

An Overview of Azide-Free methods Utilizing Tosylhydrazones for the Synthesis of 1,2,3-Triazole

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ABSTRACT

1,2,3-triazoles are nitrogen-containing heterocyclic compounds with several applications in the agrochemical and pharmaceutical sectors, which have drawn the curiosity of organic researchers in their synthesis. While traditional techniques frequently use sodium azide (NaN_3) as a starting material, concerns about its toxicity and safety, have prompted researchers to develop azide-free approaches. This overview emphasizes tosylhydrazones as essential antecedents for the synthesis of 1,2,3-triazole molecules.

Keywords : 1,2,3-triazoles, tosylhydrazone, azide-free, nitrogen heterocycles.

I. INTRODUCTION

1,2,3-triazoles are heterocyclic nitrogen-containing compounds that are key building blocks of numerous herbicides, insecticides, and pharmaceutical medicines. 1,2,3-triazoles are bioactive molecules showing antibacterial [1], antitubercular [2], antiplasmodial [3], antioxidant [2], anticancer [4], antiviral [5] and anti-inflammatory properties [6].

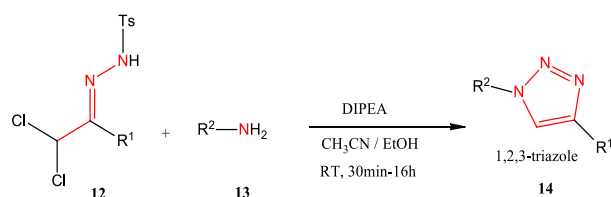
Several approaches have been studied and described for the synthesis of 1,2,3-triazole compounds [7,8,9,10,11,12] and fused 1,2,3-triazoles [13,14,15,16]. One of the such classical method is Huisgen 1,3-dipolar cycloaddition [17,18], that is versatile and commonly employed method for synthesizing 1,2,3-triazole molecules, involving the addition of a 1,3-

dipole (typically an azide) and a dipolarophile (typically an alkyne or alkene) to yield a 1,2,3-triazole ring. In 2002, Sharpless alternatively described a CuAAC (Copper-Catalyzed Azide-Alkyne Cycloaddition) method [19] as a variation of the Huisgen cycloaddition and is commonly referred to as "click chemistry" where a copper (I) catalyst is employed to induce the reaction between azides and alkynes to generate 1,2,3-triazoles. This technique is highly selective and widely utilized for triazole formation.

The majority of other methodologies also use hazardous azide molecules which are challenging to handle and not appropriate for industrial scale-up owing to their explosive and toxic nature [20].

To avoid the use of azide molecules, various azide free approaches [21] has been reported for synthesis of

In 2012, Van Berkeland co-workers [26] determined the scope and limitations of the Sakai's work by reacting α,α -dichlorotosylhydrazone **12** with variety of primary amines **13** in Acetonitrile/Ethanol solvent mixture (1:1 v/v%) and 6eq of N,N-Diisopropylethylamine base at ambient temperature to form triazoles **14** (Scheme 5) in good to excellent yield. Electron-rich and electron-poor Anilines, benzyl amines and aliphatic amines, all gave the corresponding triazoles in good to excellent yields.

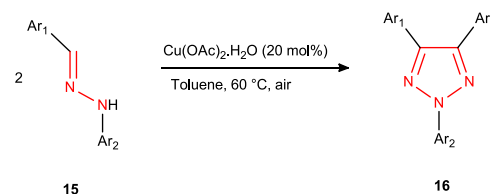


Scheme 5: Van Berkel's 1,2,3-triazole synthesis reaction by using α,α -dichloro ketone tosylhydrazone

In 2012, Guru and Punniyamurthy [27] explained a novel copper(II)-catalyzed aerobic oxidative process for synthesizing 2,4,5-triaryl-1,2,3-triazoles **16** from bisarylhyazones **15** as starting precursor under moderate conditions for reaction (scheme 6). The most effective conditions for the reaction was using bisarylhyazone in toluene with 20 mol% Cu(OAc)₂·H₂O in air at 60 °C to generate 1,2,3-triazole in 75% yield. The scope of the reaction leads to the identification of DABCO and dioxane as suitable bases and solvents, respectively, whereas inorganic bases were discovered to be ineffective. The catalytic activity of additional copper sources, like CuCl, Cu(OAc)₂, Cu(OTf)₂, CuI and CuCl₂ was investigated, and Cu(II) salts were shown to be superior than Cu(I) salts in terms of yielding triazoles.

