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REVIEW ARTICLE

SYNTHESIS OF TRIAZOLES: AN OVERVIEW

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ABSTRACT

Azoles are five-membered cyclic compounds containing one or more heteroatoms in the ring, at least one of which must be nitrogen. The rings contain the maximum number of non-cumulative double bonds consistent with the normal valencies of the ring atoms. The diversity of chemical structures of the Triazoles family and their useful biological activities made these compounds attractive targets in synthetic organic chemistry. This review explores the modern pathways of the organic synthesis of Triazoles.

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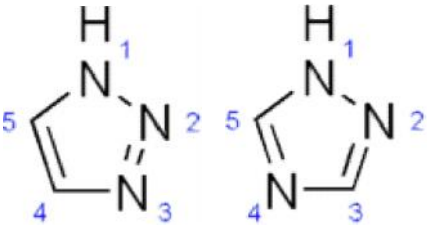
INTRODUCTION

Heterocyclic chemistry has now become a separate field of chemistry with long history, present society and future prospects. The earliest compounds known to mankind were of heterocyclic origin. Life, like ours, is totally dependent on the heterocyclic compounds, it takes birth with purine/pyrimidine bases, nourishes on carbohydrates and in case of disease, is cured from medicines, many of which are heterocyclic in nature. Today, the heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as into the related fields such as biochemistry, polymers and material sciences. The name triazole was first given to the carbon nitrogen ring system $C_2N_3H_3$ by Bladin who described its derivatives in early 1885, although the structures reported slightly incorrect. An alternative name, pyrrodiazole was given by Andreocci in 1889 regarding it as a member of a class of compounds analogous to pyrrole. A little interest emerged in this field from about 1925 to 1946. The successors of Andreocci carried out most intensive investigations of the chemistry of 1,2,4-triazoles. The chemical industry got renewed attention in the synthesis of both simple and fused triazole systems after the discovery that certain triazoles capable of inhibiting fog formation in photographic emulsions and some others being useful herbicides and convulsants. All triazoles are of synthetic origin and there is no triazole ring system detected as yet in nature. 1,2,4-Triazole is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1,2,4-Triazole is a basic aromatic heterocycle. 1,2,4-Triazole derivatives find use in a wide variety of applications, most notably as antifungals such as fluconazole and itraconazole. 1,2,4-Triazoles can be prepared using the Einhorn–Brunner reaction or the Pellizzari reaction (Potts 1961).

The two isomers are



1, 2, 3-Triazole 1, 2, 4-Triazole

Triazoles are the class of heterocyclic compounds, which are under study since many a years. Its diversity in showing the pharmacological activities is mind blowingly identified well by the medicinal chemists. Triazole, with many a compounds as incorporating with other heterocyclic nucleus, hydrazides, substituted triazoles are some of great uses which fascinates the chemists to continue research on it and find out more hidden potentials of this nucleus. The azide alkyne Huisgen cycloaddition is a mild and selective reaction that gives 1,2,3-triazoles as products. The reaction has been widely used in bioorthogonal chemistry and in organic synthesis. Triazoles are relatively stable functional groups and triazole linkages can be used in a variety of applications (for example, replacing the phosphate backbone of DNA.

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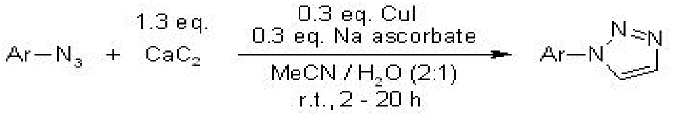
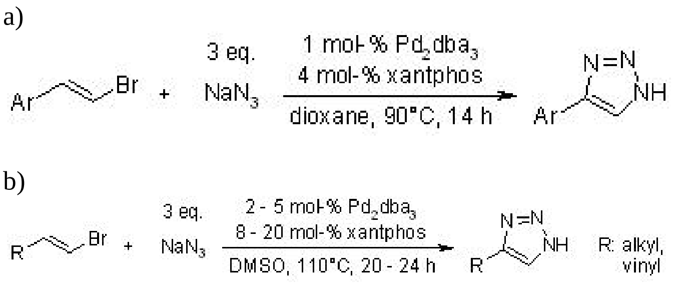
Modern Synthetic Pathways of Triazoles

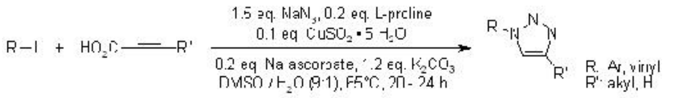
The synthesis of 1-monosubstituted aryl 1,2,3-triazoles was achieved in good yields using calcium carbide as a source of acetylene. The copper-catalyzed 1,3-dipolar cycloaddition reactions were carried out without nitrogen protection and in a MeCN-H2O mixture (Jiang, *et al*., 2009).



