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Green Approach in Click Chemistry

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Abstract

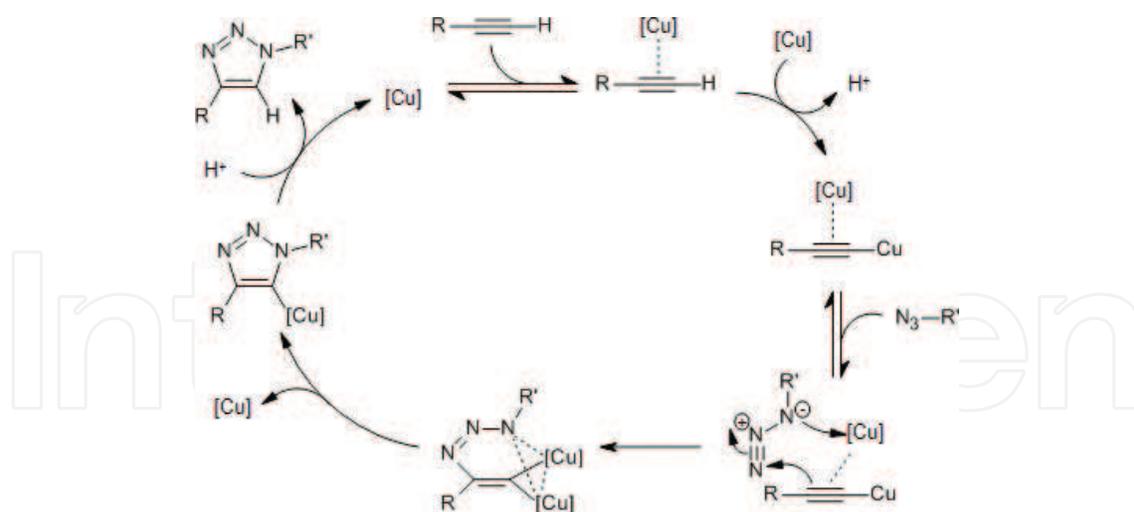
The aim of the topic on click chemistry is used to synthesize various derivatives of 1, 2, 3-triazol-1-yl piperazine, 1, 2, 3-triazol-1-yl quinoxaline, one pot 1,2,3-triazole and bistriazole. These various synthesized compounds were biologically active such as antimicrobial, anti-oxidant, anticancer, antiviral, anti HIV and antitubercular activates. The heterocyclic compounds which are pharmacological active were synthesized by the Cu (I)-catalyzed Huisgen 1, 3-dipolar cycloaddition is a major example based on the click chemistry philosophy. The click chemistry in a broad sense is about using easier reactions to make compounds for certain functions of drugs. The click chemistry used as a green synthesis, because it allows the basic principles of green chemistry given by Anastas and Warner.

Keywords: click reaction, sodium ascorbate, copper sulphate, water, room temperature

1. Introduction

In 2001, a Nobel Prize winner K. Barry Sharpless published a landmark review describing a new strategy for organic chemistry [1]. Click reaction advantages of that are high yielding, wide in scope, create only inoffensive byproducts that can be removed without chromatography, are stereo specific, simple to perform, and can be conducted in easily removable or benign solvents.

The environmentally amiable route to carbon-hetero atom bond formation, described as a click chemistry, has become known as a fast, modular, wide in scope, efficient, reliable, simple to perform to the synthesis of novel compounds with desired functionalities [2]. The name "Click Chemistry" was coined to describe this guiding principle – a principle born to meet the demands of modern day chemistry. Among the listed click reactions, Huisgen 1, 3-dipolar cycloaddition between an azide and alkyne have been widely explored due to, among others, its efficiency, versatility and inertness toward other functional groups.



Mechanism of the click Chemistry

Rulf Huisgen reported that copper (I) salts were able to accelerate the rate of reaction. More importantly, at room temperature or at moderate temperature, the copper catalyst directs the formation of only one of them regioisomers, the 1, 4-disubstituted as shown in [3, 4].

