CHAPTER- III

SECTION-A

III.A. A brief review on tetrazoles, synthesis and its applications

III.A.1. Tetrazole

Tetrazoles are heterocyclic compounds which have broad spectrum of biological activities such as antifungal, antiviral, antibacterial, antiulcer, anti-inflammatory, etc. 5-substituted-1H-tetrazoles can act as explosives, lipophilic spacers and finds use in material science. It is a precursor for synthesizing several nitrogen containing heterocycles used as ligands in coordination chemistry. Tetrazoles are used in medicinal chemistry as a metabolically stable carboxylic acid surrogates. It is an important intermediate for the transformation to other heterocycles. Tetrazoles are emerging to be used in pharmaceutical and material science for new application because tetrazoles are resistive to different chemical environment. 5-substituted tetrazoles have a free N-H bond, usually referred as tetrazolic acids. There is an equal tautomeric isomers of 1H- and 2H- tetrazoles. It is also known as imidoyl azides. Tetrazole is a synthetic five-membered heterocycle having four nitrogen atoms (1) (**Fig. III.A.1**). Tetrazoles are usually explosive and unknown in nature. Tetrazole (m.p.157-158∘C) is a white to pale yellow in colour, crystalline solid having a characteristic smell. It is soluble in water and alcohol.

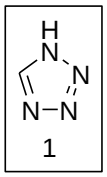


Fig. III.A.1. Tetrazole

III .A.2. Biological activities of tetrazoles

Tetrazoles are the heterocycles most used in medicinal and industrial field due to isosteric substituents for carboxylic acids.[1] It also acts as analytical reagents and plays important role in biological applications.[2, 3] 1-substituted 1H-1,2,3,4-tetrazoles were reported to be a special category because of their biological activity.[4] Tetrazoles play an important role as pharmacophores and as metabolic surrogates of carboxylic acid in several therapeutic agents which is essential for treatment of cancer, hypertension, AIDS, bacterial infection and allergies.[5,6] Well known drugs, Losartan(2) , Valsartan (3) and pamiroplast (4) are currently used as antihypertensive and 2-arylcarbapenem as antibiotic, are tetrazole structure containing compounds.[7,8]

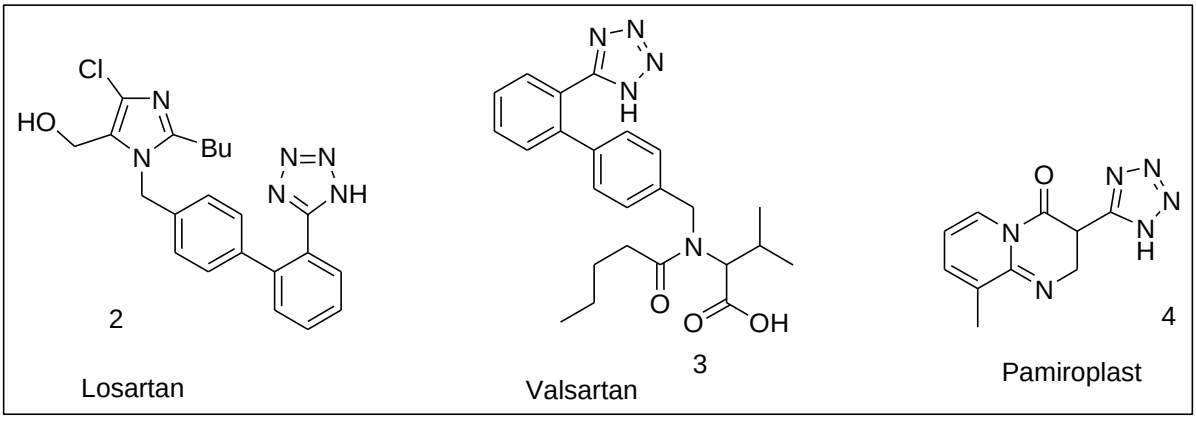


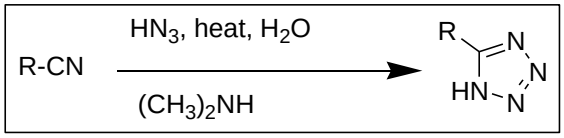
Fig. III.A.2. Example of tetrazole containing drugs

