



Syntheses and biological activities of 1,4-disubstituted-1,2,3-triazoles

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ABSTRACT

This review on 1,4-disubstituted 1,2,3-triazoles deals with the different pharmacological significance and a detailed synthetic approaches used to synthesize 1,4-disubstituted triazoles. The near perfect, easy, stereo specific and robust method of synthesis of triazoles draw attention of researchers to exploit the property of this heterocyclic building block in various fields.

Keywords: 1,4-Disubstituted 1,2,3-triazole, synthesis, biological activity.

INTRODUCTION

Triazole,[1] also known as pyrroldiazole, is a heterocyclic organic compound containing a five member ring with three nitrogen atoms and two carbon atoms. There are two isomeric compounds 1,2,3- triazole and 1,2,4-triazole (**Figure 1**) with molecular formula C₂H₃N₃.

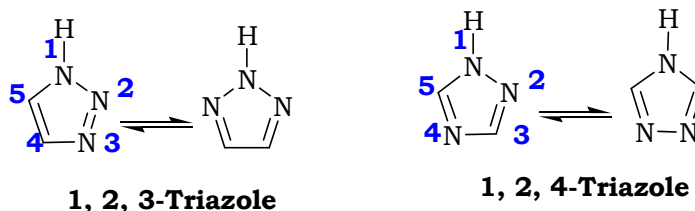


Figure 1 Chemical structures of 1,2,3-triazole and 1,2,4-triazole

Triazoles, although not available in nature, occupy a conspicuous place in various domains e.g. bioactive molecules, optical brightening agents, corrosion inhibitors, additives, dendrimers, polymers, liquid crystals and supramolecular chemistry [2-5]. At present there is increasing number of applications in numerous other areas of modern chemical sciences.

Since a large number of 1,2,3- triazoles exhibit various biological effects, it seems pertinent in this connection to review briefly earlier reports on biological activity of this privileged frame work.

Biological activities of 1,4-disubstituted 1,2,3-triazoles:

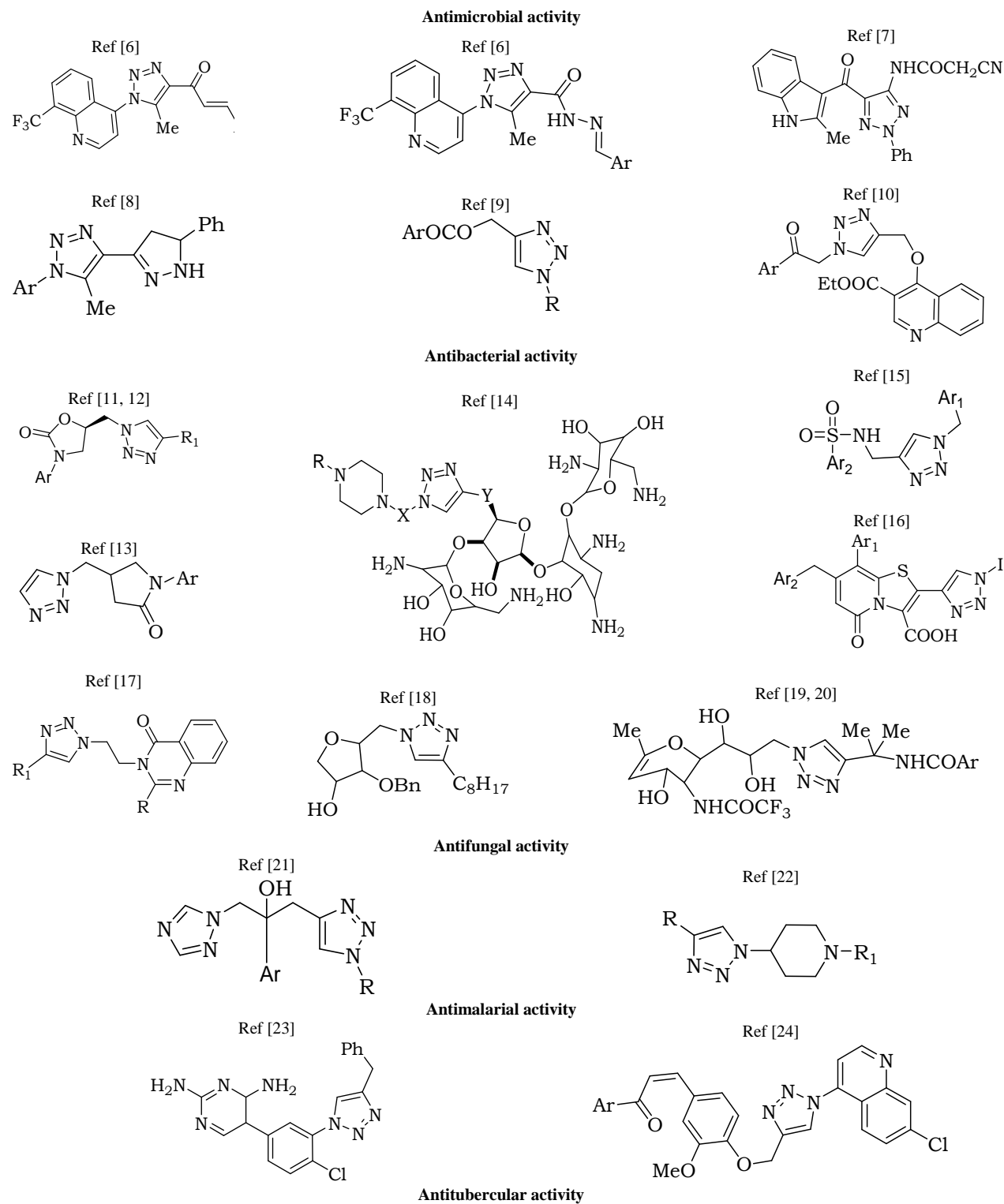
1,2,3-Triazole based heterocycles are considered important in the field of medicinal chemistry due to the presence of following features:

