we examined the loading of catalyst and reduced the amount of catalyst by 20% and it has been found that it also afforded good conversion (Table II.1, entry 8). But when 10 mol% of catalyst was used, yield was only 44% (Table II.1, entry 9). However, while performing the reaction under completely solvent-free condition at 140 ^oC for 24 h using 50 mol% catalyst (Table II.1, entry 11), no product was formed and in absence of catalyst only oxime was formed (Table II.1, entry 10).

Table II.1. [a]Optimisation of reaction condition for synthesis of 5-substituted 1*H*-tetrazole



Entry	Catalyst (mol%)	Solvent	Time (h)	[b]Yield (%)
1	50	Methanol	8	Only oxime
2	50	Ethanol	8	Only oxime
3	50	Water	8	trace
4	50	Acetonitrile	8	Only oxime
5	50	Toluene	8	Only oxime
6	50	DMF	8	74

7	50	DMF	5	74
8	**20**	**DMF**	**5**	**72**
9	10	DMF	12	44
10	none	DMF	24	Only oxime
[c]11	50	Neat	24	trace

The bold significance represents the most optimized condition;

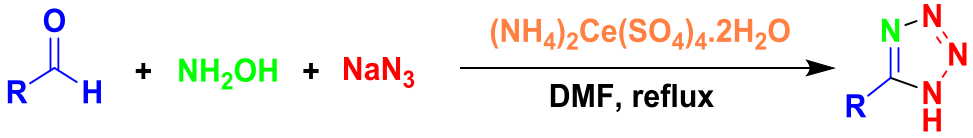
[a]Reaction of Benzaldehyde (1 mmol), hydroxylamine hydrochloride (2 mmol) and sodium azide (2 mmol);

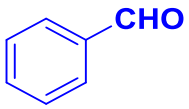
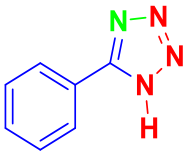
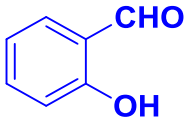
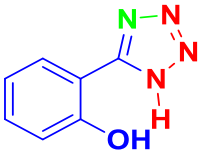
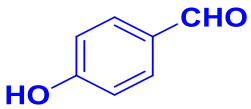
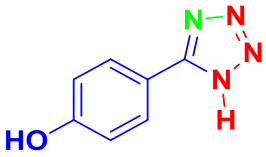
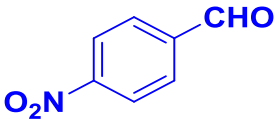
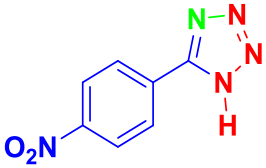
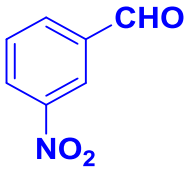
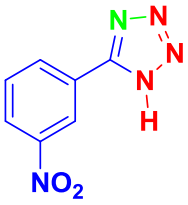
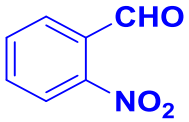
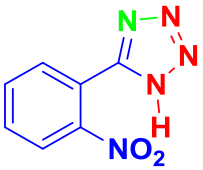
[b]Isolated yield after column chromatography;

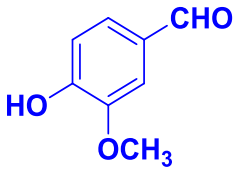
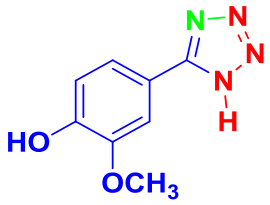
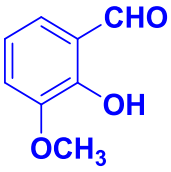
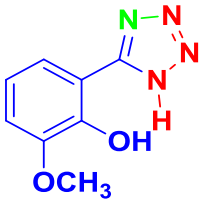
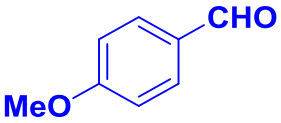
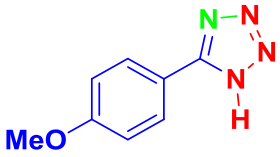
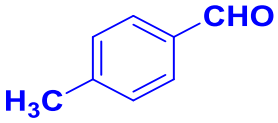
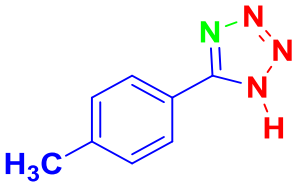
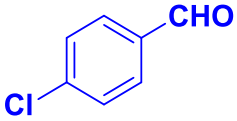
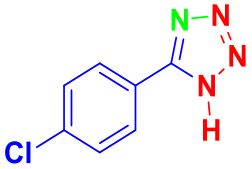
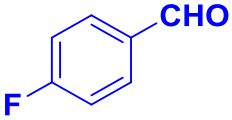
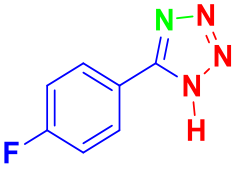
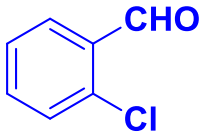
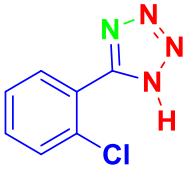
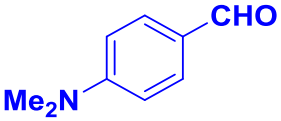
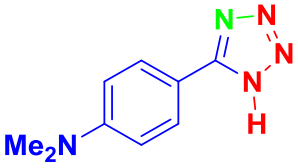
[c]Reaction was performed at 140 ^{o}C

