SYNTHESIS AND CHARACTERIZATION OF 1,2,3-TRIAZOLES THROUGH INTER AND INTRAMOLECULAR AZIDE-ALKENE CYCLOADDITION

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IN

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Submitted by

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(Ref.No:26657/Ph.D.K2/Chemistry/Full-Time/January-2018)

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CERTIFICATE

This is to certify that the thesis entitled, **"Synthesis and characterization of 1,2,3-triazoles through inter and intramolecular azide-alkene cycloaddition"** submitted by **Mr. R. Rengasamy** to Bharathidasan university for the award of the **Degree of Doctor of Philosophy in Chemistry** is a record of original and independent research work carried out by the candidate under my supervision during the period of 2018-2022. This work has not formed the basis for the award of any Degree, Diploma or any other similar title.

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DECLARATION

I hereby declare that the thesis entitled, **"Synthesis and characterization of 1,2,3-triazoles through inter and intramolecular azide-alkene cycloaddition"** is a record of work done by me in PG & Research Department of Chemistry, Rajah Serfoji Government College (Autonomous), Thanjavur - 613 005 during the period of 2018-2022. The investigation, collection of data and the results reported in my thesis are entirely original to the best of my knowledge and have been carried out by me independently. I also declare that the work has not formed in full or part the basis for award of any previous research degree.

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Dedicated

To

My Parents

ABSTRACT

This thesis is comprised of five chapters. The first chapter encapsulates the pivotal role of 1,2,3-triazoles in various fields of science and a detailed survey on the synthetic methods available in the literature. Second chapter elaborates the synthesis of 1,4-disubstituted 1,2,3-triazoles from decarboxylative azide-alkene cycloaddition of substituted cinnamic acids and organic azides. Third chapter explains CuO nanoparticles catalyzed synthesis 1,4,5-trisubstituted 1,2,3-triazoles by deacylative azide-alkene cycloaddition of benzylidene diketones with organic azides. Apart from 1,2,3-triazoles, preparation of enamines is also described in this chapter. Fourth chapter presents the one-pot two step synthesis of 1,2,3-triazole fused benzodiazepines through azidation followed by intramolecular azide-olefin oxidative cycloaddition under catalyst-free condition. Fifth chapter is comprised of the summary and conclusion.

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(R.RENGASAMY)

CONTENTS

LIST OF ABBREVIATIONS

AAC	Azide-alkyne cycloaddition
AOC	Azide-olefin cycloaddition
OAOC	Oxidative azide-olefin cycloaddition
EAOC	Eliminative azide-olefin cycloaddition
BOR	Bestmann-Ohira reagent
CAN	Ceric ammonium nitrate
CuO	Copper oxide
NPs	Nanoparticles
AcOH	Acetic acid
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
t-Bu	Tertiary butyl
t-BuOH	Tertiary butyl alcohol
tert	Tertiary
THF	Tetrahydrofuran

t-Bu	Tertiary butyl
Equiv.	Equivalent
Calcd	Calculated
FT-IR	Fourier-transform infrared
NMR	Nuclear Magnetic Resonance
^{1}H	Hydrogen-1 (or) Proton
^{13}C	Carbon-13
IR	Infra-Red
MHz	Mega Hertz
Hz	Hertz
ppm	Parts-per-million
d	Doublet
dd	Doublet of doublet
s	Singlet
m	Multiplet
q	Quartet
t	Triplet
TMS	Tetra methyl silane
HRMS	High Resolution Mass Spectroscopy
M^{+}	Molecular ion
EI	Electron ionization
ESI	Electrospray ionization

m/z	Mass/Charge
g	Gram
h	Hour
min.	Minute
mL	Milliliter
mol	Mole
mmol	Millimole
t-BuOOH	Tertiary butyl hydroperoxide
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
$K_2S_2O_8$	Potassium persulfate
$NaBH_4$	Sodium borohydride
NaOCl	Sodium hypochlorite
Na_2SO_4	Sodium sulphate
NH_4Cl	Ammonium chloride
HCl	Hydrochloric acid
TBAF	Tetrabutylammonium fluoride
TBAB	Tetrabutylammonium bromide
BTAB	Benzyltrimethylammonium bromide
CTAB	Cetyltrimethylammonium bromide
TEAC	Tetraethylammonium chloride
Oxone	Potassium peroxymonosulfate
Ph	Phenyl

Bn	Benzyl
PTSA	p-Toluenesulfonic acid
M.p	Melting point
rt	Room temperature
TLC	Thin Layer Chromatography
IL	Ionic Liquid

LIST OF SYMBOLS

α	**Alpha**
β	**Beta**
γ	**Gamma**
δ	**Delta (Chemical shift)**
J	**Coupling constant**
υ	**Nu (Wavenumber)**
°C	**Degree Celsius**
%	**Percentage**
D	**Debye**
T	**Temperature**

1. INTRODUCTION

1.1 1,2,3-TRIAZOLES

The triazole is a five membered heterocycle, bearing three nitrogen atoms and two carbon atoms. It occurs in two regioisomeric forms, i.e. 1,2,3-triazole and 1,2,4-triazole (Figure 1.1).

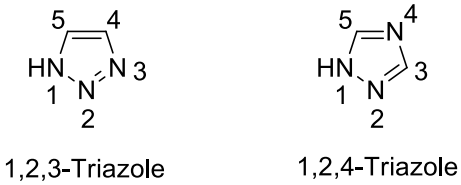


Figure 1.1 Regioisomeric forms of triazole

1.2 TRIAZOLES IN BIOLOGY

The contemporary organic chemistry focuses on the synthesis of molecules possessing medicinal, pharmaceutical, agrochemical and other applications. The efficacy of any molecule is measured in terms of non-toxic, low dosage and effective binding to a specific receptor site in order to suppress the reproduction of hazardous microorganisms. A certain functional group in a strategic position is required for each organic molecule to show the activity. In that perspective, 1,2,3-triazole based heterocyclic compounds were found to be quite promising.

1.2.1 TRIAZOLES AS AMIDE SURROGATES

Despite being devoid of natural origins, 1,2,3-triazole motifs have been found to be effective amide surrogates in bioactive molecules. Because of the large dipole moment (5.0 Debye), which is significantly higher than amide dipole moments of 3.7-4.0 Debye [1]. These dipole moments allow the triazole to act as a donor or acceptor in hydrogen bonding interactions, depending on the interacting partner (Figure 1.2) [2].

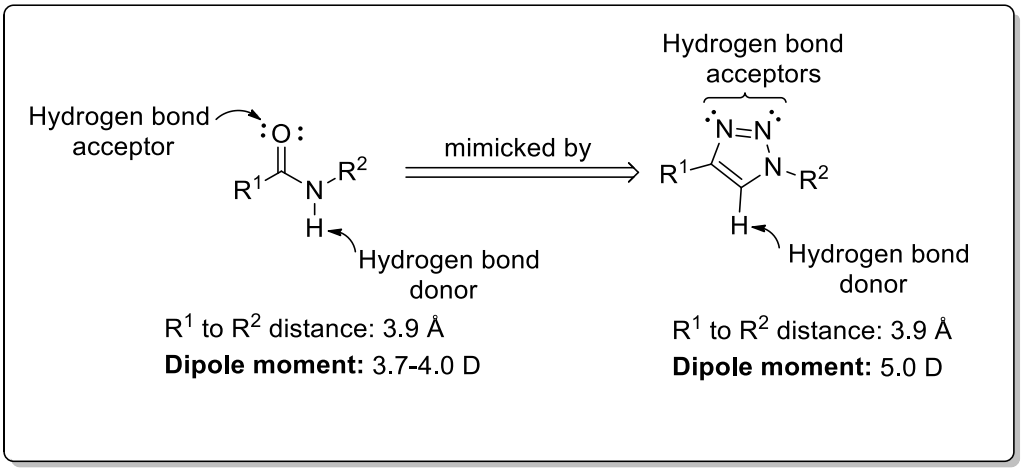


Figure 1.2 Comparison of 1,2,3-triazole ring to amide bond

1.2.2 BIOLOGICALLY ACTIVE 1,2,3-TRIAZOLES

1,2,3-Triazoles display a wide spectrum of biological activities such as anticancer, anti-HIV, antileishmanial, antimalarial, antiparasitic, antiviral, antimicrobial, antidiabetic, antifungal, antitubercular and antibacterial activities [3-10]. Some of the 1,2,3-triazole-based marketed drugs are showcased in figure 1.3. Radezolid is an antibacterial agent of biaryloxazolidinone, Carboxyamidotriazole (CAI) is an anticancer agent and Tertiarybutyldimethylsilylspiroaminooxathioledioxide (TSAO) is an anti-HIV agent while Tazobactum, Cefatrizine and Rufinamide are *β*-lactum antibiotics prominently known for their antibacterial activities [11-16].

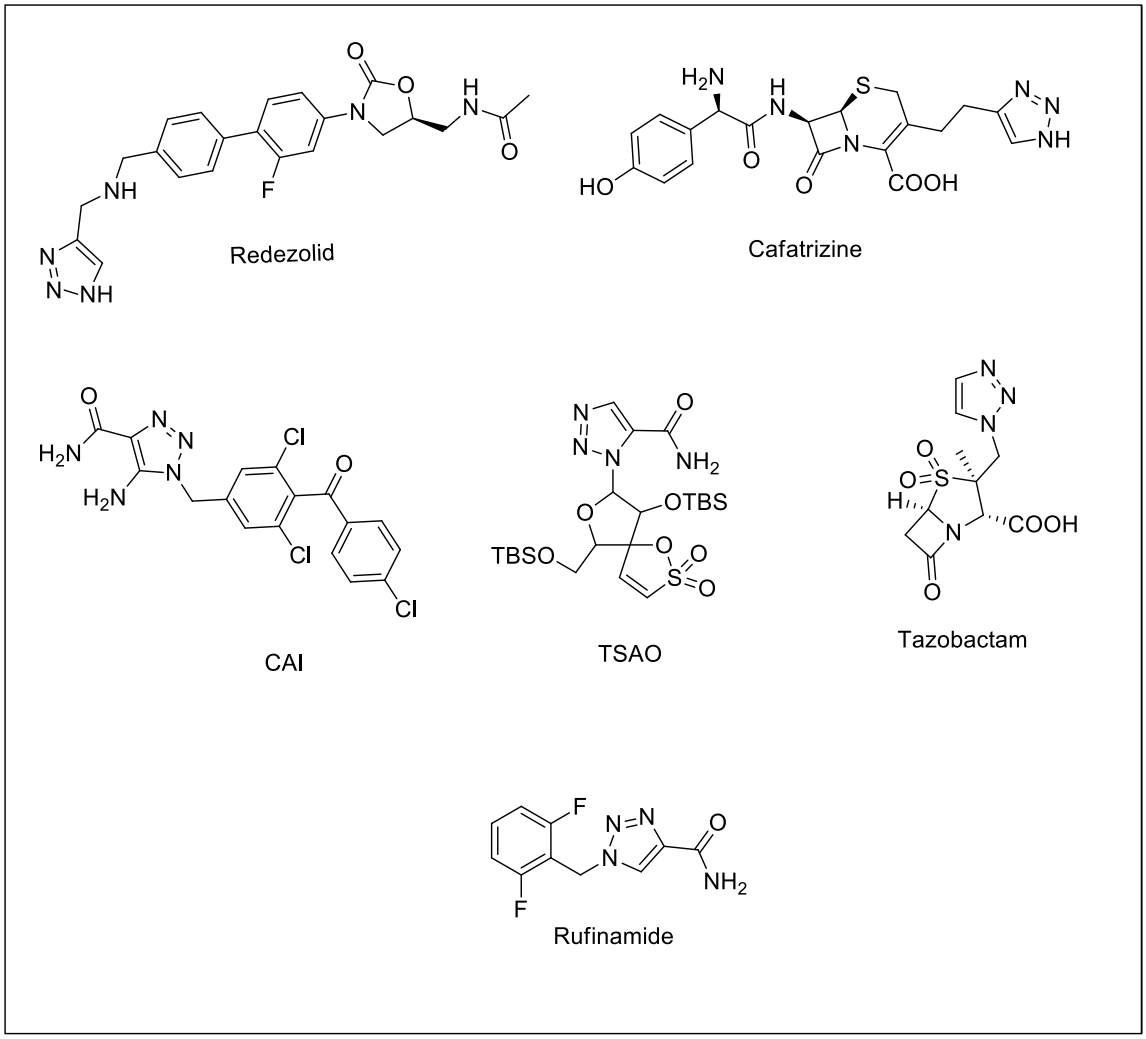


Figure 1.3 1,2,3-triazole-based marketed drugs

In addition, some of the triazole containing leads in medicinal chemistry are are displayed in (Figure 1.4).

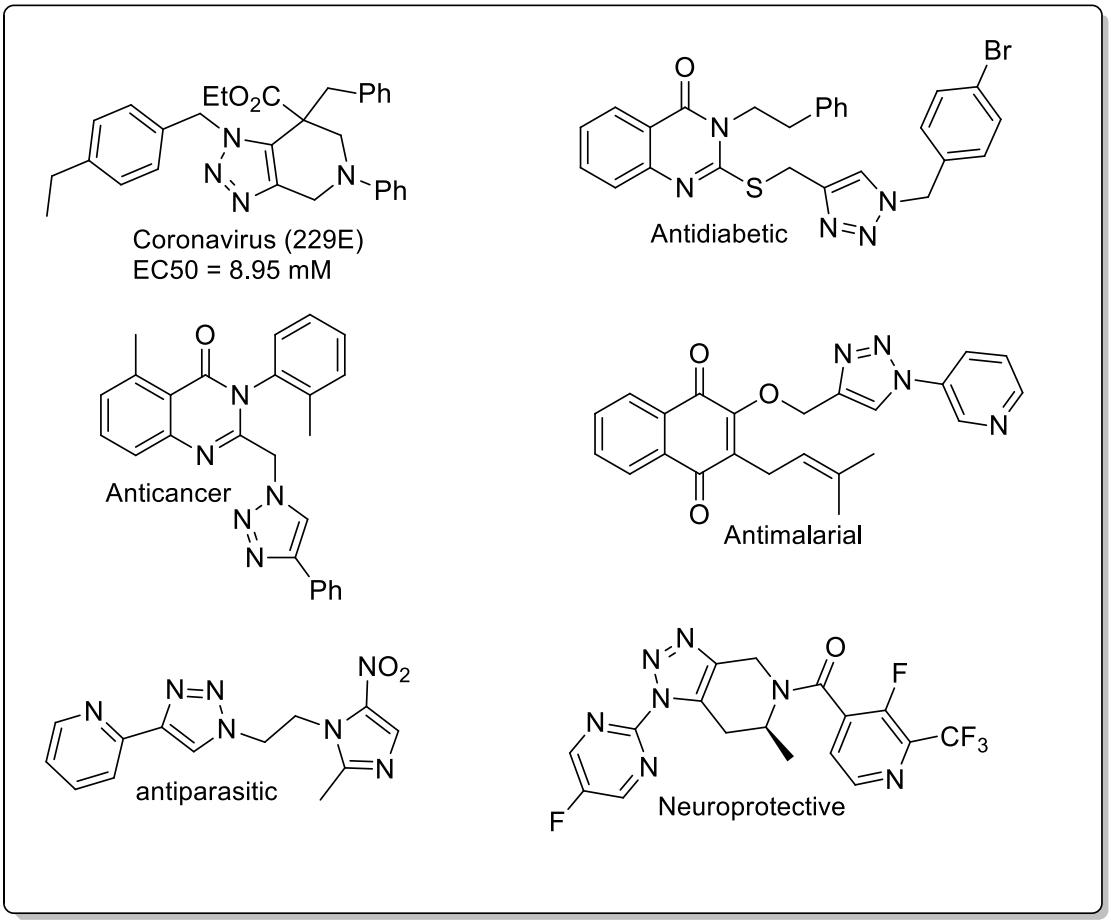


Figure 1.4 Triazole containing leads in medicinal chemistry

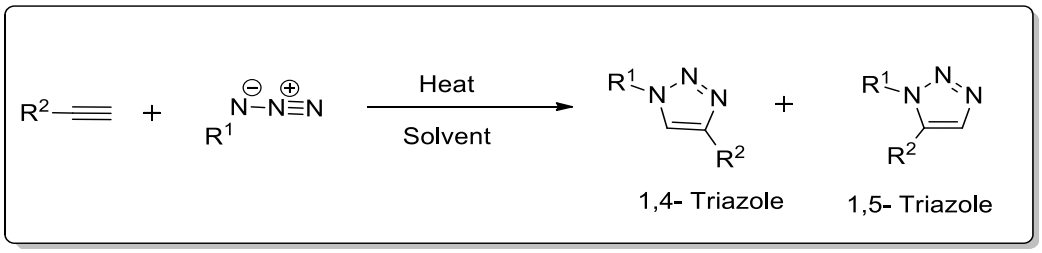
1.3 OTHER APPLICATIONS OF 1,2,3-TRIAZOLES

Apart from biology, 1,2,3-triazoles have unveiled new horizons in various areas such as materials [17-19], polymers [20-22] and supramolecules [23-25]. Interestingly they are used as valuable synthons in chemical synthesis [26-27]. Besides that, they have enormously contributed to the industry also as photo stabilizers, corrosion inhibitors, dyes, fluorescent whiteners and optical brightening agents [28].

1.4 HUISGEN 1,3-DIPOLAR CYCLOADDITION

The first Azide-alkyne cycloaddition was reported by Michael in 1893 where 1,2,3-triazole was achieved from diethyl acetylenedicarboxylate and phenyl azide [29]. Sixty years later, Huisgen cycloaddition (often refers to [3+2] cycloaddition of alkyne

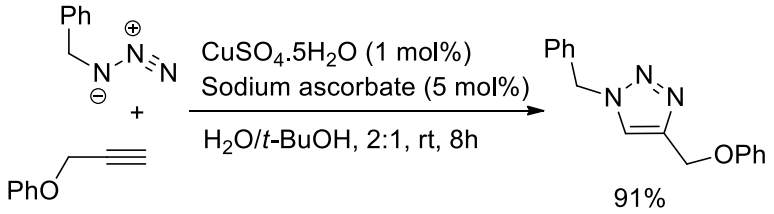
and organic azide giving 1,2,3-triazole) was reported and this reaction was believed to be a non-concerted reaction [30-31]. Moreover, this reaction (Scheme 1.6) furnishes the mixture of regioisomers (1,5- and 1,4-disubstituted-1,2,3-triazoles) [32-33]. This lack of regioselectivity and high thermal requirement were considered to be the drawbacks of Huisgen cycloaddition. When the Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) was reported in 2002, these drawbacks were solved [34].



Scheme 1.6 Lack of regioselectivity in Huisgen cycloaddition

1.5 COPPER(I)-CATALYZED AZIDE-ALKYNE CYCLOADDITION

CuAAC was first reported independently by Meldal and Sharpless [35-36] in 2002 and immediately it drew worldwide attention. The speciality of CuAAC is, its incredible selectivity towards 1,4-disubstituted 1,2,3-triazole. Moreover, this reaction proceeds under mild conditions displaying a versatile functional group tolerance (Scheme 1.7). Nobel laureate K. B. Sharpless coined the jargon "Click chemistry" [37] in 2001 to describe reactions that are high yielding, broad in scope, generate harmless by-products, needles of chromatographic methods and performable in benign or easily removable solvents.

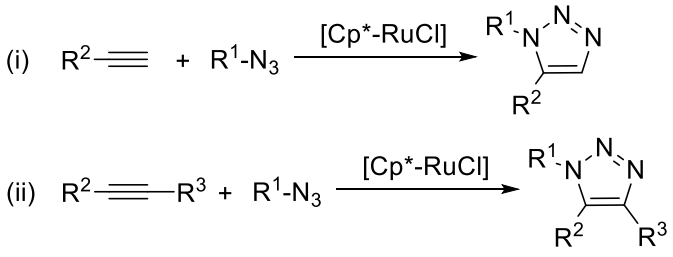


Scheme 1.7 Preparation of 1,4-disubstituted-1,2,3-triazoles by CuAAC

Meldal's CuAAC involves CuI, DIPEA and acetonitrile at room temperature to achieve the 1,4-disubstituted 1,2,3-triazole in moderate yield. Along with 1,4-disubstituted 1,2,3-triazole, by-products of oxidative coupling (caused by the dissolved oxygen in the system) also were detected. The easiest method to achieve 1,4-disubstituted 1,2,3-triazoles was the one reported by Sharpless. He used copper(II) acetate or copper(II) sulphate pentahydrate in H_2O/*t*-BuOH mixture at RT in the presence of sodium ascorbate (a mild reductant) without using any additives or ligands. In this reaction, Cu(I) salts also can be used in conjunction with sodium ascorbate, which can reduce any oxidised Cu(II) species into the catalytically active Cu(I) species. However, CuAAC is limited only to terminal alkynes and it is not applicable to internal alkynes. Moreover, the toxicity of copper to both the bacterial [38] and mammalian cells [39] restricts the usage of CuAAC beyond certain level.

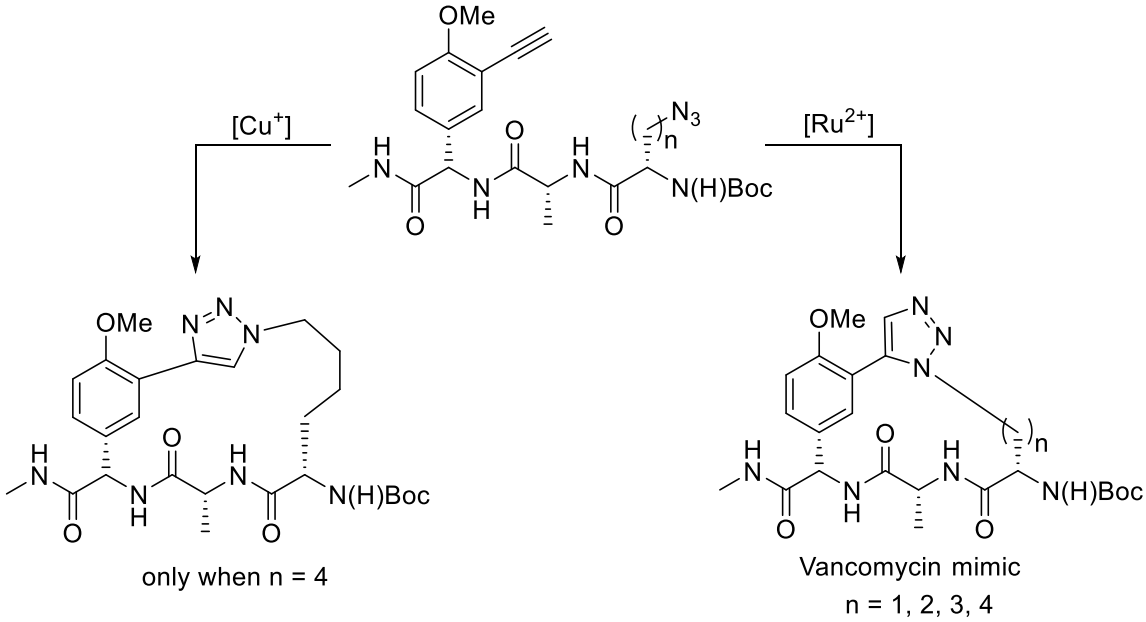
1.6 RUTHENIUM-CATALYZED AZIDE-ALKYNE CYCLOADDITION

While CuAAC was selective to 1,4-isomer, ruthenium(II) catalyzed azide-alkyne cycloaddition (RuAAC) reported by Fokin in 2005 was selective to the complementary 1,5-isomer of disubstituted 1,2,3-triazoles. Moreover, RuAAC was found to be compatible with terminal as well as internal alkynes [40].



Scheme 1.8 RuAAC of terminal alkynes and internal alkynes

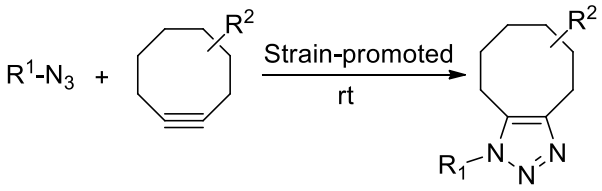
Zhang *et al.* has powerfully demonstrated the selectivity of CuAAC and RuAAC through the synthesis of vancomycin mimics (Scheme 1.9) [41].



Scheme 1.9 Synthesis of vancomycin mimics *via* CuAAC and RuAAC

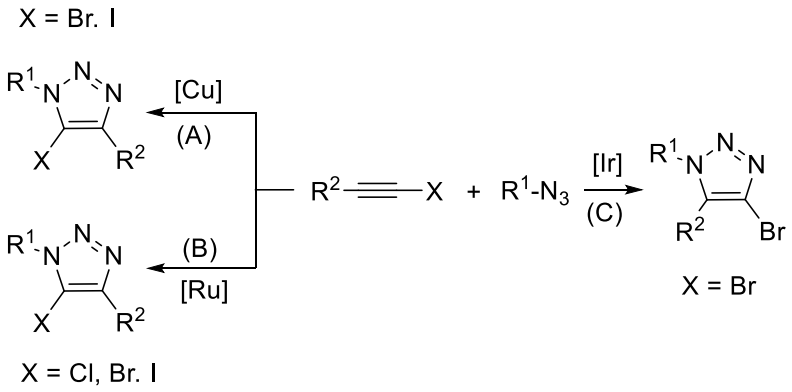
1.7 STRAIN-PROMOTED AZIDE-ALKYNE CYCLOADDITION (SPAAC)

Bertozzi reported the metal-free azide-alkyne cycloaddition using cyclooctynes in 2004 [42-43] since the cyclooctynes have an inherent strain to promote the cycloaddition (Scheme 1.10). By inserting substituents close to the triple bond, the inherent strain in the cyclooctynes was found to be increasing [44]. However, the limitation of SPAAC is the production mixture of regioisomers in the case of substituted cyclooctynes.



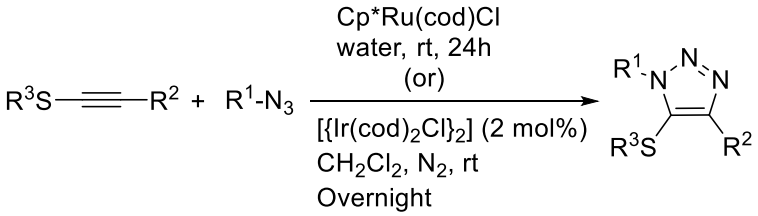
Scheme 1.10 Strain promoted, metal-free azide-cyclooctyne cycloaddition

In the case of halo alkynes, both CuAAC and RuAAC were selective to 5-halo-triazoles while IrAAC furnishes 4-bromo-triazoles (Scheme 1.11). The resulting halotriazoles can be functionalized further into fully substituted 1,2,3-triazoles [45-48].



Scheme 1.11 Regioselective synthesis of halo-triazoles

Subsequently, electron rich internal alkynes such as thioalkynes also were subjected to azide-alkyne cycloaddition. Ding *et al.* used iridium catalyst [49] while Lopez and Mascarenas and co-workers [50] employed ruthenium-catalyst and accomplished 5-thio-1,2,3-triazoles (Scheme 1.12).

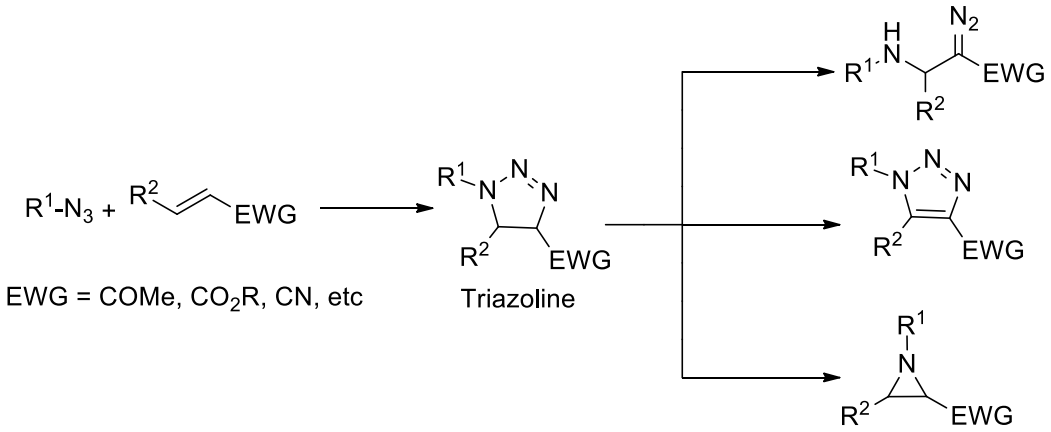


Scheme 1.12 Metal catalyzed azide-thioalkyne cycloaddition

1.8 AZIDE-OLEFIN CYCLOADDITION

Even though CuAAC and RuAAC could render efficient avenues to access 1,2,3-triazole with remarkable regioselectivity, the need for alternative methods remained unabated. Because the cytotoxicity of copper, high price of ruthenium catalyst and poor accessibility of alkynes emphasise the need of new methods. In the

case of SPAAC, poor regioselectivity looms as an unresolved problem despite the fact that it is metal-free. In response to this overwhelming demand, olefins were envisaged in the place of alkynes to access the 1,2,3-triazoles. Pioneer research on azide-olefin cycloaddition was carried out by Huisgen [51] and L'abbe [52] with azides and electron deficient olefins to form triazolines. These triazolines are generally unstable and they often crumble into different products (Scheme 1.13) depending upon the reaction conditions [53-59].

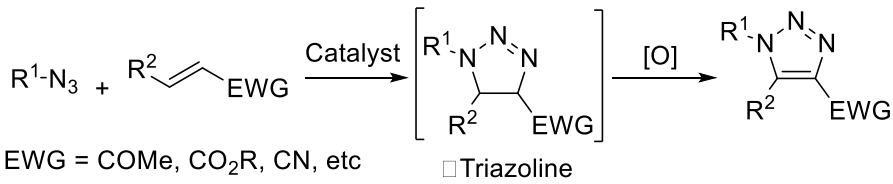


Scheme 1.13 Azide-olefin cycloaddition and the decomposition of trizoline

Nevertheless, methods to aromatize the unstable triazolines into stable triazoles were sought out by a few research groups. Finally this search culminated in the development of Oxidative Azide-Olefin Cycloaddition (OAOC) and Eliminative Azide-Olefin Cycloaddition (EAOC).