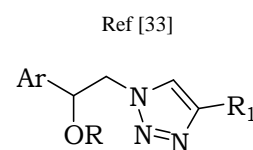
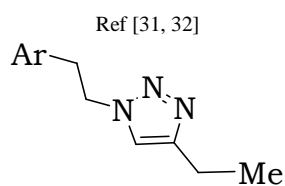
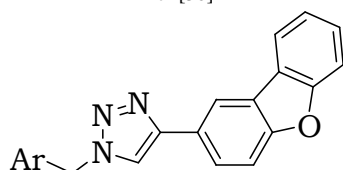
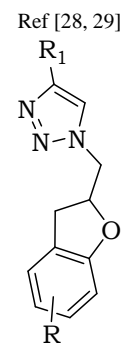
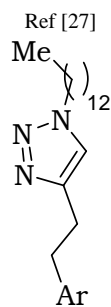
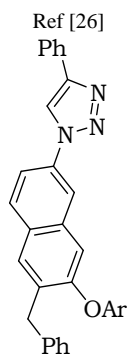
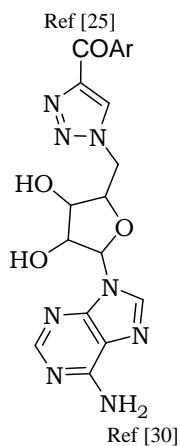
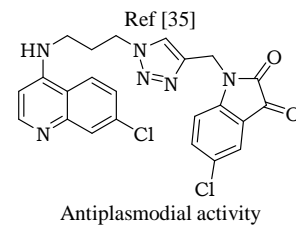
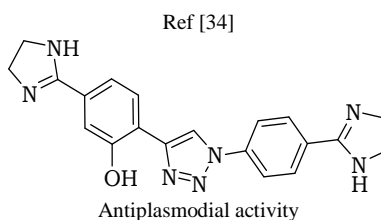
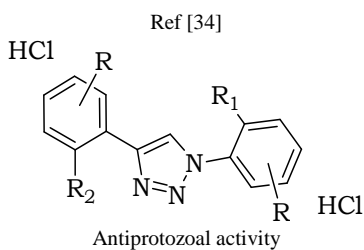
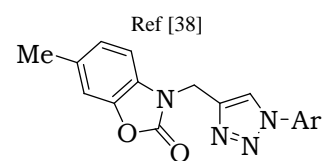
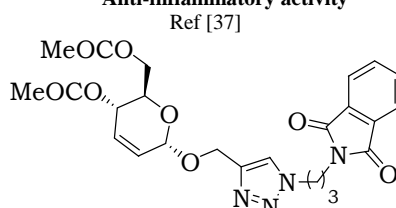
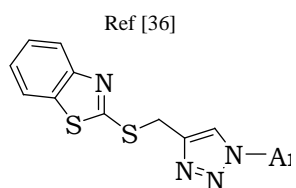
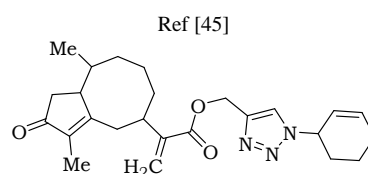
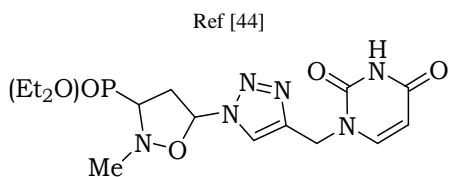
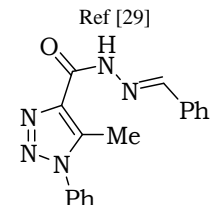
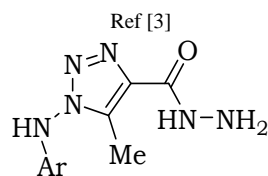
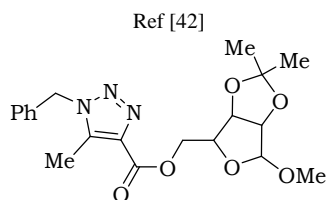
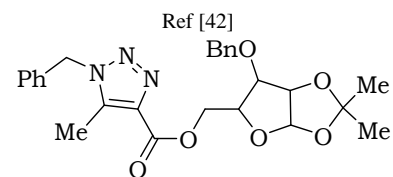
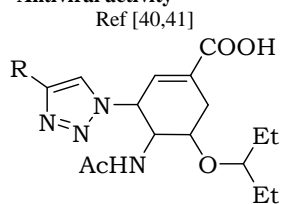
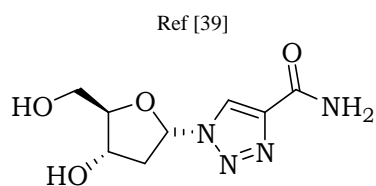
- Stable to reduction and oxidation
- Stable to hydrolysis under acidic and basic condition
- Forms strong H-bonding
- Has high dipole moment (-5D)
- Participates in π - π stacking

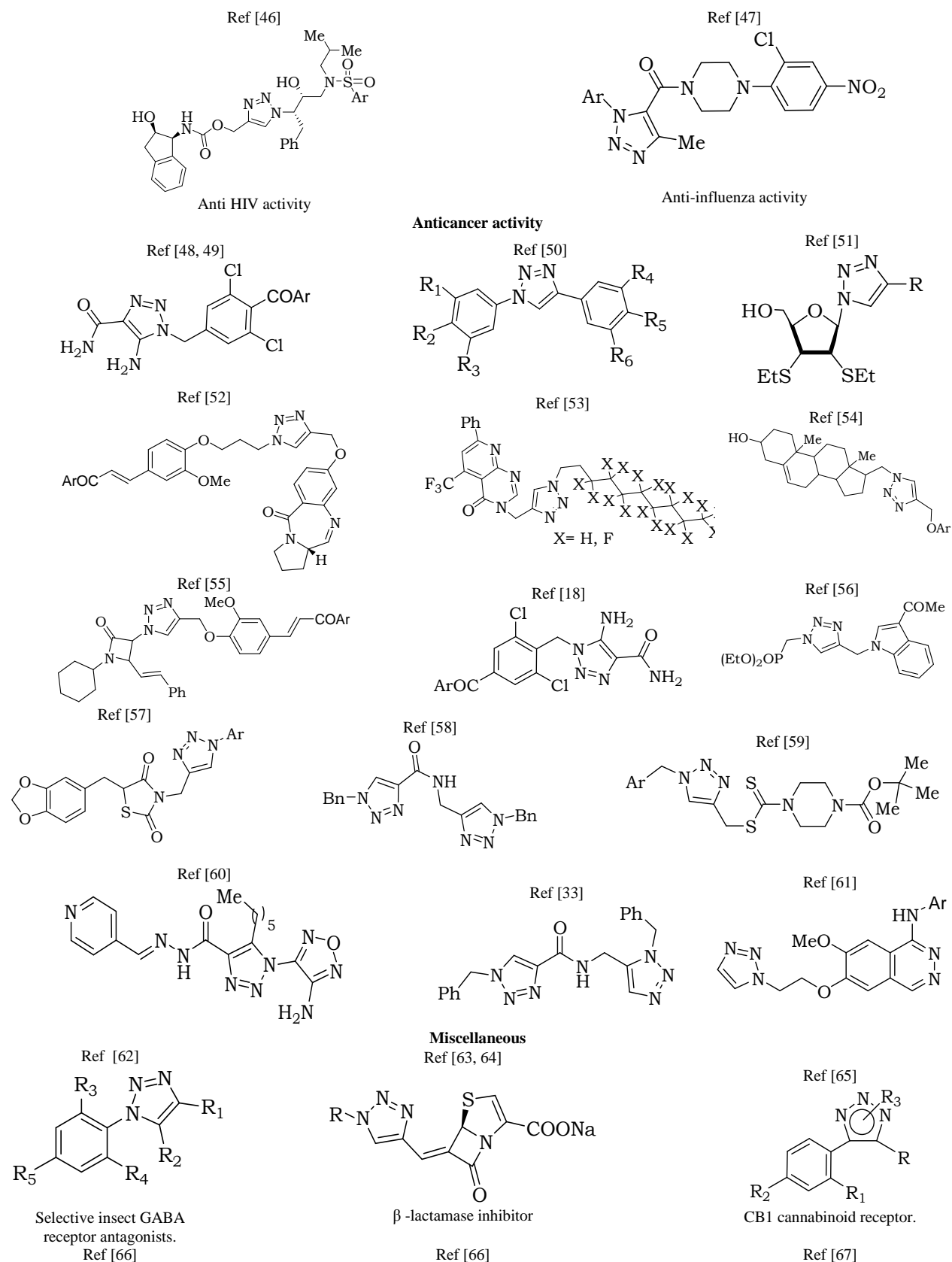
- Bioisostere of peptide linkage, aromatic ring, double bonds & imidazole ring
- Can be used as linker