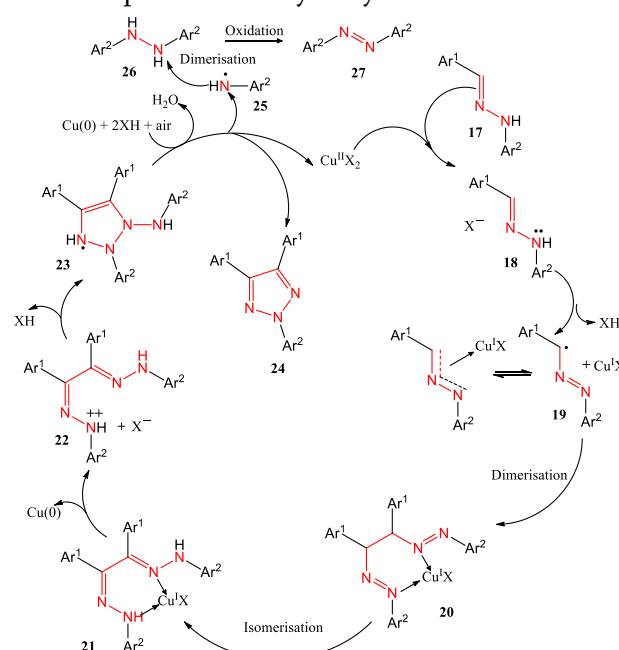
Bisarylhyazones with electron-withdrawing substituents on the arenes gave triazoles in 56-90% yields, whereas bisarylhyazones with electron-donating substituents on the aryl rings gave triazoles in 45-87% yield. Furthermore, bisarylhyazone with both electron-withdrawing and electron-donating

substituents on the arenes could produce the desired triazoles in 66% yield.



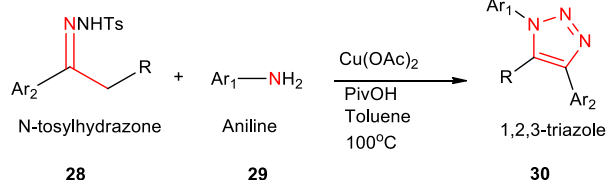
Scheme 6: Guru's Copper(II)-catalyzed synthesis of 2,4,5-triaryl-1,2,3-triazoles from bisarylhyazones

Guru proposed the mechanism for catalytic cycle for synthesis of 1,2,3-triazoles where single-electron transfer to Cu(II)X₂ from bisarylhyazones **17** generated radical cation **18**, followed by elimination of HX to produce intermediate **19**, which undergoes dimerization to the form **20**, which further generate the intermediate **21** by isomerisation. The intermediate **21** converts to radical cation **22** due to reductive elimination of elemental copper by single-electron transfer, further cyclisation of **22** after elimination of HX generates **23**, which eliminates the radical intermediate **25** and finally afford desired 1,2,3-triazole **24**. The radical intermediate **25** undergoes dimerization to afford **26** which easily converts into stable azo compound **27** by air oxidation. The active copper (II) species get generated by reoxidation of reduced copper (0) species in air and thus complete the catalytic cycle.



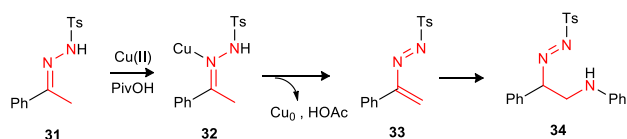
Scheme-7: Guru's proposed Catalytic Cycle for the Synthesis of Substituted 1,2,3-Triazoles

In 2013, Chen et al. [28] suggested a copper-catalyzed regioselective approach for the synthesis of 1,4-disubstituted and 1,2,5-trisubstituted 1,2,3-triazoles **30** by reacting N-tosylhydrazones **28** and anilines **29**. They also discovered that 1,2,3-triazoles can be produced in high yields when aniline is electron rich. Aniline with electron withdrawing substituents in the para position reacts more slowly than aniline with electron withdrawing substituents in the meta position. The steric bulk of anilines have less of an influence on the reaction. The disubstituted anilines also demonstrate cyclization.