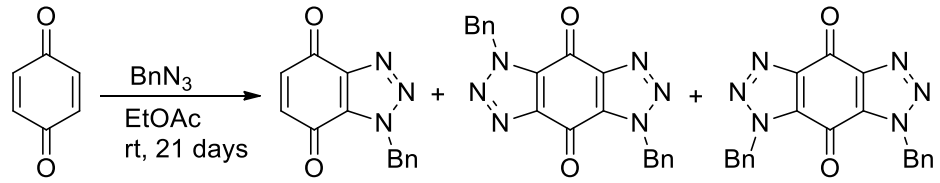
1.8.1 OXIDATIVE AZIDE-OLEFIN CYCLOADDITION (OAOC)

In this approach, the unstable triazoline formed by azide-olefin cycloaddition is concomitantly oxidized into the required 1,2,3-triazole (Scheme 1.14). The olefins employed here are activated olefins (olefins bearing electron withdrawing group).

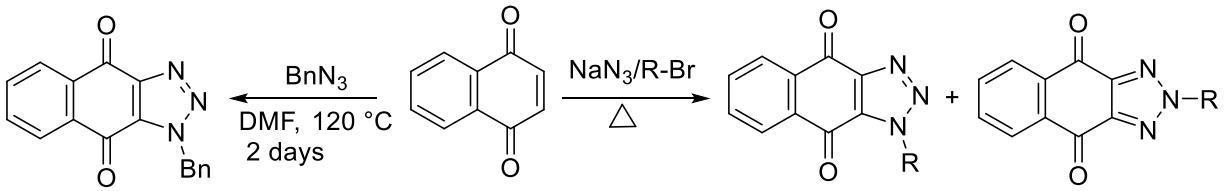


Scheme 1.14 Synthesis of 1,2,3-triazole through OAOC

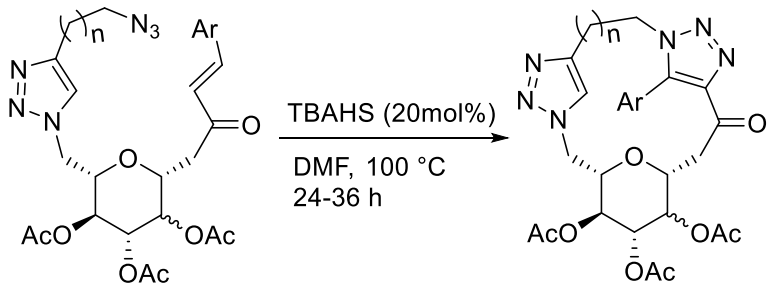
OAOC of 1,4-benzoquinone and benzyl azide was reported by Marminon *et al.*, under catalyst-free condition to yield the mixtures of benzotriazole-4,7-diones [60].



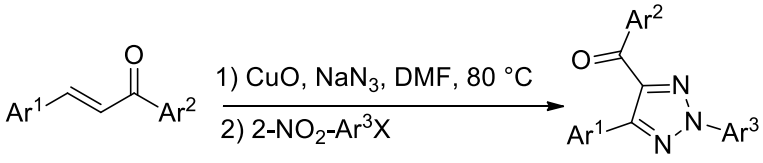
Chang and singh described the catalyst-free oxidative cycloaddition of 1,4-naphthoquinone with benzyl azide to produce 1-benzyl-1H-naphtho[2,3-d][1,2,3]triazole-4,9-dione [61-62].



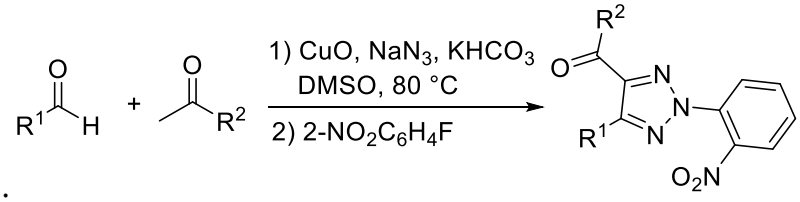
Ajay *et al*. described a new method for making macrocyclic glycoconjugates using TBAHS catalyzed intramolecular azide-enone cycloaddition [63].



Zhang *et al*. demonstrated a one-pot synthesis of *N*-2-aryl-substituted-1,2,3-triazoles through CuO nanoparticles catalyzed OAOC of chalcones followed by arylation of triazole by 2-nitroarylhalides [64].



Liu *et al.* reported the same reaction again through a one-pot reaction involves acetophenones, benzaldehydes, sodium azide and aryl halides to produce 2,4,5-substituted 1,2,3-triazoles [65].



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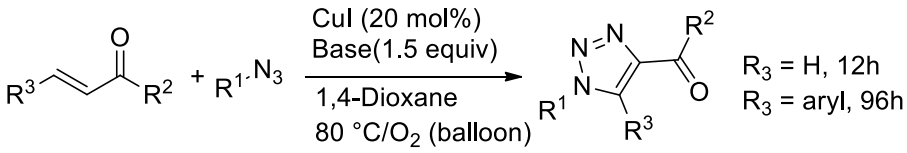
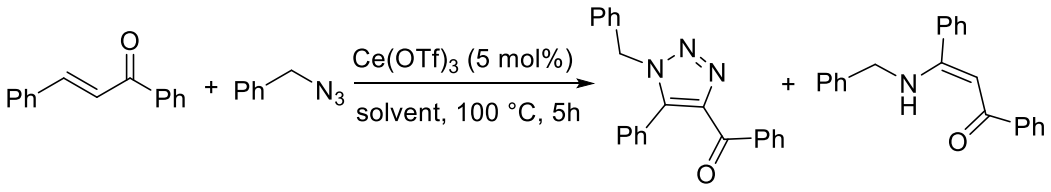
Janreddy et *al*. reported the copper(I)-promoted OAOC for the regioselective synthesis of 1,4-disubstituted/1,4,5-trisubstituted-1,2,3-triazoles in basic medium under oxygen atmosphere [66].

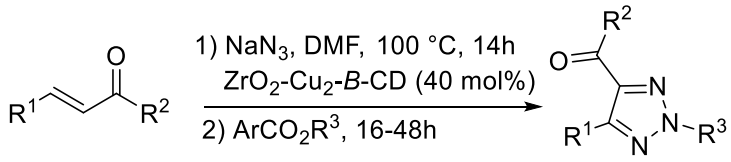


Xie *et al*. reported a tunable synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and Z-*β* -aryl enaminones using $Ce(OTf)_3$ catalyst. In toluene medium, 1,2,3-triazole was produced through OAOC, while Z-*β*-aryl enaminone was furnished in DMF medium through 1,2-*H* migration on triazoline [67].

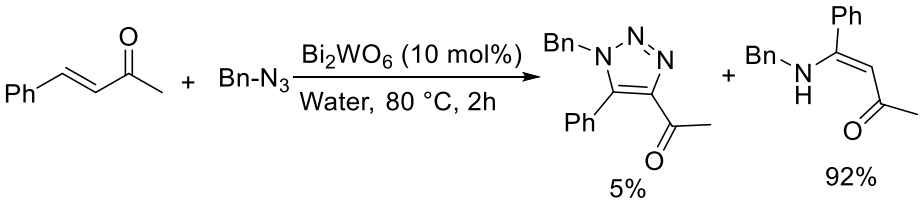


Solvent	1,2,3-Triazole	(*Z*)-Enaminone
Toulene:	85%	<5
DMF:	<5	82

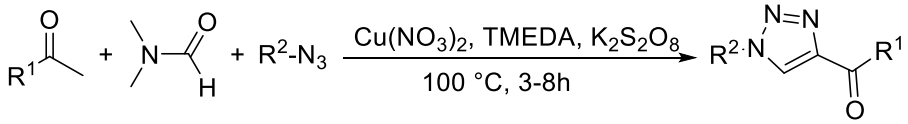
Girish *et al.* reported a one-pot synthesis of *N*-2-alkyl substituted-1,2,3-triazoles by OAOC catalyzed by ZrO_2 nanoparticle-supported Cu(II)cyclodextrin followed by triazole alkylation by alkyl benzoates [68].



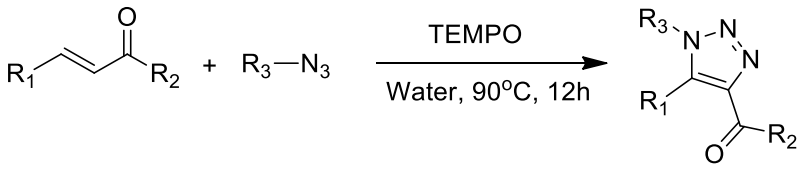
Paplal *et al.* reported the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles and *Z*-*β*-aryl enaminones catalyzed by Bi_2WO_6 nanoparticles under aqueous medium [69].



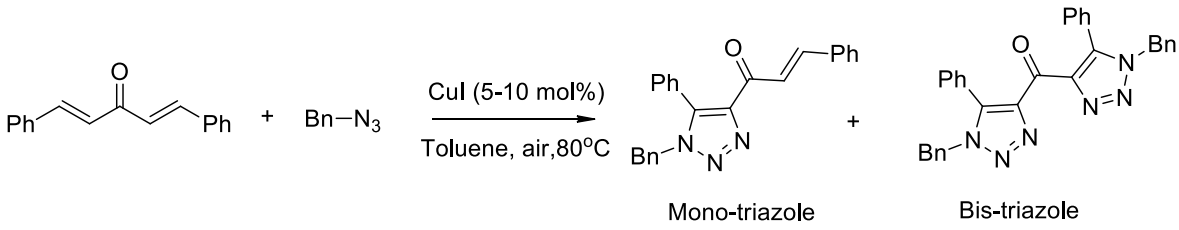
Liu *et al.* disclosed copper-catalyzed three-component reaction of methyl ketones, organic azides and DMF for the synthesis of 4-acyl-1,2,3-triazoles. This reaction proceeds through oxidative cross-dehydrogenative coupling and OAOC sequence [70].



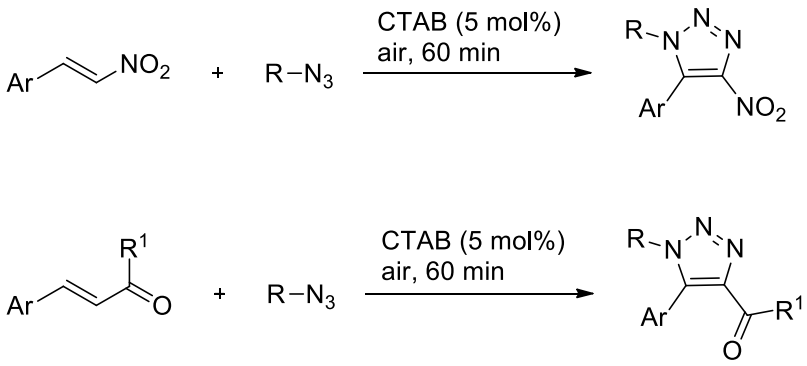
Gangaprasad *et al.* reported TEMPO catalyzed and aqueous mediated synthesis of disubstituted and trisubstituted 1,2,3-triazoles through OAOC of organic azides and electron deficient olefins [71].



Naimish *et al.* reported the copper-catalyzed oxidative azide-olefin cycloaddition of dibenzylidene acetones with azides to achieve mono- and bis-(1,4,5-trisubstituted-1,2,3-triazoles) [72].

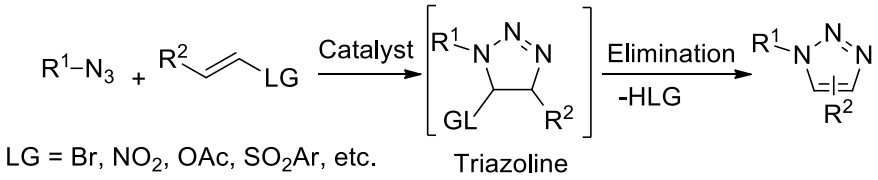


Vadivelu *et al.* reported an organocatalytic mechanochemical method for the OAOC of *β*-nitrostyrenes/chalcones with organic azides for the synthesis of 4-nitro triazoles and 4-acyl triazoles [73].



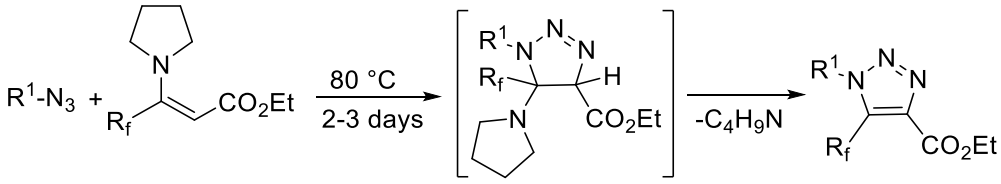
1.8.2 ELIMINATIVE AZIDE-OLEFIN CYCLOADDITION (EAOC)

In this strategy, olefin carrying a leaving group such as nitro, sulfone, acetate, alkoxy, amino, etc., would be subjected to [3+2] cycloaddition with azide followed by the concomitant elimination of the leaving group from the resulting triazoline furnishes the required 1,4 or 1,5-disubstituted-1,2,3-triazole (Scheme 1.15).

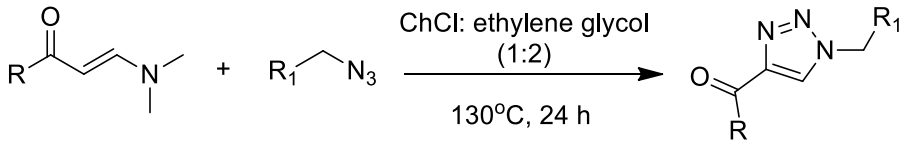


Scheme 1.15 Synthesis of 1,2,3-triazoles by EAOC

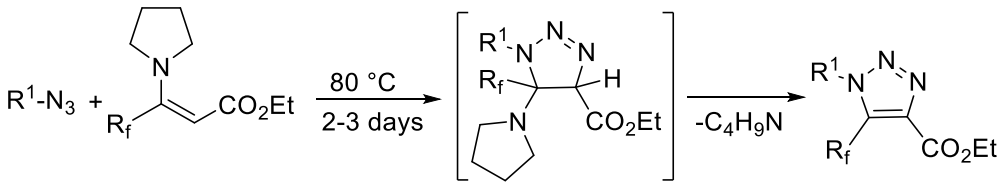
In 2003, Peng *et al.* demonstrated the EAOC on (*Z*)-ethyl 3-fluoroalkyl-3-pyrrolidino-acrylates and prepared 5-fluoroalkylated-1,2,3-triazoles in good yields under thermal condition [74].



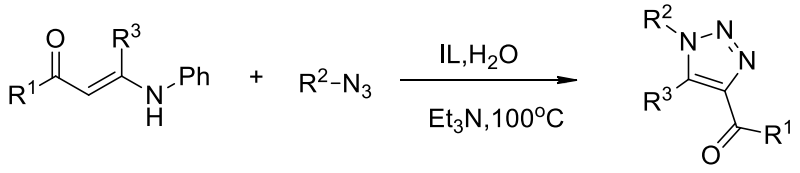
Martins *et al.* reported a green method of synthesizing 4-acyl-1,2,3-triazoles using a deep eutectic solvent system [75].



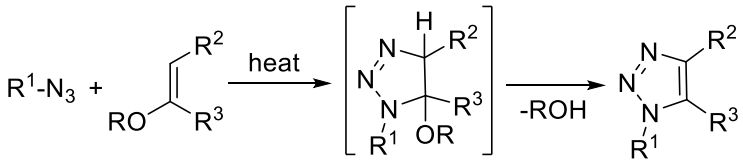
Peng *et al.* reported the regiospecific and catalyst-free eliminative [3+2] cycloaddition reaction for the synthesis of 5-fluoroalkylated-1,2,3-triazoles from push pull olefin and organic azide [76].



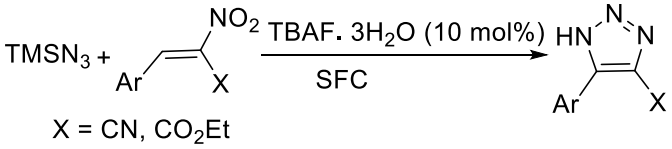
De Nino *et al.* reported a regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazoles from aryl azides and enaminones. The use of an ionic liquid in the presence of water and trimethylamine is crucial for the progress of the reaction. The process, cascades through water-promoted 1,3-dipolar cycloaddition followed by a base-promoted retroaza-Michael reaction [77].



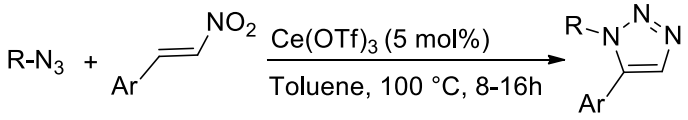
Roque *et al*. demonstrated the EAOC on enol ethers under thermal conditions to produce 1,4-disubstituted-1,2,3-triazoles [78].



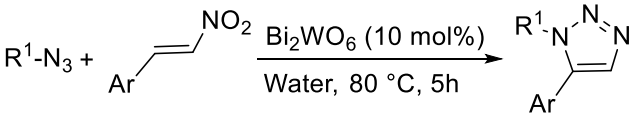
Amantini and Vaccaro reported the TBAF-catalyzed EAOC of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with $TMSN_3$ under solvent-free condition to achieve 4-aryl-5-cyano- (or 4-aryl-5-carbethoxy-N*H*-1,2,3-triazoles [79].



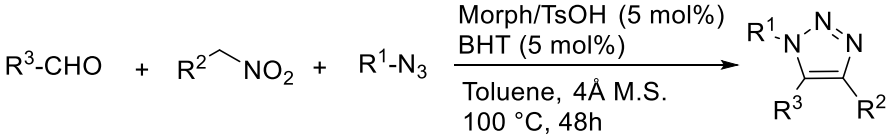
Wang *et al*. described EAOC on *β*-nitrostyrene using $Ce(OTf)_3$ catalyst and prepared 1,5-disubstituted-triazoles in excellent yields [80].



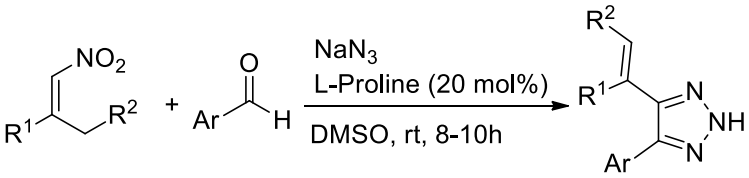
Paplal *et al*. reported the synthesis of 1,5-disubstituted triazoles *via* aqueous mediated, nano-Bi_2WO_6 catalyzed EAOC of *β*-nitrostyrenes and azides [81].



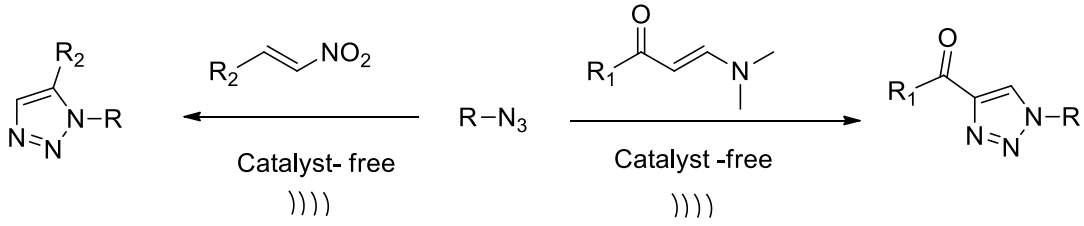
Thomas *et al*. demonstrated the preparation of 1,4,5-trisubstituted triazoles through one-pot Knoevenagel condensation followed by EAOC from aldehydes, nitroalkanes and organic azides [82].



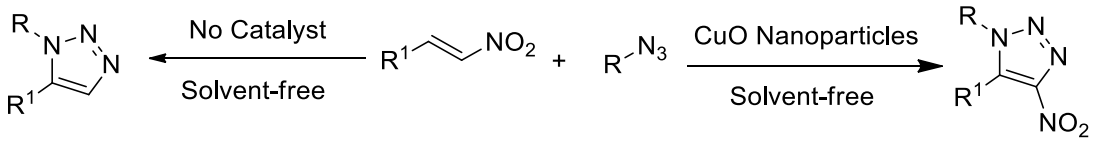
Sengupta *et al*. reported the preparation of 4-vinyl-substituted-N*H*-triazoles through a multicomponent cascade reaction involves Henry reaction followed by EAOC catalysed by L-proline [83].



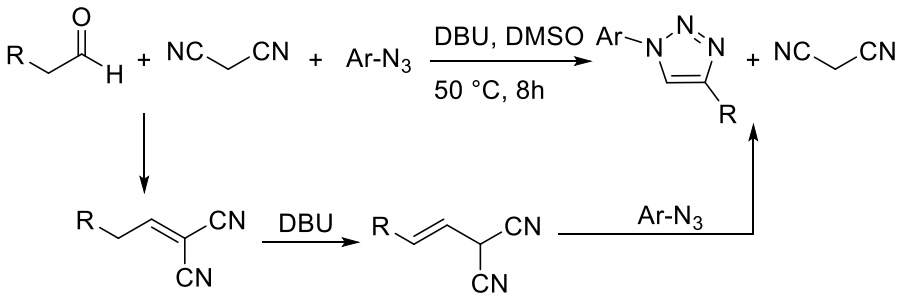
Kiranmye *et al.* reported a catalyst-free and ultra sound assisted EAOC of azides with *β*-enaminones/nitroolefins for the synthesis of 1-4-disubstituted and 1,5-disubstituted-1,2,3-triazoles [84].



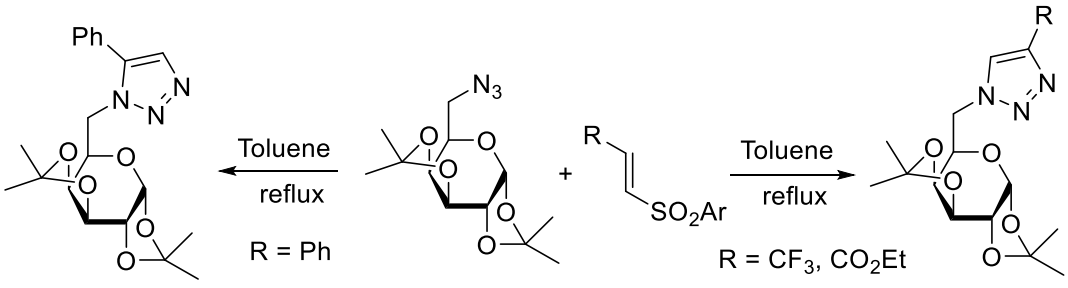
Gangaprasad *et al.* reported a tunable synthesis of 1,5-disubstituted 1,2,3-triazloles through OAOC and EAOC of nitroolefins and organic azides under solvent-free condition. In the presence of the catalyst (CuO nanoparticles), nitro group was retained in the product while it got eliminated in the absence of the catalyst [85].



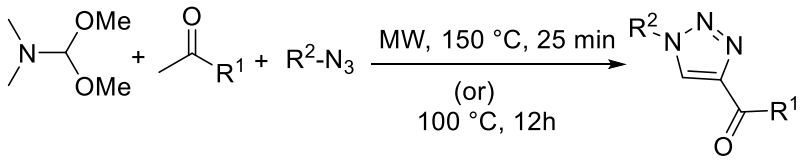
A DBU catalyzed, one-pot inverse-electron-demand EAOC approach involves malononitriles, aldehydes and aromatic azides was described by Ali *et al*. to access 1,4-disubstituted 1,2,3-trizoles [86].



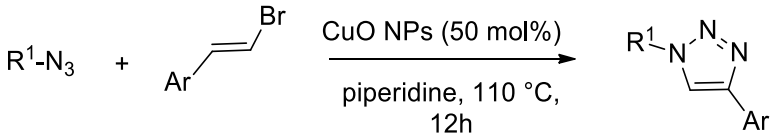
Sahu *et al.* demonstrated the EAOC of vinyl sulfones and the azides derived from carbohydrates. Regioselectivity of this reaction could be dictated by varying the substituents on the alkene [87].



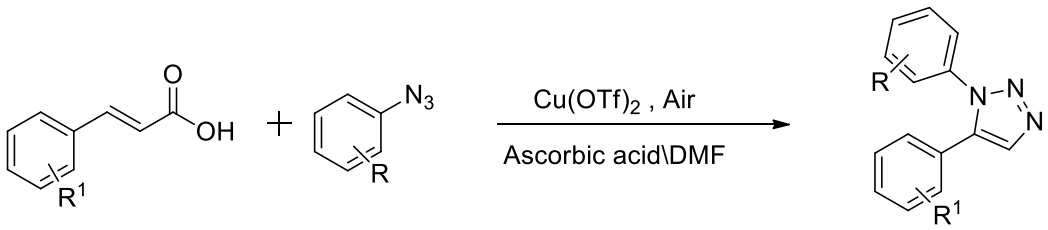
To synthesize 4-acyl-1,2,3-triazoles, Thomas *et al*. described a domino reaction between DMF acetal, ketone and organic azide. In this reaction, the EAOC of enaminone formed *in situ* leads to the required 4-acyl-1,2,3-triazoles [88].



Paul Raj *et al*. reported the commercially available heterogeneous CuO nanoparticles catalyzed EAOC of *β*-bromostyrenes under piperidine medium [89].

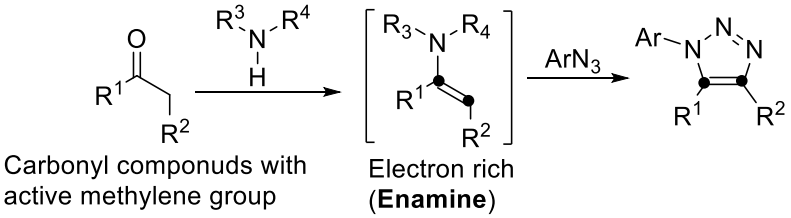


Kumar *et al.* have demonstrated the copper catalyzed decarboxylative cycloaddition of cinnamic acids with aryl azides for the synthesis of 1,5-disubstituted 1,2,3-triazole [90].



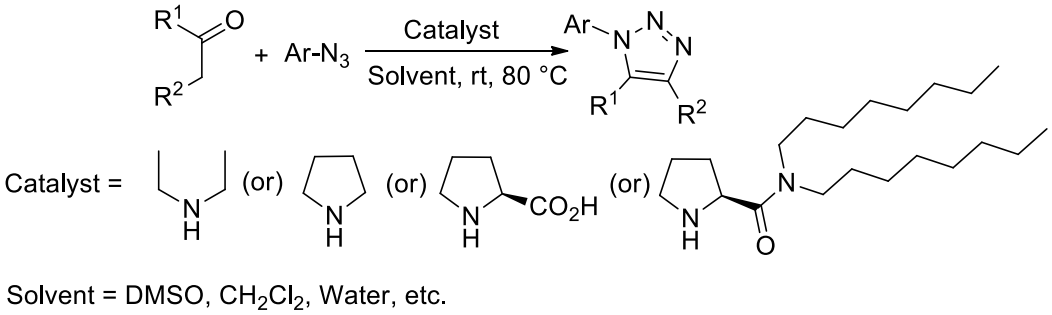
1.8.3 ORGANO CLICK REACTION

In the presence of organocatalysts (amine bases), the *in situ* generated enamines/ iminium ions/enolates from carbonyl compounds will undergo EAOC or OAOC with aryl azides to produce the 1,2,3-triazoles (Scheme 1.16) [91].

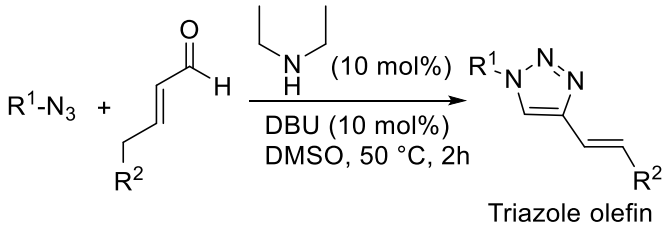


Scheme 1.16 Organo Click reactions *via* enamine intermediate

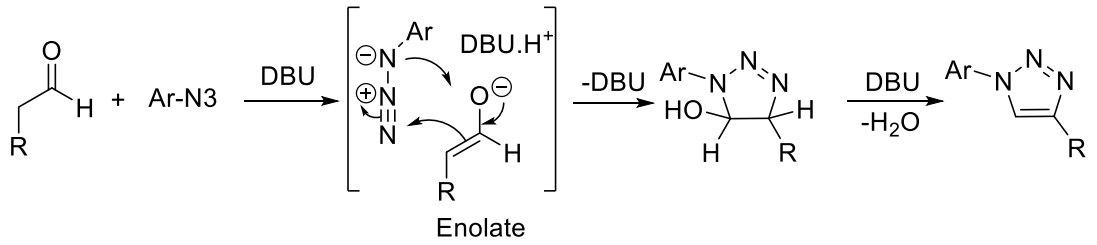
Wang, Bressy and Ramachary have pioneered in this area where they have mainly used enolizable carbonyl compounds and aryl azides [92-97].



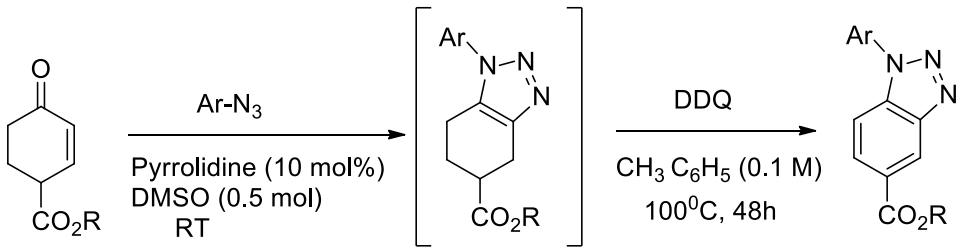
In the presence of diethylamine, Li *et al.* achieved the vinyltriazoles from *α,β*-unsaturated aldehydes and organic azides [98]. Here, the dienamines formed *in situ* undergoes EAOC with azides to furnish the vinyl triazoles.