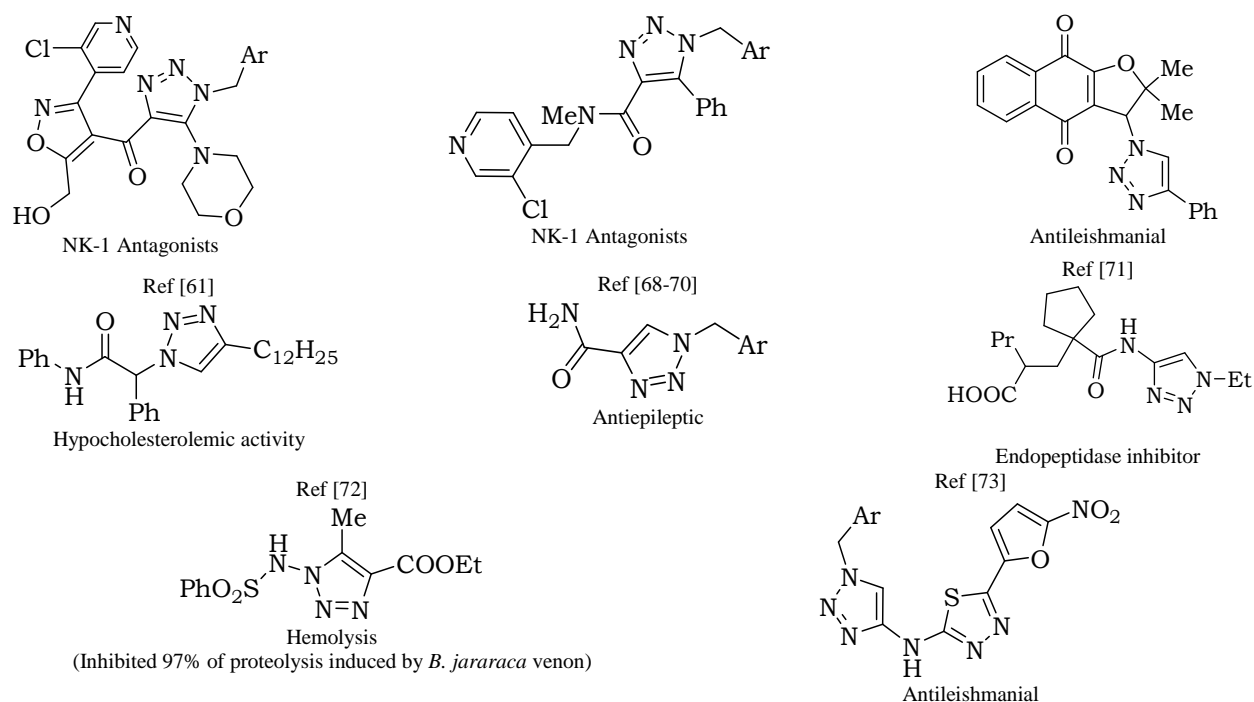
Biological activities of 1,4-disubstituted 1,2,3-triazoles are listed as follows (**Table 1**)

Table 1 List of biologically active 1,4-disubstituted 1,2,3-triazoles



**Other microbial activities****Anti-inflammatory activity****Antiviral activity**





Synthesis:

Following methods are available in the literature to synthesize 1,2,3- triazoles.

I Cycloaddition reactions between azide and alkyne to give triazole

Probably the most efficient method for the synthesis of 1,2,3-triazoles is the dipolar [3+2] cycloaddition of organic azides and alkynes. Several approaches were found in the literature which differs in solvents, catalysts and reaction conditions (**Figure 2**) summarizes few of those.

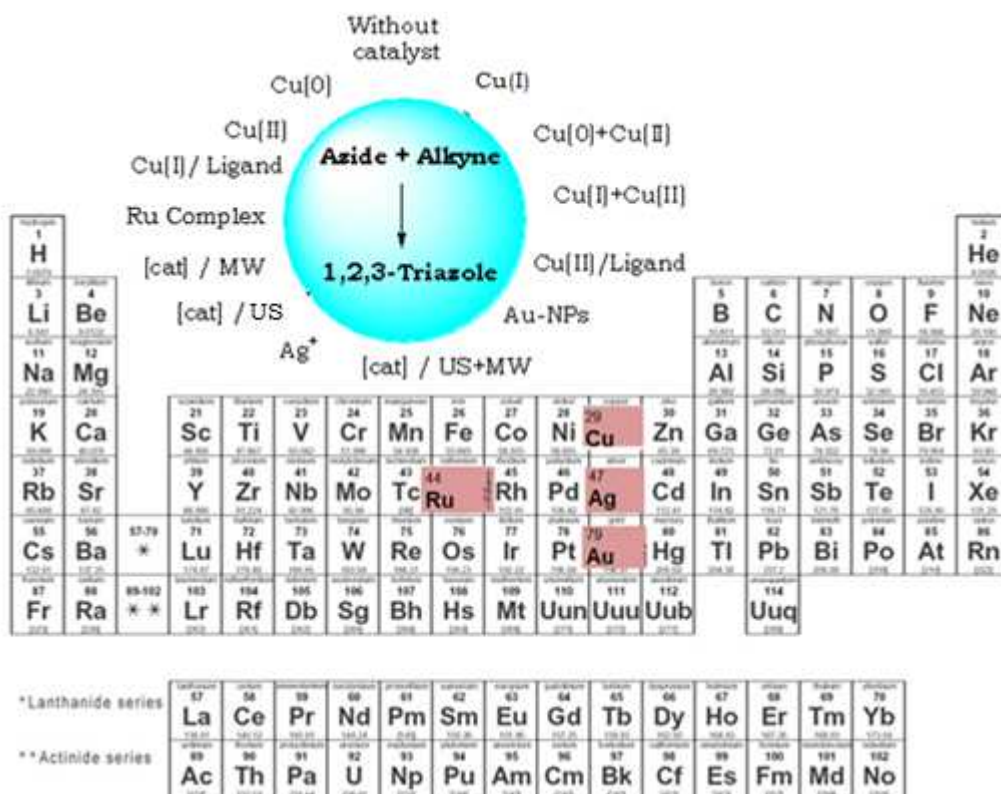
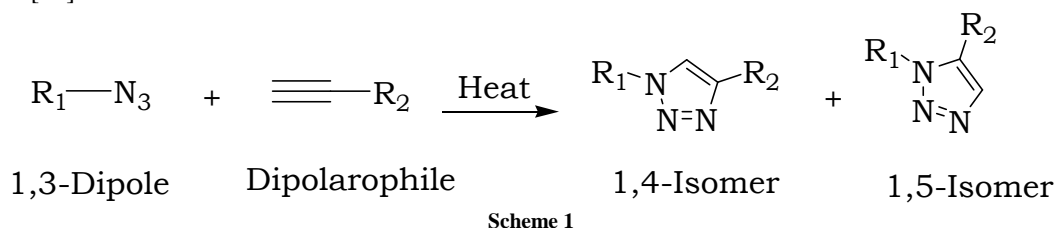


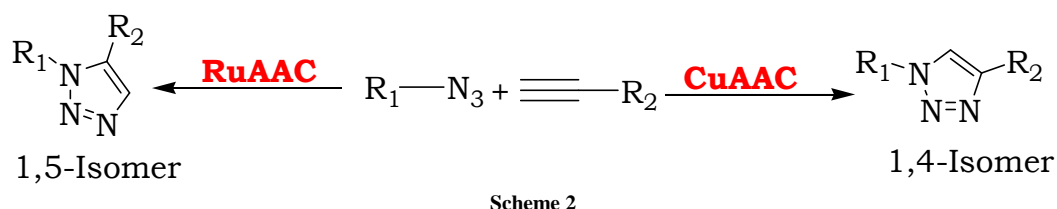
Figure 2 Different conditions and most often used metal salts for azide-alkyne cycloaddition to synthesize 1,2,3-triazole

A. Without catalyst

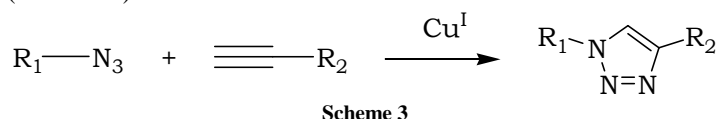
The classical Huisgen-type thermal 1,3- dipolar cycloaddition of azide and terminal alkyne, [74,75] resulted in 1:1 mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles (**Scheme 1**). Degl'Innocenti and his co-workers heated different azides with acetylenic silyl ketones under reflux in toluene to afford 1-substituted-1,2,3-triazolyl-4- and -5-acylsilanes [76].

**B With catalyst**

Over the years different catalysts were discovered for azide-alkyne cycloaddition. In this section we intended to give an overview of important developments of catalysts highlighting mainly 1,4-disubstituted 1,2,3-triazoles not 1,5-disubstituted regioisomer. From the literature survey it was found that copper catalysed reaction (CuAAC) mainly gives 1,4-isomer where as ruthenium proceeds 1,5-regioisomer (RuAAC) [77] (**Scheme 2**).