Scheme 8: Chen's copper mediated synthesis of 1,2,3-triazoles from N-tosylhydrazones and anilines

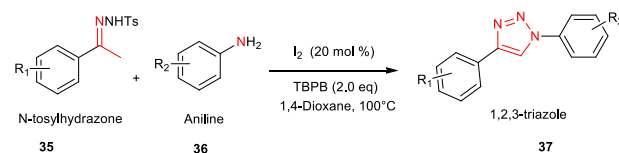
Chen's mechanistic investigations speculate, that in the presence of $\text{Cu}(\text{OAc})_2$ and PivOH, the N-tosylhydrazone **31** may isomerize to **32**, which undergoes oxidation to produce a 1-tosyl-2-vinyldiazene **33**, which further forms intermediate **34** by aza-Michael addition with aniline (scheme 9). The desired triazole is produced by copper catalysed cyclisation of intermediate **34**.



Scheme 8: Chen's plausible intermediates in the formation of 1,2,3-triazoles

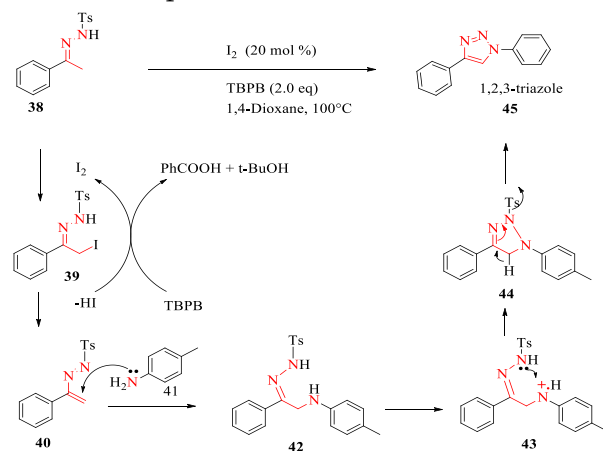
In 2014, Cai et al [29] described a metal free and azide free approach for the synthesis of 1,2,3-triazoles **37** by oxidative formal [4 + 1] cycloaddition of N-tosylhydrazones **35** with anilines **36** mediated by I_2 and TBPB. When electron-donating groups, halogen-substituted substrates, and ortho- or meta- CH_3 substituted N-tosylhydrazones substrates were

utilized, the results were identical. The alkene and alkyne functional groups can be tolerated by the reaction conditions.



Scheme 9: Cai's I_2 /TBPB mediated oxidative reaction of N-Tosylhydrazones with Anilines

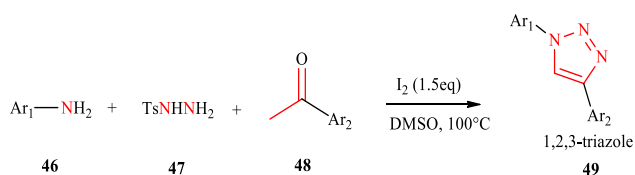
The Cai et al proposed a plausible mechanism in which an iodinated intermediate **39** is created from N-tosylhydrazone **38**, in the presence of I_2 and subsequent removal of HI forms the azoalkene **40** along with TBPB assisted oxidation of I^- to I_2 catalytic cycle. The intermediate **42** is generated by adding aniline **41** to the azoalkene **40**, which is then oxidized in basic condition to give the corresponding radical cation **43**, followed by intramolecular addition to produce intermediate **44**, followed by subsequent oxidation to produce the desired 1,2,3-triazole **45**.