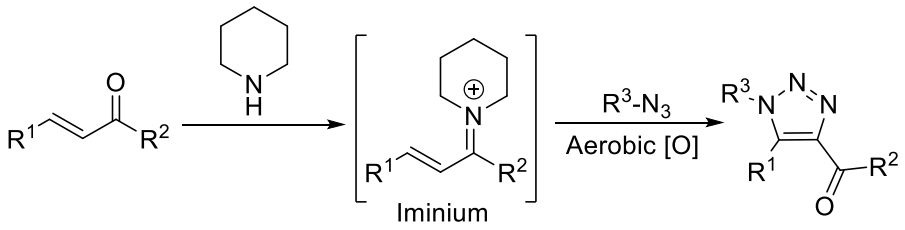
In the presence of DBU, Ramachary *et al*. have achieved a regioselective preparation of 1,4-disubstituted-1,2,3-triazoles *via* an organoclick reaction involves enolate ion and aryl azide [99].



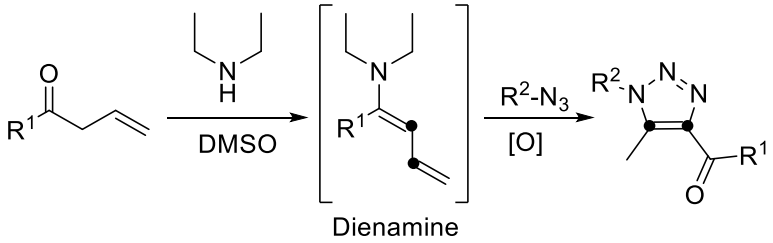
Ramachary *et al.* described the preparation of *N*-arylbenzotriazoles through one-pot azide-olefin cycloaddition followed by DDQ promoted oxidative aromatization of cyclic enones [100].



Li *et al*. reported an organocatalytic reaction involves OAOC to prepare 1,4,5-trisubstituted 1,2,3-triazoles from *α, β*-unsaturated ketones and azides through iminium catalysis [101].

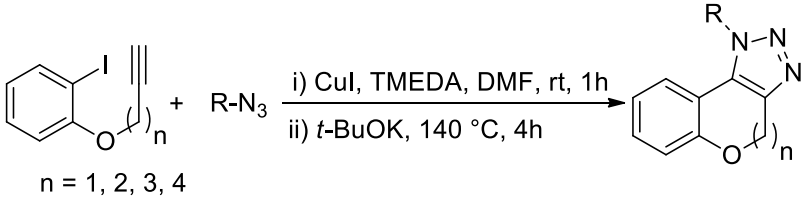


Li *et al*. reported a regioselective synthesis of 4-ketotriazoles *via* organoclick reaction of organic azides with allyl ketones [102].

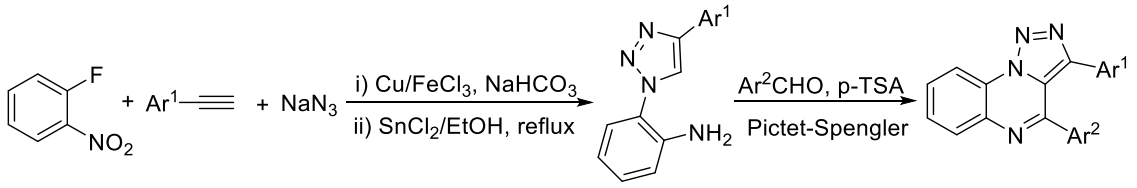


1.9 SYNTHESIS OF 1,2,3-TRIAZOLE-FUSED HETEROCYCLES

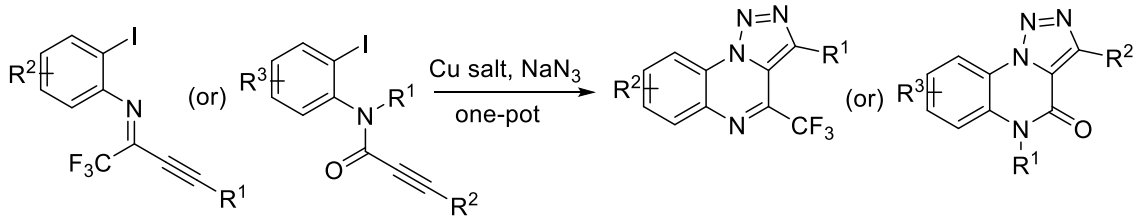
Nagarjuna Reddy *et al*. achieved the synthesis of 1,2,3-triazole fused oxygen heterocycles through CuAAC followed by intramolecular direct arylation in one-pot [103].



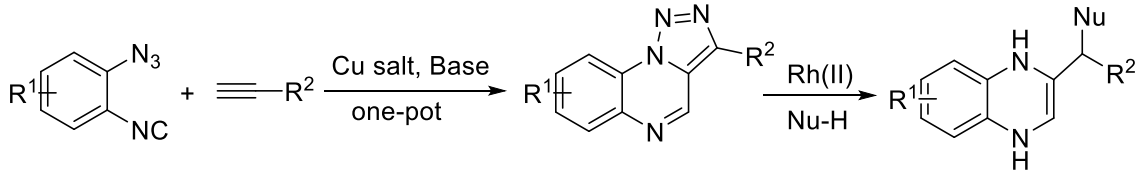
Saha *et al*. described a one-pot synthesis of 1,2,3-triazolo[l,5-a]quinoxalin-4-one through CuAAC, nitro reduction and Pictet-Spengler cyclization sequence [104].



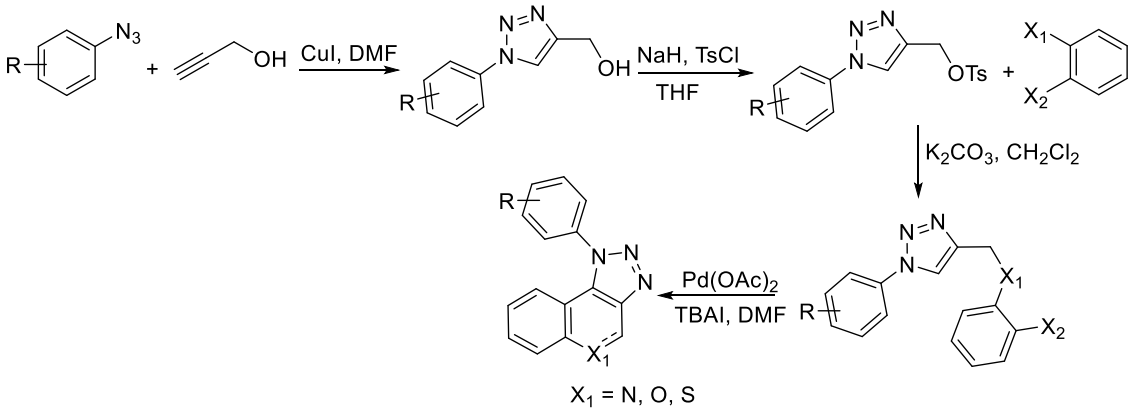
Chen and Yan used Cu(I)-catalyzed cascade reactions of 1,1,1-trifluoro-*N*-(2-iodophenyl)but-3-yn-2-imines and N-(2-iodophenyl) propiolamides with sodium azide to produce 1,2,3-triazole fused piperazine derivatives through cycloaddition-intramolecular Ullmann coupling sequence [105-106].



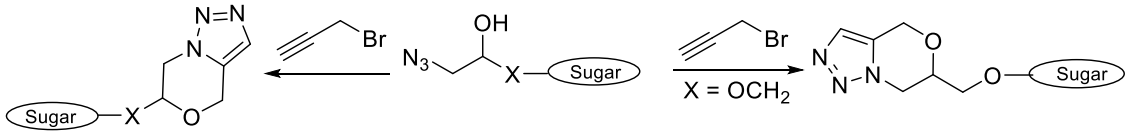
To make the 1,2,3-triazolo[1,5-a]quinoxalines, Li *et al.* employed a tandem cyclization involves terminal alkynes and 1-azido-2-isocyanoarenes. Subsequently, *via* Rh(II)-catalyzed carbenoid insertion, these fused triazoles are further transformed into quinoxaline derivatives [107].



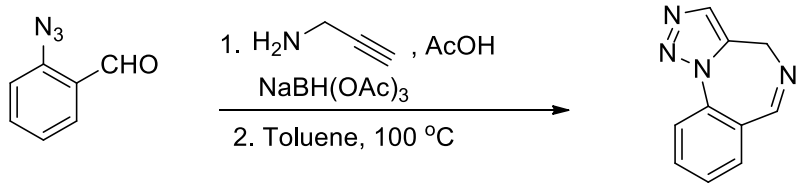
Chen *et al*. described a multi-step process for the synthesis of 1,2,3-triazole fused chromenes, quinolines and thiochromenes using CuAAC followed by palladium catalyzed intramolecular arylation[108].



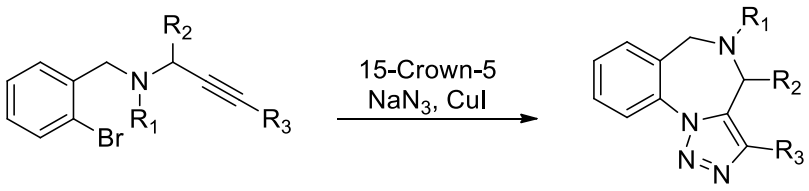
Tiwari *et al.* described the synthesis of *C*- and *O*-glycosylmorpholinefused triazoles from propargyl bromide and sugar derived 1,2-azido alcohols *via* one-pot propargylation and intramolecular azide-alkyne cycloaddition [109].



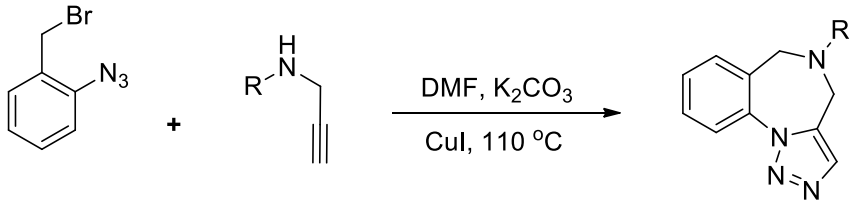
Donald *et al*. have reported the synthesis of triazoles fused benzodiazepines through reductive amination followed by intramolecular azide-alkyne cycloaddition [110].



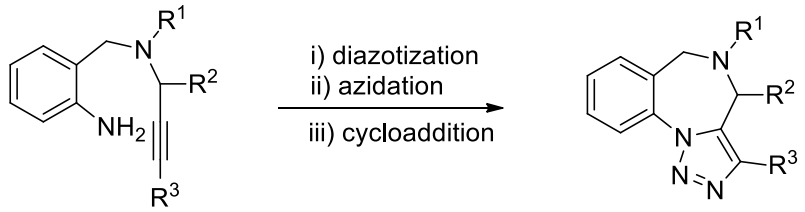
Eycken's group have reported a protocol involving copper catalyzed intramolecular azide-alkyne cycloaddition to access the triazole fused benzodiazepines [111].



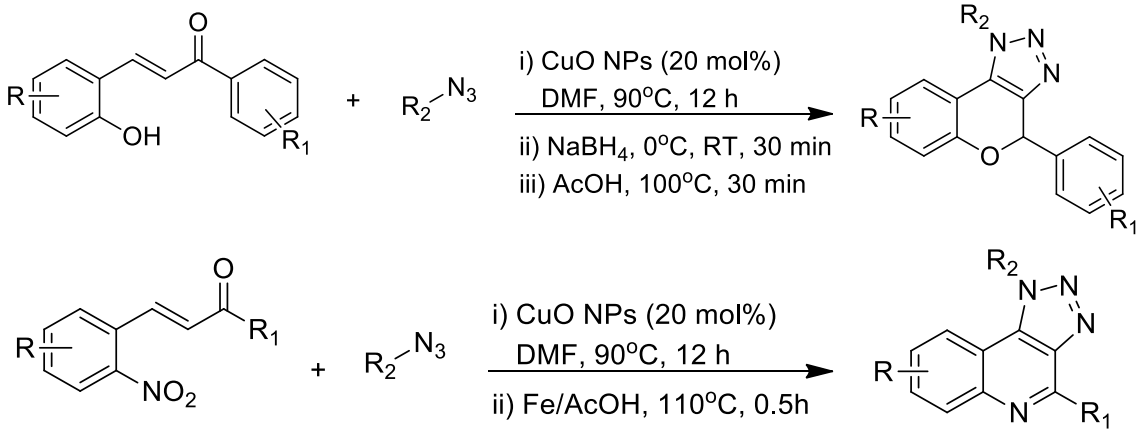
Majumdar *et al.* reported the synthesis of triazolo[1,5-*a*][1,4]benzodiazepines by copper catalyzed tandem Ullmann C–N coupling followed by azide-alkyne cycloaddition [112].



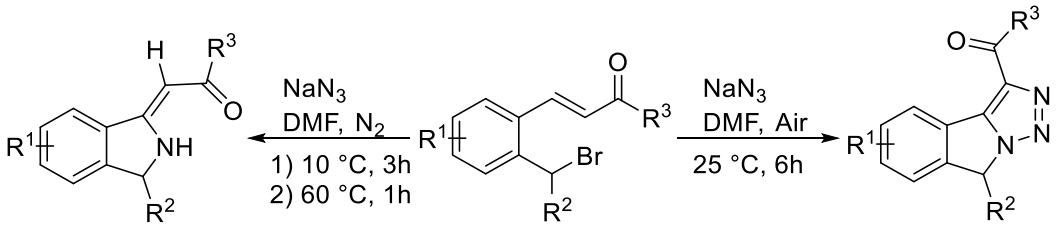
Sudhapriya *et al.* reported the synthesis of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines by sequential diazotization, azidation and intramolecular azide-alkyne cycloaddition [113].



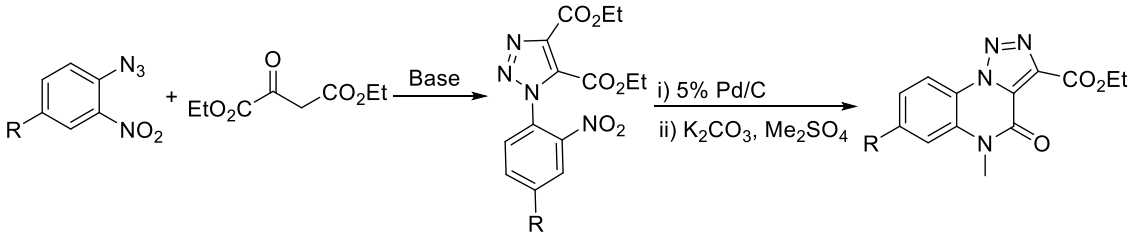
Gangaprasad *et al.* reported a one-pot oxidative azide-olefin cycloaddition followed by intramolecular reductive cyclization to access 1,2,3-triazole-fused quinolines/ chromenes [114].



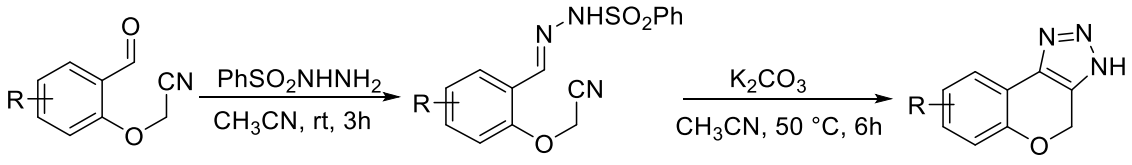
Xie and Pan reported a tunable synthesis of indole fused 1,2,3-triazoles and isoindolines through intramolecular OAOC under catalyst-free condition only by varying reaction temperature and gaseous atmosphere [115].



Bertellia *et al.* reported synthesis of 1,2,3-triazolo[l,5-a]quinoxalin-4-one derivatives from 2-nitrophenyl azides and carbonyl compounds *via* EAOC followed by nitro reduction and N-acylation [116].



Mani *et al*. disclosed the synthesis of triazole-fused chromenes by intramolecular [3+2] cycloaddition between diazo compounds and a nitriles. In this strategy, diazomethanes generated *in situ* undergoes intramolecular [3+2] cycloaddition with cyano group [117].



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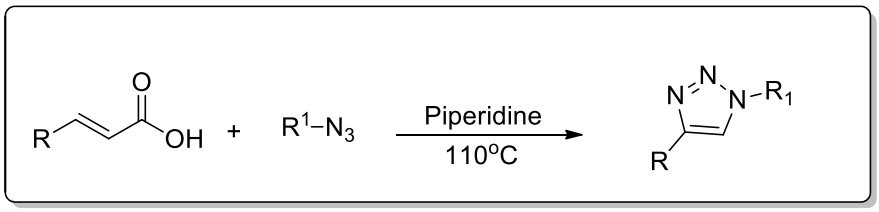
2. A novel route to 1,4-disubstituted-1,2,3-triazoles through metal-free decarboxylative azide-alkene cycloaddition

2.1 Introduction

This chapter presents the synthesis of 1,4-disubstituted 1,2,3-triazoles by decarboxylative [3+2] cycloaddition of organic azides and cinnamic acids under metal-free condition.



Scheme 2.1 Decarboxylative azide-alkene cycloaddition of cinnamic acids and organic azides.

2.2 Results and Discussion

The preliminary optimization was initiated with cinnamic acid (**1a)** and benzyl azide (**2a)** as model substrates to fix the appropriate condition. We started with copper iodide as catalyst (0.1 eq.), potassium carbonate as base (1.0 eq.) and DMSO (2.0 mL) as the solvent at 110^{o}C. When the reaction was prolonged for 24 h, the required 1,2,3-triazole (**3a)** was obtained in 20% yield (Table 2.1, entry 1). Initially the product was confirmed by comparing its melting point with that of the value in the liturature (126-128 ^{o}C). The product was characterized by ^{1}H NMR and ^{13}C NMR and XRD. In ^{1}H NMR (figure 2.1), the compound exhibits a singlet at δ 7.66 ppm representing one proton present in the triazole ring. Another characteric peaks is benzylic protons which appear at δ 5.57 ppm as a singlet. The aromatic protons come at 7.81-7.30 ppm. Apart from these signals, no signals corresponding to the olefin (δ 5.90-6.30 ppm) were observed. In ^{13}C NMR (figure 2.2) totally 11 signals were observed. The signal at 54.25

ppm indicates the presence of benzylic carbon, 119.5 ppm to 129.2 ppm which was indicate the aromatic carbons, 130.5 ppm indicate the C-5 carbon of triazole moiety and 134.7ppm quaternary carbon of benzylic aromatic group finally the characteristic peak of 148.6ppm point out the C-4 carbon of triazole ring. Finally, the desired product was unambiguously ascertained by single crystal XRD (figure 2.3).

Subsequently, other Cu species including CuCl, Cu(powder),CuOnano particles and $Cu(OTf)_2$ were also examined for improving the conversion (Table 2.1, entries 2-5). Among all of these catalysts, CuCl was found to be convincing since it showed a better yield of the product (Table 2.1, entry 2). Hence, fixing CuCl as catalyst, we tested the other solvents such as DMF, toluene, THF and water monitored the outcome (Table 2.1, entry 6-9). To our disappointment, these solvents could not impose any pronounceable change in the conversion.

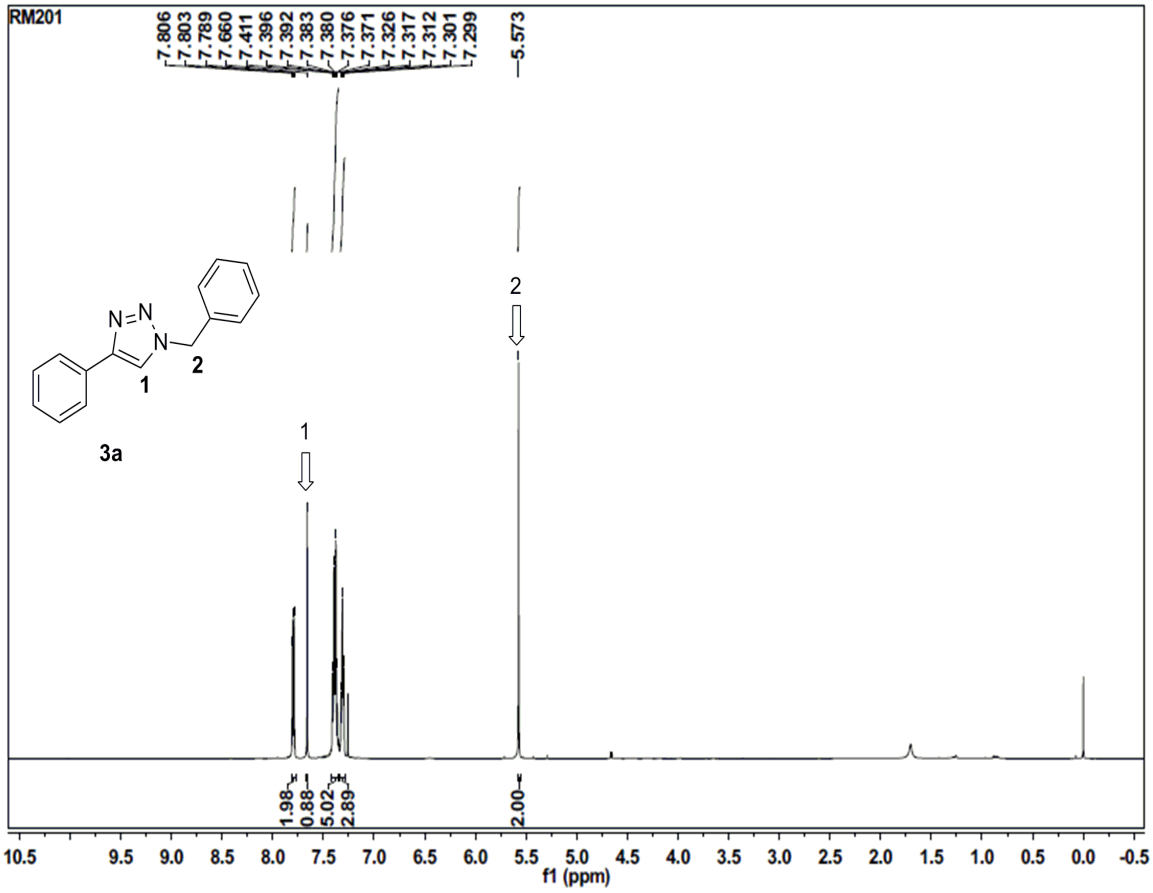


Figure 2.1 ^{1}H NMR of 1,4-diphenyl-1H-1,2,3-triazole(3a) in $CDCl_3$

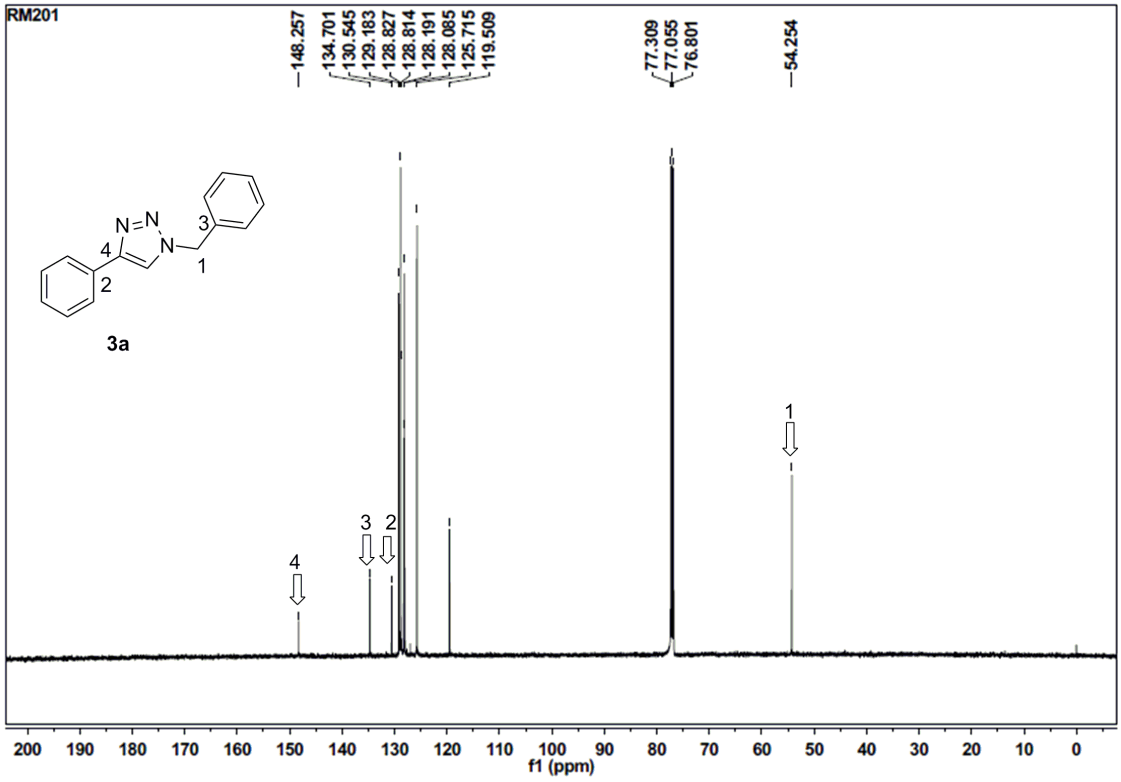
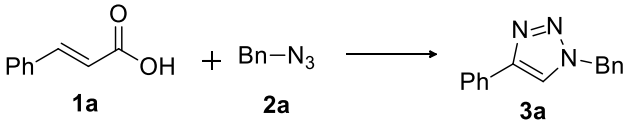


Figure 2.2 ^{13}C NMR of 1,4-diphenyl-1H-1,2,3-triazole(3a) in $CDCl_3$

On the other hand, substantial improvement was noticed when the reaction was performed under solvent-free condition (Table 2.1, entry 10). Spurred by this, we varied the bases such as Potassium *t*-butoxide, sodium bicarbonate, DABCO, DBU, pyridine and piperidine under solvent-free condition and monitored the outcome (Table 2.1, entries 11-16). To our surprise, the reaction performed in the presence of piperidine managed to furnish the corresponding product **3a** in 68% (Table 2.1, entry 16). Hence, fixing piperidine as base, when we tested the reaction in the absence of catalyst, we observed an unexpected spike in the efficiency of this protocol registering 92 % yield of the product (Table 2.1, entry 17). When we reduced the duration of the reaction from 24h to 16h, 14h and 12h, we resolved to fix 14h as the suitable time duration to carry out this reaction (Table 2.1, entries 18 to 20). While reduced the amount of the base further, 0.5 equivalent and 0.25 equivalent, 93% yield of **3a** was obtained in the case of 0.5 equivalent of piperidine. (Table 2.1, entry 21 and entry 22). Fixing the quantity of base (0.5 eq) and time 14h, we varied the temperature and monitored the outcome. While raising the temperature to 120^{o}C, there was no pronounceable change in the yield (Table 2.1, entry 23), while reducing the temperature to 100^{o}C, the yield dropped apparently (Table 2.1, entry 24). Hence, we resolved to perform the reaction in the presence of 0.5 equivalent of piperidine for a duration of 14h at 110^{o}C (Table 2.1, entry 21).

Table 2.1 Optimization of decarboxylative azide-alkene cycloaddition.[a]



1a 2a 3a

Entry	Catalyst (eq.)	Base (eq.)	Solvent (mL)	Time (h)	Temperature (^oC)	Yield 3a (%) [b]
1	CuI	K_2CO_3	DMSO	24	110	20
2	CuCl	K_2CO_3	DMSO	24	110	30
3	Cu Powder	K_2CO_3	DMSO	24	110	26
4	CNP [c]	K_2CO_3	DMSO	24	110	23
5	$Cu(OTf)_2$	K_2CO_3	DMSO	24	110	Trace
6	CuCl	K_2CO_3	DMF	24	110	09
7	CuCl	K_2CO_3	Toluene	24	110	Trace
8	CuCl	K_2CO_3	THF[d]	24	110	08
9	CuCl	K_2CO_3	Water	24	110	Trace
10	CuCl	K_2CO_3	-	24	110	42
11	CuCl	K^tOBu	-	24	110	18
12	CuCl	$NaHCO_3$	-	24	110	Trace
13	CuCl	DABCO	-	24	110	Trace
14	CuCl	DBU	-	24	110	Trace
15	CuCl	Pyridine	-	24	110	25
16	CuCl	Piperidine	-	24	110	68
17	-	Piperidine	-	24	110	92
18	-	Piperidine	-	16	110	94
19	-	Piperidine	-	12	110	85
20	-	Piperidine	-	14	110	93
21	-	**Piperidine[e]**	-	**14**	**110**	**93**
22	-	Piperidine[f]	-	14	110	81
23	-	Piperidine[e]	-	14	120	91
24	-	Piperidine[e]	-	14	100	82

[a] A mixture of Cinnamic acid (1mmol), benzyl azide (1.5 mmol), catalyst (0.1 mmol), base (1.0 mmol) and solvent (2.0 mL) were heated. [b] Isolated yields. [c]CNP = CuO Nanoparticles. [d] Reaction was performed in sealed tube. [e] 0.5 equivalent of base. [f] 0.25 equivalent of base.