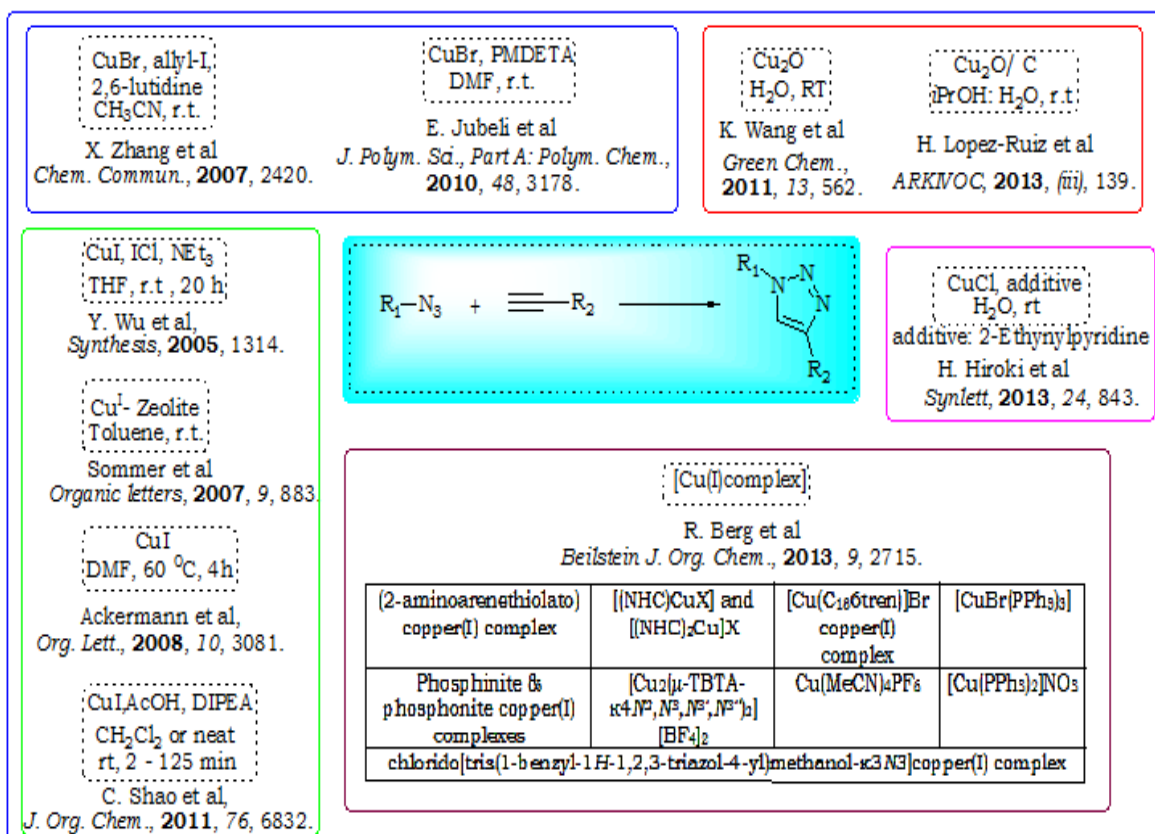
**i. Copper****Cu (I) as a catalyst**

K. Barry Sharpless and co-workers reported [78] the synthesis of a regioisomeric 1,4-disubstituted 1,2,3-triazole by using the copper(I) catalyst. This cycloaddition reaction between azides and terminal alkynes, called 'click chemistry', copper (I)-catalyzed azide alkyne cycloaddition (CuAAC) to give 1,4-disubstituted 1,2,3-triazoles under mild reaction conditions (**Scheme 3**).



As it is not possible to give a complete account of azide-alkyne cycloaddition only few developments of this field have been incorporated.

Scheme 4 represents a comprehensive collection of different CuAAC using copper(I) species eg. CuCl, CuBr, CuI and Cu₂O as catalyst. As Cu (I) is unstable, stabilizing ligands or additives were also used to improve the performance.



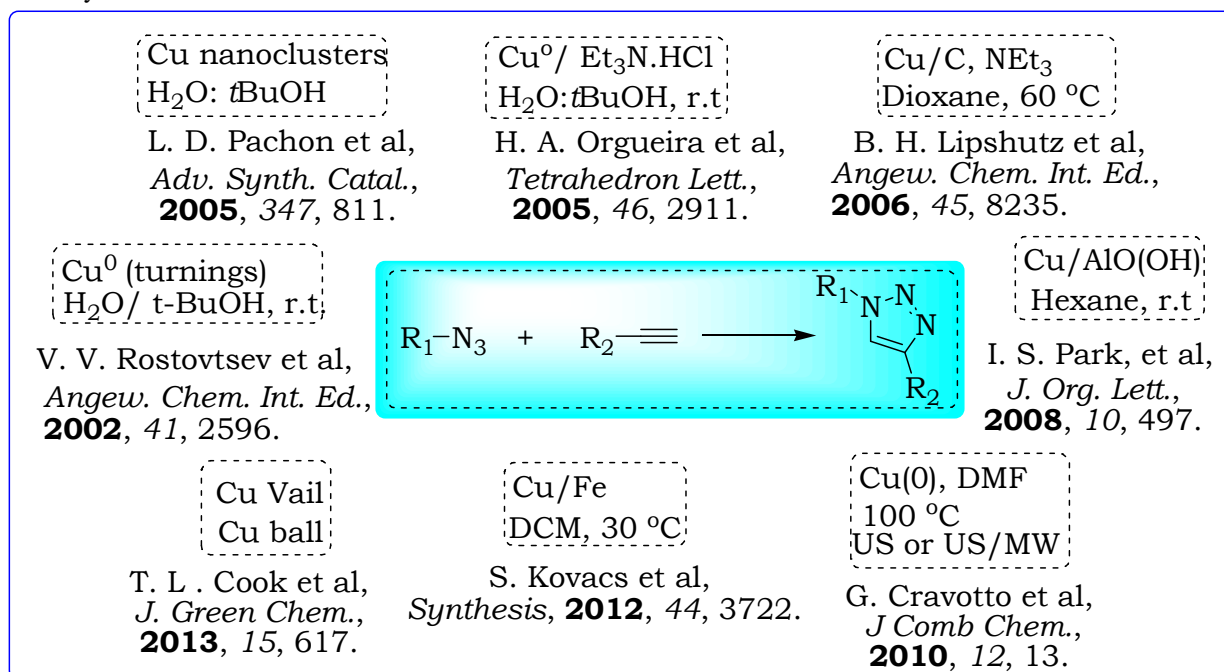
Scheme 4

Cu (I) species, the actual catalyst in CuAAC reaction was generated *in situ* mainly either by

- Cu(0) and a oxidising agent (or)
- Cu⁺² and a reducing agent.

Cu (0) as pre-catalyst

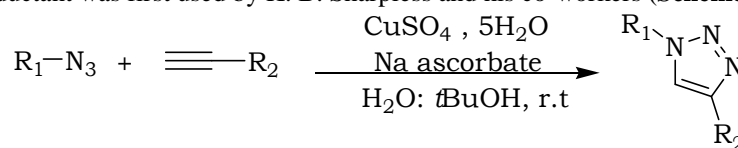
Scheme 5 represents the important achievements in construction of 1,2,3-triazoles using Cu(0) pre-catalyst during last ten years.