1.1. Huisgen 1, 3-dipolar cycloaddition reaction

Rolf Huisgen, is a German chemist his major achievements was the development of the 1,3-dipolar cycloaddition reaction, also known as the Huisgen cycloaddition or Huisgen reaction. The Huisgen 1, 3-dipolar cycloaddition reaction of organic azides and alkynes, has gained considerable attention in recent years due to the introduction in 2001 of Cu (I)-catalysis by Sharpless, a major improvement in both reaction rate and chemoselectivity of the reaction, as realized by the Meldal and the Sharpless laboratories. The great success of the Cu (I)-catalyzed reaction is a quantitative, very robust, insensitive, general and orthogonal ligation reaction and use for even bio-molecular ligation [5].

1.2. Importance of Huisgen 1, 3-dipolar cycloaddition

Thermodynamic and kinetically favorable (50 and 26 kcal/mol, respectively), Regiospecific, Chemoselective, 10^7 rate enhancement over non-catalyzed reaction and triazole stable to oxidation and acid hydrolysis.

One pot reactions are reactions where three or more substrates combine in one step to give a product that contains essential parts of all of them [6]. The idea of using a one pot reactions followed by a Huisgen [3+2] copper catalyzed reaction was first presented by Barbas and coworkers.

1.3. Synthesis of 1, 4-disubstituted 1, 2, 3-triazoles with copper catalyst

The copper (I)-catalyzed union of terminal alkynes and organic azides to give 1, 4-disubstituted 1, 2, 3-triazoles (as shown in **Figure 1**) exhibits remarkably broad scope and exquisite selectivity. Particularly, 1, 4-disubstituted 1, 2, 3-triazole fragment exhibit is useful for potent biological properties.

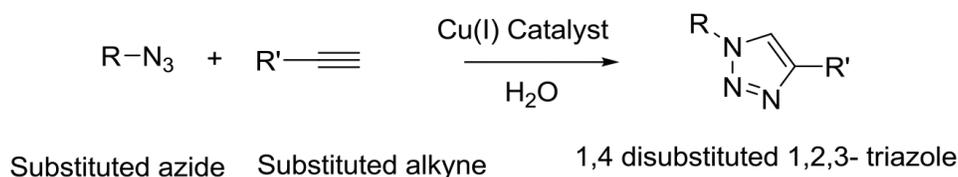


Figure 1. Copper catalyzed azide-alkyne cycloaddition.

1.4. Significance of Cu (I)-catalyzed for azide-alkyne cycloaddition reaction

Rulf Huisgen 1, 3-dipolar cycloaddition reaction is the copper (I)-catalyzed in which organic azides and terminal alkynes are combined to form 1, 4-regioisomers of 1, 2, 3-triazoles as sole products. This reaction is better termed the Copper (I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC). The Cu (I) species may either be introduced as preformed complexes, or are otherwise generated in the one pot reaction itself by one of the following ways: A copper compound in the (+2) oxidation state is added to the reaction in presence of a reducing agent of sodium ascorbate which reduces the Cu from the (+2) oxidation state transfer to the (+1) oxidation state.

1.5. Synthesis of 1, 5-disubstituted 1, 2, 3-triazoles without copper catalyst

There are reported that the formation of regioselective 1, 5-disubstituted triazoles (as shown in **Figure 2**) being mediated by Torne [7, 8], or stereoelectronic effects, but only under harsh conditions. The chemoselectivity of the 1, 3-dipolar cycloaddition enables a convergent synthetic route to the requisite triazole.

The cycloaddition was affected by the catalyst RuCl (PPh₃), which had been reported to be effective for the cycloaddition of secondary azides. The disadvantages of 1, 5-disubstituted 1, 2, 3-triazole are not stable, so we have selected 1, 4-disubstituted 1, 2, 3-triazole.

1.6. Click chemistry acts as a green approach

Click Green chemistry has been in place for long as a scientific term without much advantages until recent times when everything wants or needs to be “green”. To be scientific, not fancy here, we have try to connect and compare these two, using the “Principles of Green Chemistry”, by Anastas and Warner [9].