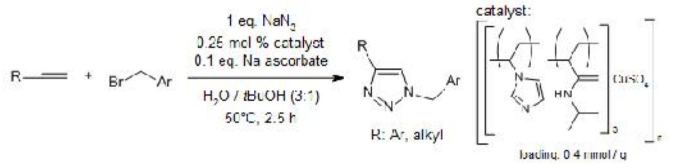
A Pd-catalyzed synthesis of 1H-triazoles from alkenyl halides and sodium azide represents a completely new reactivity pattern in the context of Pd chemistry. (Barluenga, *et al*., 2006).



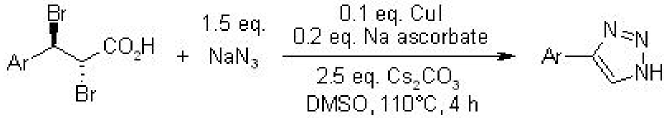
A tandem catalysis protocol based on decarboxylative coupling of alkynoic acids and 1,3-dipolar cycloaddition of azides avoids usage of gaseous or highly volatile terminal alkynes, reduces handling of potentially unstable and explosive azides to a minimum, and furnishes various functionalized 1,2,3-triazoles in excellent yields and a very good purity without the need for additional purification. (Kolarovic, *et al.*, 2011).



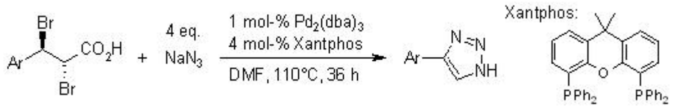
Self-assembly of copper sulfate and a poly (imidazole-acrylamide) amphiphile provides a highly active, reusable, globular, solid-phase catalyst for click chemistry. The insoluble amphiphilic polymeric imidazole Cu catalyst drove the cycloaddition of various of alkynes and organic azides at very low catalyst loadings and can be readily reused without loss of activity to give the corresponding triazoles quantitatively (Yamada, *et al*, 2012).



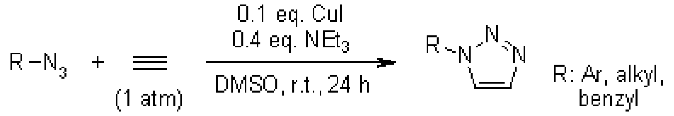
4-Aryl-1H-1,2,3-triazoles were synthesized from anti-3-aryl-2,3-dibromopropanoic acids and sodium azide by using inexpensive copper(I) iodide as the catalyst in the presence of cesium carbonate as base and DMSO as solvent (Jiang *et al*., 2010).



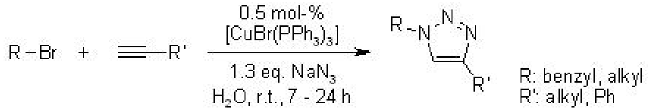
4-Aryl-1H-1,2,3-triazoles were synthesized from anti-3-aryl-2,3-dibromopropanoic acids and sodium azide by a one-pot method using N,N-dimethylformamide as solvent in the presence of Pd2(dba)3 and Xantphos (Zhang *et al*., 2010).



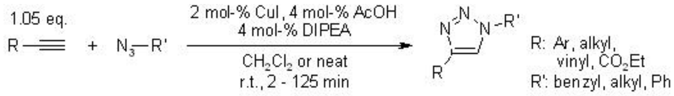
1-Substituted-1,2,3-triazoles were conveniently synthesized from the corresponding aromatic and aliphatic azides in the presence of acetylene gas using mild, copper(I)-catalyzed 'click chemistry' (Wu *et al*, 2009).



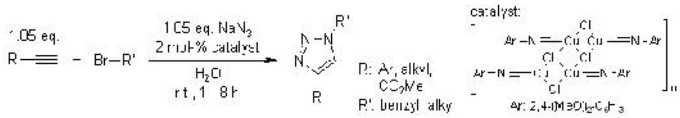
A true Click catalytic system is based on commercially available [CuBr(PPh3)3]. This system is active at room temperature, with catalyst loadings of 0.5 mol % or less, in the absence of any additive, and it does not require any purification step to isolate pure triazoles (Lal and Díez-González, 2011).



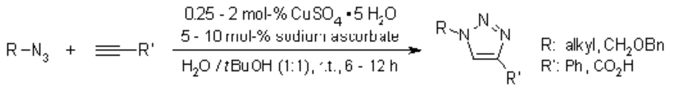
Acid-Base Jointly Promoted Copper (I)-Catalyzed Azide-Alkyne Cycloaddition (Shao *et al*, 2011).