III.A.3. Application of tetrazole in organic synthesis

The tetrazole moiety shows versatile application in different field. This nitrogen rich system is mainly used in pharmaceutical[9] because there is a similarity between tetrazole and carboxylic acid group where medicinal chemist are interested. They have synthesized a lot of substituted tetrazole as important medicinal agent, e.g. a series of 5-phenyl-1-acyl-1,2,3,4-tetrazoles were synthesized through condensation of 5-phenyl-1,2,3,4-tetrazoles with different acylating agents.[10] Tetrazole plays an important role in coordination chemistry. Coordination complex with tetrazole moiety is important field of medicinal chemistry. Tetrazoles form complexes with metal ions, Cu(Ⅱ), Ni(Ⅱ), Co(Ⅱ) and Zn(Ⅱ) which acts as ligands in e.g. Cefazolin antibiotic, that shows better antibacterial activity than non coordinated one.[11] Tetrazoles are versatile intermediate which give rise to substituted tetrazoles and other 5-membered heterocyclic ring through Huisgen rearrangement.[12]

III. A.4. Classical method for the synthesis of tetrazole

Tetrazole was first prepared in 1932 by the reaction of hydrazoic acid (HN_3) with organic cyanides.[13] This process was believed to occur through concerted 1, 3-dipolar cycloaddition reaction.Subsequent work-up process provided the tetrazolic acid. (**Scheme.III.A.1**)



Scheme III. A.1. Synthesis of tetrazole by hydrazoic acid with cyanide

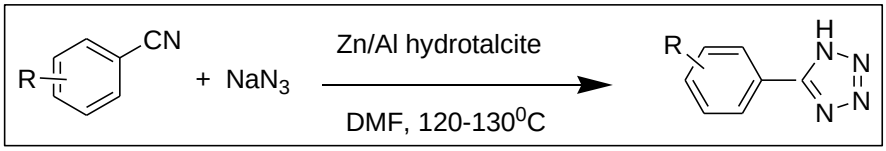
Literature study reveals that, classically, tetrazoles were synthesized by the cycloaddition of cyanides with metal azides. But due to toxic and explosive nature nature of cyanide and azides respectively, lot of catalytic methods have been introduced using different type of azides with nitriles. However, due to some drawbacks of previous methodologies, a number of new methodologies for the synthesis of tetrazoles have been developed from the combination of some different functional groups.

III.A.5. Modern methods for synthesis of tetrazole derivatives

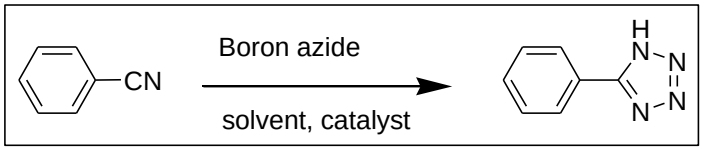
III.A.5.1. Synthesis of tetrazoles from the reaction of cyanides with azides under different catalytic conditions

To overcome the drawbacks of the classical method of synthesizing tetrazole derivatives, the development of new protocols was necessary. Use of the combination of cyanides with azides is one of the simple method for the synthesis of tetrazole derivatives. There are several catalytic process mentioned in the literature for the synthesis of tetrazole derivatives so as to minimize the drawbacks of the classical method such as Zn/Al hydrotalcite catalyzed synthesis of 5-substituted 1H-tetrazoles from the reaction of aryl nitrile and sodium azide [14] (**Scheme. III.A.2**), $CuSO_4.5H_2O$ catalyzed synthesis of 5-substituted-1H-tetrazole from the reaction of aryl or alkyl nitriles with sodium azide in DMSO,[15] $AgNO_3$ catalyzed preparation of 5-substituted-1H-tetrazole through [3+2] cycloaddition reaction of nitriles with sodium azide,[16] synthesis of 5-substituted 1H-tetrazole from the reaction of boron-azides and nitriles (**Scheme. III.A.3**.),[17] Activated Fuller's earth catalyzed synthesis of 5-aryl 1H-tetrazole from nitrile and sodium azide (**Scheme. III.A.4**.),[18] Glycerol mediated, catalyst free synthesis of 5-substituted 1H-tetrazole,[19] Zinc chloride catalyzed, solvent free synthesis of 5-substituted 1H-tetrazoles,[20] Synthesis of 1,5-disubstituted tetrazoles by palladium-catalyzed Suzuki coupling reaction (**Scheme. III.A.5**.),[21] Pb(Ⅱ) salt catalyzed synthesis of 5-substituted 1H-tetrazoles