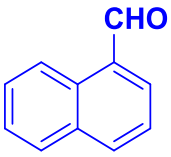
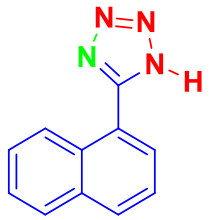
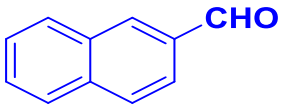
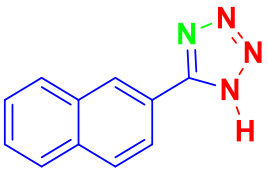
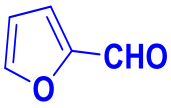
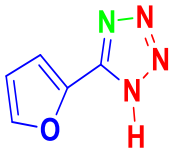
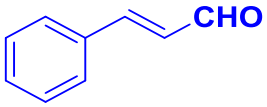
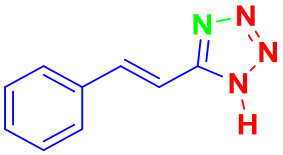
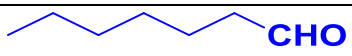
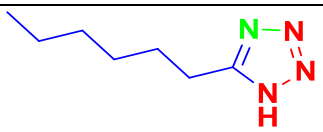
For the generalization of our protocol, aldehydes (1-19) were treated with $NH_2OH.HCl$ and NaN_3 under optimized condition and a large variety of tetrazole derivatives were formed which is listed in Table II.2. This strategy was general for a range of aldehydes having electron donating and withdrawing group on benzene ring as well as naphthyl, heterocyclic ring and also effective for aliphatic aldehydes. Best result was observed for aldehydes having electron withdrawing groups. Steric hindrance played an important role on the yield and time of the reaction which is evident for 2-nitrobenzaldehyde and 4-nitrobenzaldehyde. 4-nitro benzaldehyde gave excellent yield (Table II.2, entry 4) whereas 2-nitro benzaldehyde (Table II.2, entry 6) gave poor yield. Same result was also observed for 4-chlorobenzaldehyde (Table II.2, entry 11) and 2-chlorobenzaldehyde (Table II.2, entry 13). Aldehydes having electron donating group gave lower yield (Table II.2, entry 10). 2-naphthyldehyde (Table II.2, entry 16) gave good yield whereas 1-naphthyldehyde (Table II.2, entry 15) gave poorer yield and the reason for this may be due steric hindrance. We have performed this method also on vanillin and *o*-vanillin. *o*-Vanillin (Table II.2, entry 8) gave better yield than vanillin (Table II.2, entry 7). Similar result was also observed for 2-hydroxy and 4-hydroxybenzaldehyde. 2-hydroxybenzaldehyde gave better yield (Table II.2, entry 2) than 4-hydroxybenzaldehyde (Table II.2, entry 3). This was due to presence of hydroxyl group at 2-position and it increases the electrophilicity of carbonyl carbon of aldehyde by H-bonding whereas at 4-position it shows only electron donating property. The same skeleton is present in *o*-vanillin and vanillin moiety respectively and we obtained same type of result.

Table II.2. [a]Synthesis of diversified 5-substituted 1*H*-tetrazole derivatives



Entry	Reactant	Time (h)	Product	[b]Yield (%)
1		5		72
2		6		69
3		8		63
4		9		68
5		7		74
6		10		54

7		10		60
8		7		72
9		8		65
10		9		59
11		6		66
12		10		68
13		12		trace
14		9		64

15		12		trace
16		8		65
17		6		58
18		5		61
19		10		trace

[a]Reaction condition: Aldehyde (1 mmol), hydroxylamine hydrochloride (2 mmol), sodium azide (2 mmol) and $(NH_4)_4Ce(SO_4)_4.2H_2O$ (20 mol%) in DMF under reflux condition;

[b]Isolated yield after column chromatography.