Having fixed the optimized condition, we applied it to various substrates (Scheme 2.2). Fixing the benzyl azide (**2a**), we varied many substituted cinnamic acids and the results are reported in scheme 2.2. As stated in the optimization table, 93 % of product (**3a**) was obtained with cinnamic acid (**1a**). When 4-chlorocinnamic acid was used, yield of the corresponding triazole**3b** was improved little more. In the case of bromo substitution, remarkable decline of yield of the triazole**3c** was observed. In the case of 3-bromocinnamic acid, yield of the product **3d** plummeted furthermore. When 2,4-dichloro cinnamic acid was employed, a big surge in the yield of the product was observed than monochloro substitution **3e**. On the other hand, electron donating substituents like methoxy group could achieve substantially good yield 81% of product **3f**. On the contrary, isopropyl group which is also an inductive electron donating group pronounceably reduces the efficiency as depicted by the slump of yield of **3g**. Other acrylic acids such as 3-(2-naphthyl) acrylic acid and 3-(2-furyl) acrylic acid also could not show the same potential of cinnamic acid (**1a**) which is evident from the yields of **3h, 3i** and **3a**. In continuation, various azides were examined with cinnamic acid (**1a**). 4-Methylbenzyl azide registers the highest yield of 99% whereas 4-methoxy benzyl azide could furnish only 89 % of the corresponding triazoles**3j** and **3k**. When aliphatic azides such as phenethylazide and*n*-octylazide were studied, phenethylazide managed to give substantially better efficiency than *n*-octylazide as depicted from the yields of **3l** and **3m.** In the case of phenyl azide , similar efficiency reminiscent of the octylazide was observed as the yields of **3m** and **3n** are very closer. When phenethylazide was subjected to react with 4-chloro, 4-bromo and 4- methoxycinnamic acids, chloro substitution let to a remarkably higher yield of the product **3o** while bromo and methoxy substitutions furnish similar yields of products **3p** and **3q**. Similarly, when 4-methylbenzyl azide was treated with different cinnamic acids such as 4-chloro,

3-bromo, and 4-methoxy cinnamic acids, better result was abserved in the case of 4-methoxycinnamic acid as testified from the yields of the corresponding triazoles**3r**, **3s** and **3t**. When octylazide was treated with 4-chloro cinnamic acid, 91% of the triazole**3u** was obtained. This is remarkably different from the yield of **3m.**

The structure of the triazole prepared by this method was unambiguously ascertained by single crystal XRD (Fig 2.3).

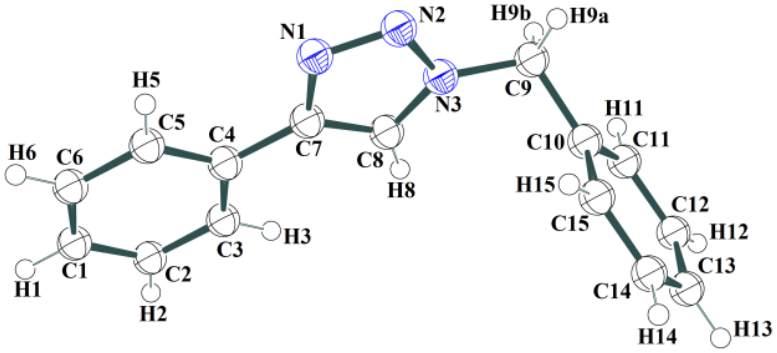
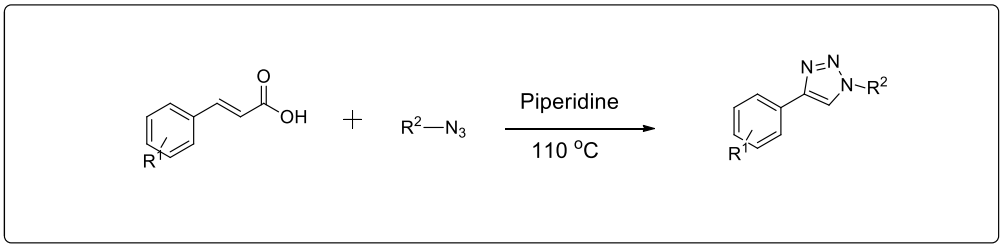
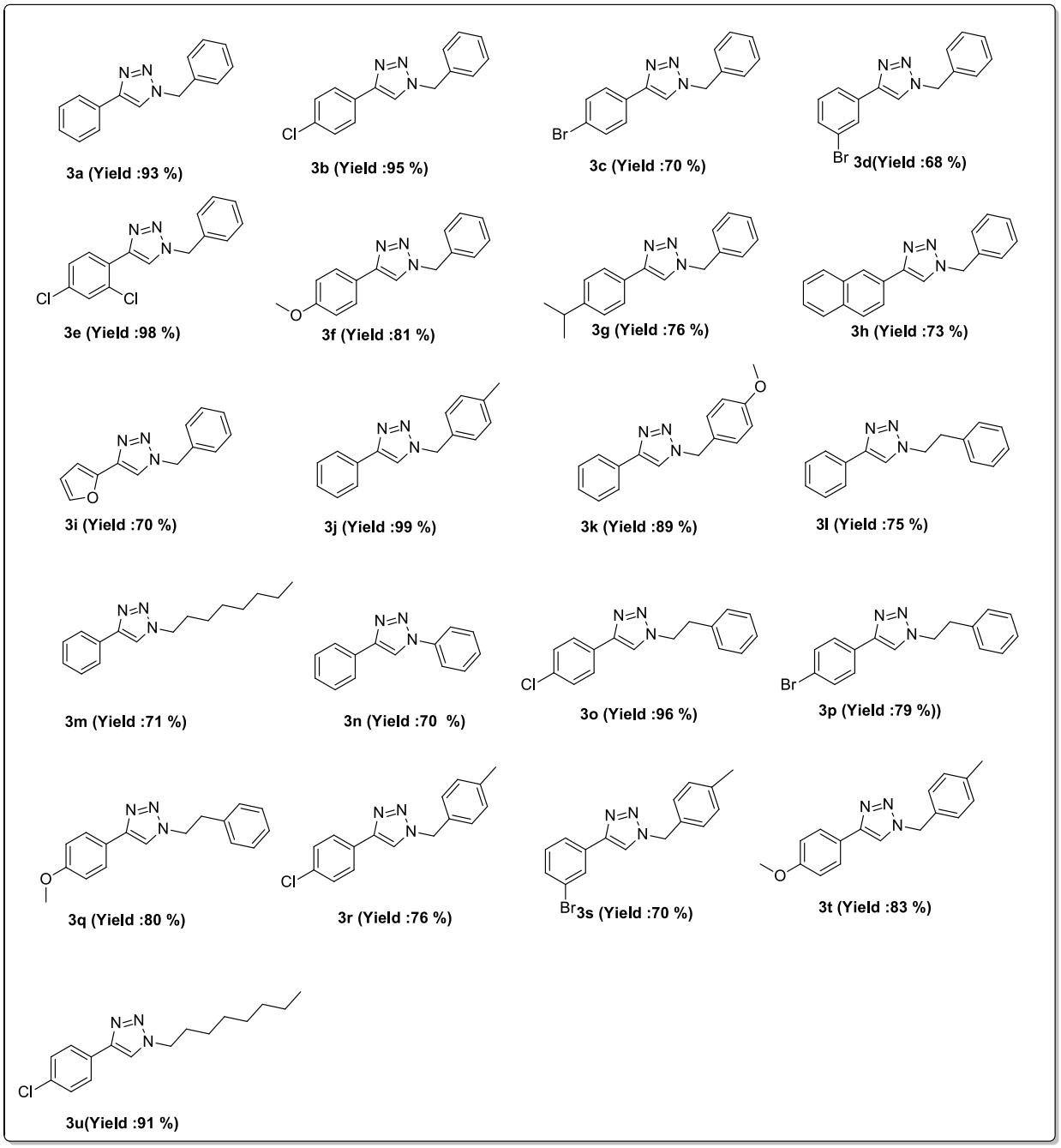


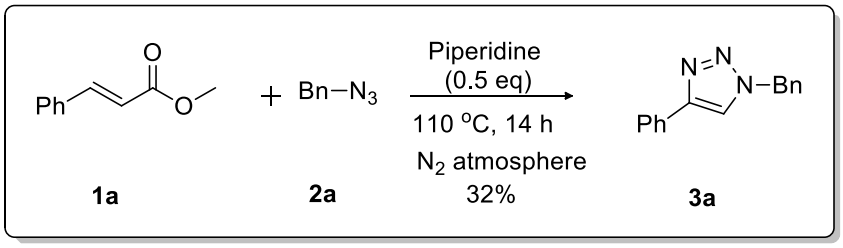
Figure 2.3 ORTEP diagram of 3a.



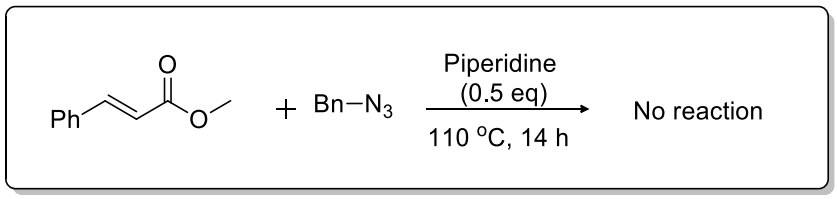


Scheme 2.2 Decarboxylative azide-alkene cycloaddition of cinnamic acids and organic azides.

In order to get the mechanistic insight, we performed the decarboxylative cycloaddition of (**1a)** with (**2a)** under nitrogen atmosphere. To our surprise only 32% of the triazole **3a** was observed which emphasizes the pivotal role of oxygen in this transformation (Scheme 2.3).



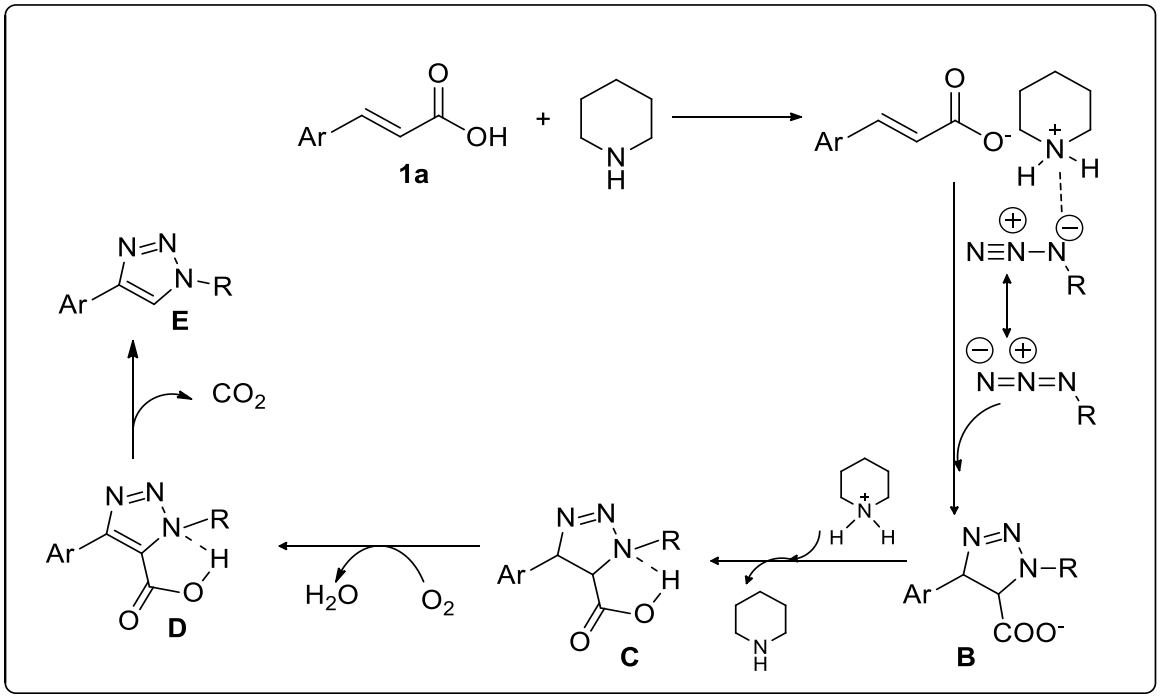
Scheme 2.3 Decarboxylative azide-alkene cycloaddition under nitrogen atmosphere.



Scheme 2.4 Decarboxylative azide-alkene cycloaddition on cinnamic ester.

No reaction took place when the reaction was performed on methyl cinnamate in the place of cinnamic acid (Scheme 2.4). Moreover, since only 0.5 equivalent of piperidine is used, it is inferred that the piperidine is consumed and regenerated in the course of the reaction. Another observation is, as soon as the reagents were added, heat was evolved which in indicates the neutralization reaction between the cinnamic acid and piperidine. From these above observations, we propose the following mechanism (Scheme 2.5). The azide alkene cycloaddition takes place on the carboxylate ion formed from the acid-base neutralization reaction and furnishes the triazoline **B**. Protonation on the carboxylate ion of **B** by the piperidinium ion leads to the triazoline **C**. We presume that the intramolecular hydrogen bonding between the carboxylic acid and the nitrogen of **C** is responsible for the regioselectivity of this cycloaddition. This

idea was corroborated by the reaction of methyl cinnamate with benzylazide (Scheme 2.4). In continuation, the concomitant oxidation and decarboxylation leads to the required 1,2,3-triazole **E**.



Scheme 2.5 Proposed mechanism for the decarboxylative azide-alkene cycloaddition.

2.3 Conclusion

A novel method was developed to achieve a collection of 1,4-disubstituted 1,2,3-triazoles from decarboxylative azide-alkene cycloaddition of substituted cinnamic acids and organic azides. This method assures the complementary regioselectivity to the preceding method. Metal- free condition and easy accessibility of the starting materials are also the salient attributes of this protocol.

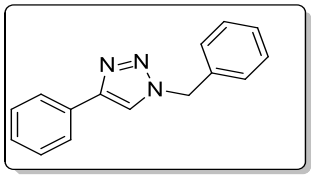
2.4 Experimental Section

All basic chemicals and solvents were purchased from Avra Synthesis private Ltd. and Sigma-Aldrich private Ltd. Analytical TLC was carried out using plastic sheets precoated with silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) and compounds were visualized by irradiation with UV light and/or by treatment with iodine. Column chromatography was performed with silica gel (230-400 mesh, Avra, India) using n-hexane: EtOAc mixture. All melting points were measured in GUNA instrument using open capillaries and are uncorrected. NMR spectra (^{1}H and ^{13}C NMR) spectra were obtained in BRUKER spectrometer (500 MHz for proton and 125 MHz for carbon). Proton chemical shifts (δ) are relative to internal standard TMS (δ = 0.00) and presented in parts per million (ppm). Coupling constants (*J*) are given in hertz (Hz) and spin-spin splitting were given as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). HRMS were recorded on a BrukermicroTOF-QII (ESI) spectrometer.

2.4.1 General Procedure for the Synthesis of 1,4-disubstituted-1,2,3-triazole

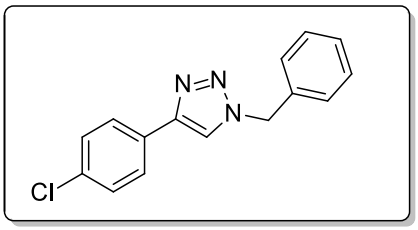
A mixture of Cinnamic acid (1.0 mmol), organic azides (1.5 mmol), piperidine (0.5 mmol) were heated at 110 °C for 14h. Completion of the reaction was monitored by TLC and the reaction mixture was cooled to room temperature and purified by column chromatography.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole(3a) [1,3]



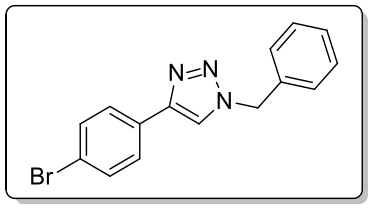
White solid; **M.p**.:126-128 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.80 (d, *J* = 8.5 Hz, 2H), 7.66 (s, 1H), 7.41-7.37 (m, 5H), 7.33-7.29 (m, 3H), 5.57 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 148.3, 134.7, 130.5, 129.2, 128.82, 128.81, 128.2, 128.1, 125.7, 119.5, 54.3.

1-Benzyl-4-(4-chlorophenyl)-1*H*-1,2,3-triazole(3b) [1,3]



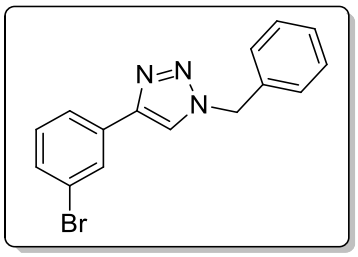
Pale brown solid; **M.p**.: 138-140 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* =8.5 Hz, 2H), 7.65 (s, 1H), 7.40-7.34 (m, 5H), 7.32-7.30 (m, 2H), 5.56 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.2, 134.5, 133.9, 129.2, 129.0, 128.9, 128.8, 128.1, 126.9, 119.6, 54.3.

1-Benzyl-4-(4-bromophenyl)-1*H*-1,2,3-triazole(3c) [1]



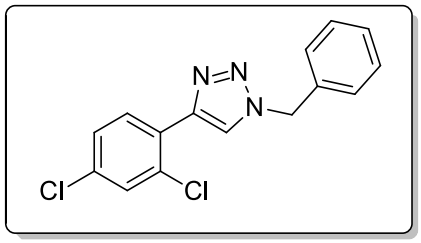
Pale brown solid; **M.p**.: 142-143 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.74-7.65 (m, 3H), 7.41-7.35 (*m*, 4H), 7.32-7.30 (*m*, 2H), 5.57 (*s*, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.2, 134.5, 131.9, 129.2, 129.0, 128.9, 128.1, 127.2, 126.9, 119.6, 54.3.

1-Benzyl-4-(3-bromophenyl)-1*H*-1,2,3-triazole(3d) [3]



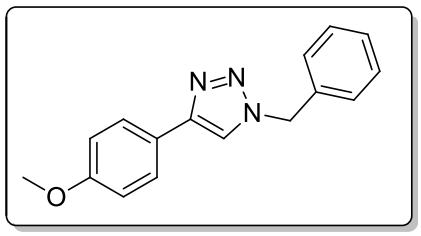
Pale brown solid; **M.p**.: 166-168 ^{o}C;**^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.94(t, *J* = 1.5 Hz, 1H), 7.73 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.69 (s, 1H), 7.44-7.37(m,4H),7.32-7.29 (m, 2H), 7.26 (dd, *J* = 8.0, 6.0 Hz, 1H),5.57(s,2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 146.8, 134.5, 132.6, 131.1, 13.4, 129.3, 128.9, 128.6, 128.2, 124.2, 122.9, 119.9, 54.4.

1-Benzyl-4-(2,4-dichlorophenyl)-1*H*-1,2,3-triazole(3e) [3]



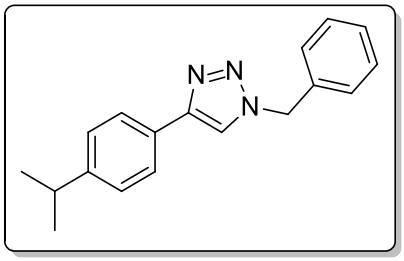
Pale brown solid; **M.p.:**137-138^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.21 (d, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 7.44-7.26 (m, 7H),5.61 (s, 2H); **^{13}C NMR** (125MHz, $CDCl_3$): δ (ppm) 143.6, 134.5, 134.2, 131.6, 130.6, 129.9, 129.2, 128.9, 127.9, 127.9, 127.6, 123.1, 54.3.

1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole(3f) [1]



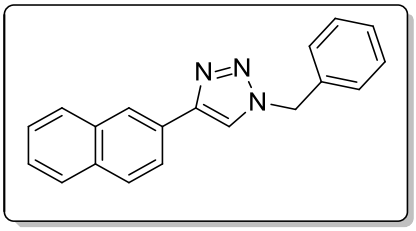
Light yellow solid; **M.p**.: 134-135 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J* = 9.0 Hz,2H), 7.59 (s, 1H), 7.38-7.34 (m,3H), 7.29-7.26 (m,2H), 6.92 (d, *J* = 9.0 Hz,2H),5.54 (s,2H),3.81(s,3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 159.6, 148.1, 134.8, 129.1, 128.7, 128.1, 127.0, 123.3, 118.8, 114. 2, 55.4, 54.1.

1-Benzyl-4-(4-isopropylphenyl)-1*H*-1,2,3-triazole(3g)



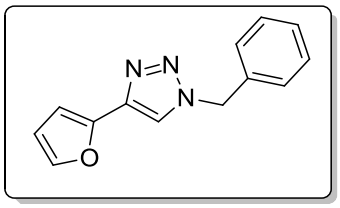
Light yellow solid; **M.p**.: 95-98 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 8.0 Hz,2H), 7.62 (s, 1H), 7.39-7.35 (m,3H), 7.30-7.25 (m, 4H), 5.57 (s, 2H), 2.94-2.89 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 149.1, 148.3, 134.8, 129.2, 128.8, 128.1, 128.0, 126.9, 125.7, 119.2, 54.2, 33.9, 23.9; **HRMS(ESI)**: *m/z* calcd. for $C_{18}H_{19}N_3$ $(M+H)^+$:278.1656, found:278.1579.

1-Benzyl-4-(naphthalen-2-yl)-1*H*-1,2,3-triazole(3h) [1,3]



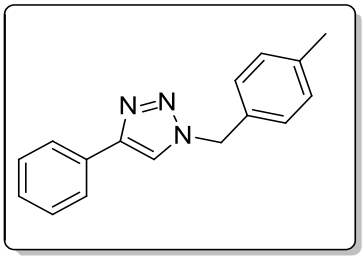
White solid; **M.p**.: 176-178 ^{0}C;**^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.31 (d, *J* = 4.5 Hz, 1H), 7.91-7.81 (m,5H), 7.50-7.44 (m, 2H), 7.42- 7.33 (m, 5H), 5.61 (d, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 148.1, 134.7, 133.4, 133.0, 129.1, 128.7, 128.5, 128.1, 128.0, 127.9, 127.7, 126.4, 126.1, 124.3, 123.8, 119.9, 54.2.

1-Benzyl-4-(furan-2-yl)-1*H*-1,2,3-triazole(3i)



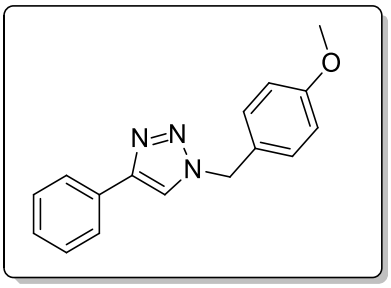
White solid; **M.p.:** 80-82 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.62 (s, 1H), 7.41-7.37 (m, 4H), 7.30 (d, *J* = 6.5 Hz, 1H),6.82 (s, 1H), 6.47 (d, *J* = 1.0 Hz, 1H), 5.57 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 146.2, 142.0, 140.9, 134.4, 129.2, 128.9, 128.1, 119.1, 111.5, 106.6, 54.3. **HRMS(ESI):***m/z* calcd. for $C_{13}H_{11}N_3O$ (M^+): 225.0569, found: 225.0902.

1-(4-Methylbenzyl)-4-phenyl- 1*H*-1,2,3-triazole (3j) [1]



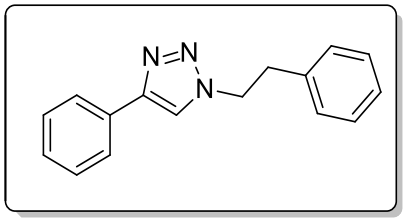
Pale yellow solid; **M.p**.:88-90 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.78 (d, *J* = 8.0 Hz, 2H), 7.64 (s, 1H), 7.38 (t, *J* = 7.5 Hz,2H), 7.29 (t, *J* = 8.0 Hz, 1H),7.21-7.17 (m, 4H), 5.51 (s, 2H), 2.35 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 148.2, 138.8, 131.2, 130.6, 129.8, 128.8, 128.2, 125.7, 119.5, 119.5, 54.1, 21.2.

1-(4-Methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole(3k) [1]



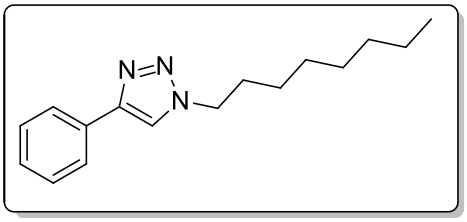
Light white solid; **M.p**.:136-138^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.78 (d, *J* = 7.5 Hz, 2H), 7.62 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32-7.26 (m, 3H), 6.91 (d, *J* = 7.0 Hz, 2H),5.50 (s, 2H),3.81 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 159.9, 148.1, 130.6, 129.7, 128.8, 128.1, 126.6, 125.7, 119.3, 114.5, 55.4, 53.8.

1-Phenethyl-4-phenyl - 1*H*-1,2,3-triazole(3l) [1]



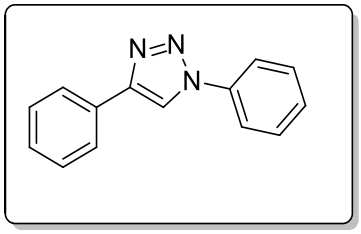
Yellow solid; **M.p**.:136-138 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 7.0 Hz, 2H), 7.47 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33-7.25 (m, 4H), 7.12 (d, *J* = 7.0 Hz, 2H), 4.61 (t, *J* = 7.0 Hz, 2H), 3.24 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.5, 137.1, 130.7, 128.9, 128.8, 128.7, 128.1, 127.2, 125.7, 120.0, 51.8, 36.8.

1-Octyl-4-phenyl-1*H*-1,2,3-triazole(3m) [3]



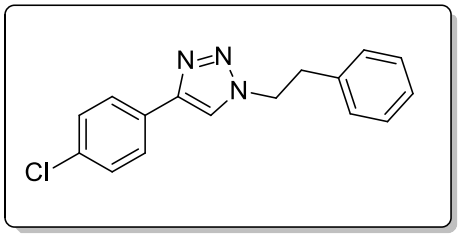
White solid; **M.p.**: 77-78 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.84 (d, *J* = 7.0 Hz, 2H), 7.75 (s, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 1H),4.39 (t, *J* = 7.5 Hz, 2H), 1.95-192 (m, 2H),1.34-1.23 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.7, 130.7, 128.8, 128.1, 125.7, 119.4, 50.5, 31.7, 30.4, 29.1, 29.0, 26.5, 22.6, 14.1.

1,4-Diphenyl - 1*H*-1,2,3-triazole(3n) [1]



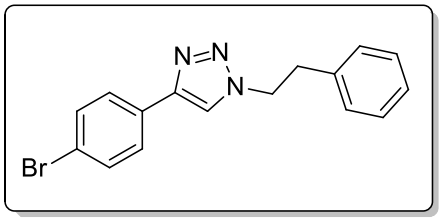
White solid; **M.p.**:180-182^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.20 (s, 1H), 7.92 (d, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.0 Hz, 2H), 7.48-7.45 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 148.4, 137.1, 130.3, 129.8, 128.9, 128.8, 128.5, 125.9, 120.6, 117.6.

4-(4-Chlorophenyl)-1-phenethyl- 1*H*-1,2,3-triazole(3o)



Light yellow solid; **M.p.**: 102-104 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 7.5 Hz, 2H), 7.47 (s, 1H), 7.40-7.24 (m, 5H), 7.11 (d, *J* = 7.0 Hz, 2H), 4.59 (t, *J* = 7.5 Hz, 2H),3.22 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.5, 137.1, 130.7, 128.9, 128.8, 128.7, 127.2, 127.1, 126.9, 125.7, 120.0, 51.7, 36.8; **HRMS(ESI)**: *m/z* calcd. for $C_{16}H_{14}ClN_3$ $(M+H)^+$: 284.0677, found: 284.0876.

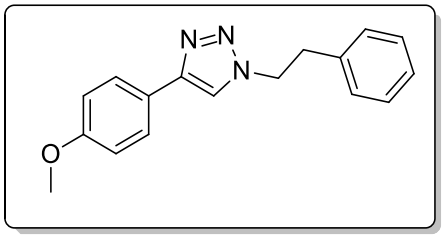
4-(4-Bromophenyl)-1-phenethyl-1*H*-1,2,3-triazole(3p) [6]



Brown solid; **M.p.**: 153-154 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 7.5 Hz, 2H), 7.47 (s , 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32-7.23 (m, 3H), 7.12 (d, *J* =

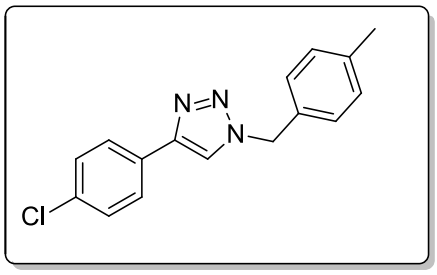
7.0 Hz, 2H), 4.61 (t, *J* = 7.5 Hz, 2H), 3.23 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.5, 137.1, 130.7, 128.9, 128.8, 128.7, 128.1, 127.2, 125.7, 120.0, 51.8, 36.8.

4-(4-Methoxyphenyl)-1-phenethyl-1*H*-1,2,3-triazole(3q)[1]



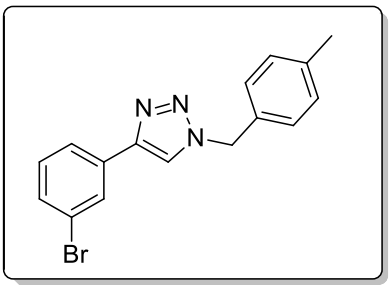
White solid; **M.p.**:138-140^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.69 (d, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 7.31-7.25 (m, 3H), 7.13 (d, *J* = 7.0 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 2H), 4.60 (t, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 3.23 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 159.5, 147.4, 137.1, 128.9, 128.8, 127.1,127.0, 123.4, 119.2, 114.2, 55.3, 51.7, 36.8.

4-(4-Chlorophenyl)-1-methylbenzyl-*H*-1,2,3-triazole(3r)



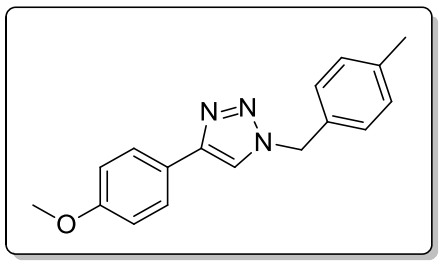
Yellow solid; **M.p.**:138-140 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 7.0 Hz, 2H), 7.62 (s, 1H), 7.36 (d, *J* = 7.0 Hz, 2H), 7.22-7.18 (m, 4H), 5.52 (s, 2H), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 147.1, 138.9, 133.8, 131.5, 129.9, 129.1, 129.0, 128.2, 126.9, 119.5, 54.1, 21.2; **HRMS(ESI)**: *m/z* calcd. for $C_{16}H_{14}ClN_3$ $(M+H)^+$: 284.0941, found :284.0876.