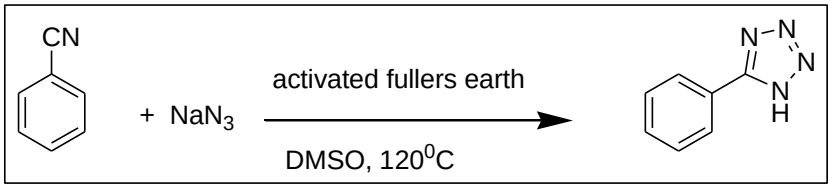
from nitriles and sodium azide,[22] Synthesis of 2-aryl-2H-tetrazoles through regioselective [3+2] cycloaddition reaction of arenediazonium salt with trimethylsilyldiazomethane (**Scheme. III.A.6**.),[23] Cyanuric chloride catalyzed, metal free synthesis of 5-substituted-1H-tetrazole,[24] Nano TiO_2/SO_4^{2-} catalyzed synthesis of 5-substituted-1H-tetrazoles,[25] Ag nanoparticle catalyzed synthesis of 5-substituted 1H-tetrazoles,[26] Ceric ammonium nitrate supported HY-zeolite catalyzed synthesis of tetrazole,[27] Silica supported lanthanum triflate catalyzed synthesis of 5-substituted-1H tetrazole (**Scheme .III.A.7**.),[28] nano copper oxide catalyzed synthesis of tetrazoles,[29] $CuFe_2O_4$ nanoparticles catalyzed synthesis of 5-substituted 1H-tetrazoles,[30] $FeCl_3$-SiO_2 catalyzed synthesis of 5-substituted 1H-tetrazoles through [2+3] cycloaddition of nitriles with sodium azide,[31] copper catalyzed synthesis of 5-substituted 1H-tetrazoles through cycloaddition of nitriles with trimethylsilyl azide,[32] (**Scheme. III.A.8**.), nano-$TiCl_4.SiO_2$ catalyzed synthesis of 5-substituted 1H-tetrazoles.[33]



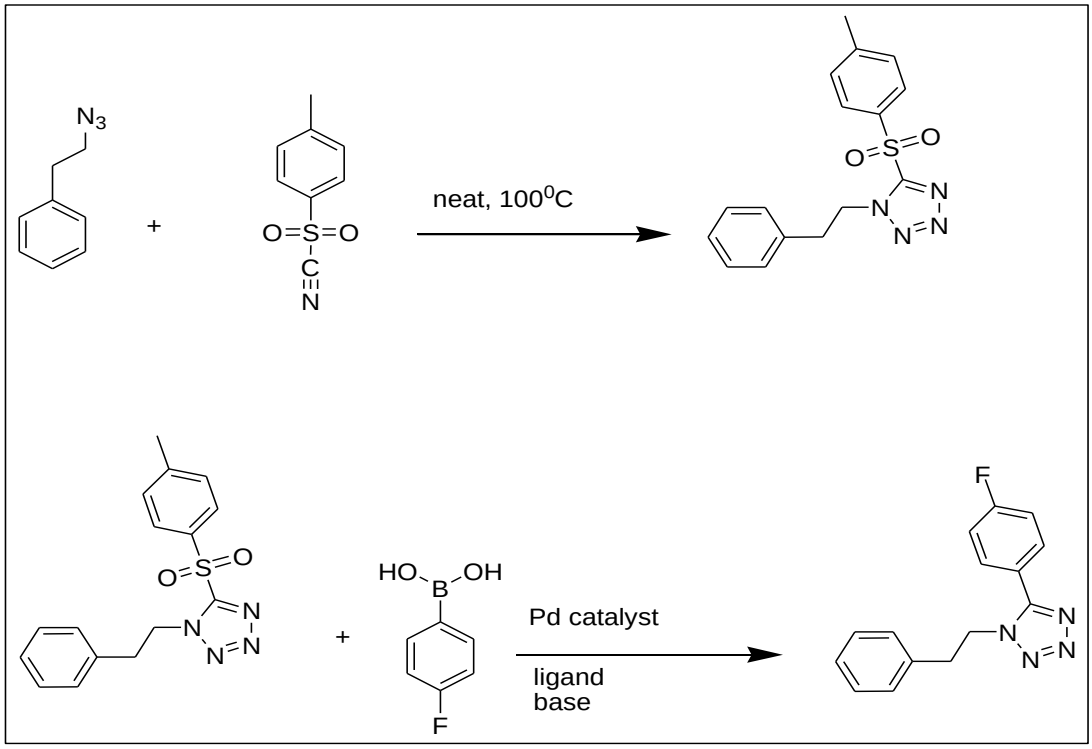
Scheme. III.A.2. Synthesis of 5-substituted 1H-tetrazole catalyzed by Zn/Al hydrotalcite