Scheme 10: Cai's plausible mechanism for 1,2,3-triazole synthesis

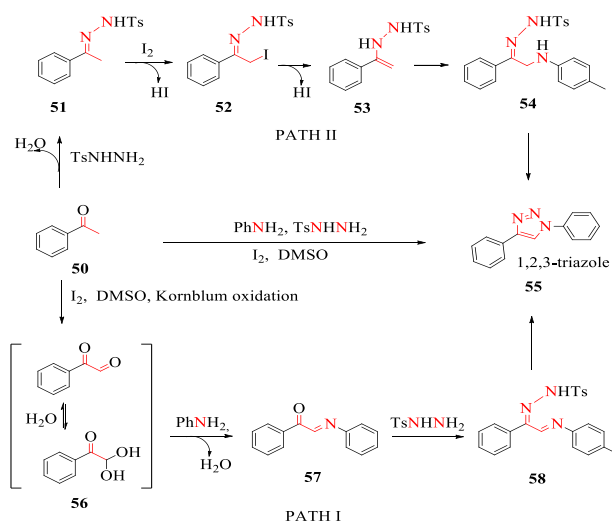
In 2014, Zhengkai Chen et al. [30] described a one-pot multicomponent, metal-free method for synthesizing 1,4-disubstituted 1,2,3-triazoles **49**, employing anilines **46**, ketones **48**, and N-tosylhydrazine **47**. As an activator, the approach employs molecular iodine. The approach tolerates a wide range of electron-drawing groups, including CF_3 , COOH , and NO_2 , and

produces high-yielding triazoles. In the case of aliphatic amines, a complicated mixture was formed, making it difficult to extract the necessary triazoles.



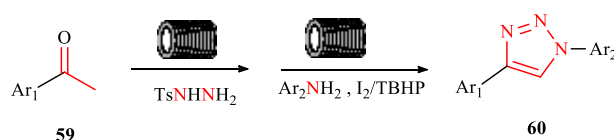
Scheme 11: Zhengkai Chen's one pot synthesis of 1,2,3-triazoles from ketones, N-tosylhydrazines and amines.

Zhengkai Chen proposed two plausible pathways (scheme 12). (Path I) In presence of iodine and DMSO phenylglyoxal intermediate **56** formed by Kornblum oxidation, which forms C-acyl imine intermediate **57** by condensation with the aniline, which further undergoes condensation with N-tosylhydrazine to form intermediate **58**. In presence of molecular iodine or oxygen, intermediate **58** undergoes cyclization and aromatization to generate the desired 1,2,3-triazole **55**. (Path 2) Alternative pathway is generation of N-tosylhydrazone **51** from arylketone and N-tosylhydrazine, which further forms intermediate **52** by subsequent α -iodination and then form intermediate **53** by elimination of HI which undergoes aza-Michael addition with aniline to form intermediate **54**. Finally in presence of iodine, the oxidative cyclisation and aromatization of intermediate **54** affords the desired 1,2,3-triazole **55**.



Scheme 12: Zhengkai Chen's proposed plausible mechanism for one pot synthesis of 1,2,3-triazoles.

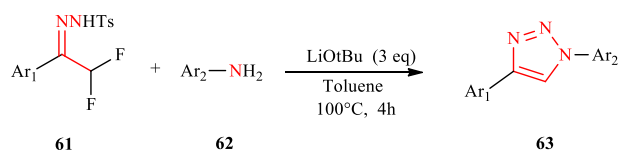
In 2016, Jiajia and co-workers [31] developed a metal and azide-free two-step continuous flow technique for the synthesis of 1,4-disubstituted 1,2,3-triazoles **60** in moderate to fair yield by reacting acetophenones **59**, tosylhydrazine, and anilines using an I_2 /TBHP catalyst (scheme 13). The reaction is not influenced by the position of the substituents on the aromatic ring of anilines, and the reaction proceeded smoothly when a more sterically restricted precursor ([1,1'-biphenyl]-2-amine) was employed. For wide variety of acetophenones substrate both electron-deficient and electron-rich substrates produced desired products in good yields. Furthermore, the use of furyl and thiophenyl groups as heterocyclic substituents resulted in better yields of triazoles.



