



A STUDY OF SYNTHESIS AND CHARACTERIZATION OF SEVERAL HETEROCYCLIC TETRAZOLES

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ABSTRACT

The aim of this study is to the in all areas of organic chemistry heterocycles play a key role, and are inextricably entangled in life processes. They contribute to the biological and industrial growth of society and to an appreciation of the life processes and attempts to enhance the quality of life. The existence and function in genetics, biochemistry, agricultural, pharmacology and other branches of science of heterocycles is recognised in all forms of organic compounds. Heterocyclic compounds are one category of organic compounds which contain or at least one of these heteroatoms in the ring or which includes carbon atoms along with other elements such as nitrogen, oxygen and sulfur. The higher polarity, water solubility and heterocyclic system reactivity are attributable to the heteroatomic presence. Heterocyclic compounds are highly structural and have demonstrated wide and economic usefulness as therapeutic agents. Many broader aspects of heterocyclic chemical science are known as general sense disciplines that affect almost all of the useful aspects of organic synthetic, medical, and biochemical, etc. Of all heterocycles, the historical production of organic synthesis is of utmost importance to scientists over the years, for thousands of sulphur and nitrogen 4, 5, or 6 component heterocyclic compounds. The major source of chemical reactions in the human body are both natural and synthetic heterocyclic compounds. In addition, all biological processes are of a chemical nature. All these fundamental types of life are built on chemical reactions involving the involvement of several heterocyclic compounds such as vitamins, enzymes, coenzymes, nuclear acids, ATP and serotone, including the provision for energy, nerve impulse transmission, vision, metabolism and transfer of hereditary material. Synthetic heterocycle treatments have widespread medicinal uses such as antibacterial, anti-pilz, anti-inflammatory, anti-viral, anthelmintic, antitumor, antitumor, anticonvulsing agents, etc. New approaches and synthetic tools for heterocyclic synthesis, using economic, efficient and green routes are now very common in organic synthesis and are advanced.

KEYWORDS: Heterocyclic Tetrazoles, organic chemistry, organic compounds, anticonvulsing agents

INTRODUCTION

Tetrazoles are a class of heterocyclic compounds rich in nitrogen. While not present in the world, tetrazoles have gained considerable popularity during the pharmacological discovery effort¹⁻². Tetrazole is used for the production of biologically active drug, as a substituent of

tetrazole for the isosteric substances of the various functional classes Tetrazole of the antibiotic β -lactum and the antivungal azole of the optically active form substances, such as TaK-456, exhibit a high degree of peroral administration against Candida, Cryptococcus and Aspergillus.

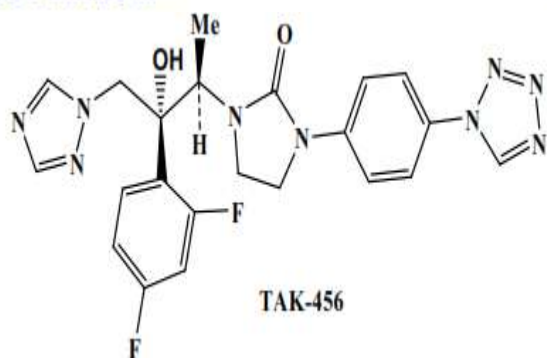


Fig. 1 Structure of tetrazole derivative, TAK-456

On the basis of TAK456, a water soluble variant TAK-457 was developed for injections. In the field of medicinal products, biochemistry, agricultural, photographic and corrosion inhibitors, the production of tetrazole chemistry is primarily related to a wide range of applications. Tetrazoles are used in drugs, propellencies, antibacterials and antibacterials, antifungal products, antiviral products, analgesic products, anti-inflammatory products, anti-inflammatory products, anti-hypertensive agents, materials research, high energies, medicinal chemistry and antimicrobials, central nervous system stimulants and sedatives, oxyders, and plant growth regulators. In addition, because of its electronic characteristics, tetrazole moieties can be used as essential synths in synthetic organic chemistry. Different tetrazoles can be used as bioisosteres to improve their usefulness for carboxylate groups. The metabolic function is constant. This function has been influenced by medication chemists to synthesise replaced tetrazoles as possible therapeutic agents, as has a clear similarity between the acidic nature of tetrazole and carboxylic. Five-aryl (1H)- tetrazoles replaced last year were more commonly referred to as non-classic carboxylic isosters. "Non-classical