Prevention: Huisgen cycloaddition reaction and high yielding.

Atom economy: Click chemistry synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

Designing safer chemicals: Huisgen reaction products should be designed to affect their desired function while minimizing their toxicity.

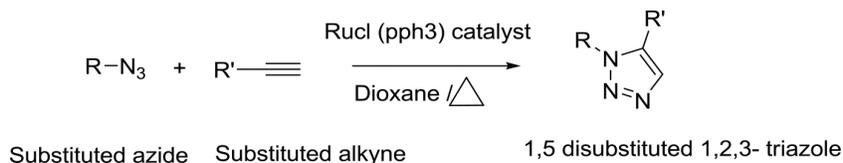


Figure 2. Ruthenium catalyzed azide alkyne cycloaddition.

Safer solvents and auxiliaries: Click chemistry in reaction medium is used water as the solvent.

Design for energy efficiency: Click chemistry is a lot of reactions can be done without much heating.

Reduce derivatives: Click chemistry is a biggest for its superior selectivity and tolerance of most functional groups.

Catalysis: Click chemistry is used for chemical or light catalysts.

Inherently safer chemistry for accident prevention: The use of azides in 1,3 dipolar cycloaddition reaction are minimize the chemical accident.

Advantages of click chemistry:

- I. The mixture owns only stable compounds.
- II. The reaction owns a high yield.
- III. To form a desired product in a simple and quantitative way.
- IV. Energetically highly favorable linking reaction.
- V. The purification can be done on large scale.
- VI. The linkage is chemoselective.
- VII. Click reaction must be of wide scope, giving consistently high yields with a variety of starting materials.
- VIII. It must be easy to perform, be insensitive to oxygen or water and use only readily available reagents.
- IX. Reaction work-up and product isolation must be simple, without requiring chromatographic purification [10].

1.7. Pharmaceutical applications of Triazoles

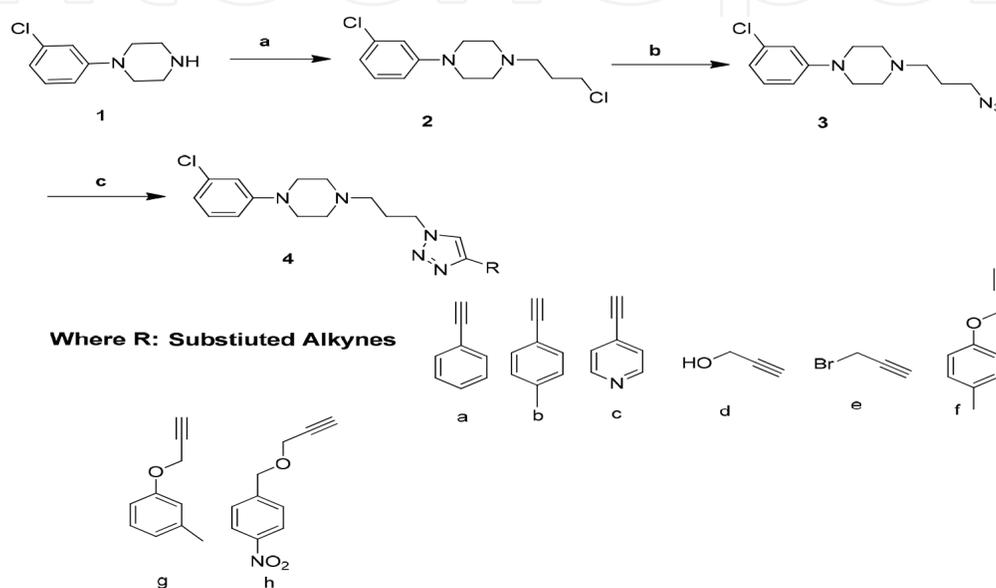
Heterocyclic compounds containing nitrogen plays an important role in agrochemical and pharmaceuticals. The basic heterocyclic rings present in the various medicinal agents are mainly 1, 2, 3-triazole and 1, 2, 4-triazole [11]. Derivatives of 1, 2, 3-triazole have found to anti-HIV, anti-allergenic, antimicrobial, cytostatic, virostatic, anti-inflammatory and antibacterial [12] activities. Triazoles are also being studied for the treatment of obesity and osteoarthritis.

