Breakthroughs in 1,2,4-Triazole Chemistry: Synthetic Innovations

Dr. Jonathan T. Whitaker
Department of Chemistry, School of Natural Sciences, University of Manchester, Manchester, UK.

ABSTRACT

The present review is a sincere attempt to compile the reported potent triazole derivatives with significant anticonvulsant action. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole & its derivatives have a wide range of application. They are predominantly among the type of compounds used such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antihypertensive, antimalarial, antianxiety, antidepressant, and antihistaminic, antitubercular agents etc.

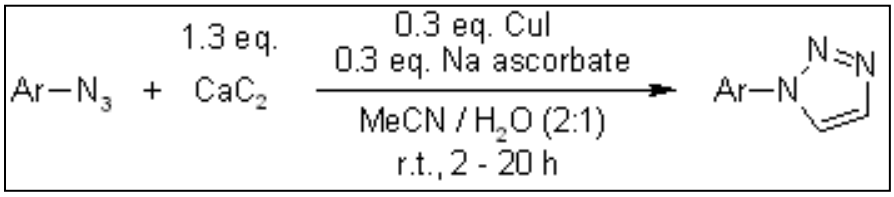
Keywords: *Heterocycles , Pharmaceutical, Triazole, Imidazoles.*

I. INTRODUCTION

The triazoles correspond to a class of five-membered heterocyclic compounds of huge significance for the preparation of new drugs with varied biological activities because they may present several structural uniqueness with the same numbers of carbon and nitrogen atoms. Due to the success of a variety of triazoles that entered the pharmaceutical sell and are still being used in medicines, many companies and research groups have exposed attention in budding new methods of synthesis and biological assessment of prospective uses for these compounds. In this review, we explored importance of article published for the 1H-1,2,3-, 2H-1,2,3-, 1H- 1,2,4- and 4H-1,2,4-triazole families, plus prototypes being considered in clinical studies between last two decades. [1].

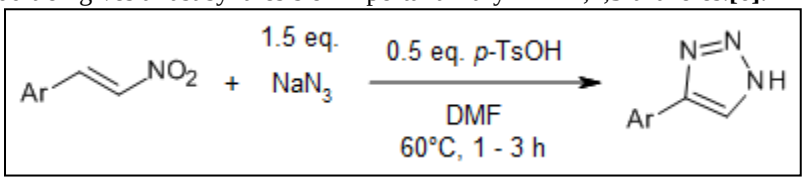
1,2,3-Triazole is a basic and incredible heterocyclic moiety. The extraordinary significance of 1,2,3-triazoles comes from not only their widespread application in cutting edge research of biological and material science,[2**]** but also their inimitable application in significant organic synthesis via distinct conversion models such as the transannulation, triazole ring opening, triazole directing group assisted C−H activation and the C−H activation-based triazolation. [3.] Because of the excellent merits of this heterocyclic scaffold, the synthetic research toward 1,2,3-triazoles has been known as a calculated issue and concerned great notice.[4]

Y. Jiang *et al* gave the synthesis of 1-monosubstituted aryl 1,2,3-triazoles was formed in good yields using CaC_2 from acetylene start. The Cu-catalyzed 1,3-dipolar cycloaddition reactions were carried out without using nitrogen protection and in a MeCN-H_2O mixture.[5].



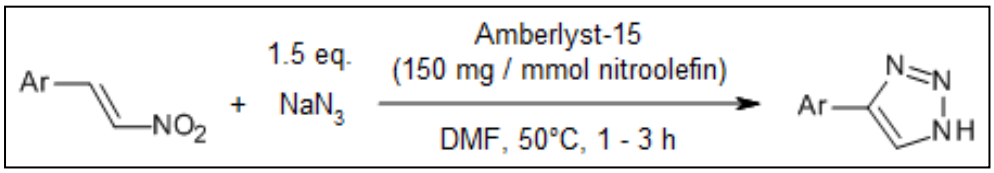
Scheme 1: Synthesis 1-monosubstituted aryl 1,2,3-triazoles

X.-J. Quan *et al* studied a p-TsOH is a vital additive in the 1,3-dipolar cycloaddition of nitroolefins and NaN_3. This p-TsOH used cycloaddition gives a fast synthesis of important 4-aryl-NH-1,2,3-triazoles.**[6].**



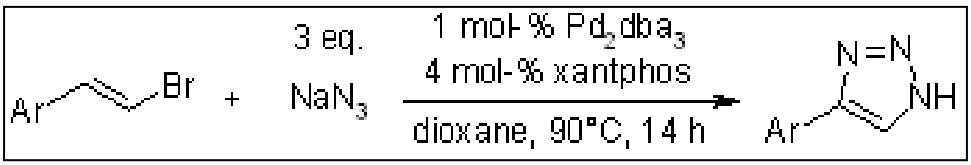
Scheme 2: Synthesis of 1,3-dipolar cycloaddition of nitroolefins and sodium azide

