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Review Article

Theme- *New horizons in chemical sciences.*
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Review on Different Recent Methods for Synthesis of Some Tetrazoles and Different Biological Activities.

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ABSTRACT

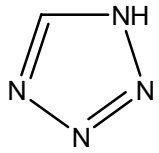
This review includes several recent methods for synthesis of tetrazoles like integrating multicomponent Ugi-azide reaction with the molecular hybridization approach[1], using tributyl tinchloride in presence of sodium azide[2], using sodium azide and triethyl ortho-formate with aromatic amines in glacial acetic acid [4], aryl tetrazole amines *via* desulphurization/substitution/electro cyclization/*C-N* cross coupling reactions from thiourea with the use of cheap, readily available and air stable copper source as catalyst[5], carboranyl tetrazoles [7], using various nitriles and sodium azide in the presence of urea and acetic acid[9], using the azido- Ugi reaction[10]. Also some tetrazole containing ligands complexes can be synthesized [6], also tetrazole amides [8]. Which showed broad-spectrum of biological properties including anti-tubercular and anti-malarial activities, and some tetrazole-based compounds have already been used in clinics for the treatment of various diseases [3] like Alzheimers's disease[1], antileukemic activity against an extensive panel of human cancer cell lines, MV4-11 AML cell line[2], , and antileishmanial activities[4], anti-allergic/anti-asthmatic ,antiviral and anti-inflammatory, anti-neoplastic activities[5], Antimicrobial activity Anti-inflammatory activity [8].

KEYWORDS

Tetrazoles, several methods, broad spectrum of activity.

1. INTRODUCTION

Tetrazole (Figure 1) is a poly-nitrogen electron-rich planar structural feature contains a five-membered ring of four nitrogen, one carbon and two hydrogen atoms. Tetrazole is a bioisostere of the carboxylic acid group, which can replace carboxyl group in drug molecules to increase lipophilicity, bioavailability and reduce side effects. Tetrazoles can interact with various enzymes and receptors in organisms through noncovalent interactions to exhibit broad biological properties. The chemistry of tetrazoles and their derivatives has garnered considerable interest over the past decades. These heterocyclic compounds play an important role in modern medicinal chemistry, organometallic and coordination chemistry, organocatalysis and chemistry of materials (e.g., as highly energetic compounds). Many current drugs such as valsartan, losartan, candesartan, azosemide, siloxithil, irbesartan, tazanolast, pentetrazole and a series of the cephalosporin b-lactam antibiotics contain the tetrazole moiety in the structure [10]. Tetrazole is an impressive functionality with diverse applications in medicinal chemistry. Research in tetrazole chemistry is found to be extremely important due to the fact that it acts as stable carboxylic acid surrogate and offers superior pharmacokinetic profile to the parent molecule[9]. Now days there are several new techniques and methods have been developed which describes synthesis of tetrazoles.



tetrazole

Fig. 1. Chemical structure of tetrazole.