Scheme 5

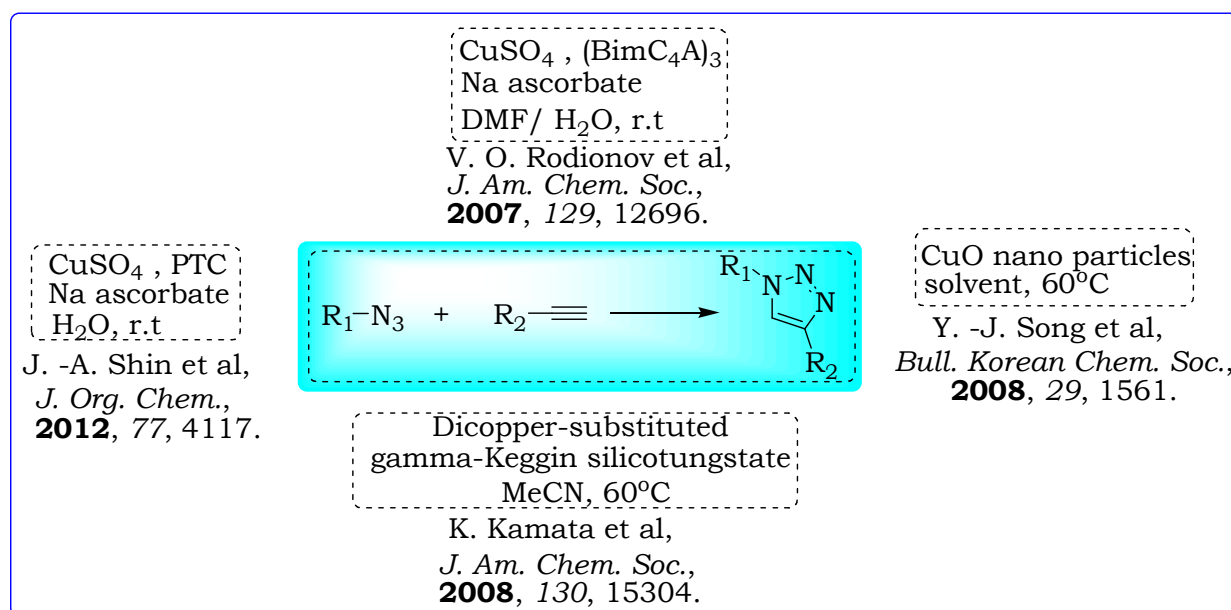
Cu (II) as pre-catalyst

Cu (II) along with a reductant was first used by K. B. Sharpless and his co-workers (**Scheme 6**) [79].



Scheme 6

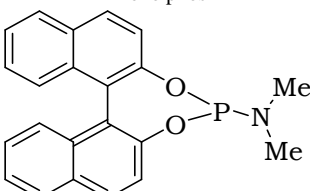
Other efficient protocols using Cu(II) are represented as follows (**Scheme 7**).



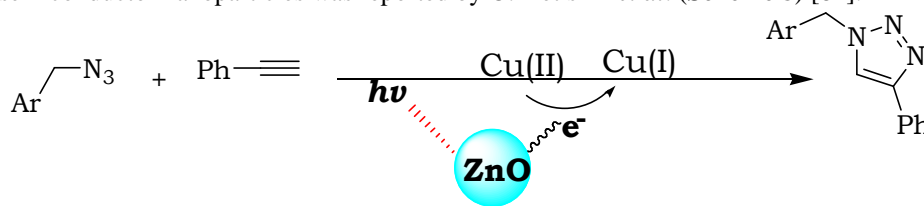
Scheme 7

In combination with copper (II) salts, ligands were added as additives, so that no oxidant can attack at the copper (I) ion. Commonly used ligands (**Table 2**) are listed below [80].

Table 2 List of ligands/additives

Tris[(1-benzyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amine (TBTA)	Tris[(1-hydroxypropyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amine (THPTA)
2-[4-{(Bis[(1- <i>tert</i> -butyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amino)methyl}-1 <i>H</i> -1,2,3-triazol-1-yl]ethyl hydrogen sulfate (BTES)	2-[4-{(Bis[(1- <i>tert</i> -butyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amino)methyl}-1 <i>H</i> -1,2,3-triazol-1-yl]acetic acid (BTAA)
3-[4-{(Bis[(1- <i>tert</i> -butyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amino)methyl}-1 <i>H</i> -1,2,3-triazol-1-yl]propyl hydrogen sulfate (BTTPS)	3-[4-{(Bis[(1- <i>tert</i> -butyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amino)methyl}-1 <i>H</i> -1,2,3-triazol-1-yl]propanol (BTTP)
Mono phos 	

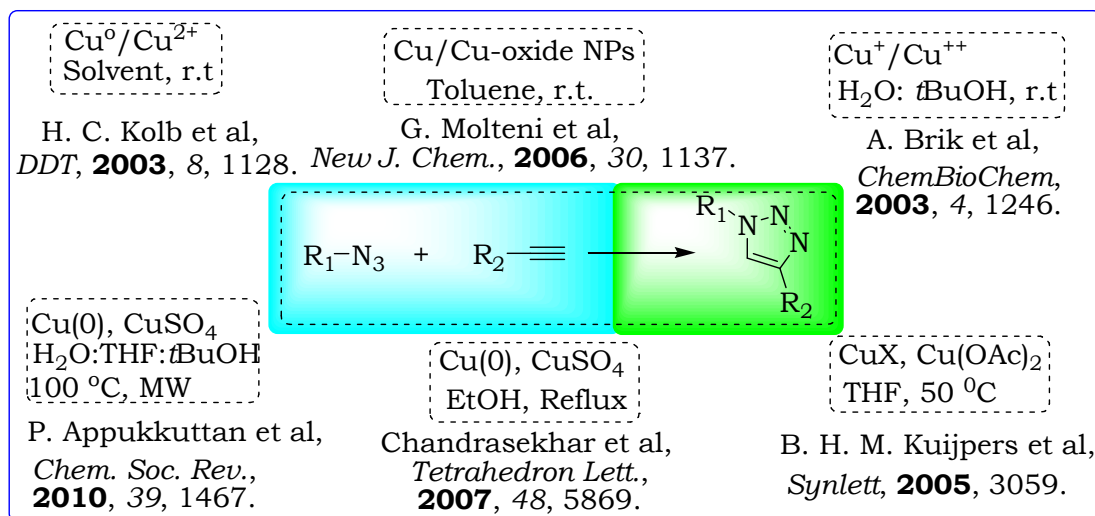
Catalytically active copper (I) species are generated *in situ* from zinc oxide nanoparticles. By using semiconductor nanoparticles as the photocatalyst, photoinduced copper(I)-catalyzed azide-alkyne cycloaddition reaction, initiated by zinc-oxide semiconductor nanoparticles was reported by O. Yetiskin *et al.* (**Scheme 8**) [81].



Scheme 8

Combination of Cu (0), Cu (I) and Cu (II) as catalyst

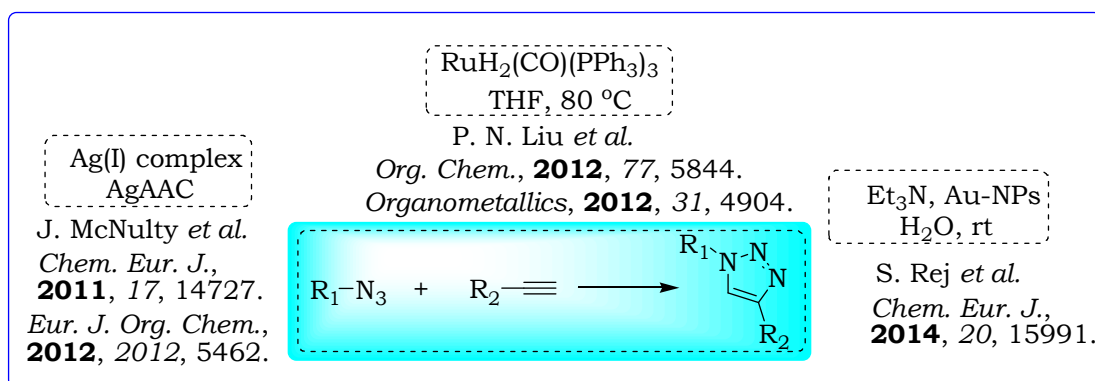
Scheme 9 represents various examples of azide-alkyne cycloaddition under the catalytic effect of dual systems e.g. (a) Cu (0) and Cu (II) and (b) Cu(I) and Cu(II).