H. Zhang *et al* studied a synthesis of N-unsubstituted 4-aryl-1,2,3-triazoles is using Amberlyst-15. The Recyclable ion exchange resin used which is reuse up to 8 times without losing catalytic activity. [7**]**

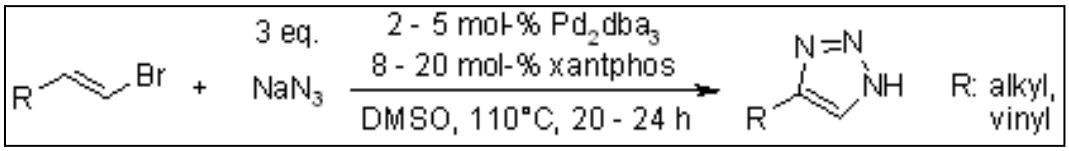


Scheme 3: Synthesis of N-unsubstituted 4-aryl-1,2,3-triazoles

J. Barluenga *et al* studied synthesis of 1H-triazoles from alkenyl halides and sodium azide in present of Pd-catalyst which was represents a completely novel[8-9**].**

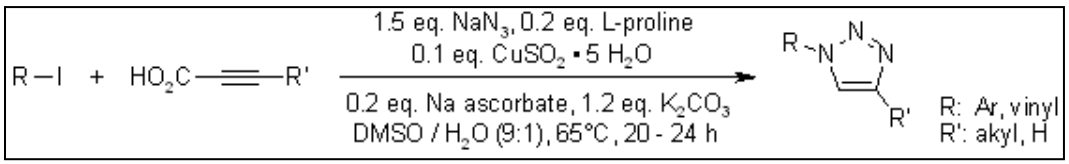


Scheme 4: Synthesis of 1H-triazoles from alkenyl halides and sodium azide



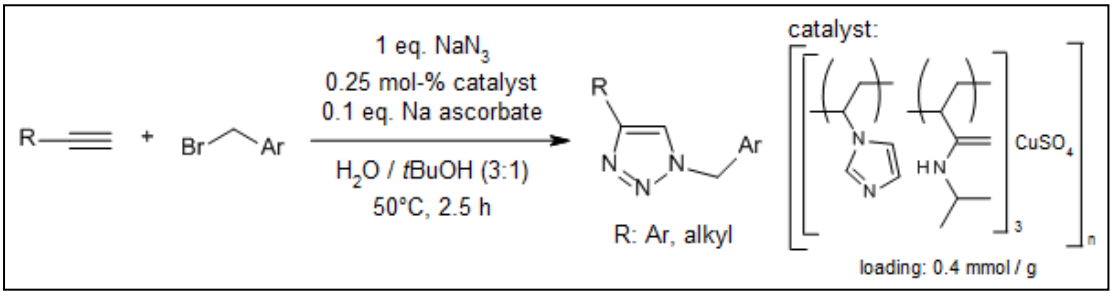
Scheme 5: One-pot synthesis of 1,5-disubstituted 1,2,3-triazoles

A. H. Banday *et al* studied a regioselective one-pot synthesis of 1,5-disubstituted 1,2,3-triazoles through N/C-heterocyclization of allenylindium bromide across aryl azides is carried out under mild conditions in aqueous medium and proceeds in good yields. [9]



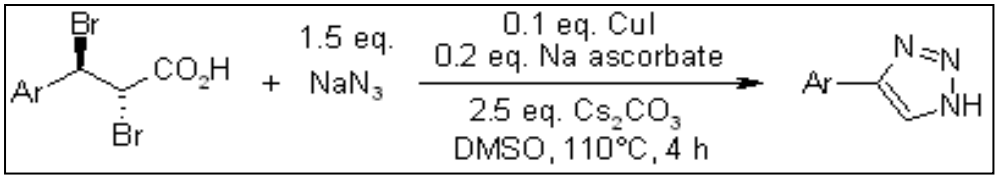
Scheme 6 : Decarboxylative coupling of alkynoic acids and 1,3-dipolar cycloaddition**.**

A. Kolarovič *et al* gave, 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 and furnishes various functionalized 1,2,3-triazoles [10].



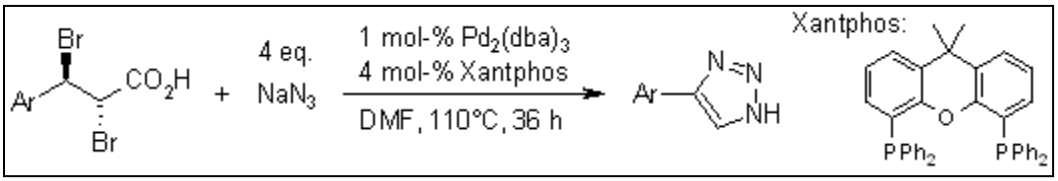
Scheme 7 : Tandem catalysis protocol based on decarboxylative couplling

Y. M. A. Yamada *et al* studied self-assembly of copper sulfate and a poly(imidazole-acrylamide) amphiphile provides 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**[11].**