isosterism" is the belief that functional groups with the same physiochemical features are interchangeable whereas the original and new compounds have identical biological activities. The steric or electronic character of non-classical isosteric replacements may or may not be identical and the number of atoms of the substituted or substituted groups may also be different. Acidic hydrogen in the position N-1 is usable with tetrazoles and 5 substituted aryl-(1H)-tetrazoles whose acidity consists largely of the substitution in position 5. The pKa values of 5-alkyl or 5-aryltetrazole and the carboxylic acids are nevertheless very similar and have thus been used as bio-isosters for carboxylic acids. The tetrazoles are ionised in the physiological pH range (~ 7.4), as are carboxylic acids, and have a planer form. At the same time, ionised tetrazoles have been shown to be lipophilic than the carboxylic acids, which in some cases allow the membrane to penetrate more easily. 5-substitutions of aryl-(1H)-tetrazoles may benefit of increased cell permeability, bioavailability and metabolic stability while retaining similar pKa values for carboxylic acids. A significant factor to account for when using tetrazoles as isosteric replacements for the carboxylic group is the delocalisation of the negative charge of the tetrazole ring. On the one hand the wide area of the molecule can prevent contact by the distribution of charges and reduce its binding capacity to the active centre. It has been observed that The pharmacological impact of the replacement of a tetrazole carboxylic group can therefore at present not be predicted in advance. The bioactivity of the product will both increase and decrease



after the introduction of the Tetrazole Ring until it disappears entirely. Nevertheless tetrazoles have become more relevant in recent years as a substitute for a carboxylic group. A variety of antihypertense preparations from Losartan and Candesartan are the best and most popular example of the tetrazole. It is believed that a losartan preparation is connected to the receptor by means of lipophilic substituents of the blocker molecule in position #2 and -4 of the imidazole in the lipophilic pockets of the receptor. In position -2, the radical hydrocarbon has been found to contain between 3 and 5 carbon atoms and to have a regular structure. There is a fundamental group in one portion of the receiver that binds to acidic molecular structure, i.e. the tetrazole ring of Losartan. In drug discovery substitution of nitrogen N-1 for 1,5-displaced tetrazols has proved useful as cisamideisosters. The preparation of imidazolyl azides is also a major application of tetrazols. Tetrazoles are typically synchronised with organic nitriles or cyanamides by means of the addition of azide ions. In the field of materials science, pharmaceutical and explosive products and photography extensive work has been carried out on the synthesis of tetrazoles. In the presence of a stoichiometric quantity, or 50 mol percent of Zn(II) salts, sharp less and coworkers reported an inventive and secure method in preparing 5-substituted (1H)-tetrazoles from the corresponding nitrates and NaN_3 . Subsequently, Amantini and coworkers reported an effective method for tetrazol synthesis by reacting to TMSN_3 by using a catalyst of 50 mol% TBAF. The efficient synthesis of tetrazols in nitril reactions

with NaN_3 with nanocrystalline ZnO and Zinc hydroxyapatite is also performed by Lakshmi Kantam and collaborators, at 120-130 oC. Most recently Jin and coworkers⁴⁹ reported the [3+2] cycloaddition of nitrates and trimethylsilyl azide to the corresponding 5-substituted (1H) tetrazoles in high yields in the presence of a CuI catalyst in DMF/MeOH. Under the mildest conditions catalysts are able to create unworkable reactions. An active field of research still lies in the production of a catalytic synthetic method for tetrazoles. In recent years, the environmental economic factors have provided heterogeneous catalysts greater importance.