II.3.2. Recyclability of catalyst

In addition, we studied the reusability of the catalyst $(NH_4)_4Ce(SO_4)_4.2H_2O$ for the synthesis of 5-phenyl-1*H*-tetrazole. The catalyst was recovered by simple filtration after completion of the reaction and reused up to five times under the optimal reaction conditions. As shown below (Figure II.4) the recovered catalyst showed good reusability with a slight decrease in yield over three runs.

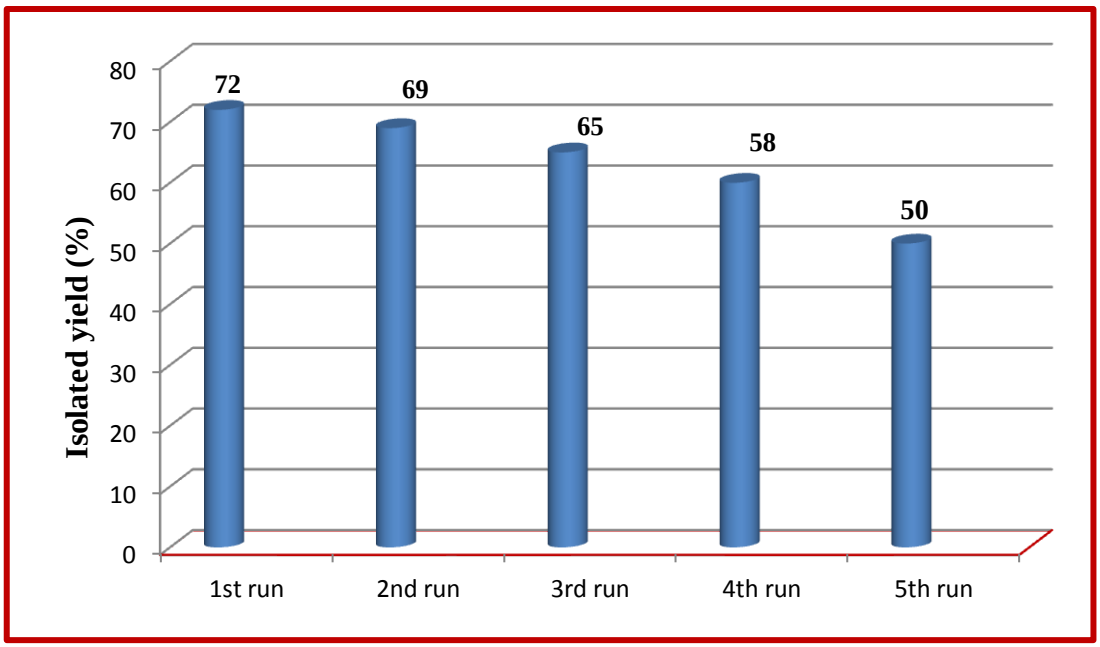
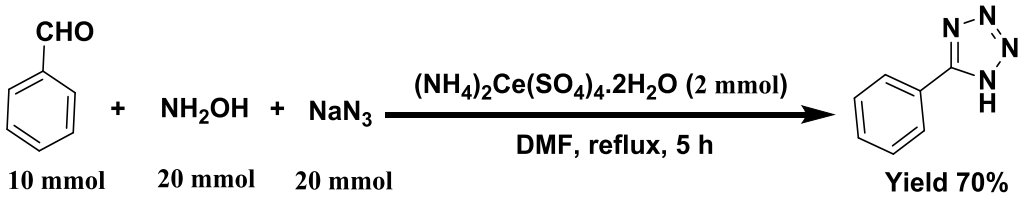