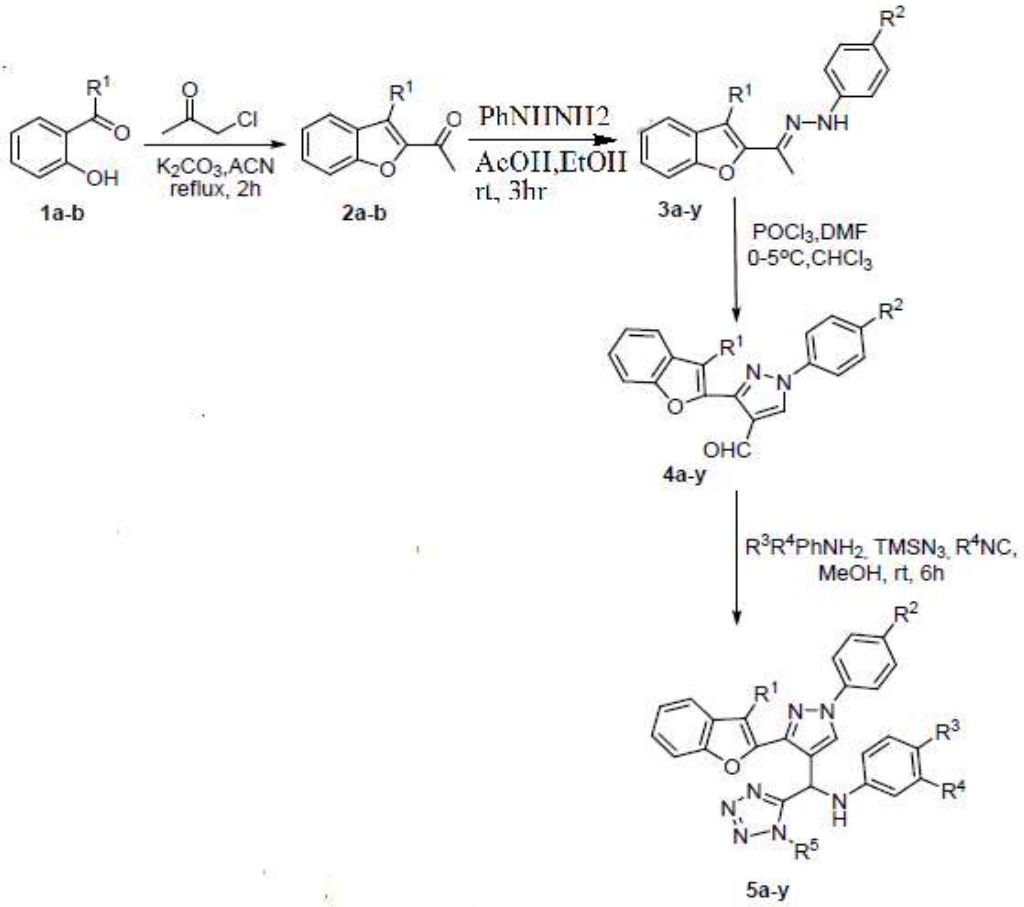
1.1. Bezofuran-tetrazole derivatives

1.1.1. Method

A series of novel Benzofuran-tetrazole derivatives were successfully synthesized by integrating multicomponent Ugi-azide reaction with the molecular hybridization approach. A number of synthesized derivatives (5c, 5d, 5i, 5l, 5q, 5s)

The detailed synthetic route for the preparation of target and intermediate compounds is outlined in Scheme 1. Initially, *o*-alkynation of salicyladehyde and 2-hydroxy acetophenone with chloroacetone in the presence of K2CO3 furnished 2-acetyl benzofuran(2a-b) *via* intramolecular cyclo condensation reaction. The compounds 3a-y were synthesized by the reaction of acetyl benzofuran with different phenyl hydrazines in ethanol and catalyticamount of acetic acid.Thehydrazone intermediates (3a-y) were then engaged in Vilsmeier-Haack reaction resulting in the formation of the intermediate aldehydic compounds 4a-y. Finally, these benzofuran-pyrazole aldehydes (4a-y) were subjected to Ugiazide reaction to give the desired hybrids 5a-y. The atom economical synthesis of target compounds was achieved by operationally

simple, metal free, multicomponent reaction. All the synthesized compounds were characterized using ^{1}H NMR, ^{13}C NMR and ESI-MS [1].



Scheme 1. Synthesis of Benzofuran-tetrazole.

1.2. Pharmacological Activity

These findings underscore the potential of these hybrids as lead molecules against Alzheimer's disease. This is characterized by the aggregation of *β*-amyloid peptide (A*β*)[1].