2. Experimental section

2.1. Synthesis of piperazine using click chemistry

In the present investigation, the synthesis of 1-(3-azidopropyl)-4-(3-chlorophenyl) piperazine were synthesized from 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine compound which

on nucleophilic substitution reaction in the presence of NaN_3 and DMSO at 40–45°C, to afford azide intermediated 1-(3-azidopropyl)-4-(3-chlorophenyl) piperazine in good to excellent yield. We have prepared the piperazine triazole by the Huisgen 1, 3-dipolar cycloaddition reaction of 1-(3-azidopropyl) 4-(3-chlorophenyl) piperazine with various substituted alkynes which was prepared reported method in the presence of Cu (I)-catalyst and we got very high yield. The continued interest for the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds, used copper sulfate with its easy availability, cheap cost and operational simplicity prompted us to explore the synthesis of 1, 3-dipolar cycloaddition reaction.



Reaction conditions: (a) 1-bromo-3-chloropropane, aq. NaOH, acetone RT, 24 h. (b) NaN_3 , DMSO, 50–55°C, 4–5 h. (c) Click reaction, R-Substituted alkynes, THF: H_2O , Copper sulfate, sodium ascorbate, RT, 10–12 h.

2.2. General procedure

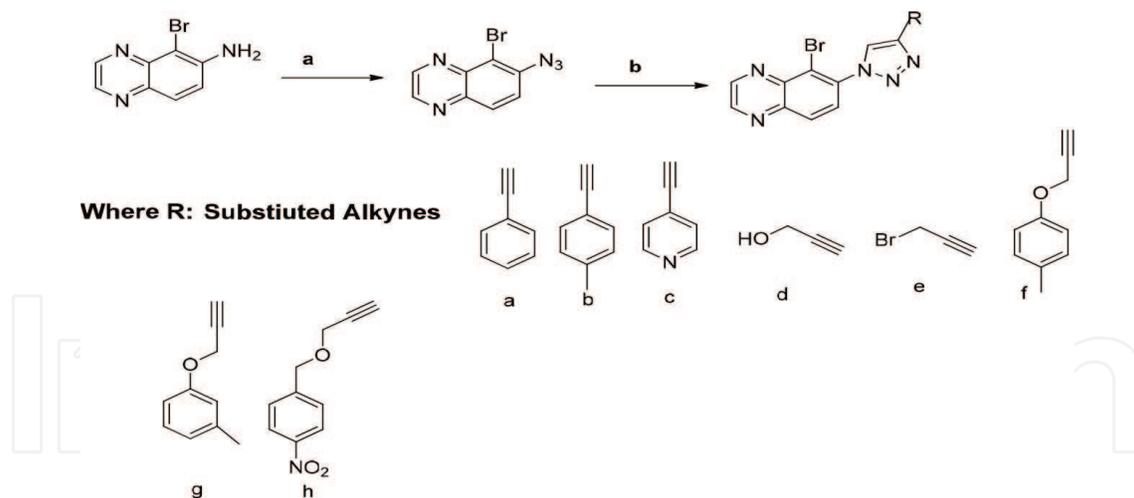
Step (i): To the solution of 1-(3-chlorophenyl)-piperazine (**1**) (0.43 mmol) in water (5 mL) was added sodium hydroxide (1.15 mmol) followed by 1-bromo-3-chloropropane (0.911 mmol) under stirring at 25–30°C. The reaction mixture was further stirred for 24 h at same temperature and progress of reaction was monitored by TLC. After completion of the reaction, the reaction mass was extracted with ethyl acetate. The organic layer was separated and dried over sodium sulfate to obtain pale yellow oily product (**2**) after evaporation of ethyl acetate.