Figure II.4. Reusability of the catalyst

II.3.3. Scale-up experiment

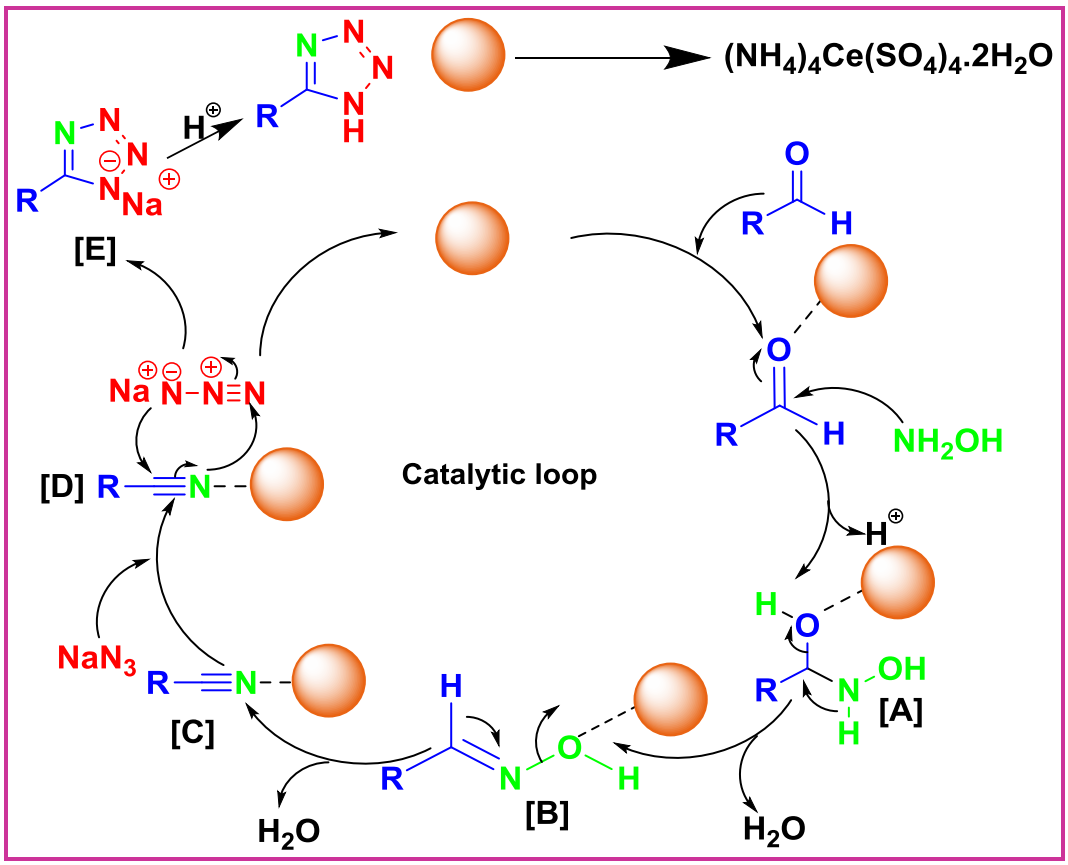
To examine the application of this methodology in large scale, the reaction was carried out in gram-scale (10 mmol scale) by taking benzaldehyde as a starting material which also afforded good yield, which is comparable to the yield obtained in small-scale reaction.



II.3.4. Mechanism

A plausible mechanism is represented in Scheme II.22. It is proposed that initially, Ce(IV) attaches with lone pair of oxygen of aldehyde and increases the electrophilicity of it. Then hydroxyl amine attacks the carbonyl carbon and form nitrile **[C]** followed by oxime **[B]** by the expulsion of water molecules. Then Ce(IV) attaches with *p*-electron cloud of the intermediate nitrile moiety **[C]**, which in turn reacts with NaN_3 for transformation into respective tetrazole. In fact, the coordination of Ce(IV) assists to activate C-N functionality to form intermediate for nucleophilic addition of NaN_3, the reaction proceeds *via* [3+2] cyclo addition pattern **[D]**. The complex on protonolysis by 35% HCl (pH of solution was adjusted in between 2 and 3)

gives **[E]**, which rearranges to produce more stable desired product, 5-substituted 1*H*-tetrazole.



Scheme II.22. Plausible mechanism for the synthesis of 5-substituted 1*H*-tetrazoles

II.4. Conclusion

In summary, a diverse array of 5-substituted 1*H*-tetrazoles were prepared from the reactions of corresponding aldehyde, hydroxylamine hydrochloride and sodium azide with the use of non-toxic, economical and reusable solid catalyst, ceric ammonium sulphate without isolation of the intermediate oximes and nitriles. The desired products were obtained in good to moderate yield, with no requirement of inert or anhydrous reaction condition and this newly developed method avoids the usage of toxic chemicals or formation of potentially explosive by-products. Replacement of toxic and expensive nitrile precursors by aldehyde is the novelty of this protocol. Simple work-up procedure, functional group tolerance have added advantages of this protocol.

II.5. Experimental Section

II.5.1. General Information

All the compounds were purchased from commercial suppliers and used without further purification. All the products were purified by column chromatography on silica gel (60-120 mesh, SRL, India). For TLC, Merck plates coated with silica gel 60, F_{254} were used. Melting point of the solid compounds was determined in concentrated H_2SO_4 bath. ^{1}H NMR and ^{13}C NMR were recorded using 300 MHz, 400 MHz and 75 MHz, 100 MHz respectively on Bruker AV 300 NMR spectrometer and Bruker AV 400 NMR spectrometer using TMS as internal standard and the HRMS was recorded using instrument of Agilent Q-TOF Mass Analyser. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