Scheme 9

ii. Other than copper

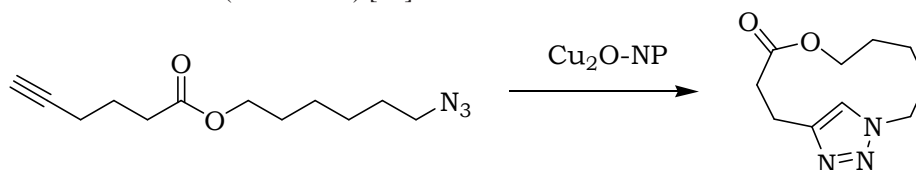
J. McNulty *et al.* developed Ag^I -catalyzed azide-alkyne cycloaddition reaction (Ag-AAC) at room temperature in presence of either a Ag^I complex of type $[\text{Ag}^I(\text{L}_2)(\text{OAc})]$ as promoter or a homogeneous silver(I) catalyst to synthesize 1,4-disubstituted triazole in high yield. In 2012, P. N. Liu *et al.* performed the same reaction in presence of ruthenium hydride complex $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ as catalyst in THF solvent (RuAAC) and surprisingly isolated 1,4-disubstituted triazole instead of expected 1,5-regioisomer in ruthenium catalyzed azide-alkyne cyclo addition. In a latest development S. Rej and his co-workers achieved regioselective azide-alkyne cycloaddition when they performed the reaction at room temperature in presence of rhombic-dodecahedral gold nanocrystals bound by {110} facets as catalyst and triethyl amine as base in aqueous medium (**Scheme 10**).



Scheme 10

C Intramolecular azide-alkyne reaction

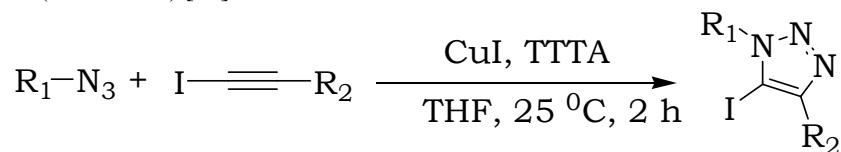
Duan *et al.* done intramolecular 1,3-dipolar cycloaddition reaction by Cu_2O nanoparticles (Cu_2O -NP) as catalyst in the presence of acetonitrile solvent (**Scheme 11**) [82].



Scheme 11

D Reaction between azide and non-terminal alkyne

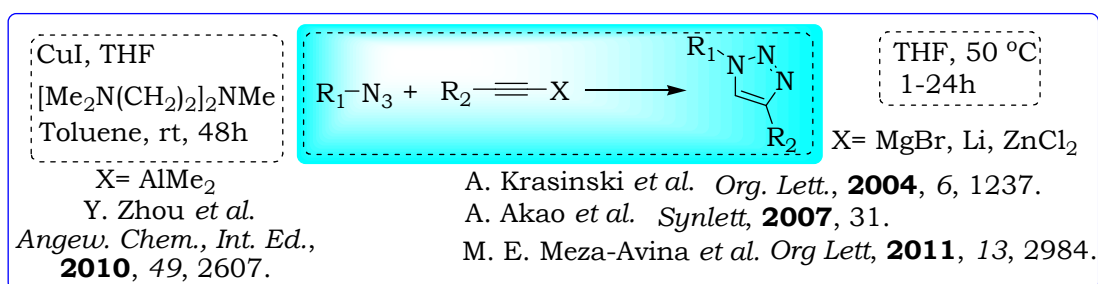
J. E Hein *et al.* performed the reaction between iodoalkynes as viable substrates for CuAAC reactions and catalytic quantities of amines like tris((1,2,3-triazolyl)methyl)amine (TTTA) as ligand, which reduces the formation of undesired byproducts (**Scheme 12**) [83].



Scheme 12

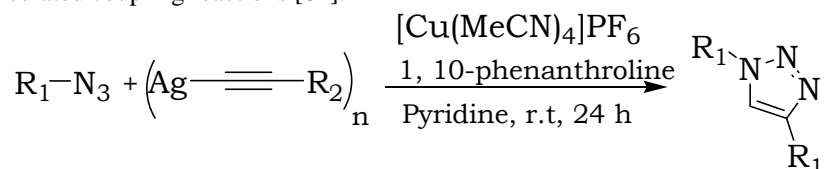
E Reaction between azide and metallated alkyne

An unanalyzed cycloaddition reaction with metallated alkynes and azides (**Scheme 13**) was done by Ankimova in 1960's. This reaction was reinvestigated in 2004 by Krasinski *et al.* The similar reaction by using lithiated alkynes and azides was done by Meza-Avina *et al.* The reaction was done with alkynylzinc or zincates with azides to form metallo triazoles. Y. Zhou *et al.* performed copper-catalyzed cycloaddition of azides with mixed-aluminum acetylides and obtained chemo- and regioselective aluminotriazoles.



Scheme 13

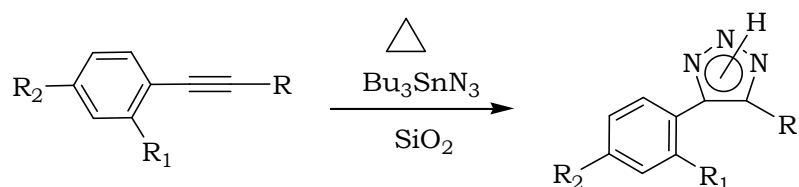
I. P. Silvestri *et al.* afford 1,4-disubstituted 1,2,3-triazoles on reacting silver acetylides and organic azides under copper (I) catalysis. Mechanistic studies implicate that the process involve transmetalation to copper acetylides prior to cycloaddition (**Scheme 14**). This demonstrates that the silver acetylides serves as suitable precursors for entry into copper-mediated coupling reactions [84].



Scheme 14

F Reaction between metallated azide and alkyne

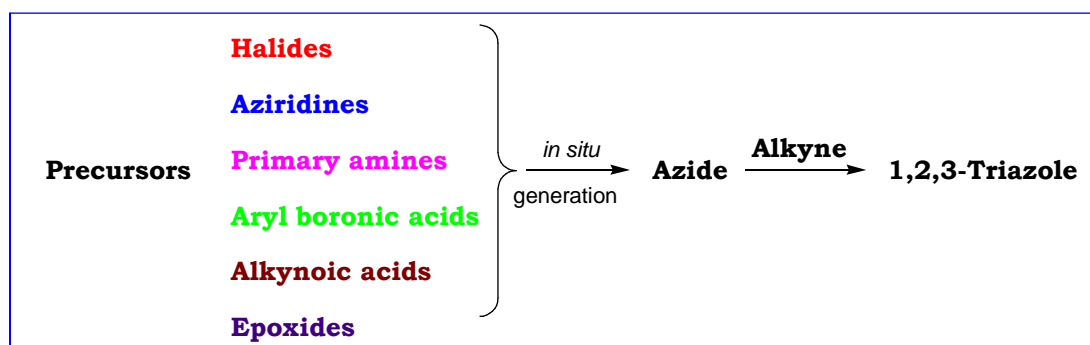
Jagerovic and his co-workers developed efficient method for 1,2,3-triazoles by cycloaddition of tri-*n*-butyltin azide with mono- or disubstituted alkynes under pressure and heating conditions (**Scheme 15**) [65].