METHODS OF PREPARATION OF SUBSTITUTED TETRAZOLES:

1. Reaction(s) of benzonitrile(s), sodium azide in presence of catalyst(s):

In the presence of many catalysts, such as iodine or silica-based sodium sulphate, the reaction of sodium azide substituted benzonitrile is beneficial to the synthesis of 5-substituted testicles, aided in Silicas by the Sulphuric acid catalyst as the heterogeneous catalyst. Similarly, different 5-(1H)-tetrazoles in solvent-free media, which are synthesised by means of montmorillonite K-10 clay as a solid recyclable heterogeneous acid catalyst, have been syntheticized by sodium azide and benzyl Nitriles with microwave radiations⁷⁷. The phosphorus pentoxide-methanic acid mixture (Eaton's reagent) is used for the cycloaddition reactions [3+2] between substituted pentoxide and methanol. Synthesis of replaced tetrazoles with ferric sulphate as a catalyst for benzonitrile & sodium azide replacement reaction. The InCl_3 [Indium (III) chloride]



catalysts of aromatic nitriles and azide were efficiently prepared with 5-substituted-(1H)-tetrazole. In the response of Di methyl formamide solvent to aromatic nitril with sodium azide, Mohite P.B.et.al reported 5-replaced tetrazole through the use of ammonium chloride as a catalyst. The use of amine salts as a catalyst for nitril and sodium azide reaction was stated to 5-substitutes by ZHU et.al. Antimony trioxide for the synthesis of 5 substitute tetrazole is used as an effective lewis acid catalyst. Velladuarian and al. The use of zeolites and sulfated zirconia of CoY zeolites respectively reported synthesis of the substituted tetrazoles. Patil et.al⁸² was recorded for ammonium acetate mediated synthesis. Mesoporous ZnS nanospheres Lang et al⁸³ and Chermahini et al have been documented for highly active heterogeneous and metal modified clay (montmorillonite K-10), including Cu²⁺, Fe³⁺, Ni²⁺ and Zn²⁺. The treatment of replaced nitriles by sodium azide and triethyl ammonium chloride in nitrobenzene in the microwave reactor is used to prepare five-substituted tetrazoles in very good yields and short periods of reaction⁸⁵. Sterical tetrazoles and disabled tetrazoles can be prepared by electron-donation groups.

2. Reaction between aromatic amine, triethyl ortho formate and sodium azide in presence of catalyst:

Series of 5-substituted-(1H)-1,2,3,4-tetrazole compounds have been synthesized in good yields from amines, tri ethyl ortho formate and sodium azide through the catalyzed reaction with Yb(OTf)₃ at 1000C, in 6 to 9 hrs.

3. Preparation of 1,5-disubstituted tetrazoles:

A general method for the synthesis of 1,5-disubstituted tetrazoles involves mild reaction conditions by using TBAB & TFA.

4. Reaction of cyanogen azide and primary amine:

The reaction of cyanogen azide and primary amines generates imidazolylazides as intermediates in acetonitrile/water. After cyclization, these intermediates gave 1-substituted aminotetrazoles in good yield.

5. Reaction of alkenes, NBS, Nitriles and tetramethyl silyl azide and Zn(OTf)₂ catalyst: A versatile and highly efficient Zn(OTf)₂-catalyzed one-pot reaction of alkenes, N-Bromosuccinamide (NBS), nitriles, and TMSN₃ gives various 1,5-disubstituted tetrazoles containing an additional α -bromo functionality of the N1-alkyl substituent.

6. Synthesis of novel tetrazolo [1, 5-a] pyridine derivatives:

The reaction of 2-halopyridines with tri methyl silyl azide in the presence of tetra butyl ammonium fluoride hydrate gives tetrazolo [1, 5-a] pyridine(s) and 8-bromo tetrazolo [1, 5-a] pyridine is further transformed into a variety of novel tetrazolo [1, 5-a] pyridine derivatives.

7. Conversion of Pyridine N-oxides were converted to tetrazolo- [1, 5-a]-pyridines:

N-oxides were converted to tetrazolo- [1, 5-a]-pyridines in good yield in the presence of sulfonyl or phosphorylazides and pyridine by heating in the absence of solvent. The Key starting material for the synthesis of substituted tetrazole(s) was substituted benzonitrile(s).



METHODS FOR THE PREPARATION OF SUBSTITUTED BENZONITRILES:

There are several method(s) to prepare the benzonitrile(s).

1. Ammoxidation of Toluene:

Ammoxidation of Toluene by vapor phase reaction of toluene with ammonia and oxygen at 400 to 450 °C.