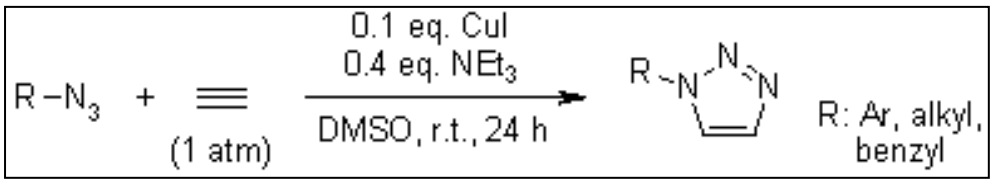
Scheme 8 : Amphiphilic polymeric imidazole Cu catalyzed cycloaddition

Y. Jiang *et al* gave 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. **[12]**



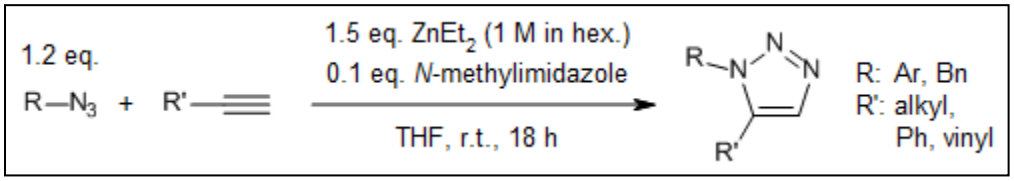
Scheme 9 : Synthesis of 4-Aryl-1H-1,2,3-triazoles using copper(I) iodide

W. Zhang W. Zhang *et al* 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 $Pd_2(dba)_3$ and Xantphos. **[13]**



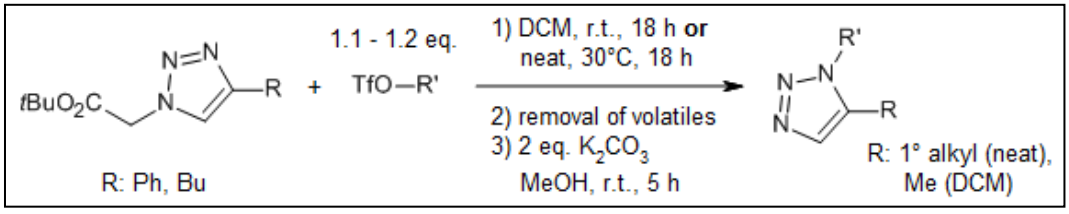
Scheme 10 : Synthesis of 4-Aryl-1H-1,2,3-triazoles using $Pd_2(dba)_3$ and Xantphos

Z.-J. Cai et al gave an efficient I_2/TBPB mediated oxidative formal [4 + 1] cycloaddition of N-tosylhydrazones with anilines represents a simple, general, and efficient approach for the construction of 1,2,3-triazoles under metal-free and azide-free conditions. **[14]**



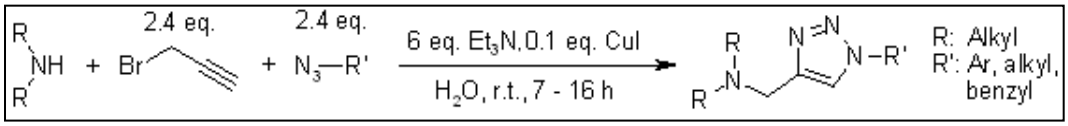
Scheme 11: Synthesis of 1,2,3-triazoles using I_2/TBPB

C. D. Smith *et al* studied a mild, zinc-mediated method for regioselective formation of 1,5-substituted 1,2,3-triazoles from a wide range of azides and alkynes works at room temperature. Additionally, the triazole 4-position can be further functionalized by reaction of the intermediate aryl-zinc with various electrophiles to accommodate a diverse three-component coupling strategy [15**].**



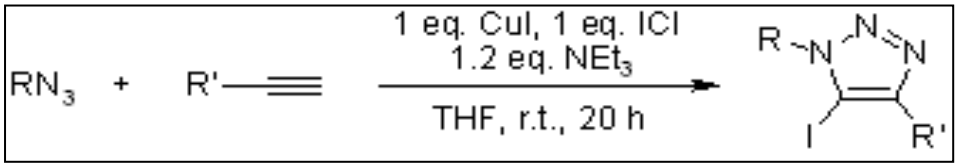
Scheme 12 : Zinc-mediated method for regioselective formation of 1,5-substituted 1,2,3-triazoles

Z.-Y. Yan *et al* 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 reward are goog atom economy, mild reaction condition and good yields [16].