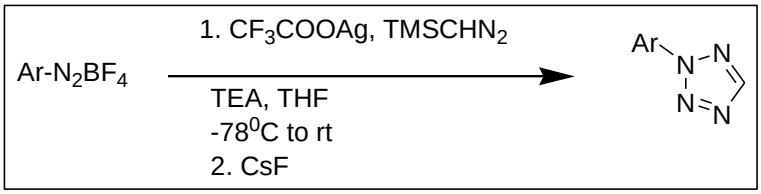
Scheme. III.A.3. Synthesis of tetrazoles catalyzed by boron azide



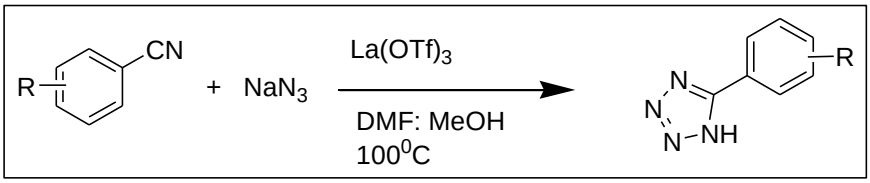
Scheme.III.A.4. Synthesis of 5-aryl-1H-tetrazole catalyzed by Activated Fuller's earth



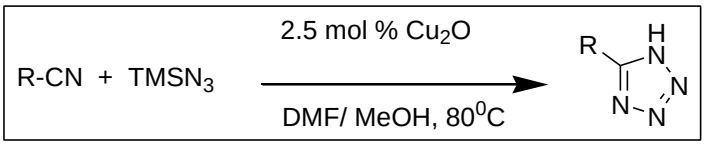
Scheme. III. A.5. Synthesis of 1, 5-substituted tetrazole by Pd catalyzed Suzuki coupling



Scheme. III.A.6. Synthesis of 2-aryl tetrazole by aryl diazonium salt



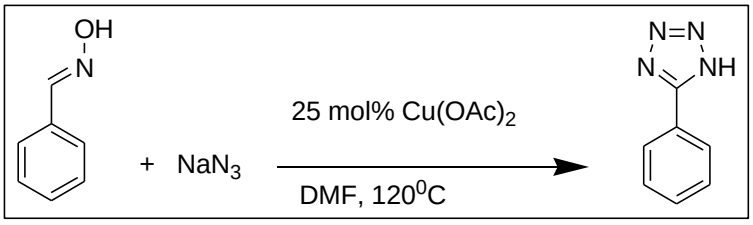
Scheme. III.A.7. Synthesis of 5-substituted tetrazole catalyzed by $La(OTf)_3$



Scheme. III.A.8. Synthesis of tetrazoles by trimethylsilylazide

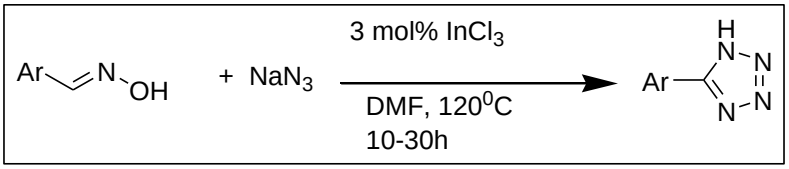
III.A.5.2. Synthesis of tetrazole derivatives from the combination of oxime and azides

Generally tetrazoles are prepared by using toxic and expensive aryl nitriles as precursors. Therefore nitriles are replaced by oximes. J.M.Nagarkar et.al.[34] synthesized 5-substituted 1H-tetrazole from the reaction of oxime with sodium azide (**Scheme. III.A.9**.)