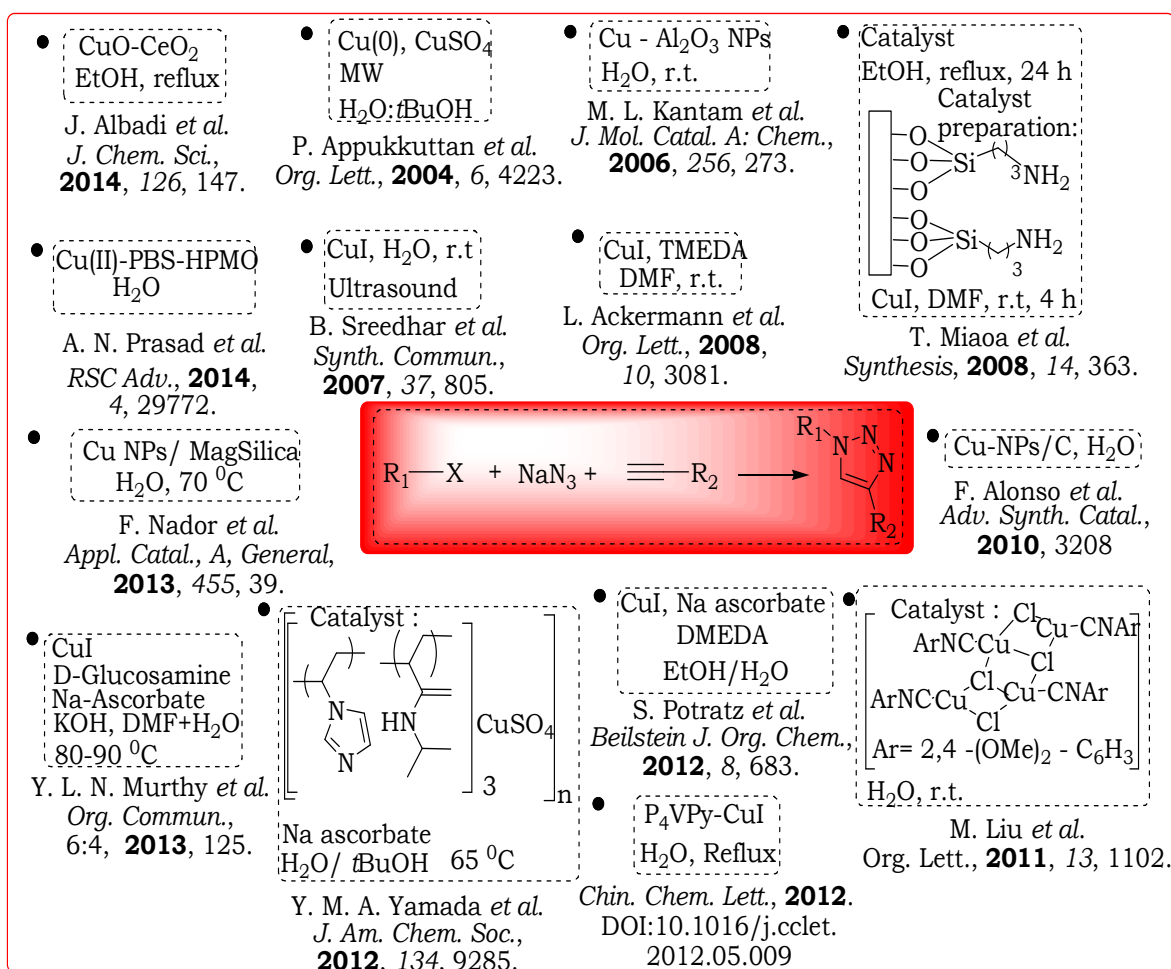
Scheme 15

G Reaction between *in situ* generated azide and alkyne**i. *In situ* generated azide**

The required azide for the reaction to afford 1,2,3-triazole molecules, was generated *in situ* from various sources (**Figure 3**).

Figure 3 *In situ* generation of azide from various sources**From alkyl/aryl halides**

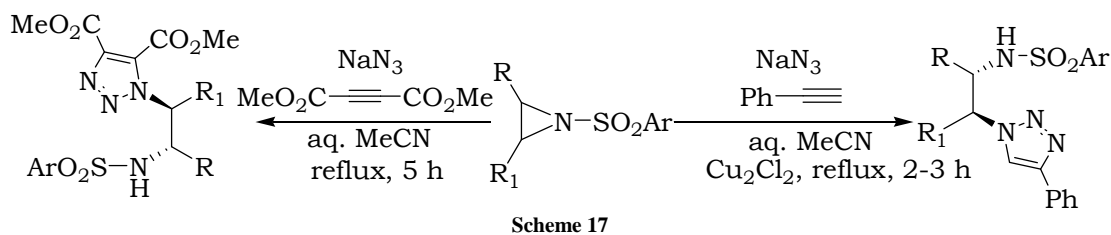
1,4-Disubstituted 1,2,3-triazoles are prepared by a multi-component reaction from corresponding alkyl/aryl halides, sodium azide, and alkynes by using different catalytic systems, on different catalyst supports like silica, alumina and poly(4-vinyl pyridine) in various solvents (**Scheme 16**).



Scheme 16

From aziridines

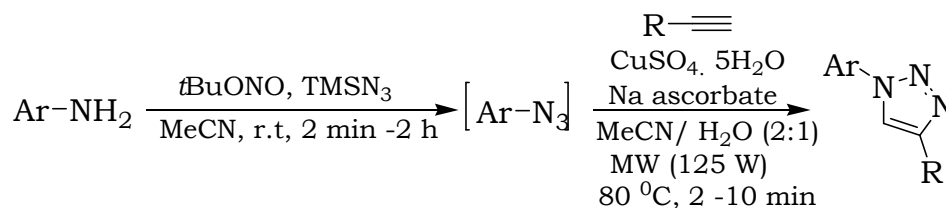
Markov and Polyakov performed one-pot synthesis of 1,2,3-triazoles by using *N*-sulfonylaziridines, phenylacetylene, NaN₃ and Cu₂Cl₂ in catalytic amounts in aqueous acetonitrile (**Scheme 17**).[85].



Scheme 17

From aniline

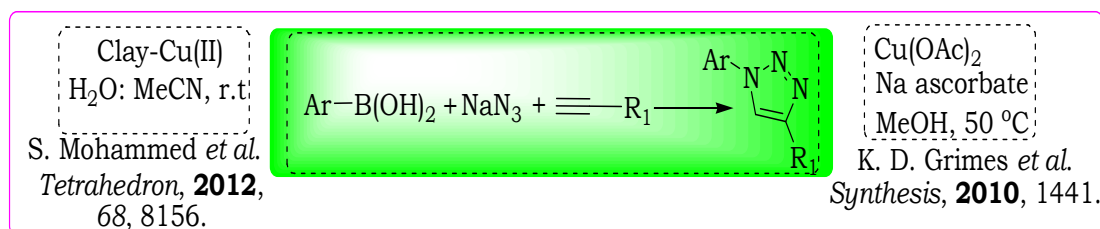
Moorhouse and Moses performed microwave irradiation to afford 1,4-disubstituted 1,2,3-triazoles. One-pot azidation of anilines generated *in situ* azides and reacted with alkynes (**Scheme 18**) [86].



Scheme 18

From boronic acids

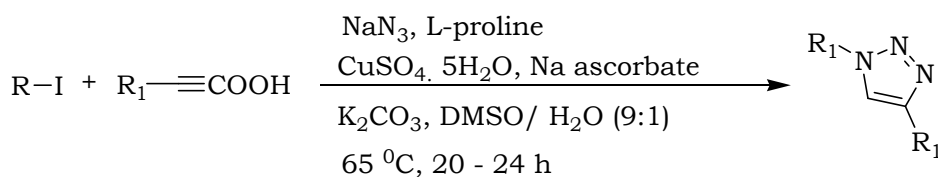
Copper(II)-catalyzed conversion of heteroaryl/aryl boronic acids, trifluoroborates and boronates into the corresponding azide derivatives, which are further converted to 1,4-disubstituted 1,2,3-triazoles, on the other hand condensation of boronic acids, alkynes and sodium azide by using catalytic amount of clay-Cu(II) catalyst was used (**Scheme 19**).