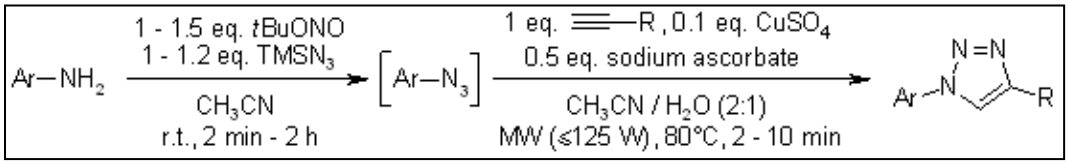
Scheme 13 : A copper(I)-catalyzed three-component reaction

Y.M. Wu *et al* developed 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. [17]



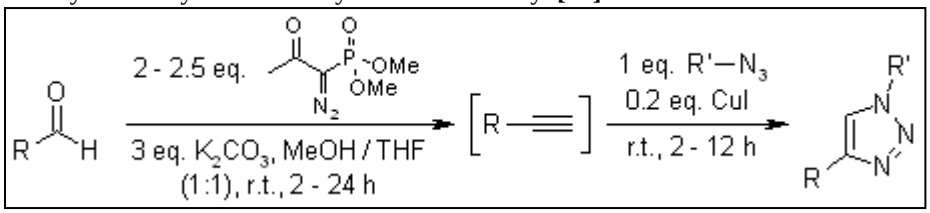
Scheme 14: 1,4,5-trisubstituted-1,2,3-triazole catalyzed by copper(I) iodide

A. D. Moorhouse et al gave 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 $TMSN_3$. **[18]**



Scheme 15 : The synthesis of 1,4-disubstituted 1,2,3-triazoles from alkynes

D. Luvino *et al* gave 1,4-disubstituted 1,2,3-triazoles via one-pot reaction for a one-carbon homologation of various aldehydes followed by Cu-catalyzed azide-alkyne click chemistry. **[19]**

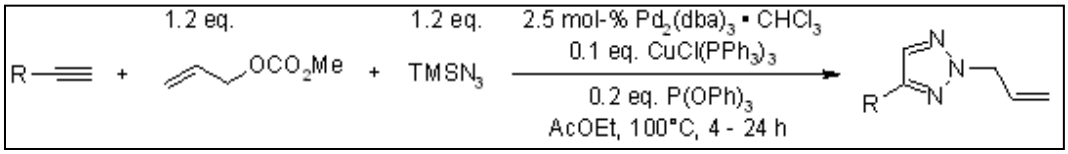


Scheme 16 : The synthesis of 1,4-disubstituted 1,2,3-triazoles

D. R. Rogue *et al* 1,2,3-Triazoles were prepared by cycloaddition of alkyl azides onto enol ethers under solvent free conditions. The 1,2,3-triazole products stand functionality that may be easily derivatized **[20].**

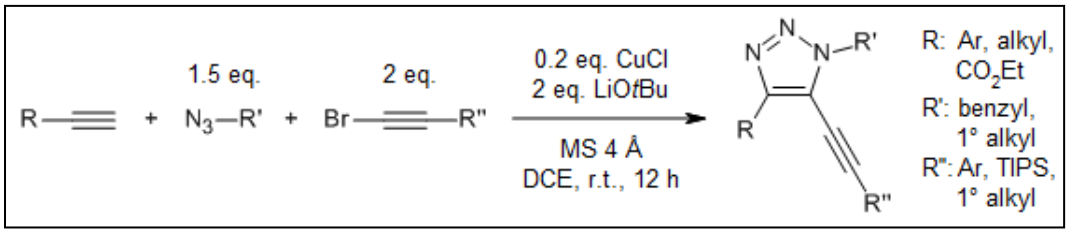
Scheme 17 : 1,2,3-Triazoles were prepared by cycloaddition of alkyl azides

S. Kamijo *et al* 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. **[21].**



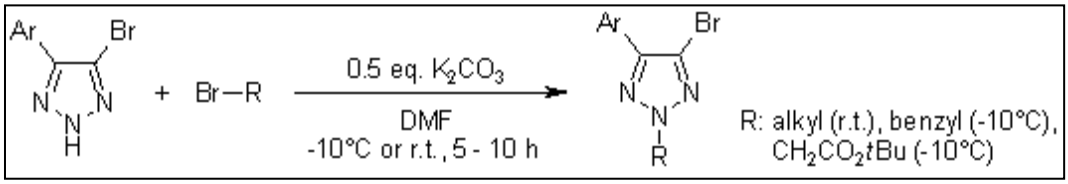
Scheme 18 : Synthesis of Triazoles via a three-component coupling reaction

W. Wang *et al* studied one-Pot Synthesis of 5-Alkynyl-1,2,3-triazoles using copper(I) as catalyzed three-Component Click/Alkynylation **[22]**



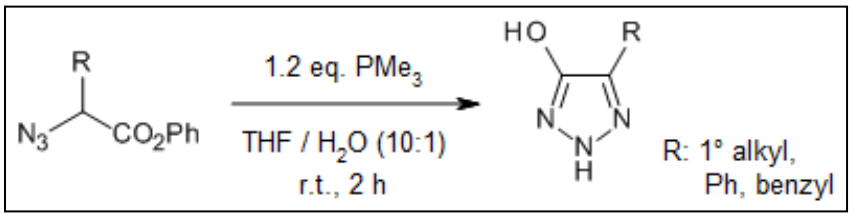
Scheme 19 : Copper(I)-Catalyzed Three-Component Click/Alkynylation