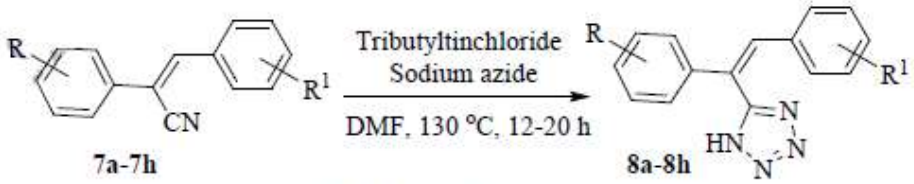
The transgenic *C. elegans* strain CL4176 exhibits temperature-inducible expression of human *β*-amyloid. This strain has been developed to express *β*-amyloid specifically in the muscles, thus, elevated *β*-amyloid in the worm which results in early paralysis makes a clear end point [1].

1.3. Novel Tetrazole Analogues of Resveratrol-

1.3.1. Method

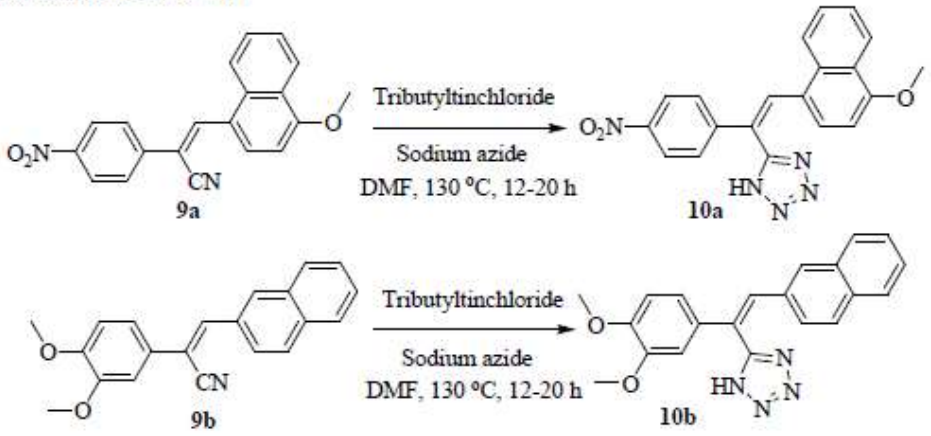
The general procedures for the synthesis of tetrazolyl analogues 8a-8h, and 10a and 10b are illustrated in Scheme 1 & 2. The synthetic strategy was based on our previous studies, which reported on a novel tributyltinazide-mediated synthesis of 1*H*tetrazolyl- *trans*-stilbenes from cyano-*trans*-stilbenes utilizing tributyltinazide as a Lewis acid in a 1,3-dipolar [3+2]

cycloaddition of azide to the cyano group of the cyanostilbene recursor.35 Thus, cyanostilbenes7a-7h and 9a and 9b were individually reacted with tributyltin chloride and sodium azide in the presence of DMF at 130 0C for 12-20 h to afford the corresponding tetrazolylstilbene analogues 8a-8h, and 10a and 10b, respectively, in 50-75% yield[2].



7a/8a: R = 4-methoxy; R^1 = 3,5-dimethoxy
7b/8b: R = 4-nitro; R^1 = 3,5-dibromo
7c/8c: R = 3,5-dibromo; R^1 = 2-methoxy
7d/8d: R = 3,4-dimethoxy; R^1 = 3,4-dichloro
7e/8e: R = 3,4,5-trimethoxy; R^1 = 3,4,5-trimethoxy
7f/8f: R = 3,4-dimethoxy; R^1 = 3,4,5-trimethoxy
7g/8g: R = 3,4,5-trimethoxy; R^1 = 4-methoxy
7h/8h: R = 3,4,5-trimethoxy; R^1 = 3-hydroxy-4-methoxy

Scheme : Synthesis of tetrazolylstilbene analogues **8a-8h** from precursor cyanostilbenes **7a-7h**



Scheme 2. Synthesis of tetrazolyl analogues.