Scheme 19

From alkynoic acids

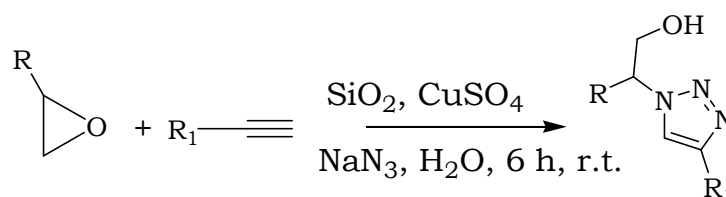
Kolarovic and his co-workers done the decarboxylative coupling of alkynoic acids and 1,3-dipolar cycloaddition (**Scheme 20**). This reaction avoids the usage of highly volatile or gaseous terminal alkynes [87].



Scheme 20

From epoxides

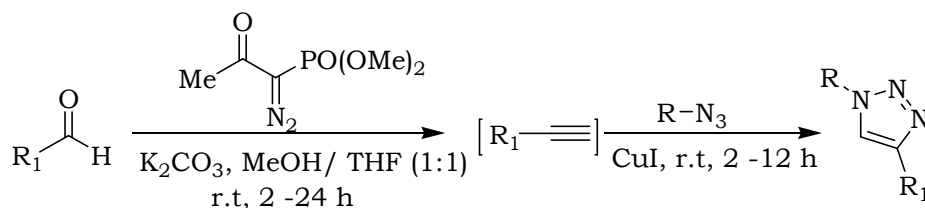
Hashjin and his co-workers done one-pot three-component condensation of alkynes, epoxides and sodium azide by using catalytic amount of $\text{SiO}_2/\text{CuSO}_4$ and ascorbic acid in aqueous medium at ambient temperature (**Scheme 21**) [88].



Scheme 21

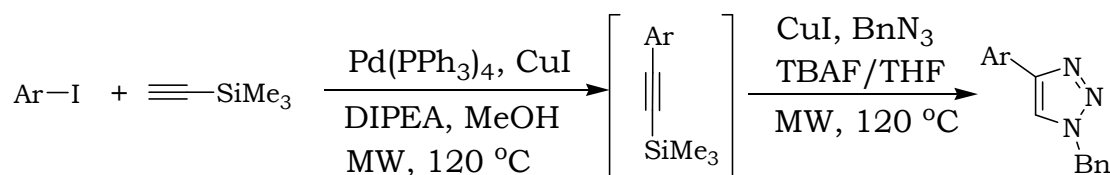
ii. In situ generated alkyne

One-pot reaction for a one-carbon homologation of various aldehydes followed by CuAAC reaction gives 1,4-disubstituted 1,2,3-triazoles without the isolation of the alkyne intermediates (**Scheme 22**) [89].



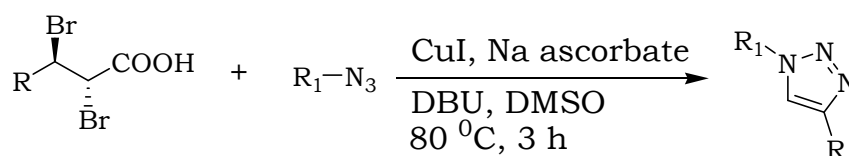
Scheme 22

F. Friscourt and G.-J. Boons performed one-pot three-step synthesis of 1,2,3-triazoles by copper-catalyzed reaction of azides with alkynes formed by a Sonogashira cross-coupling and desilylation (**Scheme 23**) [90].



Scheme 23

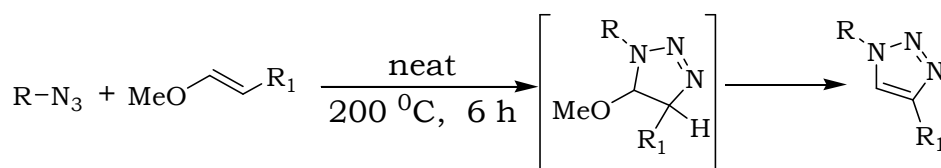
One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides in the presence of CuI in DMSO was performed by Chen and his co-workers (**Scheme 24**) [91].



Scheme 24

II Cycloaddition reactions between azide and enolethers

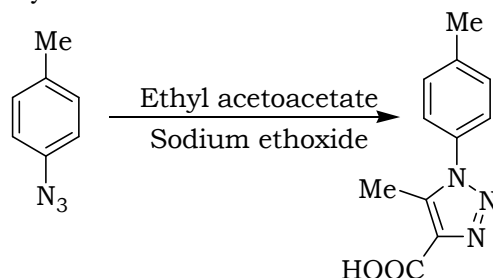
1,4-Disubstituted 1,2,3-triazoles were prepared by cycloaddition of alkyl azides and enol ethers under neat conditions (**Scheme 25**). The reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions [92].



Scheme 25

III Cycloaddition reactions between azide, ethylacetoacetate and sodium ethoxide

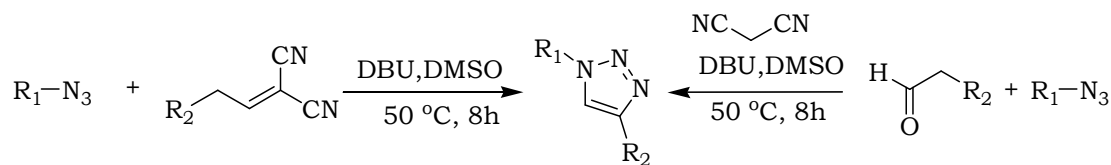
Narala *et al.* refluxed sodium ethoxide and ethylacetoacetate (2.5:1.0) in a round bottomed flask followed by the drop wise addition of 1-azido-4-methylbenzene. Reaction was carried out under N₂ atmosphere (**Scheme 26**) [93].



Scheme 26

IV Inverse electron-demand 1,3-dipolar cycloaddition

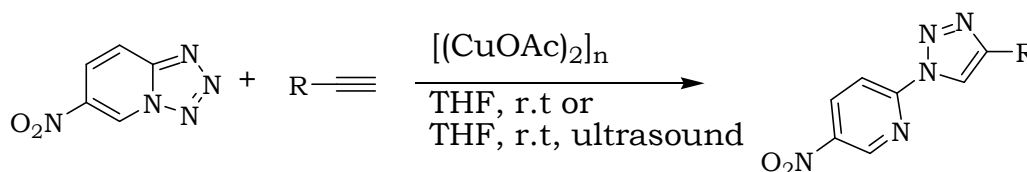
Paixao and his co-workers synthesized 1,4-disubstituted 1,2,3-triazoles by applying inverse electron-demand-1,3-dipolar cycloaddition approach. The one-pot metal-free strategy can be accomplished with various alkylidene malononitriles and aromatic azides in the presence of base (**Scheme 27**) [94].



Scheme 27

V Azide-alkyne cycloaddition by using 6-substituted tetrazolo [1,5-*a*]pyridines

6-Substituted tetrazolo[1,5-*a*]pyridines are used for azide-alkyne cycloaddition with copper(I)-catalyst. X. Wang and his co-workers observed the *in situ* formed HOAc activated 2-azidopyridine-copper(I) complex (**Scheme 28**) [95].



Scheme 28

Above mentioned reactions, performed in the presence of various solvents are listed below [96].

- | | | |
|---------------------|-----------------------------------|-------------------------------|
| ➤ THF | ➤ Pyridine | ➤ H ₂ O/ROH |
| ➤ DMF | ➤ MeCN | ➤ MeCN/H ₂ O |
| ➤ DMSO | ➤ CH ₂ Cl ₂ | ➤ Dioxane/H ₂ O |
| ➤ MeOH | ➤ H ₂ O | ➤ MeCN/H ₂ O/tBuOH |
| ➤ CHCl ₃ | ➤ DMF/Pyridine | ➤ MeCN/H ₂ O/DMSO |
| ➤ MeCN | ➤ DMF/THF | ➤ H ₂ O/ DMSO |
| ➤ Toluene | ➤ Toluene/tBuOH | ➤ H ₂ O/ tBuOH |

CONCLUSION

Overall with the above literature survey at the backdrop, it is evident that 1,2,3-triazoles are undoubtedly attractive synthetic targets as they provide various applications. The remarkable features that make 1,2,3-triazoles very special are their ability to generate structurally diverse and complex compounds.

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