4-(3-Bromophenyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole(3s)



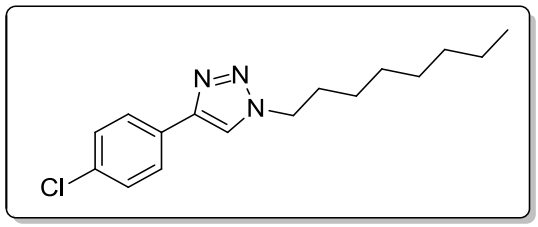
Brown solid; **M.p.**:108-109 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.72 (t, *J* = 2.0 Hz, 1H), 7.68 (dt, *J* = 7.0, 1.5, Hz, 1H), 7.64 (s,1H), 7.32 (t, *J* = 7.0 Hz,1H), 7.28-7.25 (m, 1H),7.22-7.18 (m, 4H), 5.52 (s, 2H), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 146.9, 138.9, 134.8, 132.4, 131.4, 130.1, 129.9, 128.2, 128.1, 125.7, 123.8, 119.8, 54.2, 21.2; **HRMS(ESI)**: *m/z* calcd. for $C_{16}H_{14}BrN_3$ $(M+H)^+$: 328.0184, found :328.0371.

4-(4-Methoxyphenyl)-1-4-methylbenzyl-1*H*-1,2,3-triazole(3t) [5]



Pale Yellow solid; **M.p.**:145-147 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J* = 7.0 Hz, 2H), 7.55 (s, 1H), 7.21-7.19 (m, 4H), 6.92 (d, *J* = 7.0 Hz, 2H), 5.51 (s, 2H), 3.82 (s, 3H), 2.35(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 159.6, 148.0, 138.7, 131.7, 129.8, 128.1, 126.9, 123.3, 118.6, 114.2, 55.4, 54.0, 21.2.

4-(4-Chlorophenyl)-1-octyl-1*H*-1,2,3-triazole(3u) [4]



Light Yellow solid; **M.p**.:79-81 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 8.5 Hz,2H), 7.74 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.39 (t, *J* = 7.0 Hz, 2H), 1.95-1.92 (m, 2H), 1.34-1.26 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 146.7, 133.8, 129.3, 129.0, 126.9, 119.5, 50.5, 31.7, 30.4, 29.1, 28.9, 26.5, 22.6, 14.1.

2.5 References

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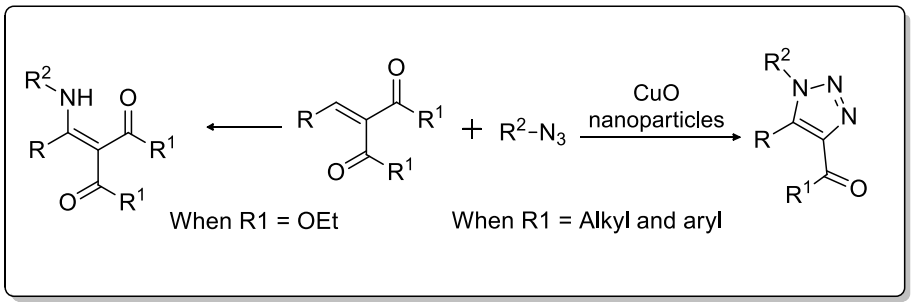
3. A tunable synthesis of 1,2,3-triazoles and enamines from azide-alkene cycloaddition

3.1 Introduction

This Chapter explains the tunablesynthesis of 1,4,5-trisubstituted 1,2,3-triazoles and enamines through [3+2] cycloaddition of activated olefins and organic azides. Triazoles were achieved from benzylidenediketones and organic azides by copper oxide nanoparticle catalysis while enamines were synthesized from benzylidenemalonates and organic azides under solvent-free and catalyst-free condition (scheme 3.1).



Scheme 3.1 Azide-alkene cycloaddition furnishing triazoles and enamines.

3.2 Results and Discussion

3.2.1 Synthesisof 1,4,5-trisubstituted 1,2,3-triazole from azide-alkene cycloaddition

At the outset, we started our investigation with the reaction of 1.0 mmol of 3-benzylidenepentane-2,4-dione (**1a**) and 1.5 mmol of benzyl azide (**2a**) in the presence of 0.1 mmol of CuO nanoparticles in 1.0 mL of DMF at 110^{o}C for 24 hours (Table 3.1). We were prompted to use CuO nanoparticles due to its heterogeneity, catalytic activity [1] and our precedent report using that catalyst[2-3]. To our excitement, we obtained the triazole (**3a**) in 38% yield (Table 3.1, entry 1). Initially the product was confirmed by melting point, and its compared with the liturature value (48-50^{o}C). The product was characterized by ^{1}H NMR and ^{13}C NMR. In ^{1}H NMR (figure 3.1). The compound exhibited a singlet at δ 2.68ppm integrating for three protons corresponds to the

ethanone protons. Another characteristic peak at δ 5.41ppm denotes the benzylic proton. The aromatic protons give the signal at 7.48-7.01ppm. The ^{13}C NMR spectrum (figure 3.2) shows totally 13 signals. Here the signal at 51.9 ppm indicates the benzylic carbon, signals from 126.0 ppm to 143.8 ppm indicate the aromatic carbons, 192.7ppm denote the carbonyl carbon and 28.0ppm represents the ethanone carbon.

When the reaction was repeated replacing CuO nanoparticle by Cu Nano powder, the yield of **3a** dwindled to 22% (Table 3.1, entry 2). On the contrary, copper powder proved to be profoundly ineffective since trace amount of **3a** only was obtained (Table 3.1, entry 3). Cu(I) salts such as CuI and CuCl also failed to make a pronounceable change in the efficacy of the reaction (Table 3.1, entry 4 and 5). Similarly, no product formation was detected when $CuSO_4.5H_2O$ was utilized (Table 3.1, entry 6). To our surprise, bulk CuO also stood ineffective since trace amount of product only was observed (Table 3.1, entry 7). In order to improve the yield, we attempted solvent variation fixing CNP as the catalyst. When the solvents such as DMSO, EtOH, MeOH, water, toluene and ethyl acetate were examined, ethanol could excel as the better one since it furnishes 23% yield of **3a** and ethyl acetate stood next to that giving 15% yield of **3a** (Table 3.1, entry 8 -13).

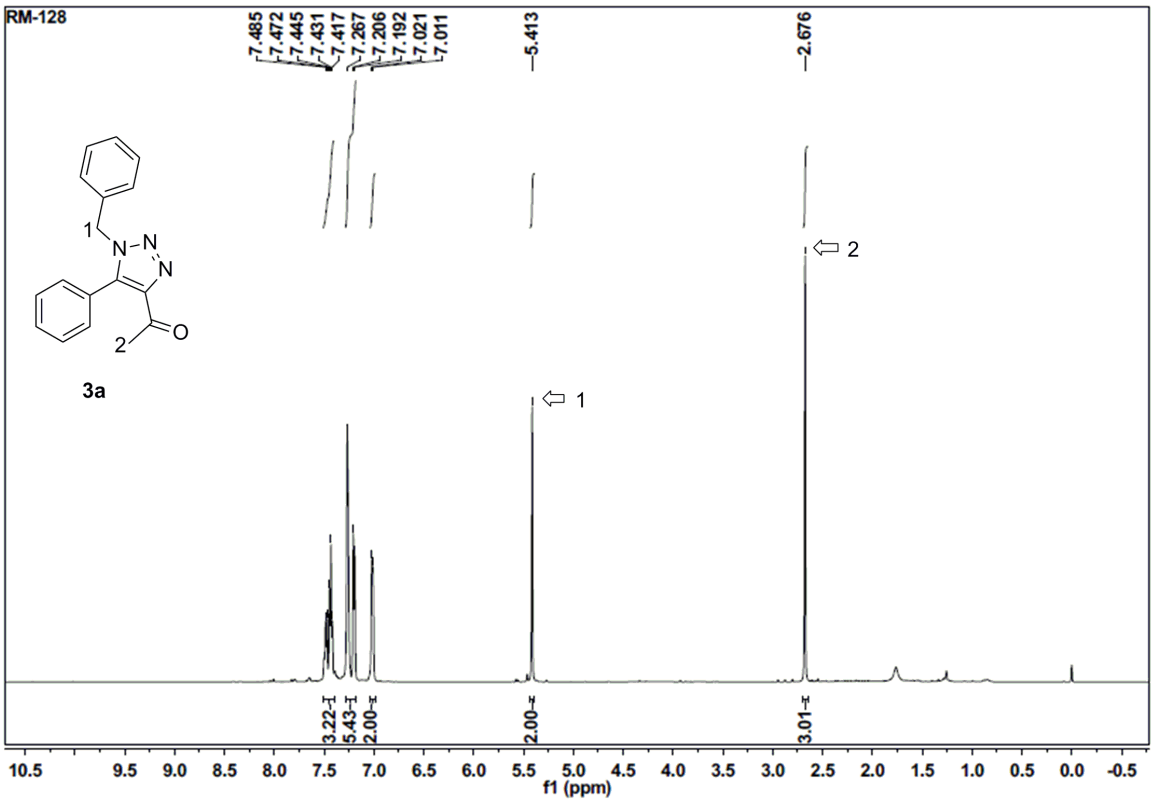


Figure 3.1 ^{1}HNMR of 1-(1-benzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone (3a) in $CDCl_3$

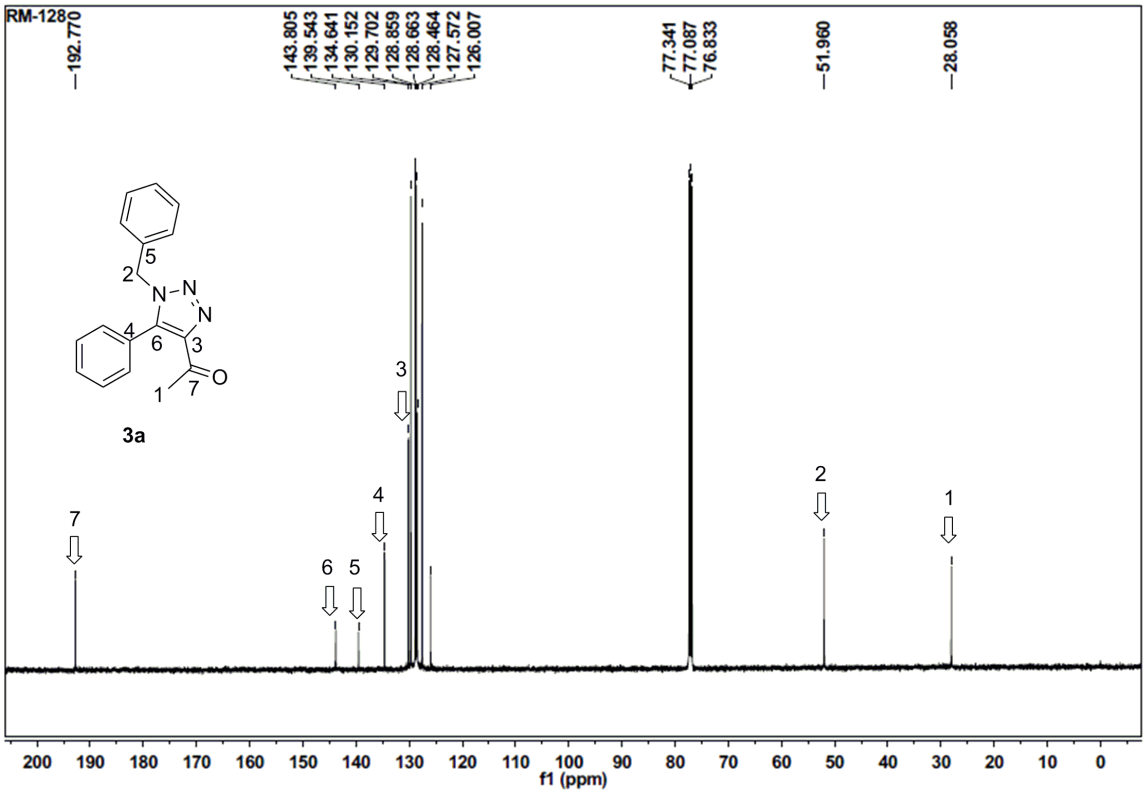
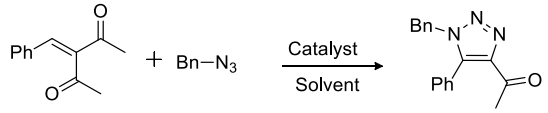


Figure 3.2 ^{13}C NMR of 1-(1-benzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone (3a) in $CDCl_3$

Eventually, it was disappointing that no product was obtained even at neat condition (Table 3.1, entry 14). Since DMF and CuO nanoparticles were proved to be the best among all the solvents and catalysts employed for this transformation, we changed the other conditions and monitored the outcome. While reducing the time duration of the reaction to 22 and 20h, we resolved to fix 22h as the duration for this reaction as the yield of **3a** was slightly higher than the other one (Table 3.1, entry 15 and 16). When the quantity of the catalyst was gradually increased from 0.1 mmol to 0.4 mmol, we decided to use 0.3 mmol of catalyst for this transformation as we inferred from the yields of **3a** (Table 3.1, entry 17 - 19).When the reaction time was increased to 48h, no significant difference was noticed in the yield (Table 3.1, entry 20). On the other hand, yield of **3a** dropped drastically to 32% when the duration of the reaction was shortened to 12h (Table 3.1, entry 21). No pronounceable difference in the yield was observed when the reaction was performed at 150^{o}C and 120^{o}C (Table 3.1, entry 22 – 23). But the yield of **3a** was reduced to 63% and 62% when the temperature of the reaction was reduced to 100^{o}C and 80^{o}C (Table 3.1, entry 24 -25). Hence, we resolved to carry out the reaction at 110^{o}C for 22h with 0.3 mmol of CNP (Table 3.1, entry 18). Having the condition optimized (Table 3.1, entry 18), we extended that condition to various olefins and azides as shown in scheme 3.2. Initially deacylativeazide-alkene cycloaddition was performed on benzyl azide (**2a**) with various benzylidenediketones.

Table 3.1 Optimization of deacylative azide-alkene cycloaddition[a]



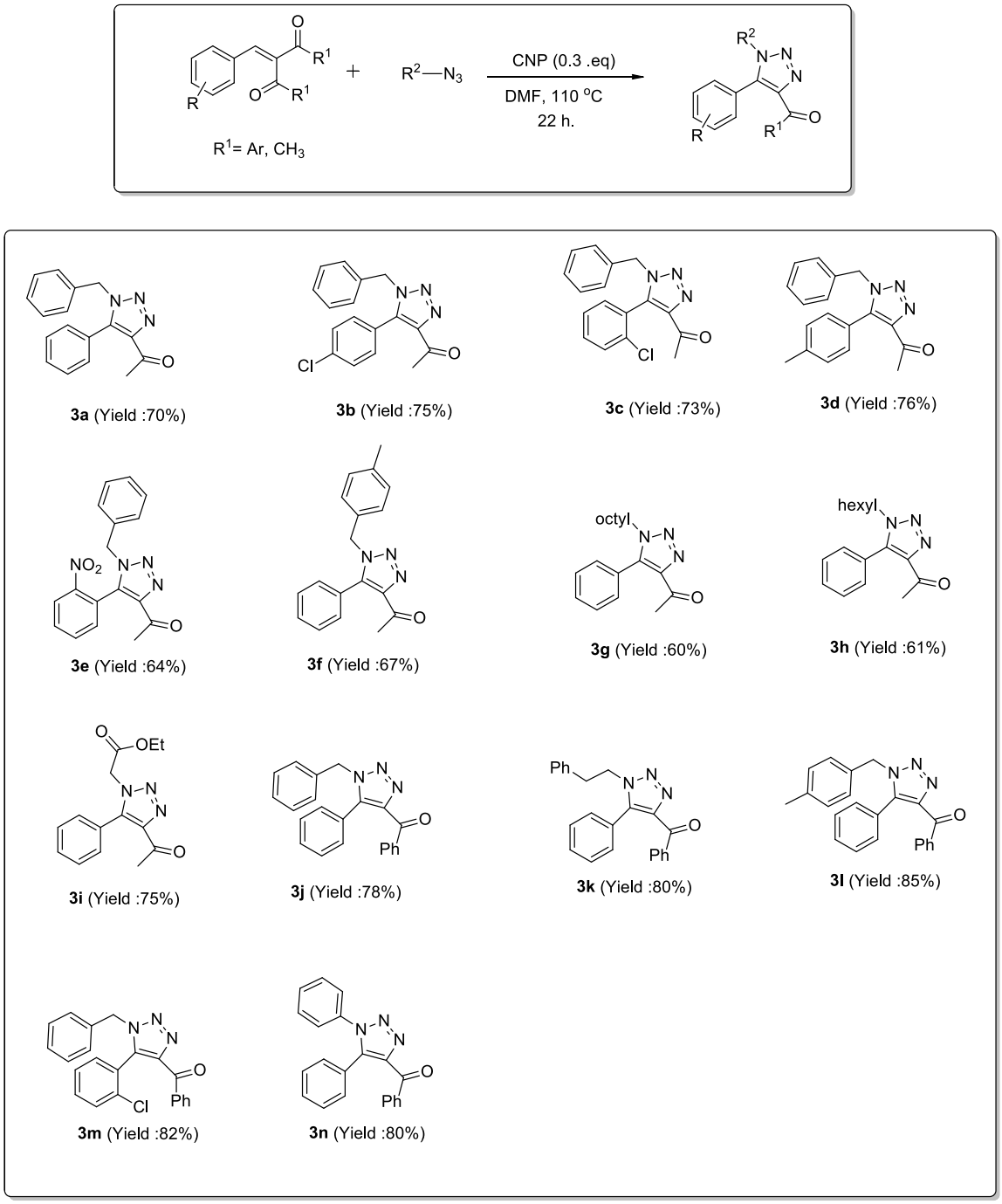
1a 2a 3a

Entry	Catalyst(eq.)	Solvent (ml)	Time(h)	Yield[b] (%) (3a)
1[c]	CNP (0.1)	DMF	24	38
2[c]	Cu* (0.1)	DMF	24	22
3[c]	Cu** (0.1)	DMF	24	Trace
4	CuI (0.1)	DMF	24	5
5	CuCl (0.1)	DMF	24	Trace
6	$CuSO_4.5H_2O$ (0.1)	DMF	24	-
7	CuO Bulk	DMF	24	Trace
8	CNP (0.1)	DMSO	24	-
9	CNP (0.1)	EtOH	24	23
10	CNP (0.1)	MeOH	24	Trace
11	CNP (0.1)	Water	24	-
12	CNP (0.1)	Toluene	24	-
13	CNP (0.1)	EtOAc	24	15
14	CNP (0.1)	Neat	24	-
15	CNP (0.1)	DMF	22	36
16	CNP (0.1)	DMF	20	30
17	CNP (0.2)	DMF	22	53
18	**CNP (0.3)**	**DMF**	**22**	**70**
19	CNP (0.4)	DMF	22	71
20	CNP (0.3)	DMF	48	72
21	CNP (0.3)	DMF	12	32
22[d]	CNP (0.3)	DMF	22	71
23[e]	CNP (0.3)	DMF	22	70
24[f]	CNP (0.3)	DMF	22	63
25[g]	CNP (0.3)	DMF	22	62

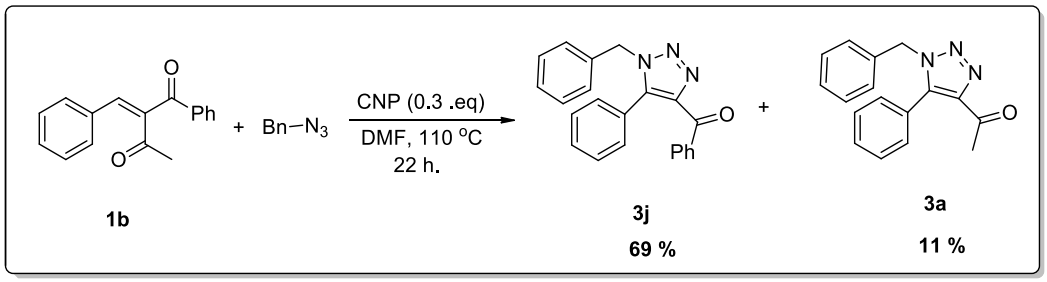
[a] Reaction condition: A mixture of olefin (1.0 mmol), azide (1.5 mmol) and catalyst were stirred in 1.0 mL of solvent for 110°C.[b] Isolated yields. [c] CNP = CuO Nanoparticle; Cu* = Cu Nano powder; Cu**= Cu powder. [d] Reaction was carried out at 150°C. [e] Reaction was carried out at 120°C. [f] Reaction was carried out at 100°C. [g] Reaction was carried out at 80°C.

As stated in the optimization table, diacetylbenzylidene (**1a**) gives 70% yield of 1,2,3-triazoles (Scheme 3.2, compound **3a**). 4-Chloro substitution in the olefin increases the yield of the product **3b** into 75%. While 2-chloro substitution slightly reduces the yield of **3c** to 73%. On the other hand, 4-methyl substitution increases the yield of **3d** to 76%. To our anticipation, electron withdrawing nitro group at the second position, significantly reduces the yield of the triazole**3e**. It is noteworthy that no deacylativeazide-alkene cycloadditon takes place when the alkyl substituted alkene-dione such as 3-propylidenepentane-2,4-dione was treated with benzyl azide. Moreover, decomposition of the starting material was detected. Subsequently, azide variation was examined on the olefin **1a**. 4-Methyl benzyl azide on reaction with **1a** furnished substantially good yield of the product **3f**. Aliphatic azides such as *n*-octylazide and *n*-hexyl azide displayed same efficiency as shown from the yields of the products **3g** and **3h**. On the other hand, when ethyl 2-azidoacetate was used, the yield of **3i** was substantially improved than **3g** and **3h**. In the place of **1a**, 2-benzylidene-1,3-diphenylpropane-1,3-dione was used against different azides and monitored the outcome.

With benzyl azide (**2a**) 78% of triazole**3j** was obtained whose yield is comparatively higher than that of **3a**. Better results were obtained in the case of phenethylazide and 4-methyl benzyl azides as inferred from the yields of **3k** and **3l**. 2-Chloro substitution on the olefin also furnished good amount of triazole**3m** with benzyl azide (**2a**). Similarly, the reaction with phenyl azide also furnished the corresponding triazole (**3n**) in good yield. When the same reaction was performed with alkene bearing unsymmetrical diketone (**1b**), acetyl group was predominantly eliminated instead of benzoyl group (Scheme 3.3).

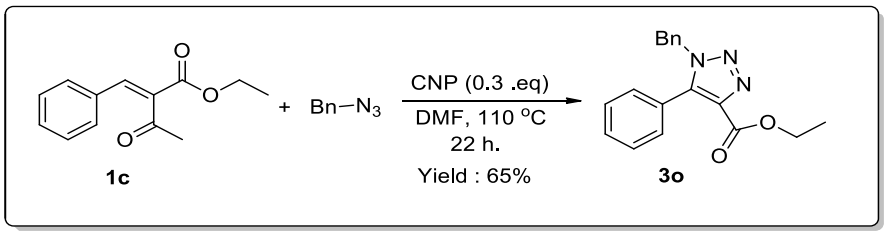


Scheme 3.2 Deacylative azide-alkene cycloaddition of benzylidene diketones and organic azides.



Scheme 3.3 Deacylative azide-alkene cycloaddition of benzylidene bearing unsymmetrical diketone and organic azides.

Similarly, in the case of the alkene connected with ester and ketone (**1c**), acetyl group was eliminated while ester group was remaining intact (Scheme 3.4).



Scheme 3.4 Deacylative azide-alkene cycloaddition of benzylidene bearing ester and ketone with organic azides.

In order to study the recyclability of the heterogeneous CuO nanoparticles, it was recovered after each cycle from the reaction mixture by simple centrifugation followed by washing with ethyl acetate and drying in vacuo (Table 3.2).

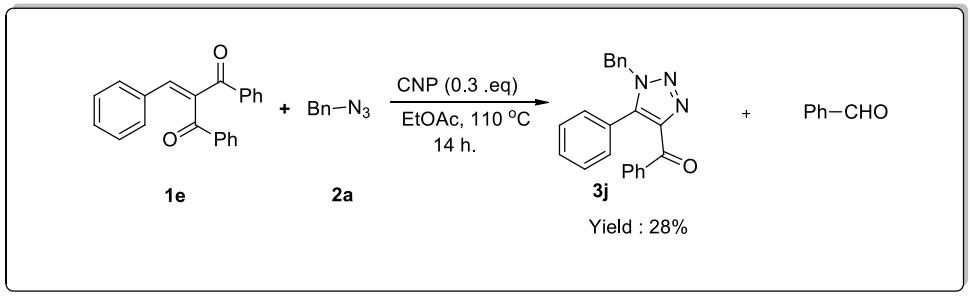
Table 3.2 Recycling of CuO nanoparticles

Entry	Catalyst recovery (%)	Cycle	Yield[c] (%)
1[a]	93	1	70
2[b]	87	2	66
3[b]	83	3	60
4[b]	75	4	56

[a]Reaction condition: **1a** (4.0 mmol), **2a** (6.0 mmol) and CuO nanoparticles (1.2 mmol) were heated at 110 ^{0}C for 22h. [b]Recovery of catalyst was done under the same reaction conditions to those of the initial run. [c]All are isolated yields.

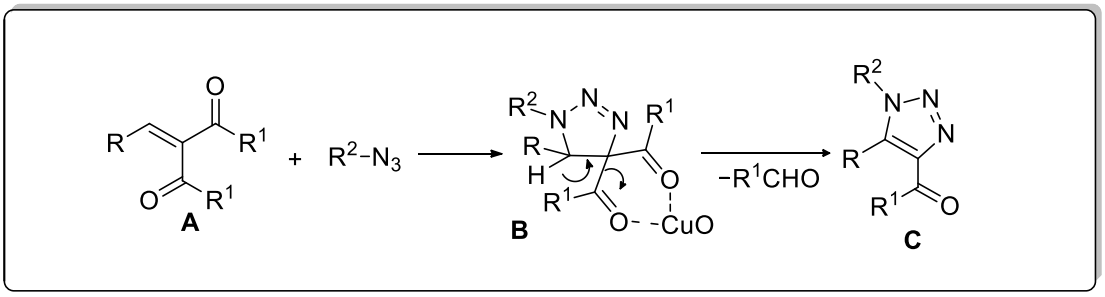
3.2.2 Proposed mechanism

In order to investigate the mechanistic pathway of this transformation, we recorded the ^{1}H NMR of the crude reaction mixture of deacylativeazide-alkene cycloaddition performed between **1e** and **2a** (scheme 3.5). The singlet at 9.92 ppm confirms the formation of benzaldehyde in this reaction (figure 3.3). Hence we were prompted to propose the mechanism as stated in scheme 3.6.



Scheme 3.5 Deacylative azide-olefin cycloaddition.

The triazoline formed from the azide-alkene cycloaddition forms a six membered cyclic transition state **B.** Concomitant elimination of aldehyde furnishes the required triazole **C** (Scheme 3.6). We presume that the difference in the electrophilicity of the carbonyl groups is responsible for the selectivity when unsymmetrical carbonyl compounds such as **1b** and **1c** are used (scheme 3.3 and scheme 3.4).