Step (ii): Sodium azide (6.5 mmol) was added to a solution of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine (**2**) (5.0 mmol) in 30 mL DMSO under stirring. The reaction mixture was stirred for 3–4 h at 50–55°C. The reaction progress was monitored by TLC. After completion of reaction, the reaction mixture was poured on crushed ice, which was extracted with ethyl acetate. The organic layer was separated and washed with water and brine solution, dried over sodium sulfate to obtain yellow oily crude product. The crude product was purified by column chromatography (ethyl acetate: n-hexane) to obtain pure yellow oily product (**3**).

Step (iii): The azide compound (**3**) (1.0 mmol) and alkyne (1.1 mmol) were dissolved in THF/H₂O (1:1), CuSO₄·5H₂O (0.05 mmol) and sodium ascorbate (0.40 mmol). The reaction mixture was stirred for 10 h at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was poured on crushed ice. The solid obtained was extracted with ethyl acetate. The organic extract was washed with water and brine. The solvent was removed under reduced pressure to afford crude product, which was purified from ethanol to obtain pure compounds.

2.3. Synthesis of quinoxaline by using click chemistry

In the present investigation, the 6-azido-5-bromo quinoxaline were synthesized from 5-bromo quinoxalin-6-amine compound, which on diazotization in the presence of concentrated sulfuric acid, water and sodium nitrite at temperature 0–5°C which undergoes and nucleophilic substitution reaction with sodium azide to afford the 6-azido-5-bromo quinoxaline in good to excellent yield. The quinoxaline 1, 2, 3 triazole derivatives were prepared by the copper catalyzed azide and alkyne cycloaddition reaction of 6-azido-5-bromoquinoxaline with various substituted alkynes were prepared by reported method using copper sulfate and sodium ascorbate in DMF:H₂O as a reaction medium at room temperature to obtain 1,2,3-triazole quinoxaline as shown scheme. The synthesized products were obtained in good to excellent yields. The progress of the reaction was monitored by TLC. Some synthesized compounds were characterized by IR, ¹H NMR, ¹³C NMR and Mass spectroscopy methods. Some synthesized compounds are antioxidant, antibacterial and antifungal activities have been evaluated.



Reaction conditions: (a) H₂O, H₂SO₄, NaNO₂, NaN₃, 0–5°C to RT, 3 h. (b) Click reaction, RTHF: H₂O, Copper sulfate, sodium ascorbate, RT, 10–13 h.

2.4. General procedure

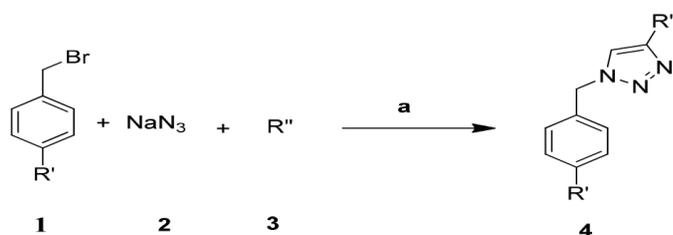
Step (i): A solution of sodium nitrate (3.13 mmol) in water (8 mL) was added dropwise to a solution of 4-amino-5-bromoquinoxaline (**i**) (2.45 mmol) in water (5 mL) and concentrated

H_2SO_4 (3 mL) at 0°C over 5 min. The reaction mixture was stirred at 0°C for 30 min. Then added solution of sodium azide (4.40 mmol) in water (5 mL). The solution was allowed to attain room temperature and keep stirring for 5 h. The progress of reaction was monitored by TLC. The reaction mass was precipitated, filtered and washed with water. Brown colored crude product was recrystallized from aqueous methanol to obtain pure azide compounds.