II.5.2. General Procedure for the synthesis of tetrazole from aldehyde

Aldehyde (1 mmol), hydroxylamine hydrochloride (2 mmol) and sodium azide (2 mmol) were added successively to a solution of $(NH_4)_4Ce(SO_4)_4.2H_2O$ (20 mol%) in 5 mL DMF. The mixture was reflux for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the solution was treated with HCl (4 N, 10 mL) and then the solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate (75:25) as eluent to afford the pure solid tetrazole. Products were characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

II.5.3. Characterization data of various tetrazole derivatives

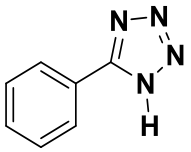
5-Phenyl-1*H*-tetrazole (Table II.2, entry 1)

White solid; M.P.: 210 ^oC;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.59-7.65 (m, 3H), 8.04-8.08 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 126.9, 127.4, 128.1, 129.3, 131.1, 134.2, 155.1;

HRMS (ESI) calculated for $C_7H_6N_4$ ($M+H^+$) 147.0670, found 147.0679.

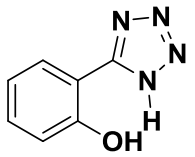


2-(1*H*-Tetrazol-5-yl)phenol (Table II.2, entry 2)

White solid; M.P.: 218 ^{o}C;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.97 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 111.0, 116.9, 119.9, 120.2, 129.5, 133.1, 152.2, 155.8.

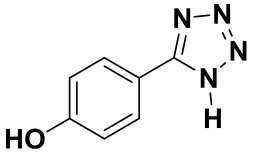


4-(1*H*-Tetrazol-5-yl)phenol (Table II.2, entry 3)

Yellow solid; M.P.: 231 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.95 (d, J = 6.8 Hz, 2H), 7.62 (d, J = 7.8 Hz, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 115.1, 116.6, 129.2, 130.8, 155.4, 160.5.

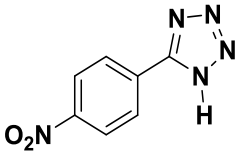


5-(4-Nitrophenyl)-1*H*-tetrazole (Table II.2, entry 4)

Yellow solid; M.P.: 216 ^{o}C;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.46 (d, J = 8.8 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 123.7, 124.8, 128.4, 129.2, 148.9, 156.0, 162.7.

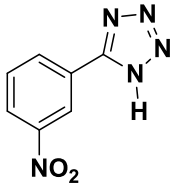


5-(3-Nitrophenyl)-1*H*-tetrazole (Table II.2, entry 5)

Yellow solid, M.P.: 106 ^{o}C;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85 (s, 1H), 8.43-8.50 (m, 2H), 7.90-7.94 (m, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 125.0, 129.1, 129.7, 134.7, 136.5, 151.8, 158.6.

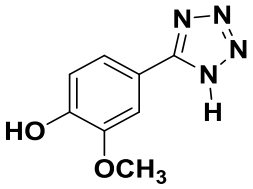


2-Methoxy-4-(1*H*-tetrazol-5-yl)phenol (Table II.2, entry 7)

Yellow solid; M.P.: 212 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.93 (s, 3H), 6.98 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 56.2, 111.1, 115.3, 116.5, 120.8, 148.5, 149.9, 155.5.



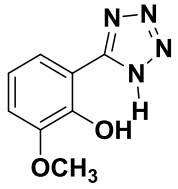
2-Methoxy-6-(1*H*-tetrazole-5-yl)phenol (Table II.2, entry 8)

White solid; M.P.: 231 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.58 (s, 3H), 7.10-7.15 (m, 1H), 6.53-6.61 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 56.6, 111.4, 114.8, 120.3, 120.9, 145.6, 148.8, 152.3;

HRMS (ESI) calculated for $C_8H_8N_4O_2$ ($M+H^+$) 193.0725, found 193.0733.

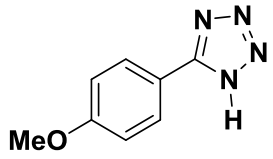


5-(4-Methoxyphenyl)-1*H*-tetrazole (Table II.2, entry 9)

Yellow solid; M.P.: 227 ^{o}C;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.85 (s, 3H), 7.97-8.01 (m, 2H), 7.16-7.19 (m, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 55.7, 113.8, 114.7, 126.7, 128.4, 129.8, 162.1, 162.9.

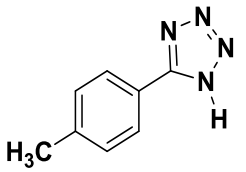


5-(4-Methylphenyl)-1*H*-tetrazole (Table II.2, entry 10)

White solid;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.39 (s, 3H), 7.42 (d, J = 7.4 Hz, 2H), 7.95 (d, J = 7.6 Hz, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 21.4, 121.7, 127.3, 130.4, 141.6, 155.4.