Scheme 3.6The proposed mechanism for the deacylative azide-olefin cycloaddition

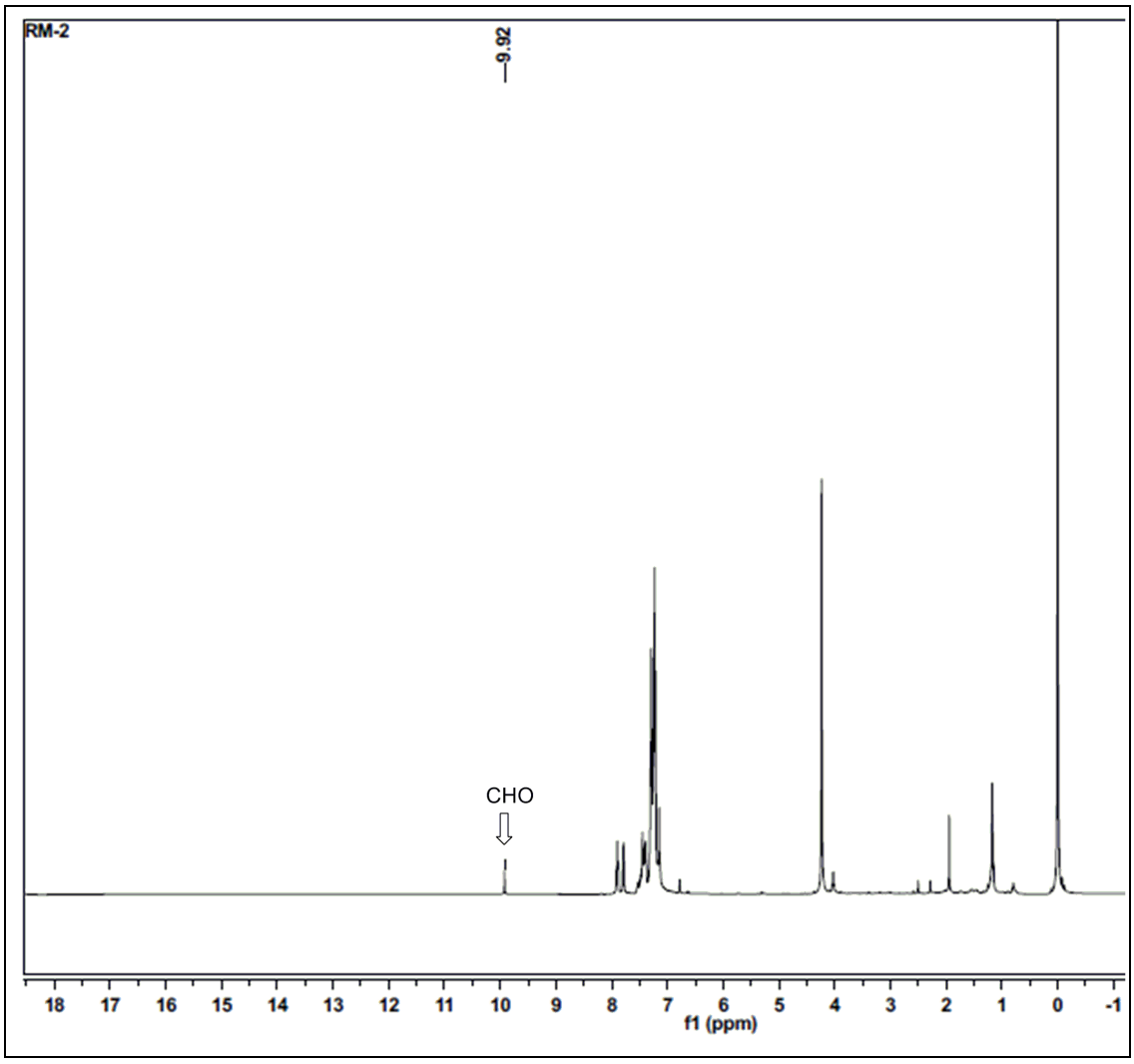
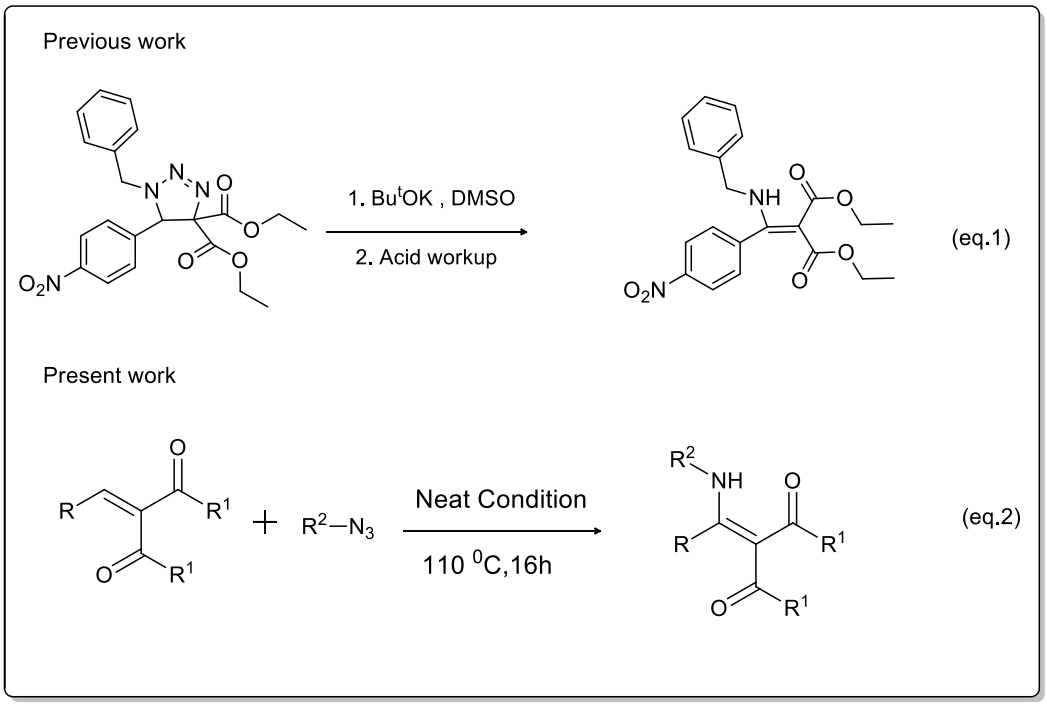


Figure 3.3 ^{1}H NMR spectrum of crude mixture compound 3j in $CDCl_3$.

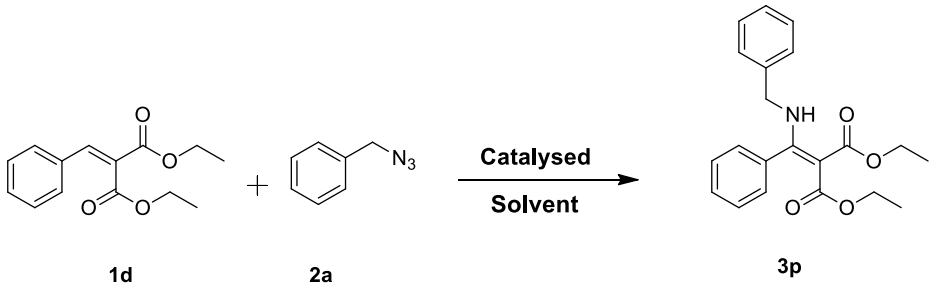
3.2.3 Synthesis of enamine from azide-alkene cycloaddition

Similarly, when deacylativeazide-alkene cycloaddition was attempted in diethyl benzylidenemalonate**(1d)**, enamine **(3p)** was obtained. Our literature perusal revealed that Prager*et al*. have reported a two-stage synthesis of enamine in which the triazoline prepared from diethyl benzylidenemalonate and benzyl azide was treated with potassium tertiary butoxide followed by trifluoro acetic acid to achieve the diethyl benzyl amino benzylidenemalonate. In spite of the usage of vigorous condition in this method, the enamine was obtained in poor yield along with 1,2,3-triazole (scheme 3.7, eq.1) [4]. After meticulous optimization on this reaction, a collection of enamines was accomplished in excellent yields by stirring olefin (1.0mmol) and azide (2.5 mmol) at 110^0C for 16 h at neat condition (scheme 3.7, eq.2).



Scheme 3.7 Azide-alkene cycloaddition on benzylidene diester.

Table 3.3 Optimization of the synthesis of enamine. [a]



1d 2a 3p

Entry	Catalyst (eq.)	Solvent (1.0 ml)	Time(h)	Temperature (^{0}C)	Yield (%)[b]
1	CuO NPS (0.3 eq)	DMF	14	90	30
2	-	DMF	14	90	32
3	-	DMSO	14	90	07
4	-	Water	14	90	52
5	-	Toluene	14	90	21
6	-	Acetonitrile	14	90	18
7	-	-	14	90	57
8	-	-	14	RT	-
9	-	-	14	110	69
10	-	-	16	110	78
11	-	-	18	110	79
12	-	-	16	110	82
13	**-**	**-**	**16**	**110**	**93**
14	-	-	16	110	94

[a]Reaction condition: diethyl benzylidenemalonate(1d, 1.0 mmol), azide (2a, 1.5 mmol) were stirred. [b] All are isolated yields.

In order to fix the standard condition for this transformation, we picked up diethyl benzylidenemalonate (**1d**, 1.0 mmol) and benzyl azide (**2a,** 1.5 mmol) as model substrates and carried out the reaction in the presence of 0.3 mmol of CuO nanoparticles in 1.0 ml of DMF at 90^{o}C for 14h. To our delight, the required enamine (**3p**) was obtained in 30 % yield (Table 3.3, Entry 1). Initially the product was characterized by ^{1}H NMR and ^{13}C NMR. In ^{1}H NMR (figure 3.4), two triplets at δ 0.81-0.78ppm and δ 1.30-1.27ppm represent the two methyl protons of the malonate. Four multiplets from δ 3.55-4.40ppm in which each multiplet integrates for one proton represent the two methylene protons. The two doublets at δ 4.20-4.23ppm and δ 5.28-5.31ppm denote the benzyl protons. The multiplets at 7.32-7.08ppm represent the aromatic protons. ^{13}C NMR (figure 3.5) shows totally 17 signals in which the signals at 13.9ppm and 13.3ppm indicate the malonate methyl carbons while the signals at 62.9ppm and 61.9ppm represent the malonate methylene carbons. The signal at 51.8ppm indicates the benzylic carbon and the eight signals at 134.3-128.1ppm denote the aromatic carbons. The two signals at 165.7ppm and 164.5ppm represent the carbonyl carbons.

Being encouraged by this intriguing result, we examined the same reaction in the absence of catalyst. Surprisingly, here also we observed that the reaction going with the same efficiency furnishing the enamine with 32% yield (Table 3.3, entry 2). So, we fixed catalyst-free condition and varied the solvents and inferred the outcome. Among the solvents such as DMSO, water, toluene and acetonitrile, water could excel as a promising medium since 52 % yield of product was achieved in water medium (Table 3.3, entry 3-6). To our curiosity, when we attempted the reaction under solvent-free and catalyst-free condition 57% yield of the product was observed (Table 3.3, entry 7).

Spurred by this interesting result, we fixed the reaction at solvent-free and catalyst-free condition, we varied the temperature of the reaction. At the room temperature, no product formation was detected while 69% yield of the product was obtained at 110^0C (Table 3.3, entry 8 - 9). Now, fixing 110^0C as the suitable temperature, when we increased the reaction time to 16h and 18h, substantial increase of yields (78% and 79 %) of the product was observed (Table 3.3, entry 10 and 11). So we decided to fix 16h as the suitable time duration for this reaction. Having optimized the time and temperature, we increased the quantity of the azide (2.0 mmol, 2.5 mmol and 3.0 mmol), remarkable enhancement in the yield was detected.

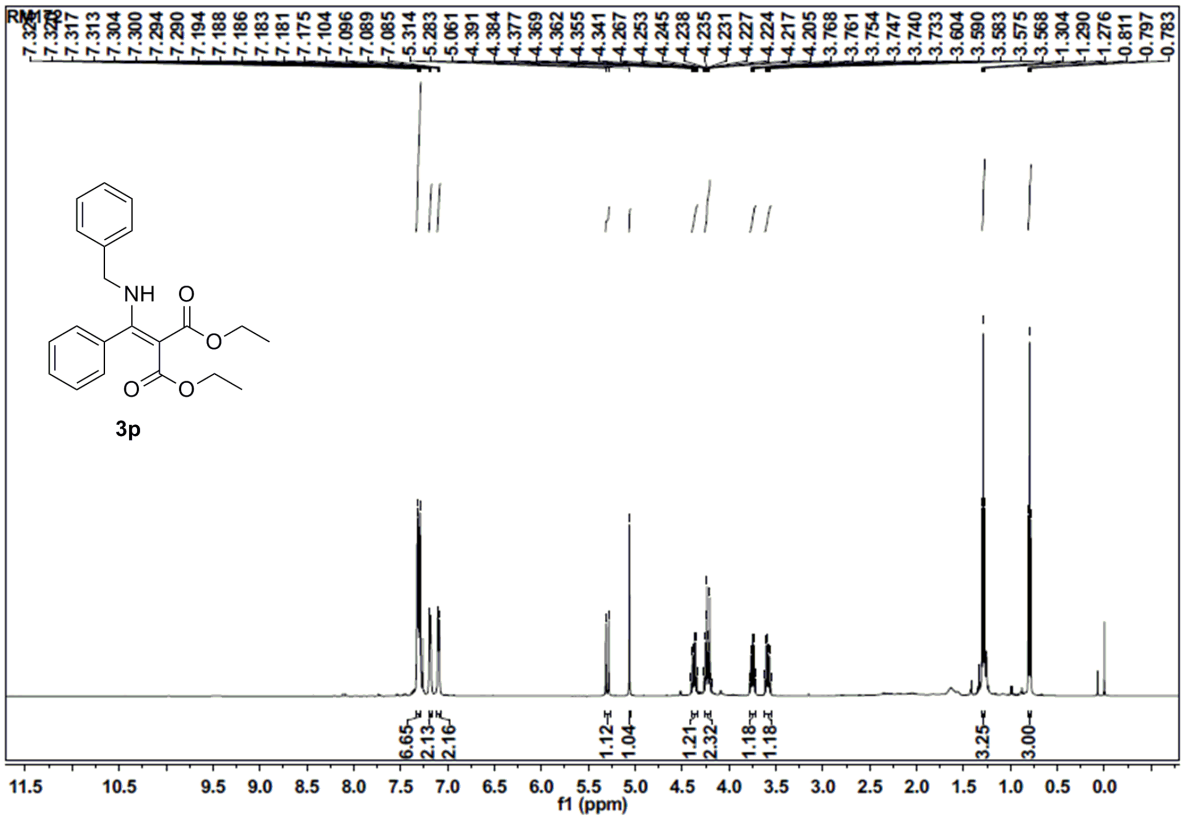


Figure 3.4 ^{1}H NMR of Diethyl 2-(benzylamino)(phenyl)methylene)malonate (3p) in $CDCl_3$

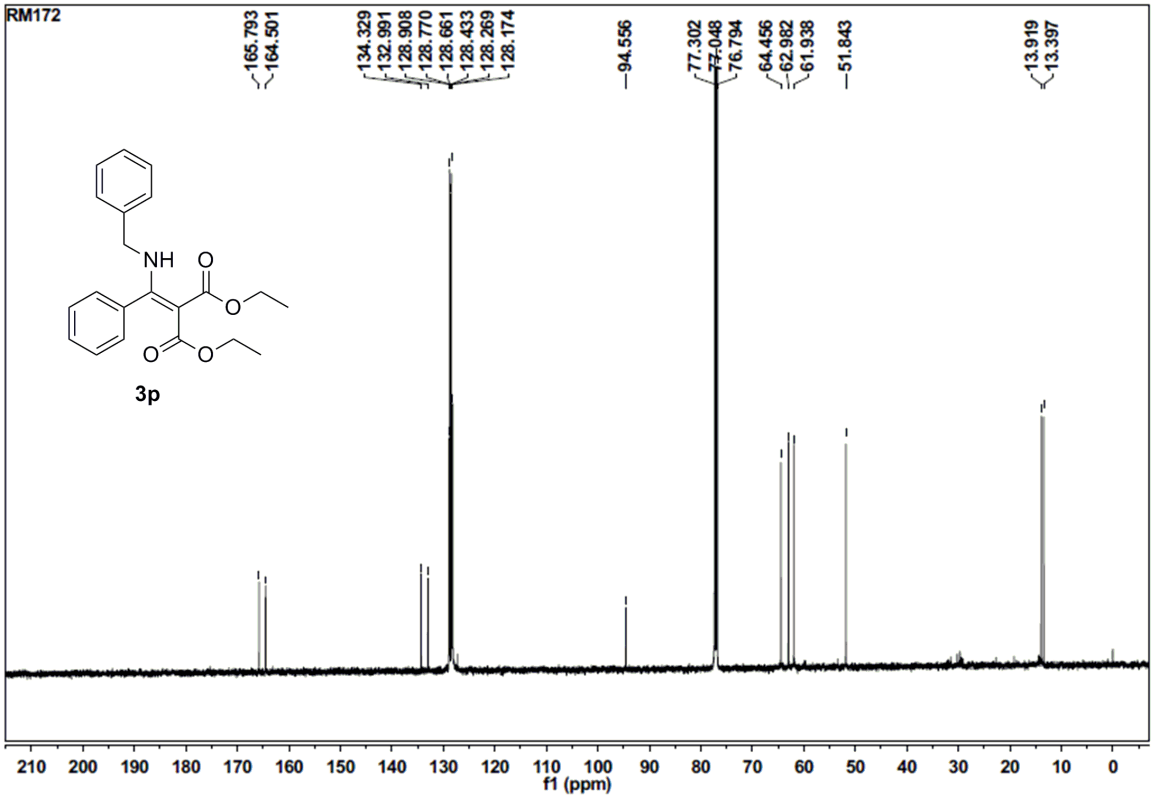
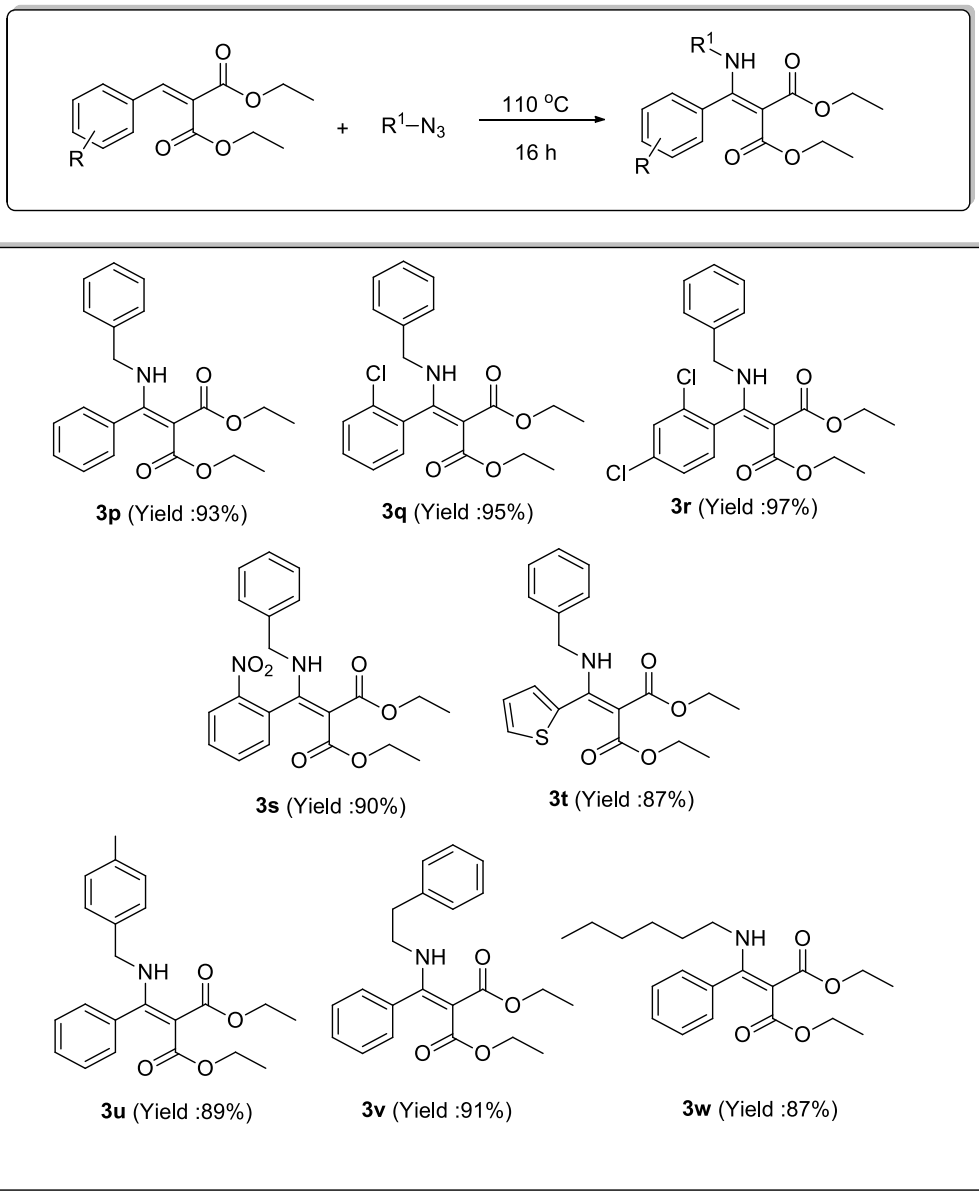


Figure 3.5 ^{13}C NMR of Diethyl 2-(benzylamino)(phenyl)methylene)malonate (3p) in $CDCl_3$

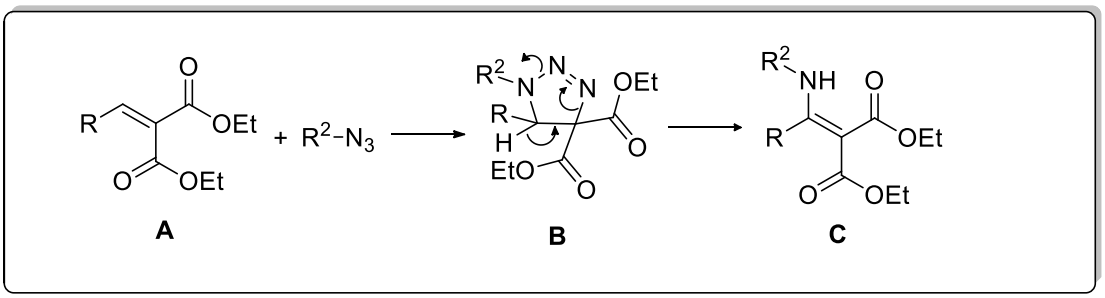
Since almost similar yields were obtained in 2.5 mmol and 3.0 mmol of azide, we resolved to fix 2.5 mmol of azide for this transformation (Table 3.3, Entry 12-14). From the observations tabulated above, Table 3.3, Entry 13 is finalized as the optimized condition for the synthesis of enamines. When benzyl azide was treated with various benzylidenediesters (Scheme 3.8), excellent yields of the corresponding enamines were obtained. Alkene **1d** furnished 93% of enamine **3p** while 2-chloro substitution on the alkene led to 95 % of enamine **3q**. 2,4-Dichloro substitution on the olefin could achieve the highest yield of 97% of the corresponding enamine **3a**. In the case of 2-nitro substitution on the olefin, efficacy decreased slightly and rendered 90% yield of the product **3s**. On the contrary, mild decrement in the efficiency of this protocol was noticed in the case of thiophene substituted olefin as shown from the yield of **3t**. Subsequently, olefin **1d** was treated with 4-methyl benzyl azide, phenethylazide and *n*-hexyl azide. In the case of *n*-hexyl azide, the efficiency was slightly diminished while the other two showcased similar efficiency as shown from the yields of **3u**, **3v** and **3w**.



Scheme 3.8 Enamine synthesis through azide-alkene cycloaddition of diethyl benzylidenemalonates and organic azides.

3.2.4 Proposed mechanism

The triazoline**B** formed from benzylidenemalonate**A** furnishes the enamine **C** by expelling the nitrogen gas (Scheme 3.9). Here also we presume that the deacylation is avoided due to the poor electrophilicity of ester groups.



Scheme 3.9The proposed mechanism for the enamine formation

3.3 Conclusion

A novel approach is developed to achieve the 1,2,3-triazoles by deacylative azide-alkene cycloaddition. To the best of our knowledge, synthesis of 1,2,3-triazoles *via* deacylativeazide-alkene cycloaddition is unknown. By this approach, various 1,2,3-triazoles bearing electron withdrawing groups such as ketones and esters are obtained simply from the benzylidenes bearing an acyl group. Easy accessibility of these alkenes and recyclability of the heterogeneous CuO nanoparticles are additional advantages of this protocol. Moreover, preparation of enamines from the azide alkene cycloaddition of benzylidenemalonates has also been demonstrated. Excellent yields, solvent-free and catalyst-free conditions foster this method to stand unique from the precedent approach for the synthesis of enamines.

3.4 Experimental Section

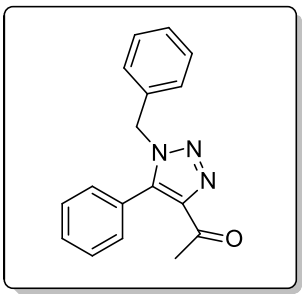
All basic chemicals and solvents were purchased from Avra Synthesis private Ltd. and Sigma-Aldrich private Ltd. CuO nano particles (particle size <50 nm, surface area 29 m^2/g) and DMF purchased from Sigma-Aldrich. Commercially available.

Analytical TLC was carried out using plastic sheets precoated with silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) and compounds were visualized by irradiation with UV light and/or by treatment with iodine. Column chromatography was performed with silica gel (230-400 mesh, Avra, India) using n-hexane: EtOAc mixture. All melting points were measured in GUNA instrument using open capillaries and are uncorrected. NMR spectra (^{1}H and ^{13}C NMR) spectra were obtained in BRUKER spectrometer (500 MHz for proton and 125 MHz for carbon). Proton chemical shifts (δ) are relative to internal standard TMS (δ = 0.00) and presented in parts per million (ppm). Coupling constants (*J*) are given in hertz (Hz) and spin-spin splitting were given as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). HRMS were recorded on a BrukermicroTOF-QII (ESI) spectrometer.

3.4.1 General Procedure for the synthesis of 1,4,5-trisubstituted1,2,3-triazole(3a-3o)

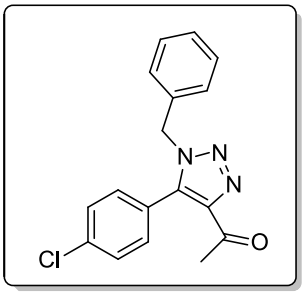
A mixture of 3-benzylidenepentane-2,4-dione (**1a**, 1.0 mmol), organic azides (**2a**, 1.5 mmol), CuOnano particles (0.3 mmol) and DMF (1.0 mL) were heated at 110°C for 22h. Completion of the reaction was monitored by TLC and the reaction mixture was cooled to room temperature and the mixture was poured to water and organic layer was extracted with ethyl acetate. The organic layer was dried with Na_2SO_4. The solvent was evaporated, and the resulting crude product was purified by column chromatography using ethyl acetate:hexane (10:90) as eluents to obtain product (**3a-3o)**.

1-(1-benzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone(3a) [5-6]



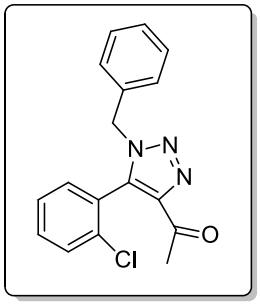
Yellow solid; **M.p**.:48-50 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.50-7.42 (m, 3H), 7.27-7.19 (m, 5H), 7.02-7.01 (m,2H), 5.41 (s, 2H),2.68 (*s*, 3H); **^{13}C NMR** (125 MHz, CDCl3) δ (ppm) 192.77, 143.81, 139.54, 134.64, 130.15, 129.70, 128.86, 128.66, 128.46, 127.57, 126.01, 51.96, 28.06.

1-(1-benzyl-5-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethanone(3b) [5-7]



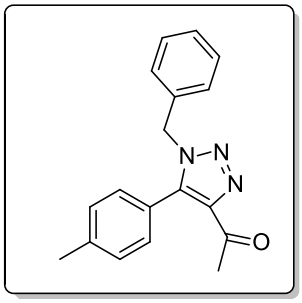
Yellow pasty oil;**^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.42 -7.39 (m, 2H), 7.29-7.26 (m, 3H), 7.14-7.11 (m, 2H), 7.03 -7.02 (m , 2H),5.41 (*s*, 2H), 2.69 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 192.85, 143.89, 138.40, 136.49, 134.47, 131.11, 129.00, 128.98, 128.62, 127.44, 124.39, 52.07, 28.01.

1-(1-benzyl-5-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethanone(3c) [5-8]



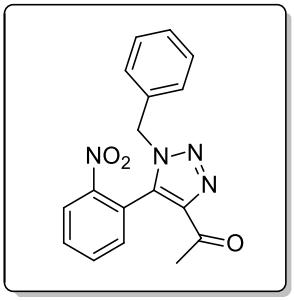
Yellow pasty oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.48 -7.46 (m, 1H), 7.43-7.40 (m, 1H), 7.28-7.18 (m, 4H), 7.00 - 6.98 (m,1H),6.94 (d, *J* = 6.5 Hz, 2H), 5.50 (d, 1H), 5.24(d,*J* = 15.0 Hz, 1H), 2.65(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 192.41, 144.84, 136.47, 133.91, 133.90, 131.55, 131.44, 128.76, 128.56, 127.97, 126.99, 125.84, 52.59, 27.74; **HRMS(ESI)**: *m/z* calcd. for $C_{17}H_{14}ClN_3O$ (M+):311.0826, found: 311.08254.

1-(1-benzyl-5-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone(3d)



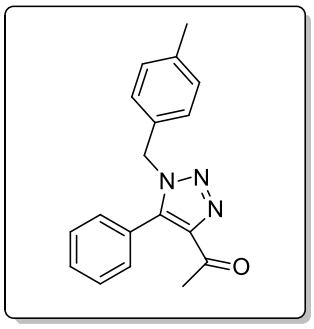
White pasty oil;**^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.29 -7.24 (m, 5H), 7.10 (d, *J*= 8.0 Hz, 2H), 7.06-7.04 (m, 2H), 5.41(s,2H),2.67(s, 3H), 2.42(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 192.81, 140.37, 139.72, 134.81,129.70, 129.59, 129.40, 128.86, 128.46, 127.57, 127.54, 122.85, 51.80, 28.10, 21.52; **HRMS(ESI)**: *m/z* calcd. for $C_{18}H_{17}N_3O$ $(M+H)^+$:292.1444, found:292.1450.

1-(1-benzyl-5-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)ethanone(3e)



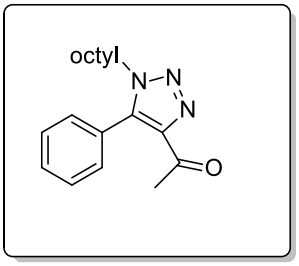
Light yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)8.23 (d, *J*= 8.0 Hz,1H), 7.70-7.61 (m, 2H), 7.28-7.22 (m, 3H), 7.02- 6.98(m, 3H),5.56 (d,*J*= 15.5 Hz, 1H), 5.30 (d, *J* = 15 Hz, 1H),2.65(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 192.94, 147.91, 136.05, 133.55, 133.46, 131.86,131.22, 128.86, 128.74,127.91,125.28,122.28, 52.91,27.44; **HRMS(ESI):** *m/z*calcd. for $C_{17}H_{14}N_4O_3(M+H)^+$:323.1139, found:323.1144.

1-(1-(4-methylbenzyl)-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone(3f)



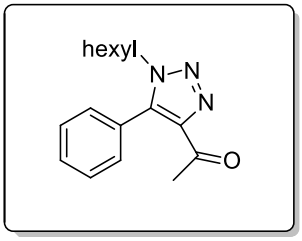
White liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.50 -7.42 (m,3H), 7.22-7.20 (m, 2H), 7.06 (d, *J*= 8.0 Hz, 2H), 6.91 (d, *J*= 8.0 Hz, 2H),5.36(s, 2H), 2.67(s, 3H),2.30(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)192.77, 143.77,139.43, 138.31, 131.66, 130.11,129.76,129.50, 128.64, 127.58,126.09, 51.74,28.04, 21.13; **HRMS(ESI)**: *m/z* calcd. for $C_{18}H_{17}N_3O$ $(M+Na)^+$: 314.1264, found: 314.1269.