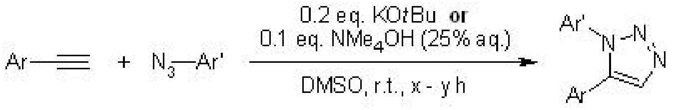
A well-defined copper(I) isonitrile complex is an efficient, heterogeneous catalyst for azide-alkyne 1,3-dipolar cycloadditions and three-component reactions of halides, sodium azide and alkynes to form 1,4-disubstituted 1,2,3-triazoles in high yields under mild conditions in water. The complex can be recycled for at least five runs without significant loss of activity by simple precipitation and filtration (Liu and Reiser, 2011).



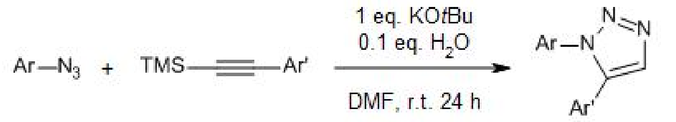
Cycloadditions of copper(I) acetylides to azides and nitrile oxides provide ready access to 1,4-disubstituted 1,2,3-triazoles and 3,4-disubstituted isoxazoles, respectively. The process is highly reliable and exhibits an unusually wide scope with respect to both components. Computational studies revealed a nonconcerted mechanism involving unprecedented metallacycle intermediates (Himo *et al.*, 2005)



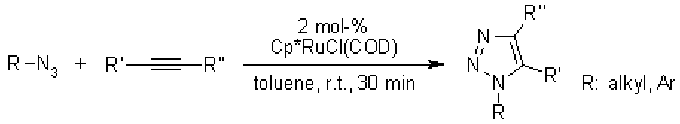
1,5-Diarylsubstituted 1,2,3-triazoles are formed in high yield from aryl azides and terminal alkynes in DMSO in the presence of a catalytic amount of tetraalkylammonium hydroxide or t-BuOK for base-labile substrates. The reaction is experimentally simple, does not require a transition-metal catalyst, and is not sensitive to atmospheric oxygen and moisture (Kwok *et al*, 2010).



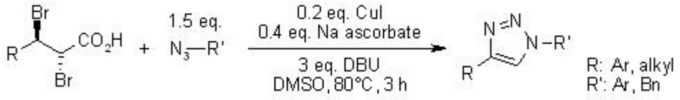
The use of t-BuOK in wet DMF as desilylating reagent in a cycloaddition reaction of aromatic azides and trimethylsilyl alkynes generated 1,5-disubstituted 1,2,3-triazoles regioselectively in good yields at ambient temperature (Wu *et al*, 2012).



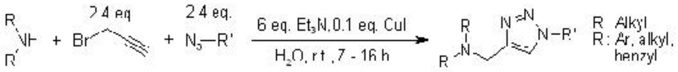
In the presence Cp*RuCl(PPh3)2 or Cp*RuCl(COD) as catalyst, primary and secondary azides react with a broad range of terminal alkynes containing a range of functionalities selectively producing 1,5-disubstituted 1,2,3-triazoles. Both complexes also promote the cycloaddition reactions of organic azides with internal alkynes, providing access to fully-substituted 1,2,3-triazoles (Boren *et al*, 2008).



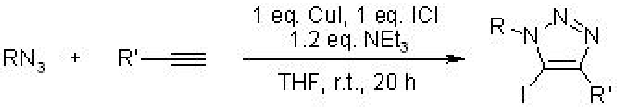
In the presence of inexpensive copper (I) iodide as the catalyst, a series of 1,4-disubstituted 1,2,3-triazoles were synthesized in a one-pot process from anti-3-aryl-2,3-dibromopropanoic acids and organic azides in dimethyl sulfoxide (Chen *et al*, 2011).



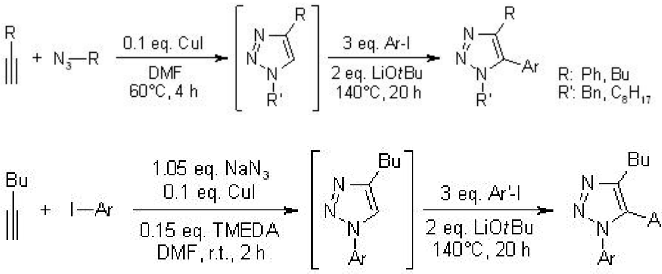
A copper(I)-catalyzed three-component reaction of amines, propargyl halides and azides forms 1-substituted-1H-1,2,3-triazol-4-ylmethyl)-dialkylamines in water. Synthetic advantages are high atom economy, low environmental impact, atmospheric oxygen, wide substrate scope, mild reaction condition and good yields (Yan *et al*, 2005).



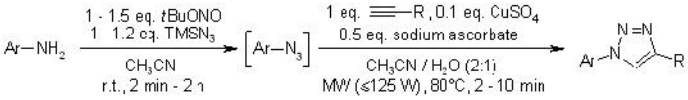
A method for the regiospecific synthesis of 1,4,5-trisubstituted-1,2,3-triazole catalyzed by copper(I) iodide was developed. This is the first example of a regiospecific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazole, which can be further elaborated to a range of 1,4,5-trisubstituted-1,2,3-triazole derivatives (Wu *et al*, 2005).