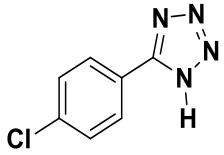


5-(4-Chlorophenyl)-1*H*-tetrazole (Table II.2, entry 11)

White solid; M.P.: 157 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.05-8.07 (m, 2H), 7.69-7.71 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 127.9, 128.4, 128.7, 129.0, 129.5, 136.1, 155.1.



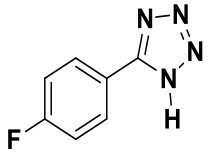
5-(4-Fluorophenyl)-1*H*-tetrazole (Table II.2, entry 12)

Yellow solid; M.P.: 186 ^{o}C;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.90-8.02 (m, 2H), 7.15-7.33 (m, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 116.6, 121.2, 130.4, 155.1, 165.6;

HRMS (ESI) calculated for $C_7H_5N_4F$ ($M+H^+$) 165.0577, found 165.0576.

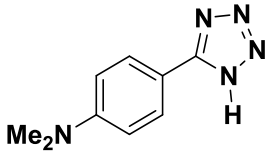


5-(*N*,*N*-dimethyl-4-phenyl)-1*H*-tetrazole (Table II.2, entry 14)

Brown solid;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.03 (s, 6H), 6.81 (d, J = 8.4 Hz, 2H), 7.83-7.96 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 111.1, 121.2, 128.4, 152.3, 155.4.



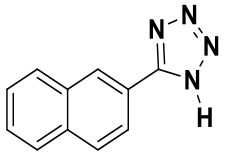
5-(Naphthalene-3-yl)-1*H*-tetrazole (Table II.2, entry 16)

Yellow solid; M.P.: 207 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.65 (d, J = 7.2 Hz, 2H), 8.03-8.26 (m, 2H), 8.67 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 122.1, 124.2, 127.8, 128.4, 129.2, 129.7, 133.2, 134.4, 155.1;

HRMS (ESI) calculated for $C_{11}H_8N_4$ ($M+H^+$) 197.0827, found 197.0827.

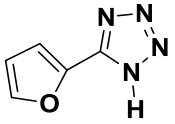


5-(Furan-2-yl)-1*H*-tetrazole (Table II.2, entry 17)

Yellow solid; M.P.: 201 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.33-7.10 (m, 1H), 7.20-7.34 (m, 1H), 7.52-8.07 (m, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 112.8, 113.4, 140.3, 146.4, 148.7.