1-(1-octyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone(3g)



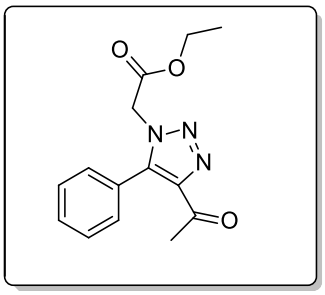
Yellow oily liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.44 -7.42 (m, 3H), 7.28-7.26 (m, 2H), 4.14 (t, *J* = 7.5 Hz, 2H), 2.60(s,3H),1.75- 1.57(m, 2H),1.21- 1.11(m , 10 H),0.78(t,*J* = 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)192.84,143.56, 139.22, 130.03, 129.55, 128.85, 128.76, 126.35, 48.23, 31.64, 29.89, 28.75, 28.02, 28.01, 26.30, 22.57, 14.06; **HRMS(ESI)**: *m/z* calcd. for $C_{18}H_{25}N_3O$ $(M+H)^+$:300.2070, found:300.2076.

1-(1-hexyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone(3h)



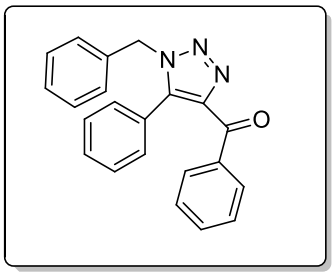
Light green oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.52 -7.50 (m, 3H), 7.35-7.33 (m, 2H), 4.22 (t, *J* = 7.5 Hz, 2H), 2.68(s, 3H),1.81- 1.73(m, 2H), 1.25- 1.18(m, 6H),0.83 (t, *J* = 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)192.90,143.56, 139.24, 130.05, 129.56, 128.78, 126.34, 48.24, 30.96, 29.90, 28.04, 26.00,22.33,13.91; **HRMS(ESI)**: *m/z* calcd. for $C_{16}H_{21}N_3O$ $(M+H)^+$:272.1757, found:272.1763.

Ethyl-2-(4-acetyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone(3i)



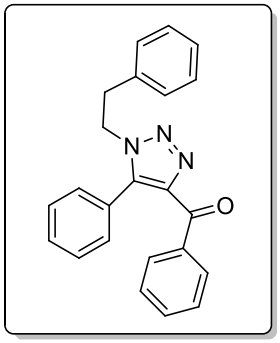
Yellow pasty liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)7.51 -7.49 (m,3H), 7.37-7.35 (m, 2H), 5.00 (s, 2H), 4.22- 4.18(q, 2H),2.70(s, 3H), 1.24 (t,*J* = 7.0 Hz , 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ(ppm)192.66, 166.03,143.51,140.30, 130.42, 129.53, 128.86, 125.53,62.54, 49.10, 28.10, 14.02; **HRMS(ESI):***m/z* calcd. for $C_{14}H_{15}N_3O_3$ $(M+H)^+$:274.1186, found:274.1191.

1-benzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone(3j)[5-8]



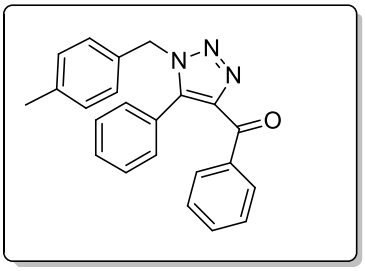
White solid; **M.p**.: 112-114^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.28 (d, *J* = 7.5 Hz, 2H), 7.58-7.56 (m, 1H), 7.49-7.43 (m, 5H), 7.30-7.25 (m, 5H), 7.07-7.05(m, 2H), 5.47(s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)186.38,143.82, 141.84, 137.11,134.68, 133.03, 130.71,130.06,129.79, 128.88, 128.70, 128.49, 128.24, 127.67, 126.37,52.04.

(1-phenethylbenzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone(3k)[5]



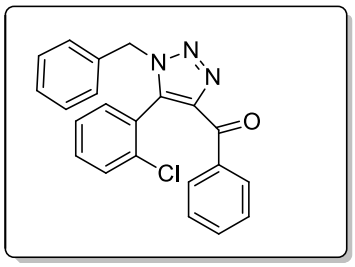
White solid; **M.p**.: 104-106 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.16 (d, *J* = 7.5 Hz, 2H), 7.48-7.45 (m, 1H), 7.38-7.28 (m, 5H), 7.11 (s, 3H), 6.92 (d, *J* = 7.5 Hz , 2H), 6.81(s, 2H), 4.36 (t, *J* = 7.0 Hz, 2H), 3.09 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 185.32, 142.31, 141.03, 136.08, 135.64, 131.93, 129.59, 128.77, 128.49, 127.73,127.67, 127.55, 127.16, 126.05, 125.17, 48.36, 35.26.

1-(4-methylbenzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone(3l)[5]



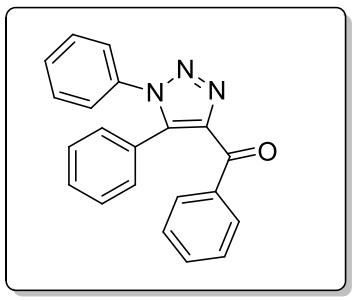
Yellow solid; **M.p.:** 110-112 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.28 - 8.26 (m,2H), 7.58-7.56 (m, 1H), 7.51-7.44 (m, 5H), 7.28-7.26 (m, 2H),7.08 (d, *J* = 7.5 Hz , 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.43(s, 2H), 2.32 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)186.43, 143.75, 141.76, 138.36, 137.11, 133.03, 131.66, 130.71, 130.04, 129.84, 129.53, 128.69, 128.23, 127.69, 126.41, 51.82, 21.17.

(1-benzyl-5-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone(3m)



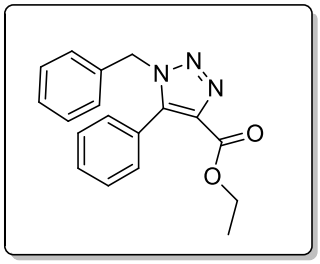
White solid; **M.p.**: 144-146 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm)8.23 (d, *J*= 8.5 Hz, 2H), 7.46-7.43 (m, 1H), 7.37-7.28 (m, 4H), 7.18-7.08 (m, 4H),6.98-6.96(m , 1H), 6.87(d, *J* = 7.0 Hz, 2H),5.45(d, *J*= 15.0 Hz, 1H), 5.18 (d,*J*= 15.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)185.93, 144.92, 138.96, 136.85, 133.98, 133.96, 133.15, 131.60,131.50,130.69, 129.90, 128.81, 128.60, 128.31,128.05, 127.02, 126.21, 52.70,52.66; **HRMS(ESI):***m/z* calcd. for $C_{22}H_{16}ClN_3O$ $(M+Na)^+$:396.0874, found:396.0879.

(1,5-diphenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone(3n) [5]



White solid; **M.p.:** 164-168 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 8.29 - 8.27 (m,2H), 7.59-7.58 (m, 1H), 7.51-7.48 (m, 2H), 7.42-7.31 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm)186.77, 143.60, 141.21, 137.20, 135.89, 133.18, 130.75, 130.25, 129.90, 129.55, 129.39, 128.53, 128.31, 126.06, 125.30.

Ethyl1-benzyl-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate(3o)

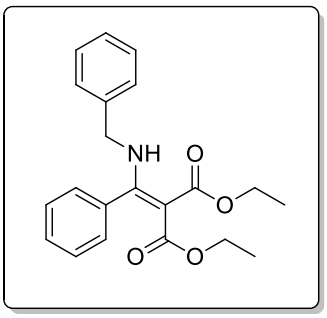


Yellow pasty oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.42-7.41 (m, 1H), 7.35-7.30 (m, 2H), 7.19-7.18 (m, 3H), 7.13-7.11 (m, 2H),5.93-5.91(m, 2H),5.36 (*s*, 2H), 4.24-4.20(q, 2H),1.18 (t , *J* =7.0 Hz,3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 160.94,141.32, 137.15, 134.62, 130.12, 129.78, 128.28, 128.54,128.44, 127.53, 125.98, 52.21, 51.05. 14.10; **HRMS(ESI):***m/z* calcd. for $C_{18}H_{17}N_3O_2$ $(M+Na)^+$:330.1218, found:330.1213.

3.4.2 General Procedure for the synthesis of enamine

A mixture of diethyl benzylidenemalonate (**1d**, 1.0 mmol) and organic azide (**2a**, 2.5 mmol) were stirred at 110^0C for 16h under neat condition. When the completion of the reaction was ensured by TLC, the reaction mixture was cooled to room temperature and purified by the column chromatography using ethyl acetate: hexane (10:90) as eluents to obtain product (**3p-3w)**.

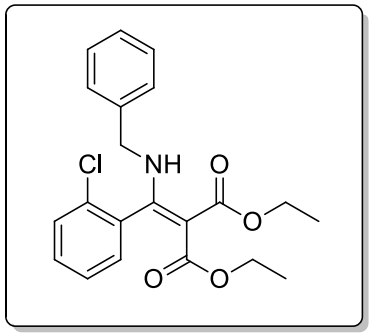
Diethyl 2-(benzylamino)(phenyl)methylene)malonate(3p)



Yellow oil liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.33-7.29 (m, 6H), 7.10-7.09 (m, 2H), 5.30 (d,*J*= 15.5 Hz, 2H), 5.06 (s, 1H),4.41-4.34(m ,1H),4.26-4.18

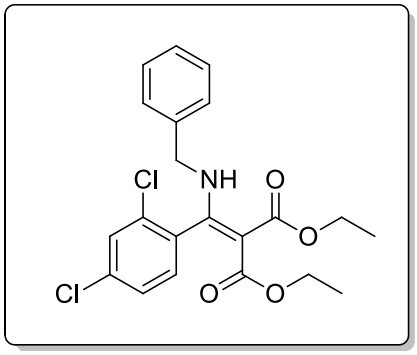
(m, 2H),3.62- 3.55(m, 1H),1.29 (t,*J*= 5.0 Hz, 3H),0.80 (t,*J*= 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 165.79, 164.50,134.33, 132.99, 128.91, 128.77, 128.66, 128.43, 128.27, 128.17, 94.56, 64.46, 62.98, 61.94, 51.84, 13.92, 13.40; **HRMS(ESI)**: *m/z* calcd. for $C_{21}H_{23}NO_4$ $(M+H)^+$:354.1717, found:354.1705.

Diethyl 2-((benzylamino)(2-chlorophenyl)methylene)malonate(3q)



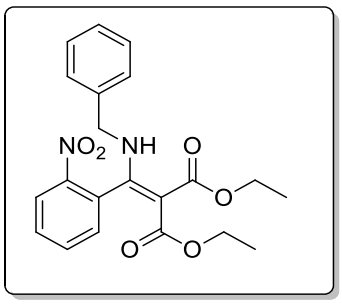
Colourless pasty oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.35-7.23 (m , 6H), 7.12-7.11 (m, 2H), 7.06- 7.05 (m ,1H) 5.77 (s,1H), 5.27 (d , *J* = 15.0 Hz, 1H), 4.36-4.21 (m, 2H),4.36-4.21 (m,2H), 3.79-3.75(m, 1H),3.62-3.59 (m,1H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 164.77,164.75, 135.13, 134.19,131.60, 129.99, 129.77,128.96,128.81, 128.38, 128.25, 127.09, 94.62, 63.10, 61.85, 60.13, 51.91, 13.92, 13.38; **HRMS(ESI)**: *m/z* calcd. for $C_{21}H_{22}ClNO_4$ $(M+H)^+$:388.1310, found:388.1315.

Diethyl 2-((benzylamino)(2,4-dichlorophenyl)methylene)malonate(3r)



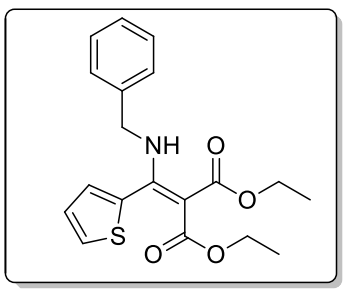
Colorless pasty oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.36-7.27 (m, 4H), 7.21 (d,*J*= 5 Hz, 1H), 7.11-7.10 (m, 2H), 7.20 (d, *J* = 8.5 Hz ,1H), 5.68 (s,1H), 5.24 (d, *J* = 15.0 Hz, 1H), 4.36-4.31 (m, 1H),4.27-4.22 (m, 2H), 3.84- 3.80(m, 1H),3.72-3.67 (m, 1H), 1.28 (t,*J*= 7.5 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 164.61, 135.82, 135.26,133.92, 130.40, 129.86,129.56,128.87, 128.41, 128.38, 127.41, 94.91, 63.24, 62.04, 59.70, 52.08, 13.91, 13.47; **HRMS(ESI)**: *m/z* calcd. for $C_{21}H_{21}Cl_2NO_4$ $(M+H)^+$:422.0848, found:422.0926.

Diethyl 2-((benzylamino)(2-nitrophenyl)methylene)malonate(3s)



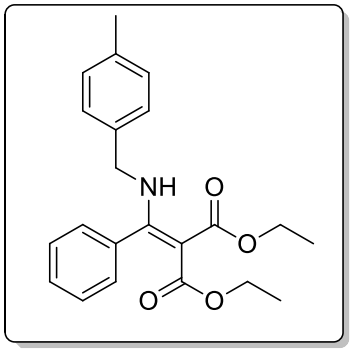
Yellow pasty oil ; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.95 (dd , *J* = 8.0 and 8.0 Hz ,1H), 7.59-7.59 (m, 1H), 7.51-7.47 (m, 1H), 7.31-7.27 (m, 4H),7.15-7.13(m,2H),5.89 (s,1H), 5.24 (d, *J* = 15.0 Hz, 1H), 4.38-4.23 (m, 2H),3.83- 3.77(m, 1H),3.64-3.58 (m,1H), 1.27 (t, *J* = 7.5 Hz, 3H), 0.85 (t,*J*= 7.0 Hz , 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 164.66, 164.55,149.59,133.81, 133.21, 129.69,129.45,129.39, 128.85, 128.50, 128.44, 124.91, 95.43, 63.31, 62.02, 59.13, 52.51, 13.89, 13.45; **HRMS(ESI)**: *m/z* calcd. for $C_{21}H_{22}N_2O_6$ $(M+H)^+$:399.1568, found:399.1556.

Diethyl 2-((benzylamino)(thiophen-2-yl)methylene)malonate(3t)



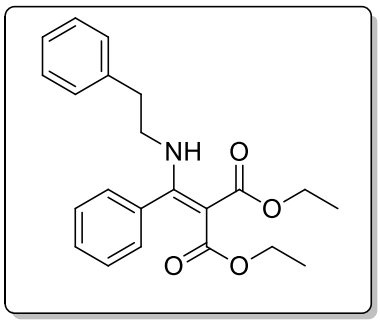
Yellow pasty oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.34-7.28 (m, 4H), 7.15-7.13 (m, 2H), 7.00- 6.97 (m,2H), 5.30 (t, *J* = 8 Hz, 2H), 4.41-4.34(m,1H), 4.31 (d, *J* = 15.5 Hz, 1H), 3.94- 3.88 (m, 1H), 3.84- 3.78 (m, 1H), 1.30 (t,*J*= 7.0 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 165.42, 164.19,135.04, 134.18, 128.82, 128.52, 128.27, 128.12, 127.25, 126.49, 94.05, 63.14, 62.30, 60.44, 51.99, 13.92, 13.54; **HRMS(ESI)**: *m/z* calcd. for $C_{19}H_{22}NO_4S$ $(M+H)^+$:360.1264, found:360.1269.

Diethyl 2-(4-methylbenzyl)amino)(phenyl)methylene)malonate(3u)



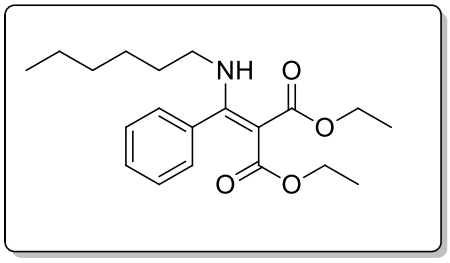
Colourless liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.33-7.31 (m, 3H), 7.20-7.18 (m, 2H),7.10- 7.09 (m, 2H),6.98- 6.96 (m, 2H), 5.28 (d, *J* = 16.5 Hz, 1H), 5.05 (s, 1H),4.41-4.34(m,1H),4.26-4.20(m, 1H), 4.16 (d, *J*= 15 Hz, 1H), 3.78- 3.71(m, 1H),3.61- 3.55 (m, 1H), 2.32 (s, 1H), 1.30(t, *J* = 7.0 Hz, 3H),0.80 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 165.86, 164.53,137.89, 133.03,131.17,129.43, 129.31, 128.87, 128.64, 128.40, 128.27, 94.45, 64.34, 62.94, 61.92, 51.56, 21.16, 13.92,13.40; **HRMS(ESI)**: *m/z* calcd. for $C_{22}H_{25}NO_4$ $(M+Na)^+$:390.1676, found:390.1681.

Diethyl 2-((phenethylamino)(phenyl)methylene)malonate(3v)



Yellow liquid;**^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.28-7.20 (m, 6H), 7.14-7.09 (m, 4H), 5.27 (s, 1H), 4.43-4.38(m,1H),4.33-4.28 (m, 1H), 4.01- 3.95 (m, 1H), 3.73- 3.70(m, 1H), 3.68-3.55 (m, 1H), 3.50- 3.44 (m,1H),3.03- 2.99 (m, 1H), 1.33(t,*J*= 7.0 Hz, 3H),0.80 (t,*J*= 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 166.03, 164.55,138.18, 133.25, 128.91, 128.85, 128.59, 128.14, 126.63, 94.47, 65.83, 63.08, 61.92, 49.48, 34.57; **HRMS(ESI)**: *m/z* calcd. for $C_{22}H_{25}NO_4$ $(M+H)^+$:368.1862, found:368.1856.

Diethyl 2-((hexylamino)(phenyl)methylene)malonate(3w)



Yellow pasty oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.27-7.24 (m, 3H), 7.15-7.14 (m, 2H), 5.26 (s, 1H), 4.38- 4.38(m, 1H), 4.26-4.09 (m, 2H), 3.74- 3.64(m, 2H),3.54-3.48 (m, 1H), 3.19-3.14 (m, 1H), 1.58-1.53 (m, 2H) 1.27 (t, *J* = 7.0 Hz, 3H), 1.22-1.19 (m, 4H), 0.82-0.77 (m, 3H), 0.74 (t, *J* = 7.0 Hz, 3H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm) 166.17, 164.72, 160.05, 133.54, 128.87, 128.58, 128.16, 94.30, 65.39, 63.03, 61.96, 48.01, 31.29, 27.60, 26.27, 22.45,13.96, 13.39; **HRMS(ESI)**: *m/z* calcd. for $C_{20}H_{29}NO_4$ $(M+H)^+$:348.2169, found:348.2175.

3.5 References

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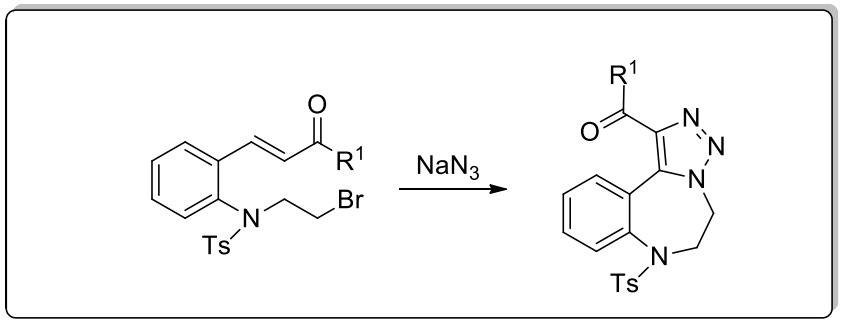
4. A New Route to 1,2,3-Triazole Fused Benzodiazepine Analogues Through Metal-free Intramolecular Azide-Olefin Oxidative Cycloaddition

4.1 Introduction

This chapter deals with the regioselective synthesis of benzodiazepine fused 1,2,3-triazoles through one-pot azidation followed by the intramolecular oxidative [3+2] cycloaddition sequence. Initially azidation of compound (**1a**) was achieved and the resultant product was subjected to intramolecular oxidative [3+2] cycloaddition to obtain the benzodiazepine fused 1,2,3-triazole (scheme 4.1).



Scheme 4.1 Synthesis of 1,2,3-triazole fused benzodiazepine

4.2 Results and Discussion

At the outset, we started our investigation by taking Olefin (**1a**) (1.0 mmol) and sodium azide**(1b**) (2.0 mmol), CuO (0.1 mmol) in 1.0 mL of DMF and heated the mixture at 90^{o}C for 6h. To our delight, we obtained 45% yield of the benzodiazepine fused 1,2,3-triazole **2a** (Table 4.1, entry 1). Initially the product was characterized by ^{1}H NMR, ^{13}C NMR and HRMS. In ^{1}H NMR spectra of (figure 4.1) the compound (**2a**), the peaks at δ 8.38-6.86ppm integrating for thirteen protons represent the aromatic protons. A broad peak at δ 4.52ppm integrated for four protons denote the two methylene protons of the diazepine ring. A singlet at δ 1.79ppm integrates for three protons indicate tosyl methyl group. Apart from the above mentioned NMR signals there were no other signals in the region around δ 5.90-6.30ppm signifying the absence

of olefinic protons. In ^{13}C NMR (figure 4.2) all together twenty lines were obtianed. The signal at 184.7ppm indicates the carbonyl carbon and the sixteen signals at 143.6-126.2ppm signify the aromatic carbons. The signal at 54.0ppm denote the methylene carbon of the diazepine ring bonded with the nitrogen of the 1,2,3-triazole while the signal at 45.0ppm represent the methylene group bonded with the tosylated nitrogen. Finally the signal at 20.9ppm indicates the tosyl methyl group. The HRMS spectrum of the compound(**2a**), exhibited the molecular ion peak at *m/z* = 445.1351 corresponding to the elemental composition $C_{24}H_{20}N_4O_3S$ $(M+H)^+$ matches with calculated value for $C_{24}H_{20}N_4O_3S$ $(M+H)^+$ is 445.1256 (figure 5.3). Based on the analysis, the structure of this compound **(2a)** was assigned as phenyl(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3] triazolo[1,5-d][1,4]diazepin-1-yl)methanone.

When the reaction was repeated by replacing CuO by other copper catalyst such as Cu powder, CuO nanoparticles, $Cu(OTf)_2$ and CuI, CuO nanoparticles could excel as the better one since it furnishes 65% yield of **2a** (Table 4.1, entry 2–5). To our surprise, 70 % yield of **2a** was achieved when the reaction was achieved in the absence of the catalyst (Table 4.1, entry 6). Fixing the catalyst-free condition, we examined other solvents such as DMSO, toluene and water none was able to act superior to DMF (Table 4.1, entry 7-9). To our disappointment, only 12 % yield of **2a** only was obtained at the neat condition (Table 4.1, entry 10). Fixing the DMF as solvent and catalyst free condition, we tested the reaction at 110^{o}C and 80^{o}C (Table 4.1, entry 11 and 12). At 110^{o}C, the yield of **2a** obtained was closer to the yield achieved at 90 ^{o}C. Subsequently, when the reaction time was tested by prolonging the reaction for 5h and 7h (Table 4.1, entry 13 and 14), we resolve to fix 6h as the suitable time duration for this transformation.

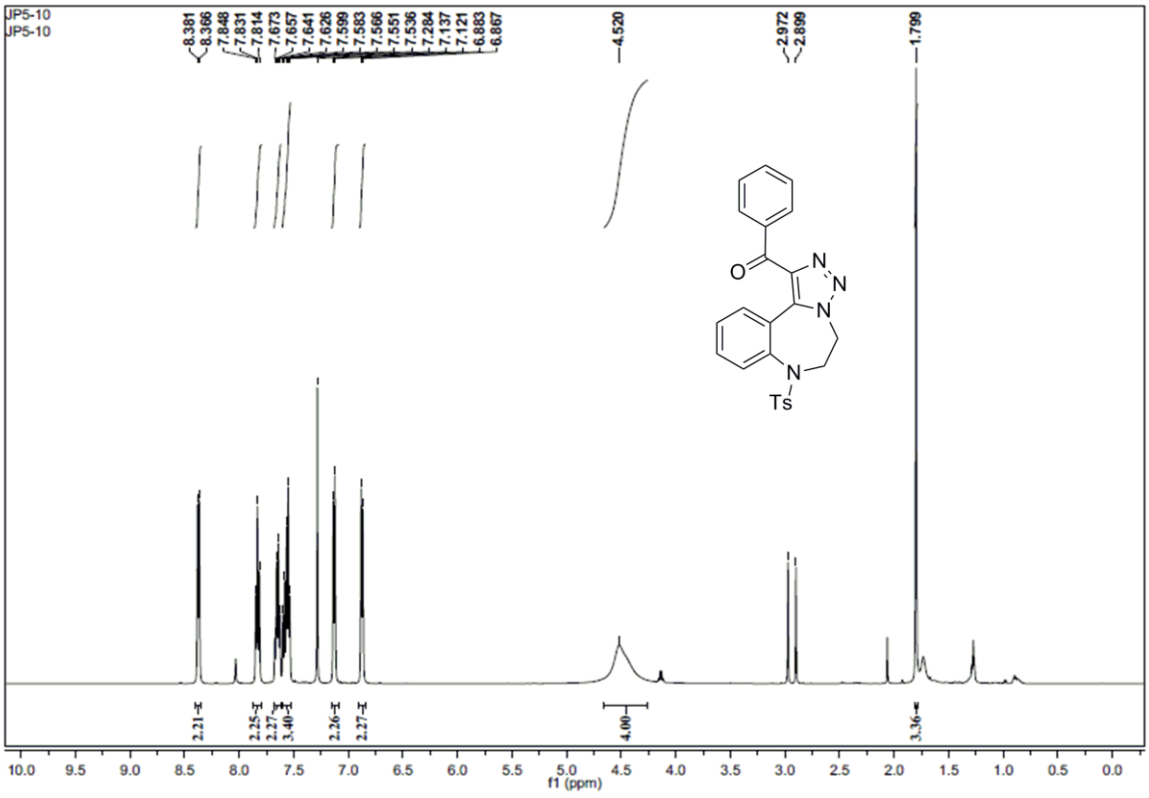


Figure 4.1 ^{1}H NMR of phenyl(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl)methanone (2a) in $CDCl_3$

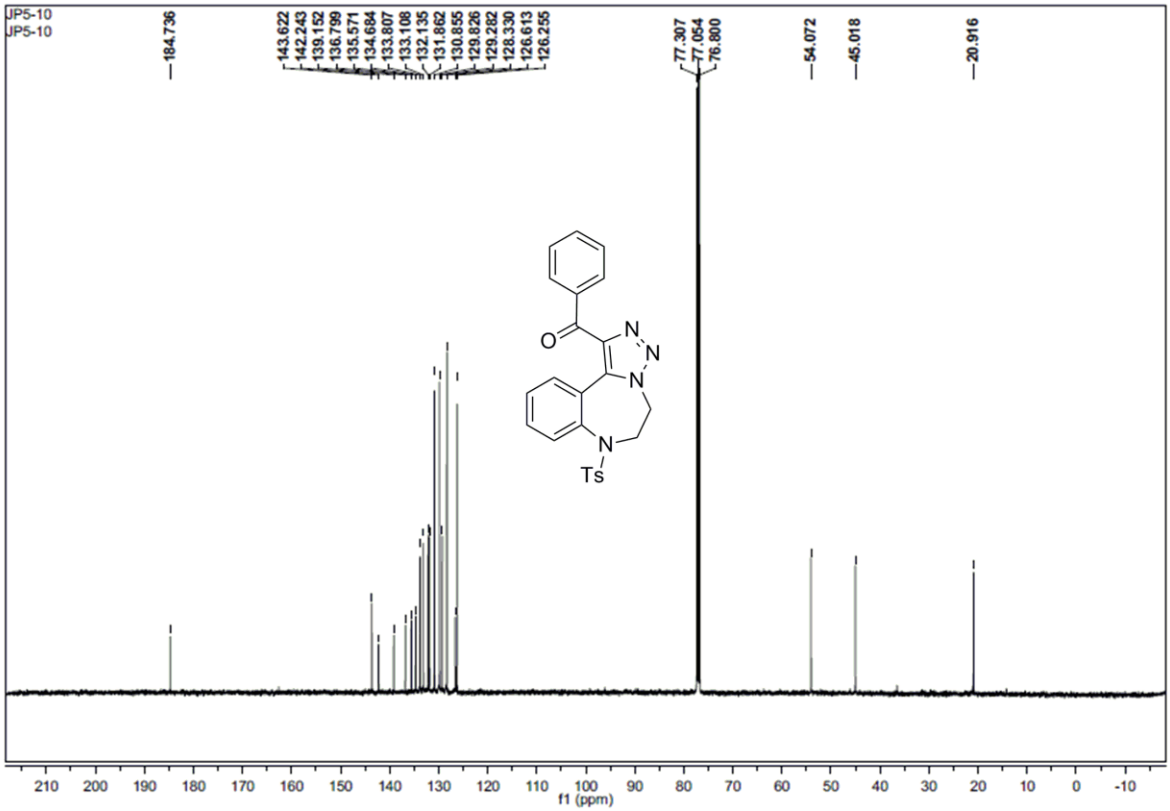


Figure 4.2 ^{13}C NMR of phenyl(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl)methanone (2a) in $CDCl_3$