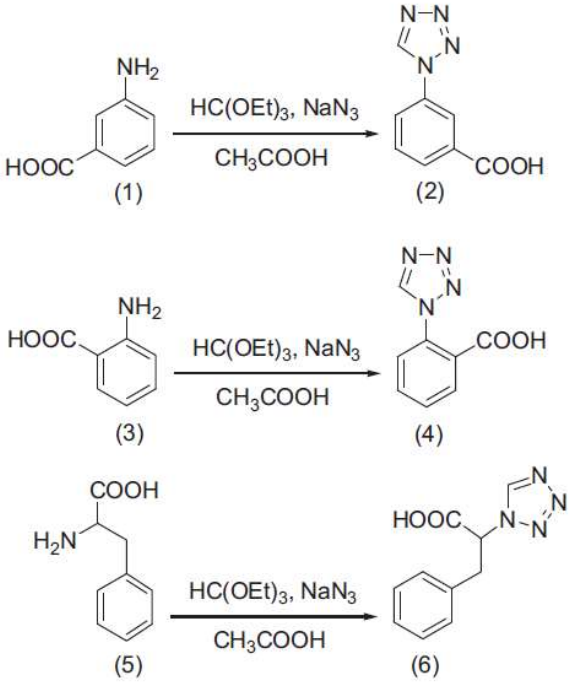
1.4. Pharmacological Activity

A series of novel tetrazole analogues of resveratrol were synthesized and evaluated for their antileukemic activity against an extensive panel of human cancer cell lines and against the MV4-11 AML cell line. These molecules were designed as drug-like derivatives of the resveratrol analogue DMU-212 and its cyano derivatives. Four compounds 8g, 8h, 10a and 10b exhibited LD50 values of 4.60 μM, 0.02 μM, 1.46 μM, and 1.08 μM, respectively, against MV4-11 leukemia cells. The most potent compounds, 8h and 10b, were also found to be active against an extensive panel of human hematological and solid tumor cell lines [2].

1.5. Synthesis of tetrazoles from aryl amine (2, 4, 6)

1.5.1. Method

In a typical experiment, glacial acetic acid (15 ml) was added to a suspension of amino benzoic acids (10 mmol) and sodium azide (10 mmol) in triethyl orthoformate (20 mmol) with constant stirring at 400 rpm. The reaction mixture was than stirred at 150 ^{0}C on an oil bath for almost 10 hours. Thin layer chromatography was constantly used to monitor the progress of the reaction. Upon completion of the reaction, a mixture of concentrated Hydrochloric acid (37%) and Water (25 ml) was poured in the flask till solid precipitates were formed. The solid precipitates formed, were separated by filtration and dried in oven at 50 ^{0}C. The synthesized tetrazole derivatives (2, 4, 6) were obtained in good to excellent yields (75%, 63%, 84%) respectively. The oven dried solid precipitates of the tetrazole derivatives (2, 4, 6) were efficiently purified by recrystallization technique [3].



Scheme 3. Synthesis of tetrazole derivatives.