X. J. Wang *et al* a reaction of 4-bromo- NH-1,2,3-triazoles with alkyl halides in the presence of K_2CO_3 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. [23]



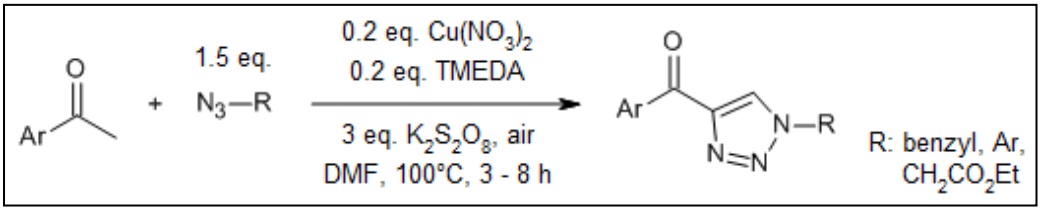
Scheme 20 : Synthesis of 2-substituted 4-bromo-1,2,3-triazoles

S. D. Taylor *et al* made the efforts to synthesized 5-substituted 2H-1,2,3-triazol-4-ols phenyl esters of α-azido acids react with trialkylphosphines in THF/H_2O. **[24]**



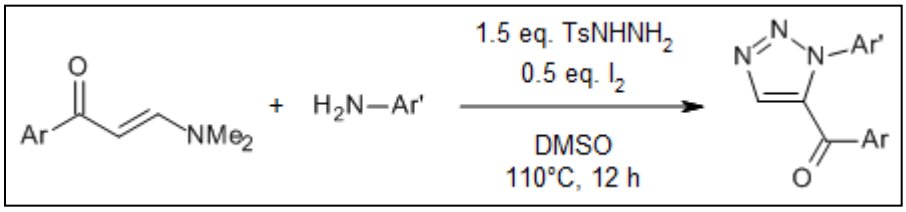
Scheme 21 : Synthesis 5-substituted 2H-1,2,3-triazol-4-ols phenyl esters

Y. Liu *et al* discovers a copper-catalyzed three-component reaction of methyl ketones, organic azides, and DMF as one-carbon (C1) donor provides 4-acyl-1,2,3-triazoles in good yields. **[25]**



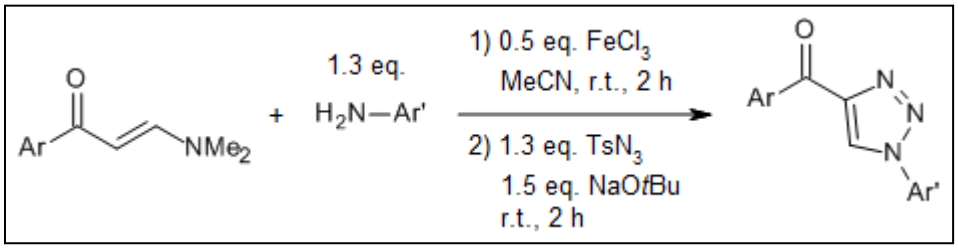
Scheme 22 : Synthesis of 4-acyl-1,2,3-triazoles

J.-P. Wan *et al* the metal and azide free method presence of molecular iodine developed the three-component reactions of enaminones, tosylhydrazine and primary amines enabled gives 1,5-disubstituted 1,2,3-triazoles.**[26]**



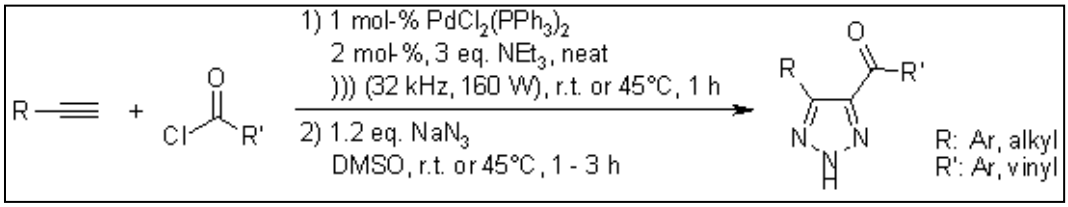
Scheme 23 : Synthesis of 1,5-disubstituted 1,2,3-triazoles

J.-P. Wan *et al* studied the synthesis of various N-substituted 1,2,3-triazoles via a key Regitz diazo-transfer process by employing t-BuONa as the base promoter. This is a domino reactions between NH-based secondary enaminones and tosyl azide. **[27]**