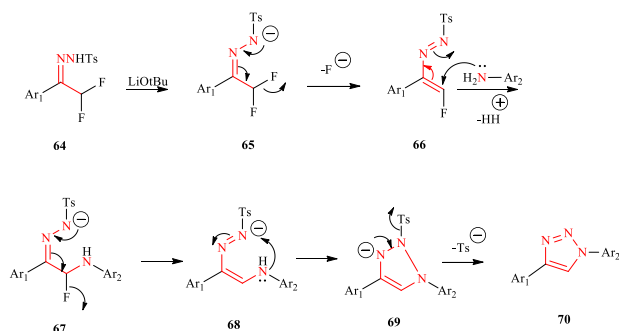
Scheme 13: Jiajia's two step continuous flow synthesis of 1,4-disubstituted 1,2,3-triazoles

In 2019, Zhou and co-workers [32] described metal free and azide free efficient protocol for synthesis of 1,4-disubstituted 1,2,3-triazole **63** by reacting novel precursor α,α -Difluoro-N-tosylhydrazone **61** and

amine **62** employing C-F bond cleavage. The scope of reaction revealed LiOtBu base affording higher yields of triazoles than other bases like Cs₂CO₃, K₂CO₃, K₃PO₄ and DIPEA in the reaction. Regarding the substrate scope of amines, electron-donating groups in aryl amines resulted in higher reaction yield and para substituted electron-withdrawing ester group, ortho-bromo aniline reduces the yield. Primary aliphatic amines are more compatible for this reaction than secondary amines. Arylamines or N-tosylhydrazones with heteroaromatic ring also produced fruitful results with higher yields of triazole. Identical results and yield was obtained for one-pot synthesis of 1,2,3-triazoles from precursor α,α -difluoro-N-tosylhydrazone.

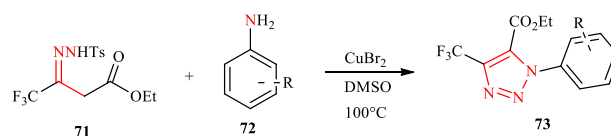


Scheme 14: Zhou's 1,2,3-triazole synthesis from α,α -difluoro-N-tosylhydrazone and amine. They proposed the reaction mechanism (scheme 15), under basic condition intermediate **65** was formed from precursor α,α -difluoro-N-tosylhydrazone **64**, further fluorine ion get released to generate azoalkene **66** which reacts with aniline via aza-michael addition to produce intermediate **67**, the subsequent C-F bond cleavage generates intermediate **68**. Finally targeted 1,2,3-triazole **70** is formed by intramolecular cyclization of intermediate **68** followed by aromatization.



Scheme 15: Zhou's proposed mechanism for synthesis of 1,2,3-triazole.

In 2021, Panish and co-workers [33] described a copper catalysed cyclisation of anilines with N-tosylhydrazones of 4,4-trifluoroacetoacetate to produce 4-CF₃triazoles with 76% yield (scheme 16). Various ortho-halo (-I, -F, Br or -Cl) substituted anilines produced identical results. Additionally the steric hindrance at ortho position to amine group also provided the same fruitful results with higher yield of target triazoles. Lower yield obtained when electron donating groups are present in anilines. Variety of functional groups like -RCOOR, -NO₂, -CN, -COOH, -RCOR etc. are exceptionally tolerated due to the milder reaction conditions.



Scheme 15: Panish's Copper-Catalyzed Synthesis of 5-Carboxyl-4-perfluoroalkyl Triazoles

IV. CONCLUSIONS

In conclusion, the azide-free techniques for the synthesis of 1,2,3-triazole compounds employing N-tosylhydrazones as antecedents constitutes a significant and promising advances in the field of organic chemistry.

The switch from conventional azide-based approaches to these greener and safer alternatives merely answers safety concerns about the usage of azides, but also provides many significant advantages. N-tosylhydrazones, that are synthesized from common carbonyl compounds, are a simple and adaptable starting material for the synthesis of 1,2,3-triazoles. Additionally, these techniques frequently utilize milder reaction conditions, making them more compatible with a wider variety of substrates and functional groups.

While these azide-free methods show great potential, it is essential to acknowledge that challenges remain especially regioselectivity, reaction optimization, and scalability. To utilize the full potential of N-tosylhydrazones as 1,2,3-triazole precursors, researchers in this field have to keep trying to develop and extend their synthetic toolset.

As scientists and researchers continue to investigate these azide-free techniques, we can anticipate new developments and advancements in the discipline of organic chemistry in the years to come that will be helpful for synthesis of many heterocyclic compounds which can be used in the field of pesticides, herbicides and pharmaceutical industries.

V. CONFLICT OF INTEREST

The author affirms that there is no conflict of interest regarding this paper.

VI. ACKNOWLEDGEMENTS

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