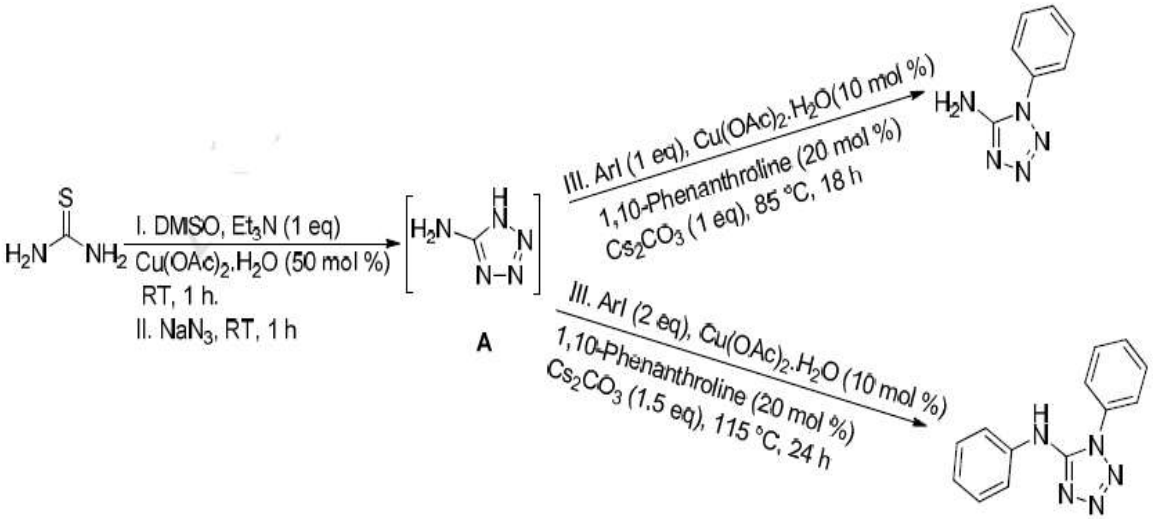
1.6. Activity

Cytotoxicity was performed using a method of Nadhman et al., 2015 but with minor modifications. Briefly, 180 mL fresh human red blood cells were washed three times at 3000 rpm with phosphate buffer solution (PBS). Using UV-visible spectrophotometry (T80, pg instruments), the released hemoglobin was assessed at 576 nm by taking the supernatant. Triton X-100 (0.1%) was taken as positive control and the red blood cell suspension in PBS without compound was used as a negative control[3].

1.7. Aryl and Di-aryl tetrazole amine

1.7.1. Method

To a stirred solution of DMSO (2-3 mL), thiourea (1 mmol, 76 mg) was added in slowly and followed by Et3N (1 mmol, 101 mg) and Cu(OAc)2.H2O (50 mol %, 100 mg) were added at room temperature. The whole reaction mixture stirred for one hour (until get the black color) at room temperature. The reaction was monitored by TLC. After completion of the reaction (monitored by TLC), to this, NaN3 (2 mmol, 130 mg) was added. Then, the reaction mixture stirred for 1 h. Later, iodobenzene (1 mmol, 204 mg), Cs2CO3 (1 mmol, 325 mg), Cu(OAc)2.H2O (10 mol %, 19.9 mg) and 1,10-phenanthroline (20 mol %, 36 mg) were added consecutively for several min and the reaction mixture was stirred for 18 h at 85 °C. The progress of the reaction was investigated by TLC (5% ethyl acetate in hexane). After completion of the reaction, the reaction mixture was transferred into centrifuged tubes and the mixture was centrifuged for 10 min by using centrifugation machine. Black color solid was settled in the bottom of centrifuged tubes. The clear solution was concentrated by using rotary evaporator and the crude mixture was purified by silica gel (60-120 mesh) column chromatography using 20% ethyl acetate in hexane as eluent [5].



Scheme 4. Synthesis of Aryl and Di-aryl tetrazole amine.