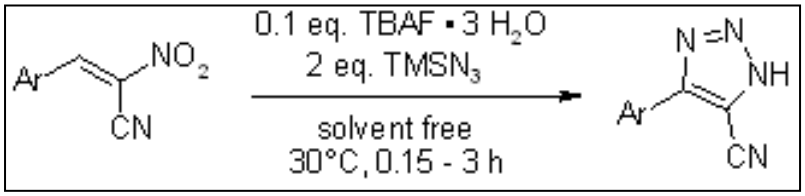
Scheme 24 : The synthesis of various N-substituted 1,2,3-triazoles

J. Li, *et al* developed a palladium-catalyzed and ultrasound mediated Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide gives 4,5-disubstituted-1,2,3-(NH)-triazoles in excellent yields. **[28]**



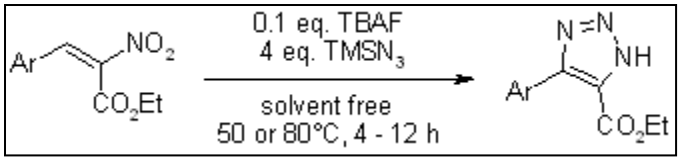
Scheme 25 : Palladium-catalyzed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition

G.-L. Wu *et al* developed the synthesis of 4,5-disubstituted 1H-1,2,3-triazoles from phosphonium salts, aldehydes, and sodium azide. An organocatalyzed coupling of the formyl group with the phosphonium group provides an olefinic phosphonium salt which is a mild and metal-free multi-component reaction. [29**]**



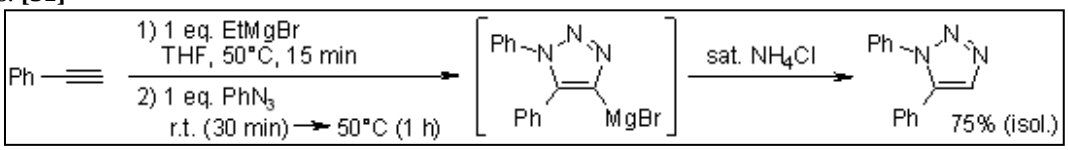
Scheme 26 : The synthesis of 4,5-disubstituted 1H-1,2,3-triazoles

D. Amantini *et al* TBAF-catalyzed [3 + 2] cycloadditions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with $TMSN_3$ gives 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1H-1,2,3-triazoles. [30**]**



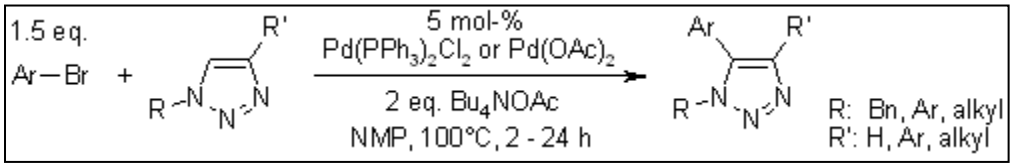
Scheme 27 : TBAF-catalyzed [3 + 2] cycloadditions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes

D. Liu *et al* preparation of Triazole-based monophosphine ligands done via cycloadditions. Palladium complexes derived from these ligands are highly active catalysts for Suzuki-Miyaura coupling and amination reactions of aryl chlorides. **[31]**



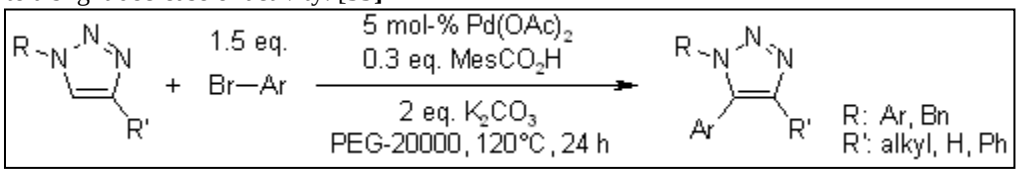
Scheme 28 : Preparation of Triazole-based monophosphine ligands

S. Chuprakov *et al* developed the synthesis of multisubstituted 1,2,3-triazoles via a direct Pd-catalyzed C-5 arylation.**[32]**



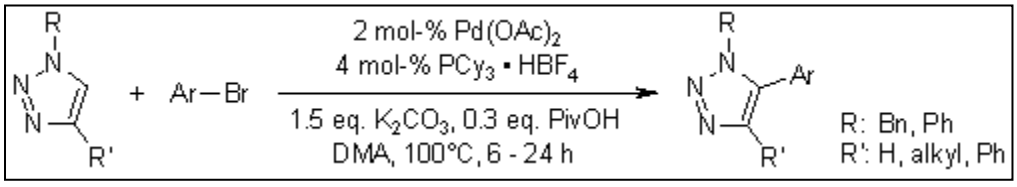
Scheme 29 : Synthesis of multisubstituted 1,2,3-triazoles

L. Ackermann *et al* discovers use of nontoxic polyethylene glycol (PEG) as solvent and $MesCO_2H$ as cocatalyst enabled user-friendly palladium(0)-catalyzed C-H bond functionalizations under air in the absence of phosphine ligands. Direct arylations of 1,2,3-triazoles gave substituted triazoles in good yields. Recycling of the catalytic system led to a slight decrease of activity. [33**]**