2. Rosenmund-Von Braun reaction:

Reaction of substituted bromo benzene and cuprous cyanide at hot condition by following Rosenmund-Von Braun reaction.

3. Thermal decomposition:

Thermal decomposition of ammonium benzoate at high temperature.

4. Synthesis of substituted benzonitriles from substituted benzaldehydes:

Reaction of substituted benzaldehyde with hydroxyl amine hydrochloride to form the oxime of the respective aldehyde. Formed oxime further dehydrated by using various dehydrating reagents like phosphorus penta oxide, triethyl amine sulphur dioxide, Zeolites, sulfuryl chloride fluoride, sulfuryl chloride, Silica gel, Mont K-10 and KSF catalyst, formic acid, potassium peroxy monosulphate, sodium sulphate & sodium bicarbonate, at various conditions gives the respective benzonitriles.

5. Synthesis of substituted benzonitriles from substituted benzoic acids:

Substituted benzoic acid (s) when treated with zinc sulphate & lead thiocyanate at high temperature gives respective substituted benzonitriles.

6. Synthesis of substituted benzonitriles by continuous flow reaction:

A continuous-flow protocol for the preparation of substituted benzonitriles

from respective substituted benzoic acid (s) has been developed by Cantillo D.et.al. The method is based on the acid-nitrile exchange reaction with acetonitrile used as the solvent and takes place without any catalyst or additives under high temperature and high pressure conditions employed at 350°C and 65 bar respectively. Where acetonitrile is in its supercritical state. The transformation of benzoic acid to benzonitrile requires 25 minutes.

7. Preparation of substituted benzonitriles by acid chloride of substituted benzoic acid(s), followed by its amide derivative and dehydration:

Mahajan & Mahalaksmi reported synthesis of 2-amino-5-chloro benzo nitrile by the reaction of 2-amino-5-chloro benzoic acid and thionyl chloride to get respective acid chloride followed by ammonia treatment to get corresponding amide. The obtained amide was dehydrated by using P₂O₅ as a dehydrating agent to yield the respective nitrile.

8. Synthesis of substituted benzonitriles by the treatment of Ionic liquid to substituted Benzoic acid(s):

Zhang Jun-li et.al¹⁰⁸ reported direct synthesis of benzonitriles from substituted benzaldehyde (s) in Ionic liquid (s)

9. Preparation of substituted benzonitriles by Sandmeyer reaction:

Aromatic nitriles are often prepared in the laboratory from the aniline(s) via diazonium salt with copper cyanide (transition metal cyanides) by sandmeyer reaction.

10. Synthesis of substituted benzonitrile (s) by the reaction of substituted benzoic acid(s) & urea at high temperature:



Christidis Y. and Meier M.110 and Davoud et.al111 reported synthesis of 3,4-bis(2-methoxyethoxy)-benzotrile by the reaction of mixture of 3,4-bis(2-methoxyethoxy)-benzoic acid and urea were heated at 220°C.

CONCLUSION

Heterocyclic compounds played a vital role in biological process and are widely spread as natural products. This is the primary explanation behind the multiple heterocycles used in our everyday lives. In producing a stable complex of metal ions in certain heterocycles, heterocycles may have great biochemical significance. Many petroleum products often contain low heterocycle levels of nitrogen and sulphur. In nature, nuclear acids, alkaloids, anthocyanin, flavones, heat and chlorophyll are commonly present in this region. Aromatic heterocycles, vitamins or hormones are found in proteins as well. If we believe that heterocyclic motifs are used in the majority of macromolecules that contain live organisms, this is not an overestimation. In biological processes, several heterocyclic compounds are the key components. The dietary inputs that act either as enzymes or as precedents are, for example, thiamine (B1 vitamin), riboflavin (B2 vitamin), nicotinamide (B3 vitamin), and pyridox (B6 vitamin). This is extremely important since collagen reactions are not only required to treat the wound and to avoid capillary bleeding, but also to prevent free radicals and oxidative stress. They also serve as an antioxidants. DNA is potentially the most essential macromolecule in existence. Pyrimidine and purine ring structures are derivatives of nucleotides. Our chromosomes are building blocks. Hema and chlorophyll

originate from large porphyrin rings composed in both plants and animals of modified pyrroleums.

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