1.8. Pharmacological Activity

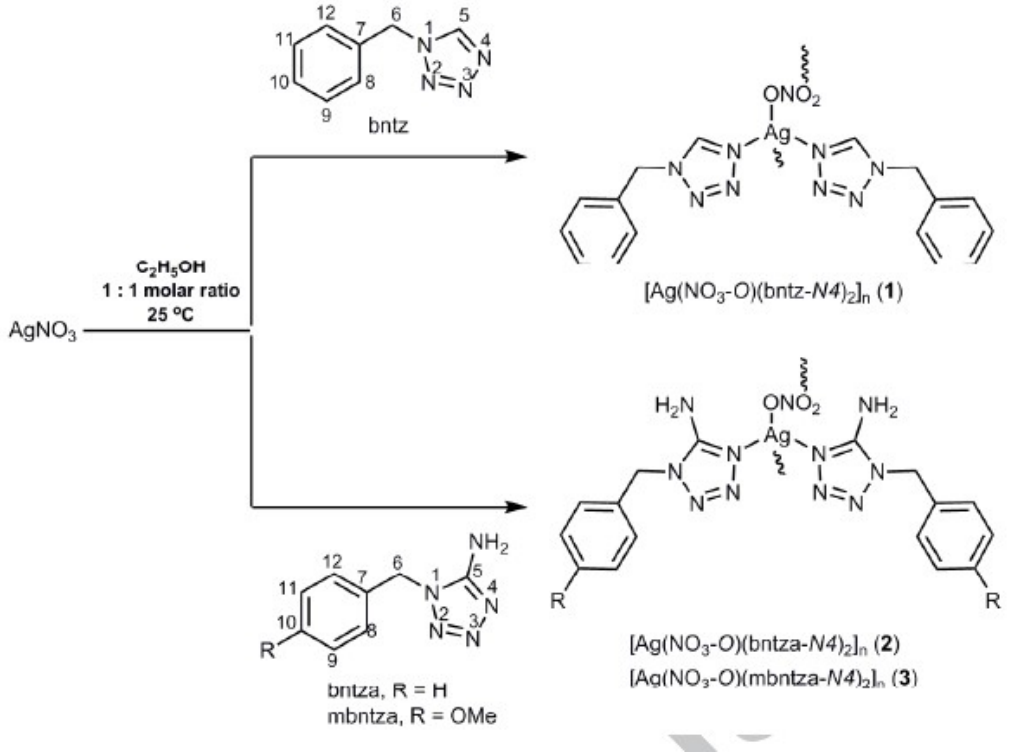
Anti-allergic / anti-asthmatic, antiviral and anti-inflammatory were performed on synthesized compounds.[5].

1.9. Silver (I) complexes with 1-benzyl-1H-tetrazoles

1.9.1. Method

The tetrazole-containing compounds, 1-benzyl-1*H*-tetrazole (bntz), 1-benzyl-1*H*-tetrazol- 5-amine (bntza) and 1-(4-methoxybenzyl)-1*H*-tetrazol-5-amine (mbntza), were synthesized by

previously described methods. These compounds were pure based on elemental microanalysis and NMR spectroscopy [6].



Scheme 5. Synthesis of Silver (I) complexes with 1-benzyl-1H-tetrazoles.

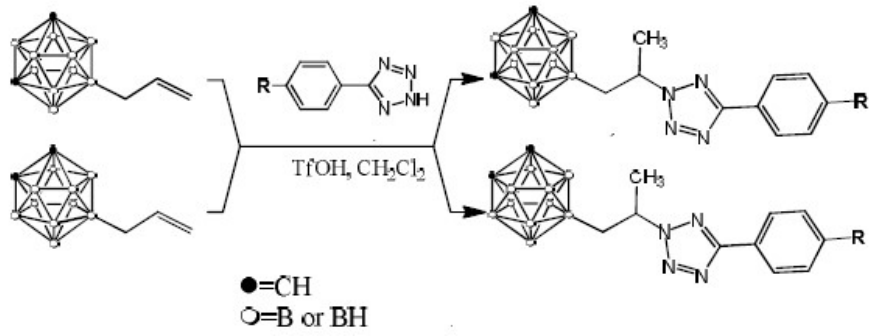
1.10. Activity

Antimicrobial studies MIC concentrations of 1 – 3 and 1-benzyl-1H-tetrazole ligands were determined according to the standard broth micro dilution assays, recommended by the National Committee for Clinical Laboratory Standards (M07-A8) for bacteria and Standards of European Committee on Antimicrobial Susceptibility Testing (v 7.3.1: Method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for yeasts) for Candida spp[6].

1.11. Carboranyltetrazoles

1.11.1. Method

To a suspension of tetrazole 1 or 2 (10.7 mmol) in dry CH2Cl2 (30 mL) triflic acid (0.6 mmol, 60 μL) was added under an argon atmosphere and mixture was stirred for 5 min. Then a solution of corresponding allylcarborane (8.9 mmol) in 20 mL of CH2Cl2 was slowly (3 h) added with stirring at 0-5 ^{o}C. After that reaction mixture was kept at room temperature for 9-11 h (R=H) and 12-14 h (R=CN). After filtration the mixture was washed with 2% NaHCO3 solution (10 mL), water (2_50 mL), dried over Na2SO4 and evaporated. The residue was treated with hexane, and the precipitate that formed was filtered off [7].