II.5.4. Scanned copies of ^{1}H and ^{13}C NMR, HRMS spectra

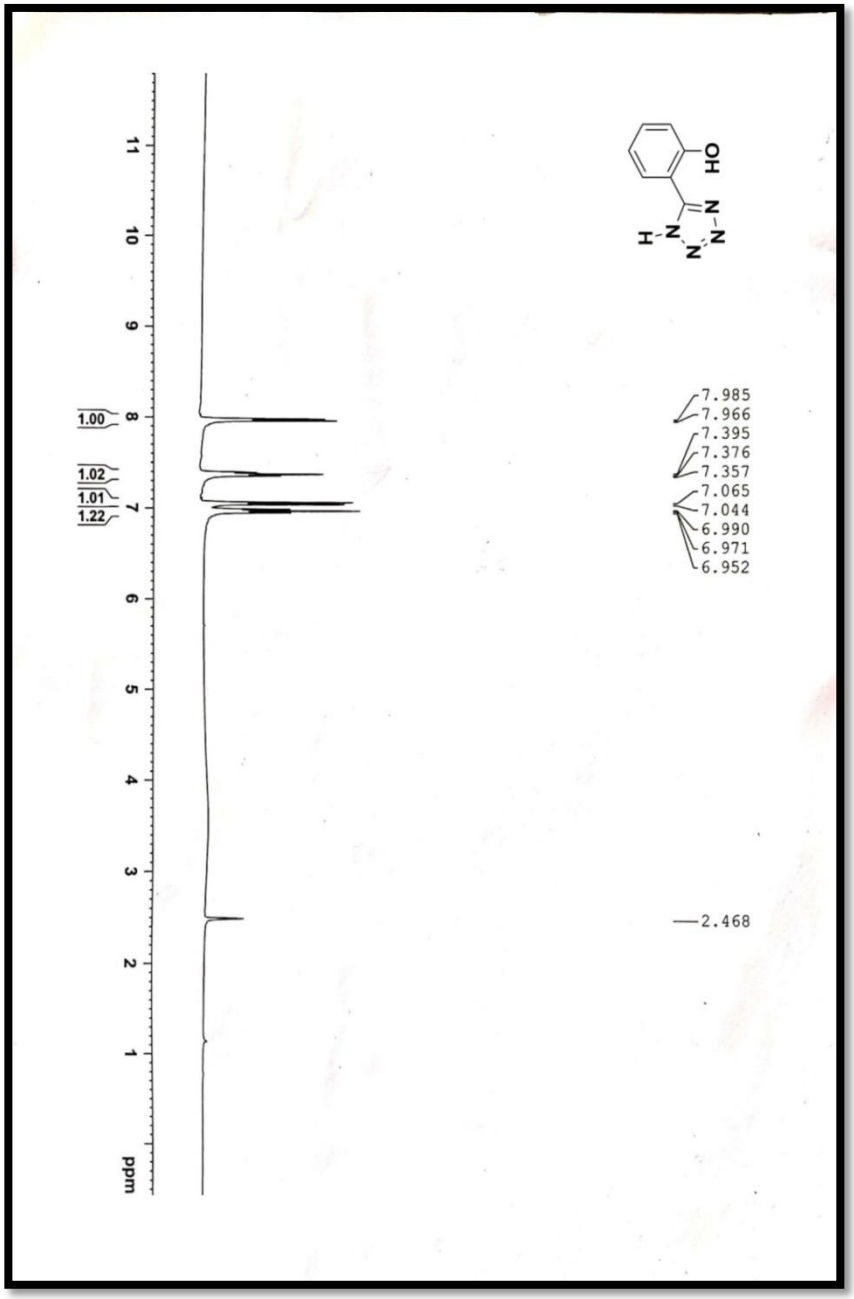


Figure II.5. Scanned copy of ^{1}H NMR of 2-(1*H*-tetrazol-5-yl)phenol

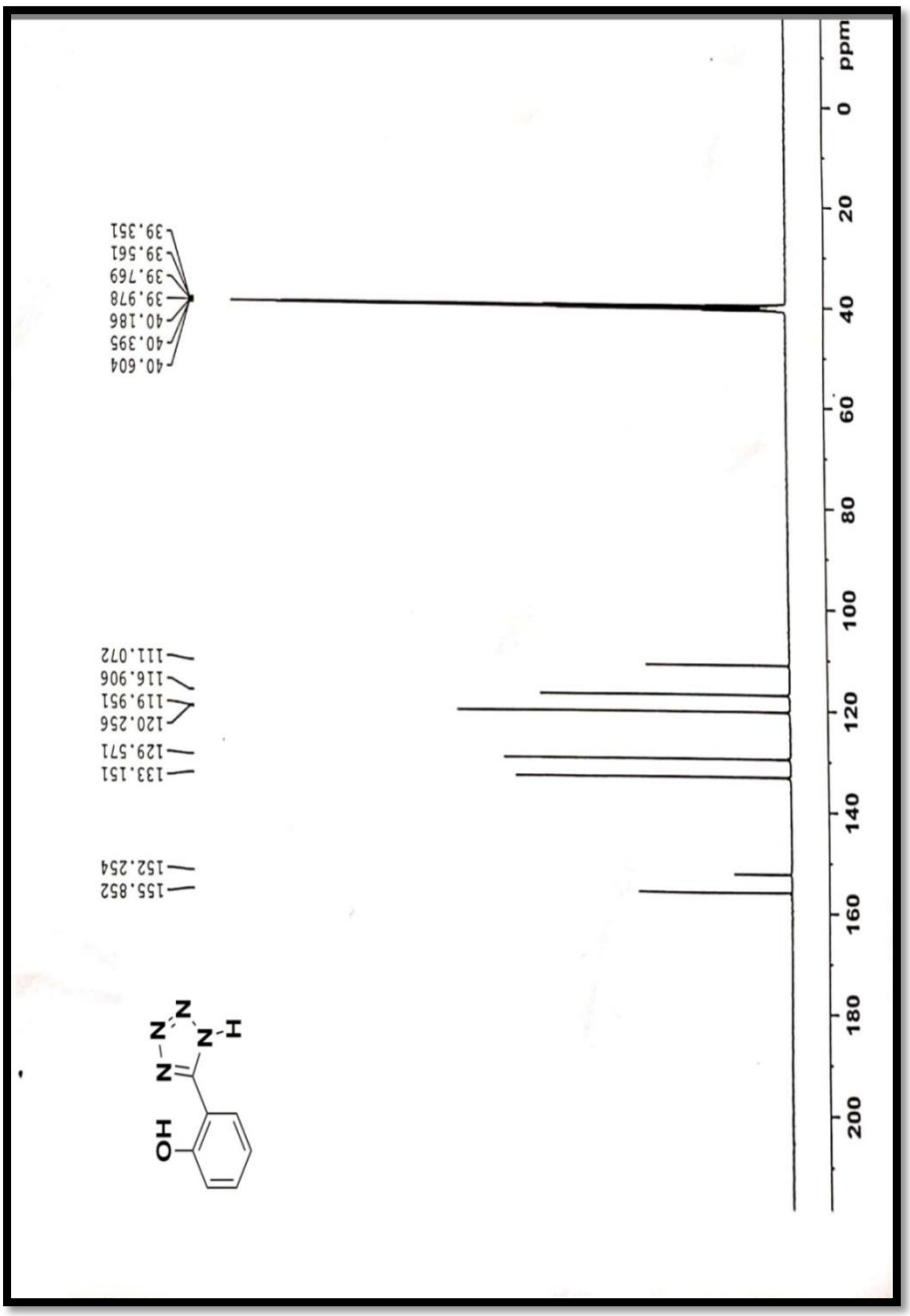