Step (ii): The azide compound (1.0 mmol) and alkyne (1.1 mmol) were dissolved in DMF/ H_2O (9:1). To this solution, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.05 mmol) and sodium ascorbate (0.40 mmol) were added. The reaction mixture was stirred for 11 h at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was poured on crushed ice. The solid product was extracted with ethyl acetate. The organic extract was washed with water and brine. The solvent was removed under reduced pressure to afford crude product, which was recrystallized from methanol to obtain pure compound.

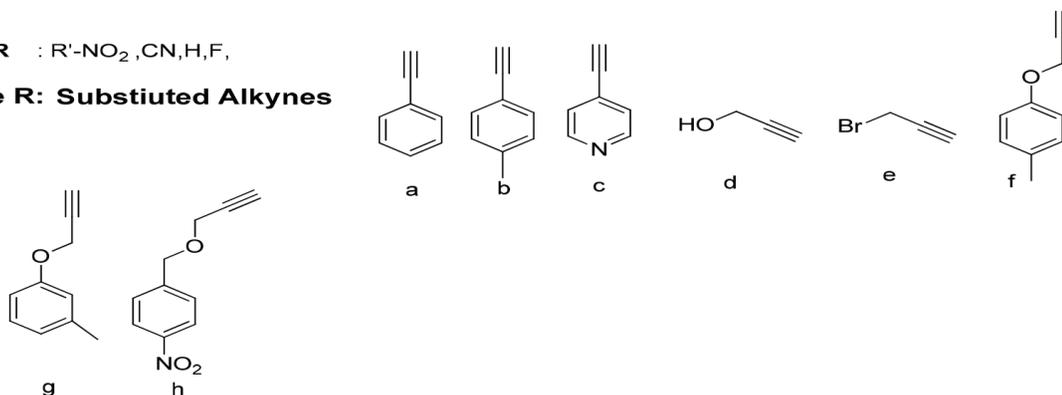
2.5. Synthesis of 1, 2, 3-triazoles by one pot method by using click chemistry

The chemoselective azide and alkyne cycloadditions at room temperature in organic medium. K. Barry Sharpless and co-workers have reported a high yielding synthesis of triazoles using a Cu (I)-catalyst with an excellent 1, 4-regioselectivity. The resulting “clicked” products can even be obtained via in situ generation of the corresponding organic azides, halides, NaN_3 in the presence of an alkyne and a copper catalyst, avoiding the need to handle azides.



Where R : $\text{R}'\text{-NO}_2, \text{CN}, \text{H}, \text{F},$

Where R: Substituted Alkynes



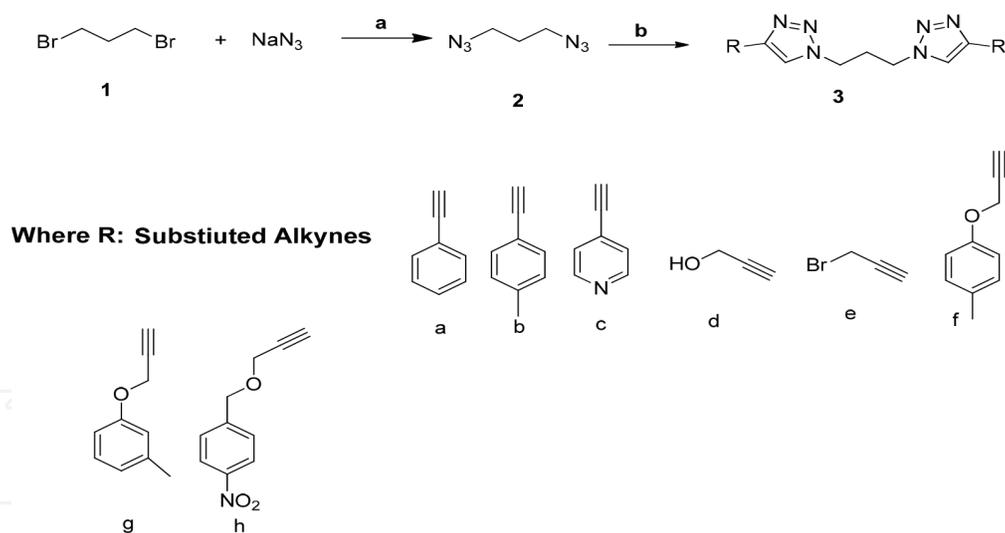
Reagent and conditions: (a) NaN_3 , CUI (10%), PEG-400.