Scheme 6. Synthesis of Carboranyltetrazoles.

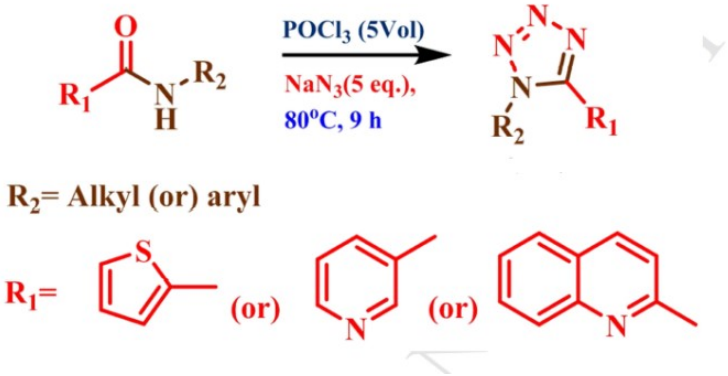
1.12. Activity

Plant growth regulators, herbicides and fungicides[7].

1.13. Tetrazoles from amide

1.13.1. Method

To an amide (1.01 mmol), phosphorus oxychloride (10.15 mmol) and sodium azide (4.06 mmol) was added. The reaction mixture was stirred for 9 hours at 80 oC under a nitrogen atmosphere and then it was cooled carefully quenched with ice water and neutralized with saturated sodium bicarbonate solution. The product was extracted with ethyl acetate (75 mL), washed with water (2 x 75 mL) and brine solution (75 mL). The organic layer was separated and dried over anhydrous Na2SO4 and concentrated under reduced pressure [8].



Scheme 7. Synthesis of Tetrazoles from amide.