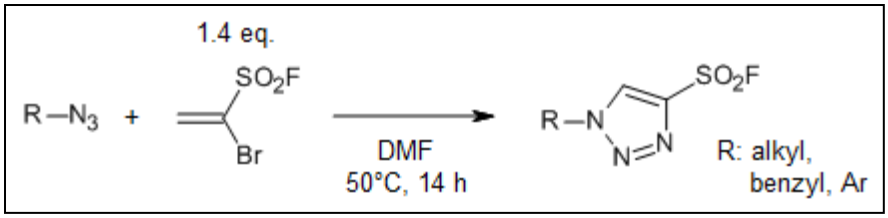
Scheme 30: Palladium(0)-catalyzed C-H bond functionalization

B. Liégault *et al* studied the palladium-catalyzed direct arylation of a broad series of heterocycles with aryl bromides utilize a stoichiometric ratio of both coupling partners, as well as a substoichiometric quantity of pivalic acid. **[34]**



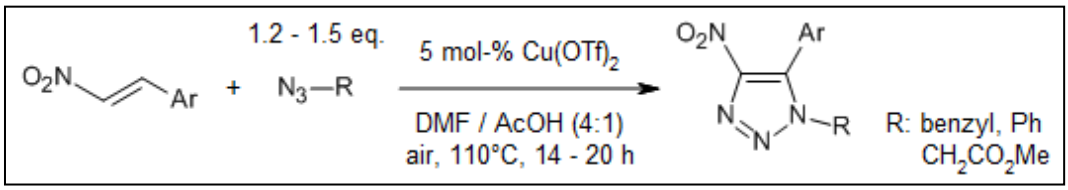
Scheme 31 : Palladium-catalyzed direct arylation

J. Thomas *et al* gives a synthesis of bromovinylsulfonyl fluoride using 4-fluorosulfonyl 1,2,3-triazoles. This is general and regioselective metal-free cycloaddition. **[35]**



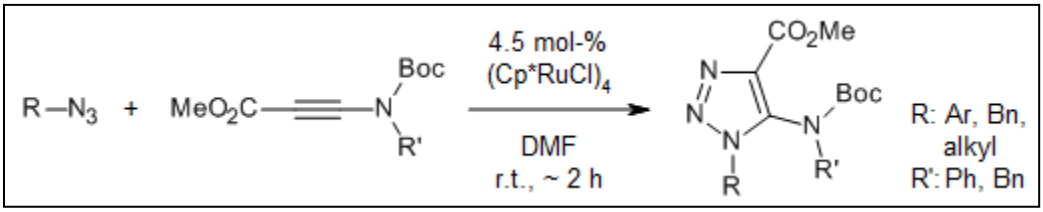
Scheme 32: Regioselective metal-free cycloaddition

Y. Chen *et al* a copper-catalyzed [3 + 2] cycloaddition/oxidation reaction of nitro-olefins with organic azides affords a broad range of 1,4(-NO_2),5-trisubstituted 1,2,3-triazoles. **[36]**



Scheme 33: Copper-catalyzed [3 + 2] cycloaddition

S. Ferrini *et al* covers ruthenium-catalyzed cycloaddition of N-Boc ynamides with azides gives protected 5-amino-1,2,3-triazole-4-carboxylic acids. The condensation of aryl or alkyl azides with N-Boc-aminopropiolates or arylynamides, the cycloaddition occurs with complete regiocontrol, while N-Boc-alkyl ynamides yield a mixture of regioisomers [37**]** and some other heterocyclic structures important towards synthetic[38-40] and biologically[41-42].



Scheme 34 : Ruthenium-catalyzed cycloaddition

II. CONCLUSION

In this present review is emphasized the synthetic chemistry, which deals with the nature of triazole nucleus is one of the most important heterocycles which is a feature of natural products and medicinal agents. Triazole nucleus is enjoying their importance as being the center of activity. The nitrogen containing heterocyclics are found in abundance in most of the medicinal compounds.

III. ACKNOWLEDGEMENTS

The author is thankful to Hon'ble Principal and Head, Department of Chemistry, JET's Z. B. Patil College, Dhule for providing the laboratory facilities.