2.6. General procedure

Substituted halide (1.0 mmol), sodium azide (1.4 mmol) and Substituted alkynes (1.1 mmol) were charged into the single neck R.B. flask contains polyethylene glycol-400 (5 mL). Catalytic amount of copper iodide (10 mol %) were added into the reaction mixture and maintain it for 6 h at 40–45°C. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was poured on crushed ice. The isolated product was extracted with ethyl acetate. The organic layer was separated and washed with water and brine solution. The solvent was removed under reduced pressure and the isolated crude product was recrystallized from ethanol to obtain pure compounds.

2.7. Synthesis of 1, 2, 3-bistriazoles by using click chemistry

Present investigation in the synthesis of 1, 2, 3-bistriazole, the most widely used is the Cu (I)-catalyzed 1, 3 dipolar cycloaddition reaction in which the condensation of a bis-halide with an substituted alkynes were prepared by reported method in the presence of NaN_3 , Na_2CO_3 , $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, ascorbic acid, DMF: H_2O , 15–20 h, r.t. We have synthesized the 1, 2, 3-bistriazole derivatives by changing the pharmacophore and changing the position of the pharmacophore on substituted alkynes. These synthesized new drug scaffold. The synthesized compounds were evaluated for antibacterial activity and carcinogenicity study.



Reagents and condition: (a) NaN_3 , DMSO, 45–50°C, 4–5 h. (b) CuI, DIPEA, DMF, 5–6 h, 55–60°C.

2.8. General procedure

To a stirred solution of 1, 3-dibromopropane (1.5 mmol) in DMF: H_2O (4:1) 15 mL; NaN_3 (3.2 mmol), Na_2CO_3 (2.2 mmol), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.6 mmol), ascorbic acid (2.2 mmol) and phenyl acetylene (3.1 mmol) were added. The reaction mixture was stirred at room temperature for 20 h. The progress of reaction monitored by TLC. Then, aqueous NH_4OH and CH_2Cl_2 were added in the reaction mixture and the organic layer was separated and washed with water, brine solution

and dried by MgSO_4 . The organic solvent was evaporated under reduced pressure to get crude product. The isolated crude product was recrystallized from ethanol to obtain pure compound.

3. Result and discussion

IR spectra of azide showed characteristic band at near region 2113 cm^{-1} due to $(-\text{N}_3)$ stretching vibrations. IR spectrums in azido and alkyne peak are disappeared to confirmed 1, 2, 3-triazole formation, of compounds. These assignments are in agreement with those observed by several research groups.

^1H NMR spectra of compounds were studied in CDCl_3 and DMSO-d_6 showed spectra the proton in triazole ring significantly observed in the region at δ 8.62–7.81 ppm and adjacent sp^2 hybridized carbon of that proton at δ 129.68–127.86 ppm in ^{13}C NMR. These findings are in agreements with those observed by different workers.

The mass spectra of corresponding 1, 2, 3-triazol-1-yl piperazine show their molecular formula weight and found to be in agreement with the literature.

4. Conclusion

We have successfully introduced azide-alkyne 1, 3-dipolar cycloaddition reaction in heterocyclic chemistry. Due to the presence of triazole it observed that enhancing the bioactivity of basic moieties at different heterocycles. We have concluded that a series of novel 1, 2, 3-triazol-1-yl piperazine, quinoxaline, one pot 1,2,3-triazole and bistriazole derivatives by using click chemistry. These derivatives we have achieved by using Husign 1, 3-dipolar cycloaddition which is green chemistry approach because of high yield, high purity, stereo specific, simple to perform, using green solvents.

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