Figure II.6. Scanned copy of ^{13}C NMR of 2-(1*H*-tetrazol-5-yl)phenol

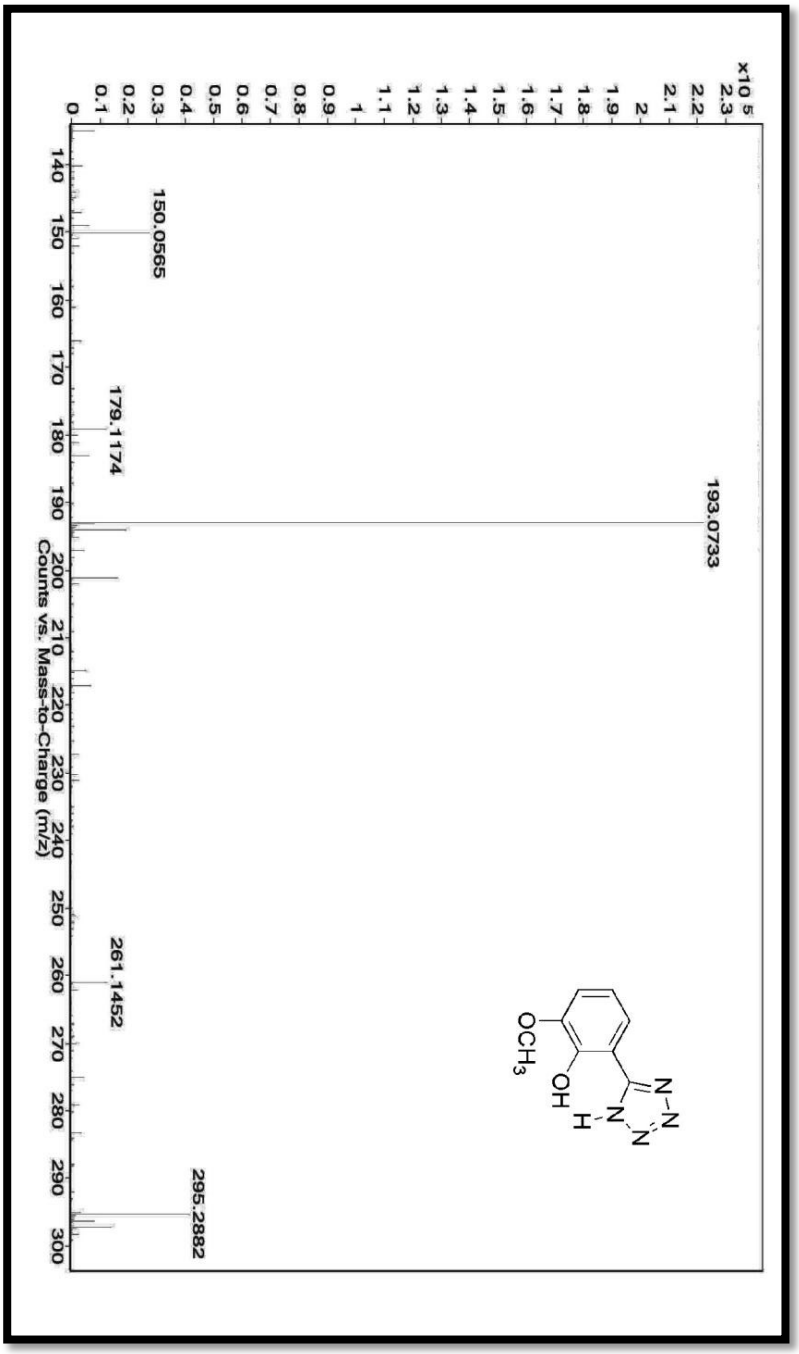


Figure II.7. Scanned copy of HRMS of 2-methoxy-6-(1*H*-tetrazole-5-yl)phenol

II.6. References

References are given in BIBLIOGRAPHY under Chapter II (page 170-173).