Scheme. III.A.9. Synthesis of 5-substituted 1H-tetrazole from oxime, catalyzed by $Cu(OAc)_2$

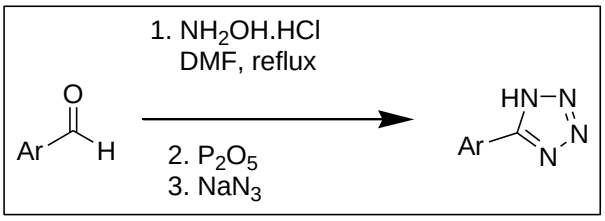
S.D.Guggilapu et.al.[35] synthesized 5-substituted 1H-tetrazole derivatives from the reaction of oxime and sodium azide catalyzed by Indium(Ⅲ) chloride, a lewis acid catalyst (**Scheme. III.A.10**.)



Scheme. III.A.10. Synthesis of 5-substituted 1H-tetrazole from oxime, catalyzed by $InCl_3$

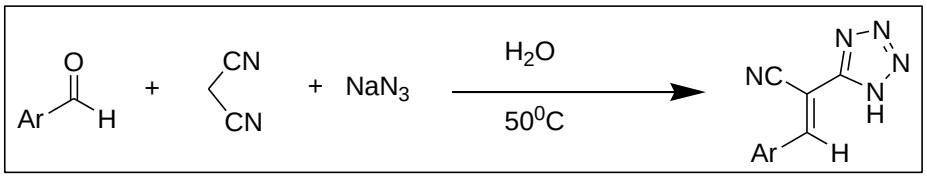
III.A.5.3. Synthesis of tetrazole derivatives from aldehydes

K.M.Khan et.al.[36] synthesized tetrazole derivatives from the reaction of substituted benzadehyde with sodium azide in presence of hydroxylamine hydrochloride and P_2O_5 in DMF under reflux condition (**Scheme. III.A.11**.)



Scheme. III.A.11. Synthesis of tetrazole derivatives from aldehyde, hydroxylamine hydrochloride, sodium azide in presence of P_2O_5

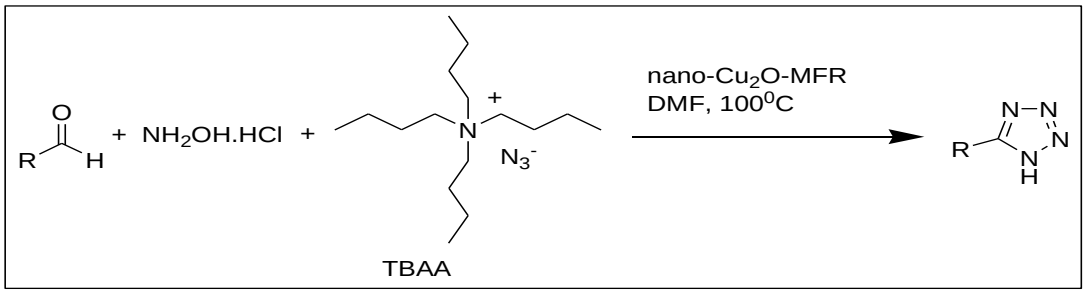
Z.N.Tisseh et.al.[37] synthesized 5-substituted 1H-tetrazole in aqueous medium without catalyst, from the reaction of aldehyde with malononitrile and sodium azide (**Scheme.Ⅲ.A.12**.). The reaction was diastereoselective.



Scheme .III.A.12. Synthesis of 5-substituted 1H-tetrazole from aldehyde, malononitrile and sodium azide in aqueous medium

S. Behrouz (2017)[38] synthesized 5-substituted 1H-tetrazole derivatives from aldehydes catalyzed by doped nano-sized Cu_2O on melamine-formaldehyde resin (nano-Cu_2O-MFR). In this three-

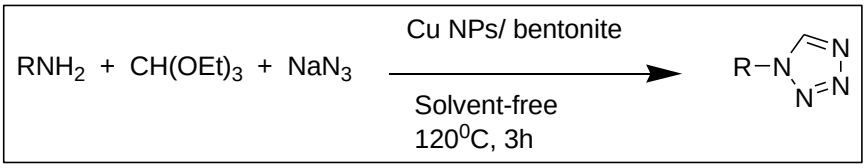
component method structurally diverse aldehydes are reacted with hydroxylamine hydrochloride and tetrabutylammonium azide (TBAA) as a source of azide, catalyzed by nano-Cu_2O-MFR(**Scheme. III.A.13**.)