REFERENCES

1. Vitor F Ferreira, David R da Rocha, Fernando C da Silva, Patrícia G Ferreira, Núbia A Boechat & Jorge L Magalhães, Expert Opinion on Therapeutic Patents Volume,2013, 23(3), 319-331
2. [(a) Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G. F.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. W.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. J. Med. Chem. 2005, 48, 5644. B. Schulze, B.; Schubert, U. S. Chem. Soc. Rev. 2014, 43, 2522.
3. Schulze, B.; Schubert, U. S. Chem. Soc. Rev. 2014, 43, 2522
4. Jie-Ping Wan, Shuo Cao, and Yunyun Liu, J. Org. Chem. 2015, 80, 9028−9033

5. Y. Jiang, C. Kuang, Q. Yang, Synlett, 2009, 3163-3166
6. X.-J. Quan, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, Org. Lett., 2014, 16, 5728-5731
7. H. Zhang, D.-Z. Dong, Z.-L. Wang, Synthesis, 2016, 48, 131-135.
8. J. Barluenga, C. Valdés, G. Beltrán, M. Escribano, F. Aznar, Angew. Chem. Int. Ed., 2006, 45, 6893-6896.][J. Barluenga, C. Valdés, G. Beltrán, M. Escribano, F. Aznar, Angew. Chem. Int. Ed., 2006, 45, 6893-6896.
9. A. H. Banday, V. J. Hruby, Synlett, 2014, 25, 1859-1862
10. A. Kolarovič, M. Schnürch, M. D. Mihovilovic, J. Org. Chem., 2011, 76, 2613-2618
11. Y. M. A. Yamada, S. M. Sarkar, Y. Uozumi, J. Am. Chem. Soc., 2012, 134, 9285-9286.
12. Y. Jiang, C. Kuang, Q. Yang, Synthesis, 2010, 4256-4260.
13. W. Zhang, C. Kuang, Q. Yang, Synthesis, 2010, 283-287.
14. Z.-J. Cai, X.-M. Lu, Y. Zi, C. Yang, L.-J. Shen, J. Li, S.-Y. Wang, S.-J. Ji, Org. Lett., 2014, 16, 5108-5111
15. C. D. Smith, M. F. Greaney, Org. Lett., 2013, 15, 4826-4829
16. Z.-Y. Yan, Y.-B. Zhao, M.-J. Fan, W.-M. Liu, Y.-M. Liang, Tetrahedron, 2005, 61, 9331-9337.
17. Y.-M. Wu, J. Deng, Y. L. Li, Q.-Y. Chen, Synthesis, 2005, 1314-1318.
18. A. D. Moorhouse, J. E. Moses, Synlett, 2008, 2089-2092.
19. D. Luvino, C. Amalric, M. Smietana, J.-J. Vasseur, Synlett, 2007, 3037-3041.
20. D. R. Rogue, J. L. Neill, J. W. Antoon, E. P. Stevens, Synthesis, 2005, 2497-2502
21. S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, J. Am. Chem. Soc., 2003, 125, 7786-7787
22. W. Wang, F. Wei, Y. Ma, C.-H. Tung, Z. Xu, Org. Lett., 2016, 18, 4158-4161
23. X. J. Wang, K. Sidhu, L. Zhang, S. Campbell, N. Haddad, D. C. Reeves, D. Krishnamurthy, C. H. Senanayake, Org. Lett., 2009, 11, 5460-5493
24. S. D. Taylor, C. R. Lohani, Org. Lett., 2016, 18, 4412-4415
25. Y. Liu, G. Nie, Z. Zhou, L. Jia, Y. Chen, J. Org. Chem., 2017, 82, 9198-9203.
26. J.-P. Wan, S. Cao, Y. Liu, J. Org. Chem., 2015, 80, 9028-9033.
27. J.-P. Wan, S. Cao, Y. Liu, Org. Lett., 2016, 18, 6034-6037
28. J. Li, D. Wang, Y. Zhang, J. Li, B. Chen, Org. Lett., 2009, 11, 3024-3027
29. G.-L. Wu, Q.-P. Wu, Synthesis, 2018, 50, 2768-2774.
30. D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, E. Zunino, L. Vaccaro, J. Org. Chem., 2005, 70, 6526-6529
31. D. Liu, W. Gao, Q. Dai, X. Zhang, Org. Lett., 2005, 7, 4907-4910.
32. S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, Org. Lett., 2007, 9, 2333-2336.
33. L. Ackermann, R. Vicente, Org. Lett., 2009, 11, 4922-4925.
34. B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, J. Org. Chem., 2009, 74, 1826-1834.
35. J. Thomas, V. V. Fokin, Org. Lett., 2018, 20, 3749-3752.
36. Y. Chen, G. Nie, Q. Zhang, S. Ma, H. Li, Q. Hu, Org. Lett., 2015, 17, 1118-1121
37. S. Ferrini, J. Z. Chandanshive, S. Lena, M. C. Franchini, G. Giannini, A. Tafi, M. Taddei, J. Org. Chem., 2015, 80, 2562-2572.
38. A. P. Rajput, D. V. Nagarale, , *Journal of Applicable Chemistry*, **2018**, 7 (6): 1592-1596.
39. A. P.Rajput, D. V.,Nagarale, *Der Pharma Chemica*, 2016, 8(8):182-186.
40. A. P. Rajput, D. V. Nagarale, *IJPC* (2016) 06 (07), 181-185.
41. A. P. Rajput, D. V. Nagarale., *Chem Sci Trans.*, 2016, 5(4), 912-917
42. D. V Nagarale, P. S Girase, *Global Journal Of Engineering Science And Researches*, **2019**, 6 (5), 187-193.