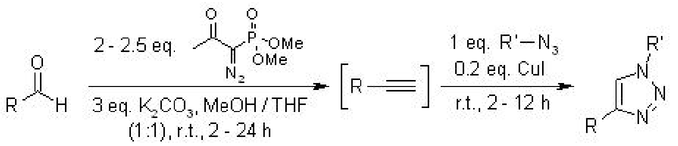
Inexpensive copper catalysts enabled modular one-pot multicomponent syntheses of fully decorated triazoles through a sustainable "click" reaction/direct arylation sequence (Ackermann *et al*, 2008).



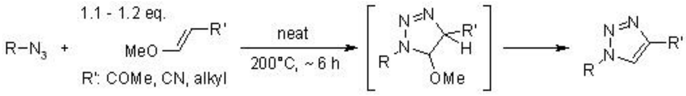
Microwave irradiation significantly enhances the rate of formation of 1,4-disubstituted 1,2,3-triazoles from alkynes and in situ generated azides. Azides are derived from an efficient one-pot azidation of anilines with the reagent combination t-BuONO and TMSN3 (Moorhouse and Moses 2008).



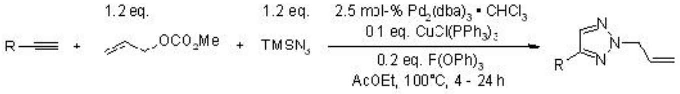
A reliable and operationally simple one-pot reaction for a one-carbon homologation of various aldehydes followed by Cu-catalyzed azide-alkyne click chemistry gives 1,4-disubstituted 1,2,3-triazoles in good yields without the need for isolation of the alkyne intermediates (Luvino *et al*, 2007).



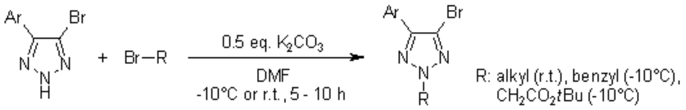
1,2,3-Triazoles were prepared in good to modest yields by cycloaddition of alkyl azides onto enol ethers under solventless conditions. The reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions and is easily scalable. The 1,2,3-triazole products bear functionality that may be readily derivatized (Rogue *et al*, 2005).



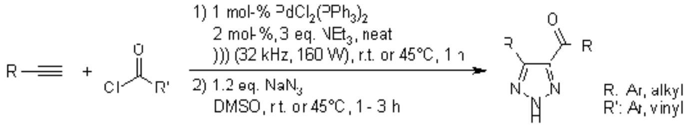
Triazoles have been synthesized via a three-component coupling reaction of unactivated terminal alkynes, allyl carbonate, and trimethylsiyl azide under Pd(0)-Cu(I) bimetallic catalysis. The deallylation of the resulting allyltriazoles is described (Kamijo *et al*, 2003).



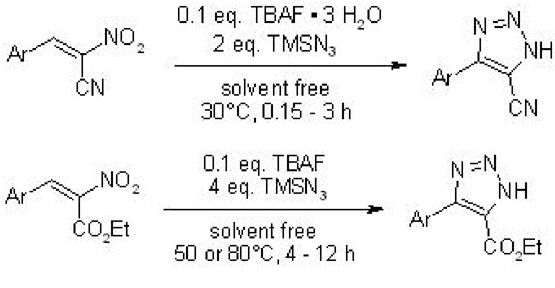
Reaction of 4-bromo-NH-1,2,3-triazoles with alkyl halides in the presence of K2CO3 in DMF produced the corresponding 2-substituted 4-bromo-1,2,3-triazoles in a regioselective process. Subsequent Suzuki cross-coupling reaction provided an efficient synthesis of 2,4,5-trisubstituted triazoles, whereas hydrogenation furnished an efficient synthesis of 2,4-disubstituted triazoles (Wang *et al*., 2009).



A palladium-catalyzed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide in one pot enables an efficient synthesis of 4,5-disubstituted-1,2,3-(NH)-triazoles in excellent yields (Li *et al*, 2009).



TBAF-catalyzed [3 + 2] cycloadditions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with TMSN3 under solvent free conditions allow the preparation of 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1H-1,2,3-triazoles under mild reaction conditions with good to excellent yields (Amantini *et al*., 2005).



Conclusion

The review summarizes with a gist that there is a strong need to synthesize various Triazoles using a household microwave oven and without the use of organic solvent, catalysts or extended heating. This will give out to emphasize the importance of Green Chemistry and also provide a fast & efficient technique to obtain the desired triazoles which gives a superior alternative to the classical synthesis without the use of poisonous and environmentally dangerous reagents.

Acknowledgement

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