Scheme.III.A.13. Synthesis of 5-substituted 1H-tetrazole from aldehydes, hydroxylamine hydrochloride and TBAA in presence of nano-Cu_2O-MFR

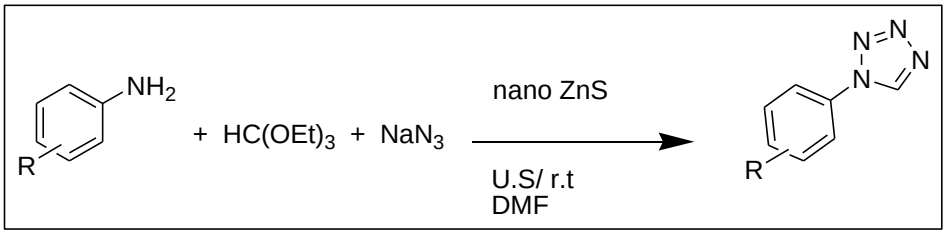
III.A.5.4. Synthesis of tetrazole derivatives from amine, hydrazides, isocyanides and primary alcohols

A.R.Vartooni et.al.[39] synthesized 1-substituted 1H-1,2,3,4-tetrazoles from amine, NaN_3, triethyl orthoformate catalyzed by Cu nano particles/bentonite (**Scheme.Ⅲ.A.14**.)



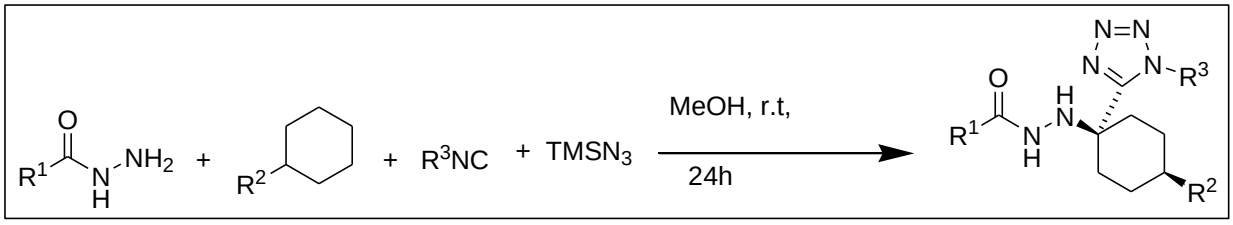
Scheme. III.A.14. Synthesis of 1-aryl-1H-1,2,3,4-tetrazole catalyzed by Cu NPs/bentonite

H.Naeimi and F.Kiani [40] synthesized tetrazoles from aryl amine and triethyl orthoformate under ultra sound irradiation catalyzed by Zinc sulfide nanoparticles (**Scheme. III. A.15**.)



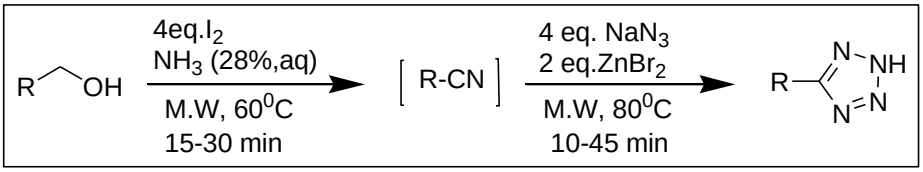
Scheme. III.A.15. Synthesis of 1-substituted 1H-1,2,3,4-tetrazoles by ZnS NPs under ultrasound irradiation

S.Ramezanpour et.al.[41] synthesized a 1,5-disubstituted diastereoselective α-hydrazino tetrazoles through four-component reaction using diverse cyclic ketones, hydrazides, isocyanides and trimethylsilyl azide at room temperature (**Scheme. III.A.16**.)



Scheme. III.A.16. Synthesis of 1, 5-disubstituted α-hydrazino tetrazoles by four-component reaction

J.J.Shie and J.M.Fang [42] explored the microwave- assisted direct transformation of primary alcohol to tetrazole derivatives in aqueous medium (**Scheme. III.A.17**.)



Scheme. III.A.17. One-pot transformation of primary alcohol into tetrazole derivatives

III.A.6. Conclusion

Tetrazoles are associated with several pharmaceutical as well as industrial applications and people have devoted themselves to develop new methodologies for the synthesis of tetrazole derivatives so that the shortcomings of the classical methods can be minimized. Literature study reveals that there are several catalytic synthetic methodologies for the preparation of tetrazole derivatives. But most of the reported processes are not so simple and cost-efficient. Based on these facts, author realized to develop a simple, cost-efficient and straight forward method for the synthesis of tetrazole derivatives, which are of the interest of sustainable development.

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