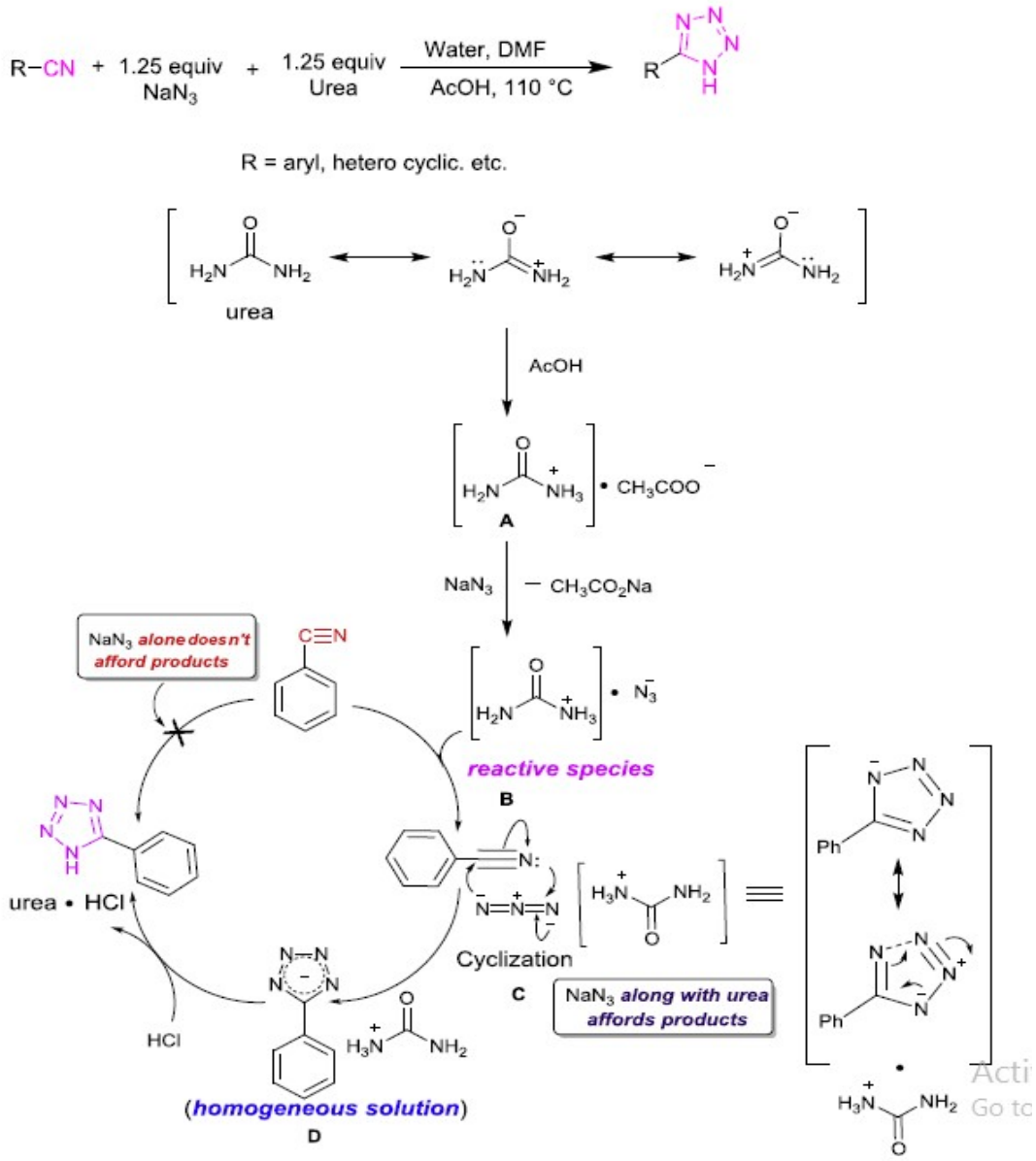
1.14. Activity

Antibacterial activity, Anti-inflammatory activity [8].

1.15. Urea mediated 5-substituted-1H-tetrazole via [3 + 2] cycloaddition of nitriles and sodium azide

1.15.1. Method

1 equivalent of nitriles, 1.25 equivalent of sodium azide and 1.25 equivalent of urea was heated at 110 ^{0}C in presence of water, DMF and acetic acid[9].



Effect of urea

Entry	Urea	Reaction time	Yield[b] (%)
1	1.25 equiv	8 h	95
2	1.0 equiv	10 h	75
3	0.5 equiv	14 h	50
4	0.2 equiv	24 h	45
5	–	24 h	0[c]

[a] Reaction conditions: Reactions were carried out on a 0.5 g scale of **1** with NaN_3 (1.25 equiv) at 110 °C;
[b] Isolated yields;
[c] No product formation.

Scheme 8. Synthesis of Urea mediated 5-substituted-1H-tetrazole via [3 + 2] cycloaddition of nitriles and sodium azide.

2. CONCLUSION

This paper gives brief account of different methods of synthesis of different tetrazoles and biological activities of tetrazoles. Treatment of organic nitriles with sodium azide in the presence of iodine or silica-supported sodium bisulfate as a heterogeneous catalyst enables an advantageous synthesis of 5-substituted 1*H*-tetrazoles. 2-Aryl-*2H*-tetrazoles are synthesized by a [3+2] cycloaddition reaction between an aryl diazonium and trimethyl silyl diazomethane. In this study Tetrazoles are an important functionality with wide-ranging applications in photography and information recording systems, pharmaceutical and material sciences and appealing ligands in coordination chemistry, Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive, antialergic, antibiotic and anticonvulsant agents, This review highlighted recent reports of antimicrobial, antifungal, anticancer, analgesic, antinociceptive, antimycobacterial, Antidiabetic, anticonvulsant, cyclooxygenase inhibitors as well as anti-inflammatory and antihypertensive activities of tetrazole.

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