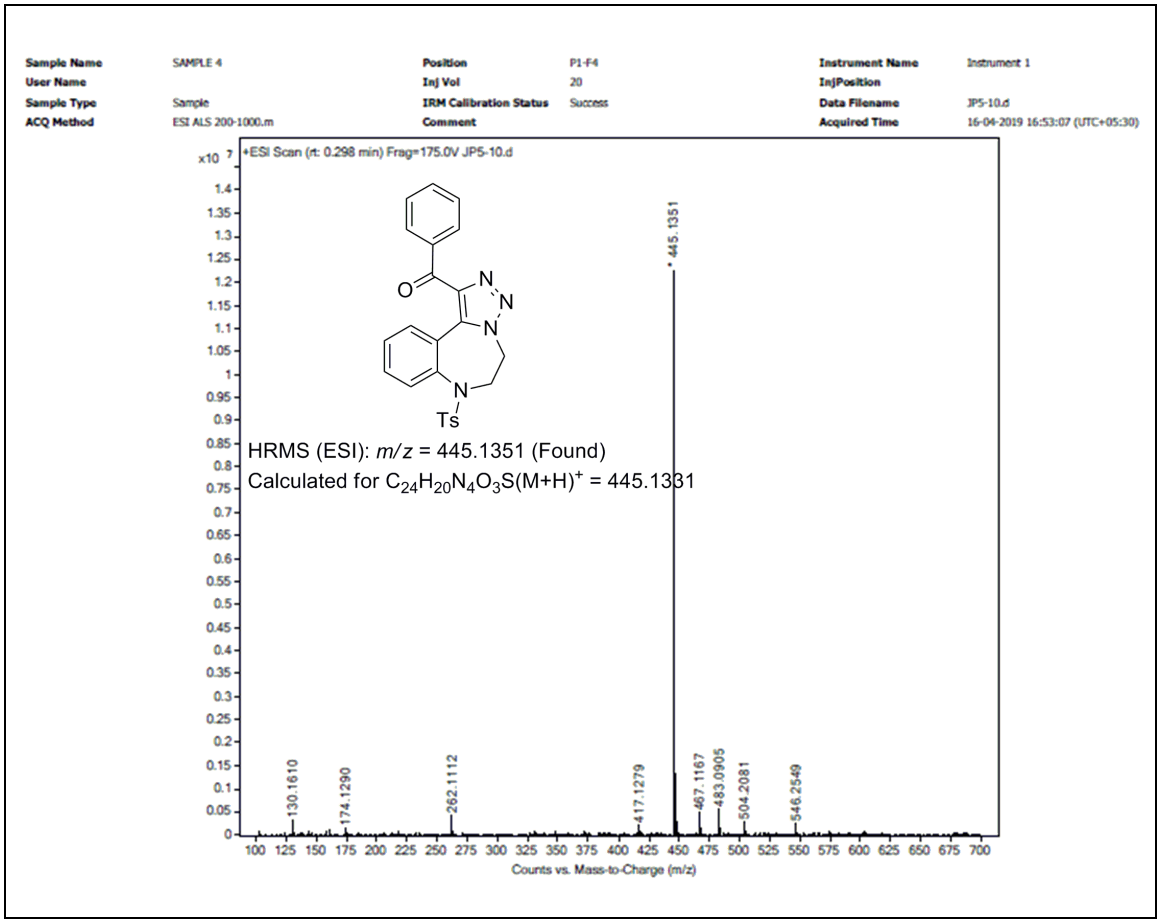
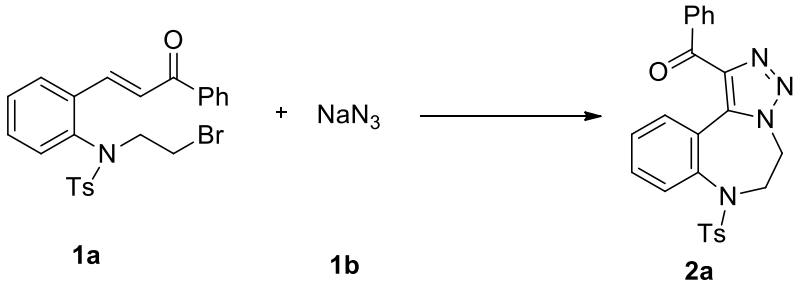


Figure 4.3 HRMS spectrum of compound (2a)

Table 4.1 Optimization of one-pot azidation in intramolecular OAOC[a]



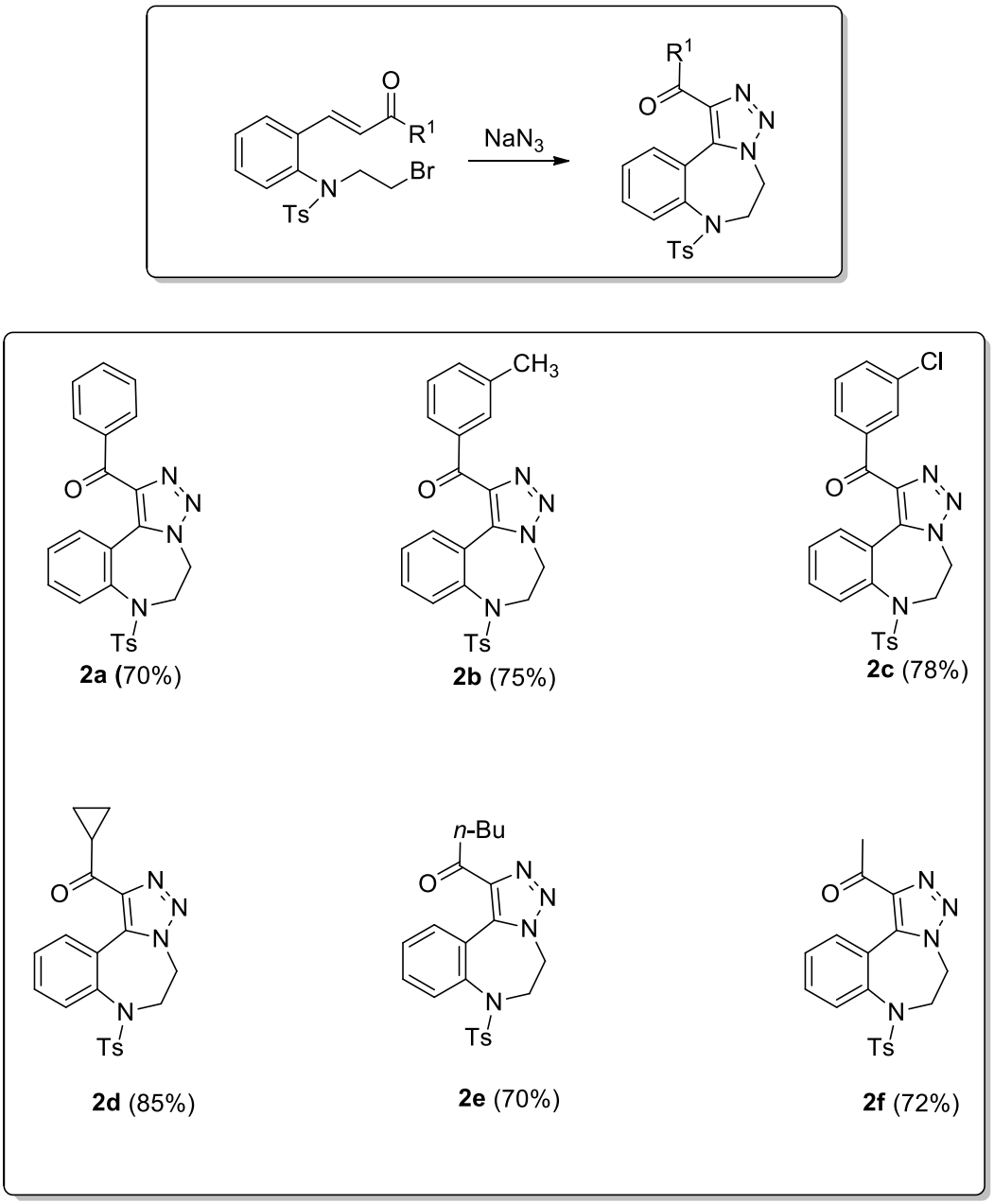
1a 1b 2a

Entry	Catalyst (0.1 eq.)	Solvent(1.0 ml)	Temperature (^{0}C)	Time (h)	Yield[b] % (2a)
1	CuO	DMF	90^{0}C	6h	45
2	Cu Powder	DMF	90^{0}C	6h	48
3	CuONps	DMF	90^{0}C	6h	65
4	$Cu(OTf)_2$	DMF	90^{0}C	6h	62
5	CuI	DMF	90^{0}C	6h	41
6	**-**	**DMF**	**90^{0}C**	**6h**	**70**
7	-	DMSO	90^{0}C	6h	46
8	-	Toluene	90^{0}C	6h	35
9	-	H_2O	90^{0}C	6h	43
10	-	-	90^{0}C	6h	12
11	-	DMF	110^{0}C	6h	71
12	-	DMF	80^{0}C	6h	63
13	-	DMF	90^{0}C	5h	65
14	-	DMF	90^{0}C	7h	70

[a]Olefin (1.0 mmol), sodium azide (2.0 mmol), catalyst (0.1 mmol) and solvent (1.0 mL) were heated. [b] Isolated yield.

Having established the optimized condition (Table 4.1, entry 6) for metal-free synthesis of 1,2,3-triazole fused benzodiazepines was applied to various substrates (Scheme 4.2). Various changes in the substitution on the ketone side of the starting material was meticulously examined. Introducing methyl substitution in the meta

position of the aryl ring, yield of the product (**2b**) improves to 75 % while chloro substitution at the same position enhances the yield of the product **2c** further more. Instead of aryl groups on the ketone side, aliphatic groups were examined. Cyclopropyl group furnishes 85 % of **2d** while *n*-butyl and methyl groups could give the corresponding products **2e** and **2f** in 70 % and 72 % yields.



Scheme 4.2 Metal-free synthesis of 1,2,3-triazole fused benzodiazepines

4.3 Conclusion

A new method has been developed to access 1,2,3-triazole fused benzodiazepines. This method involves azide-olefin cycloaddition to construct the 1,2,3-triazole moiety while the other methods utilize azide-alkyne cycloaddition. Metal-free condition and consecutive one-pot reaction sequence are the additional features to promote this method as a promising alternative to the existing methods to access the family of 1,2,3-triazole fused benzodiazepines.

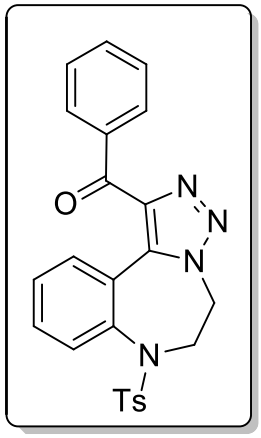
4.4 Experimental Data

All basic chemicals and solvents were purchased from Avra Synthesis private Ltd. and Sigma-Aldrich private Ltd. DMF purchased from Sigma-Aldrich. Commercially available. Analytical TLC was carried out using plastic sheets precoated with silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) and compounds were visualized by irradiation with UV light and/or by treatment with iodine. Column chromatography was performed with silica gel (230-400 mesh, Avra, India) using n-hexane: EtOAc mixture. All melting points were measured in GUNA instrument using open capillaries and are uncorrected. NMR spectra (^{1}H and ^{13}C NMR) spectra were obtained in BRUKER spectrometer (500 MHz for proton and 125 MHz for carbon). Proton chemical shifts (δ) are relative to internal standard TMS (δ = 0.00) and presented in parts per million (ppm). Coupling constants (*J*) are given in hertz (Hz) and spin-spin splitting were given as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). HRMS were recorded on a JEOL GC Made using EI Ionization and ESI techniques.

4.4.1 General Procedure for the Synthesis of benzodiazepine

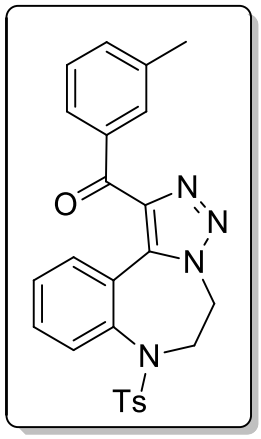
A mixture of compound (**1a**) (1.0 mmol) and sodium azide (**1b**) (2.0 mmol) in DMF (1.0 ml) was heated into 90^{o}C for 6h. After completion of the reaction, reaction mass was diluted with water and extracted with ethyl acetate (3 x 15 mL) and dried over anhydrous Na_2SO_4. The resulting crude mixture was purified by silica gel (Hexane:EtOAc) column chromatography.

phenyl(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl) methanone(2a)



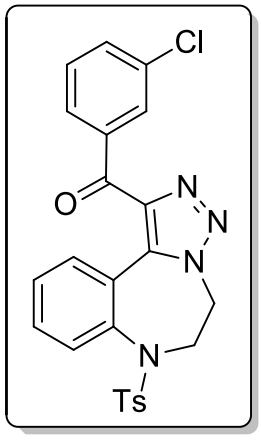
Brown solid; **M.p**: 144-146^{o}C:**^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.38-8.37 (*d*, *J*= 8Hz, 2H), 7.83 (*t*, *J*= 8Hz, 2H), 7.67-7.63 (*m*, 2H), 7.60-7.54 (*m*,3H), 7.14-7.12 (*d*, *J*= 8Hz, 2H), 6.88-6.87 (*d*,*J*= 8Hz, 2H), 4.52 (*m*, 4H), 1.80 (s, 3H):**^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) 184.7, 143.6, 142.2, 139.2, 136.8,135.6, 134.7, 133.8, 133.1, 132.1, 131.9,130.9, 129.8, 129.3, 128.3, 126.6, 126.3, 54.1,45.0, 20.9. **HRMS(ESI)**: *m/z* calcd. for $C_{24}H_{20}N_4O_3S$ $(M+H)^+$:445.1256, found:445.1351.

***m*-tolyl(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl) methanone(2b)**



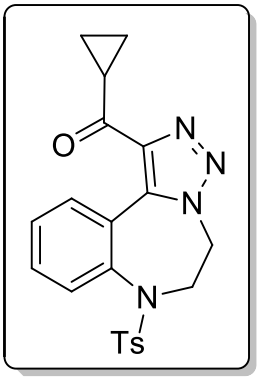
Brown solid; **M.p:** 144-146 ^{0}C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.08-8.07 (*d*, *J*=6.5Hz, 1H), 8.03 (*s*,1H), 7.73-7.71 (*m*, 2H) 7.55 (*t*, *J*=8Hz, 1H),7.49-7.45 (t, *J*=8Hz, 1H), 7.36-7.32 (m, 2H),7.03 (*d*, *J*= 8Hz, 2H), 6.79-6.77 (*d*, *J*= 8Hz, 2H), 4.41 (*m*, 4H), 2.39(s, 3H), 1.73(s, 3H):**^{13}C NMR (125 MHz, $CDCl_3$):**δ(ppm) 185.0, 143.6, 142.3, 139.1, 138.0, 136.9, 135.6, 134.7, 133.9, 133.8, 132.1,131.8, 131.2, 129.8, 129.2, 128.2, 128.2,126.6, 126.3, 54.1, 45.0, 21.5, 20.9.**HRMS(ESI)**: *m/z* calcd. for $C_{25}H_{22}N_4O_3S$ $(M+H)^+$:459.1491, found:459.1540.

(3-chlorophenyl)(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4] diazepin-1-yl)methanone(2c)



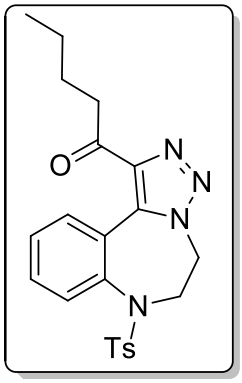
Brown solid; **M.p:** 144-146 ^{0}C: **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.36 (*m*, 1H), 8.30-8.28 (*d*, *J*=8Hz, 1H), 7.84-7.82 (*m*, 2H) 7.69-7.65 (*m*, 1H), 7.61-7.58 (*m*, 2H), 7.51-7.48 (t, 1H), 7.12(*d*, *J*=8Hz,2H), 6.89-6.87 (*d*, *J*=7.5Hz, 2H), 4.52-4.46 (*m*, 4H), 1.84(s, 3H): **^{13}C NMR (125 MHz, $CDCl_3$) :** δ (ppm) 183.3, 143.6, 141.8, 139.4, 138.3,135.7,134.7, 134.5, 133.9, 133.0, 132.1, 132. 0,130.9, 129.8, 129.6, 129.3, 129.0,126.4, 126.3, 54.1, 45.1, 20.9.**HRMS(ESI)**: *m/z* calcd. for $C_{24}H_{19}ClN_4O_3S$ $(M+H)^+$:479.0944, found:479.0963.

Cyclopropyl(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl)methanone(2d)



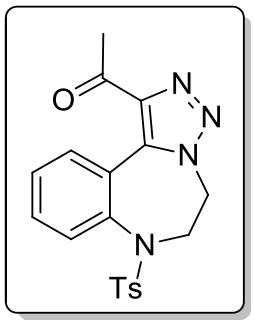
Brown solid: **M.p:** 144-146 ^{0}C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.78-7.75 (*t*, *J*= 6.5Hz, 2H), 7.63-7.60 (*t*, *J*= 8Hz, 1H), 7.55-7.52 (*t*, *J*= 8Hz, 1H) 7.10(*d*, *J*= 8Hz, 2H), 7.00 (*d*, *J*= 8Hz, 2H), 4.49 (*m*, 4H), 3.11-3.06 (*sep*, 1H), 2.36 (s, 3H), 1.22(m,2H), 1.11-1.09 (m, 2H):**^{13}C NMR (100 MHz, $CDCl_3$) :** δ (ppm) 194.0, 143.4, 142.6, 136.2, 135.6, 134.7, 133.9, 132.0, 131.8, 129.8, 129.2, 126.2, 126.1, 54.0, 45.0, 21.6, 17.9, 12.1.**HRMS(ESI)**: *m/z* calcd. for $C_{21}H_{20}N_4O_3S$ $(M+H)^+$:409.1334, found:409.1329.

1-(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl)pentan-1-one(2e)



Brown solid: **M.p:** 144-146 ^{0}C;**^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.78-7.75 (t, 2H), 7.63-7.60 (t, 1H), 7.55-7.52 (*t*, 1H) 7.11-7.10 (*d*, 2H), 7.00-6.99(*d*, 2H), 4.49 (*m*, 4H), 3.11-3.06 (*sep*, 1H), 2.36(s, 3H), 1.22(m, 2H), 1.11-1.09 (m, 2H): **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) 194.0, 143.4, 142.6, 136.2, 135.6, 134.7, 133.9, 132.0, 131.8, 129.8, 129.2,126.2, 126.1, 54.0, 45.0, 21.6, 17.9, 12.1.**HRMS(ESI)**: *m/z* calcd. for $C_{22}H_{24}N_4O_3S$ $(M+H)^+$:425.1647, found:425.1653.

1-(7-tosyl-6,7-dihydro-5*H*-benzo[*f*][1,2,3]triazolo[1,5-d][1,4]diazepin-1-yl)ethanone(2f)



Brown solid: **M.p:** 144-146 ^{o}C;**^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.77-7.73 (m, 2H), 7.62 (*t*,*J*= 8Hz,1H), 7.54 (*t*, *J*= 8Hz, 1H) 7.06 (*d*, *J*= 8Hz,2H), 6.98 (*d*, *J*= 8Hz, 2H), 4.49 (*m*, 4H), 2.53(s, 3H), 2.34 (s, 3H):**^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 191.9, 143.1, 142.2, 136.5, 135.7,134.5, 133.9, 131.9, 131.9, 129.8, 129.4, 126.3, 126.1, 54.2, 45.0, 27.8, 21.5.**HRMS(ESI)**: *m/z* calcd. for $C_{19}H_{18}N_4O_3S$ $(M+H)^+$:383.1178, found:383.1174.

5. Summary and Conclusion

This thesis presents three methods developed by us to synthesize 1,2,3-tirazles through [3+2] cycloaddition of olefins and organic azides. The first method involves the synthesis of 1,4-disubstituted 1,2,3-triazoles from decarboxylative azide-alkene cycloaddition of substituted cinnamic acids and organic azides. This method assures synthesis of 1,4-disubstituted 1,2,3-triazoles while precedent method are selective to 1,5- disubstituted triazoles. Metal-free condition and easy accessibility of the starting materials are also the added advantages of this method.

The second method involves the CuO nanoparticles catalyzed synthesis 1,4,5-trisubstituted 1,2,3-triazoles by deacylative azide-alkene cycloaddition of benzylidene diketones with organic azides. To the best of our knowledge, synthesis of 1,2,3-triazoles *via* deacylative azide-alkene cycloaddition is unknown. By this approach, various 1,2,3-triazoles bearing electron withdrawing groups such as ketones and esters can be obtained. Easy accessibility of these alkenes and recyclability of the heterogeneous CuO nanoparticles are the additional advantages of this protocol. Apart from 1,2,3-triazoles, preparation of enamines is also described by using benzylidene malonates in the place of benzylidene diketones under catalyst-free and solvent-free condition.

Third method describes the one-pot two step synthesis 1,2,3-triazole fused benzodiazepines through azidation followed by intramolecular azide-olefin oxidative cycloaddition under catalyst-free condition.

List of Publications

UGC Care List Journals

1. R. Rengasamy, K.Vijayalakshmi, N. Punitha, J. P. Raj, K. Karthikeyan, J. Elangovan, A novel route to 1,4-disubstituted-1,2,3-triazoles through metal-free decarboxylative azide-alkene cycloaddition. ***Tetrahedron Lett***. 2021, *84*,15, 3440. **E-ISSN:1873-3581**

2. R. Rengasamy, J. Paul Raj, K. Vijayalakshmi, N. Punitha, M. Kesavan, M.Vajjiravel and Jebamalai Elangovan, Tunable synthesis of 1,2,3-triazoles and enamines through deacylative azide-alkene cycloaddition. ***Eur. J. Org. Chem*.** DOI: org/10.1002/ejoc.202101470. **E-ISSN:1099-0690**

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Tunable Synthesis of 1,2,3-Triazoles and Enamines through Deacylative Azide-Alkene Cycloaddition

R. Rengasamy,[a] J. Paul Raj,[b] K. Vijayalakshmi,[a] N. Punitha,[a] M. Kesavan,[c] M. Vajjiravel,[b] and Jebamalai Elangovan*[a]

A tunable synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and enamines through [3 + 2] cycloaddition of activated olefins and organic azides is reported. Triazoles were achieved from benzylidene diketones and organic azides by copper oxide nanoparticle catalysis while enamines were synthesized from benzylidene malonates and organic azides under solvent-free and catalyst-free condition.

Introduction

For the past two decades, 1,2,3-trizoles have emerged indispensable due to their repertoire of applications in diverse fields such as drug discovery,[1] chemical synthesis,[2] bioconjugation,[3] macromolecules,[4] material science,[5] agrochemicals,[6] and polymers.[7] In addition, 1,2,3-triazoles are known to exhibit a wide spectrum of therapeutic activities such as anticancer, anti-HIV, antileishmanial, antimalarial, antiparasitic, antiviral, antimicrobial, antidiabetic, antifungal, antitubercular and antibacterial activities.[8] Some of the triazole containing leads in medicinal chemistry are displayed in Figure 1.

In spite of the traditional Huisgen azide-alkyne cycloaddition,[9] 1,2,3-triazoles were mainly prepared by copper catalyzed azide-alkyne cycloaddition (CuAAC)[10] and ruthenium catalyzed azide-alkyne cycloaddition (RuAAC).[11] CuAAC was capable of furnishing 1,4-disubstituted 1,2,3-triazoles while RuAAC was selective toward 1,5-disubstituted triazoles (Scheme 1, equation I). However, CuAAC is limited to terminal alkynes only while RuAAC is compatible with terminal as well as internal alkynes. Besides that, the cytotoxicity of copper catalysts,[12] high cost of ruthenium catalysts and poor commercial and synthetic viability of alkynes posed the overwhelming need of the alternative methods to access the 1,2,3-triazoles. In response to that, azide-alkene cycloaddition was developed in the place of azide-alkyne cycloaddition. Azide-alkene cycloaddition was executed by two methods.

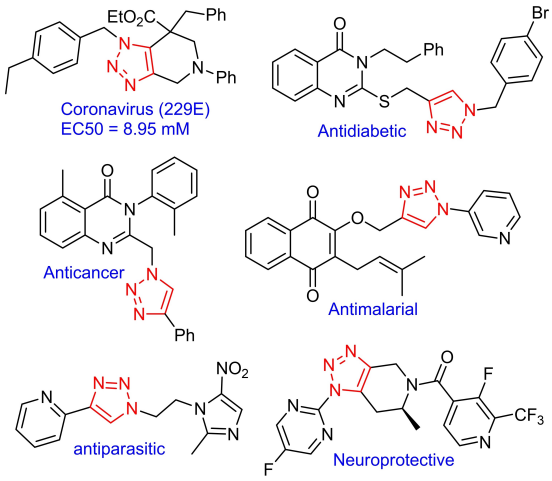
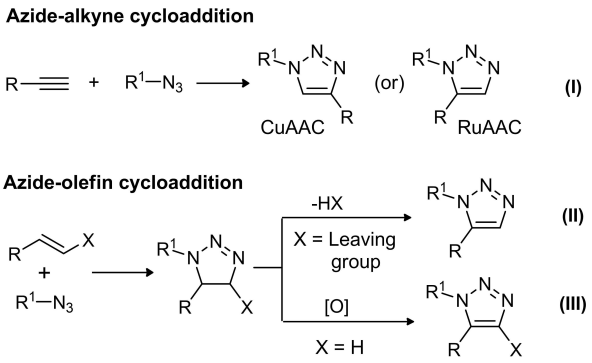


Figure 1. triazole containing leads in medicinal chemistry[8b]



Scheme 1. Background of azide-olefin cycloaddition

First one is eliminative azide-olefin cycloaddition (EAOC) where triazoline obtained by [3 + 2] cycloaddition of azide and olefin bearing a leaving group undergoes elimination and furnishes 1,2,3-triazole (Scheme 1, equation II).[13] Second one is oxidative azide-olefin cycloaddition (OAOC) where triazoline obtained by [3 + 2] cycloaddition of azide and activated olefins oxidizes into 1,2,3-triazole (Scheme 1, equation III).[14] Besides

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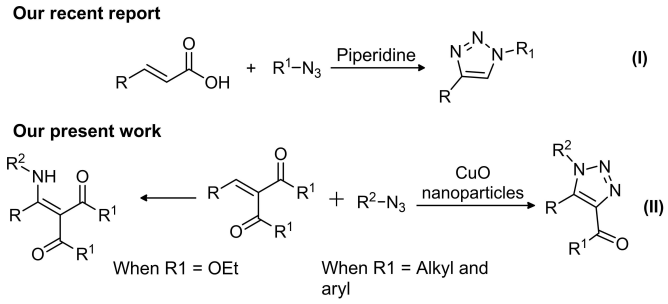
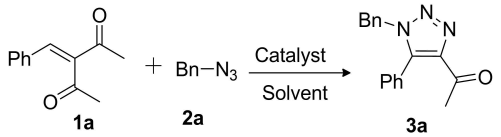
that, our research group has also substantially contributed in the field of OAOC and EAOC.[15] Another intriguing class of azide-olefin cycloaddition is 'organo click' reactions in which organo catalysts (mostly secondary amines) are employed in the place of metal catalysts[16] Recently we have reported a metal-free decarboxylative azide-alkene cycloaddition to access 1,4-disubstituted-1,2,3-triazoles (Scheme 2, equation I).[17] In continuation to that, we embarked on the cycloaddition of organic azides with benzylidenes obtained from Knoevenagel condensation of benzaldehydes and 1,3-dicarbonyl compounds. To our surprise, we obtained 1,2,3-triazoles from benzylidene diketones while we obtained enamines from benzylidene malonates (Scheme 2, equation II).



Scheme 2. Azide alkene cycloaddition furnishing triazoles and enamines.

Table 1. Optimization of deacylative azide-alkene cycloaddition.[a]



Entry	Catalyst [equiv.]	Solvent	Time [h]	Yield[b] [%] (**3a**)
1[c]	CNP (0.1)	DMF	24	38
2[c]	Cu* (0.1)	DMF	24	22
3[c]	Cu** (0.1)	DMF	24	Trace
4	CuI (0.1)	DMF	24	5
5	CuCl (0.1)	DMF	24	Trace
6	$CuSO_4.5H_2O$ (0.1)	DMF	24	–
7	CuO Bulk	DMF	24	Trace
8	CNP (0.1)	DMSO	24	-
9	CNP (0.1)	EtOH	24	23
10	CNP (0.1)	MeOH	24	Trace
11	CNP (0.1)	Water	24	–
12	CNP (0.1)	Toluene	24	–
13	CNP (0.1)	EtOAc	24	15
14	CNP (0.1)	Neat	24	-
15	CNP (0.1)	DMF	22	36
16	CNP (0.1)	DMF	20	30
17	CNP (0.2)	DMF	22	53
18	**CNP (0.3)**	**DMF**	**22**	**70**
19	CNP (0.4)	DMF	22	71
20	CNP (0.3)	DMF	48	72
21	CNP (0.3)	DMF	12	32
22[d]	CNP (0.3)	DMF	22	71
23[e]	CNP (0.3)	DMF	22	70
24[f]	CNP (0.3)	DMF	22	63
25[g]	CNP (0.3)	DMF	22	62

[a] Reaction condition: A mixture of olefin (1.0 mmol), azide (1.5 mmol) and catalyst were stirred in 1.0 mL of solvent. [b] Isolated yields. Unreacted olefin (**1a**) was detected in all the cases except entry 18, 19, 20, 22 and 23. [c] CNP=CuO Nanoparticle; Cu* = Cu Nano powder; Cu** = Cu powder. [d] Reaction was carried out at 150 °C. [e] Reaction was carried out at 120 °C. [f] Reaction was carried out at 100 °C. [g] Reaction was carried out at 80 °C.

Results and Discussion

At the outset, we started our investigation with the reaction of 1.0 mmol of 3-benzylidenepentane-2,4-dione (**1a**) and 1.5 mmol of benzyl azide (**2a**) in the presence of 0.1 mmol of CuO nanoparticles in 1.0 mL of DMF at 110 °C for 24 hours (Table 1). We were prompted to use CuO nanoparticles due to its heterogeneity, catalytic activity[18] and our precedent report using that catalyst.[15a][15b] To our excitement, we obtained the triazole (**3a**) in 38% yield (Table 1, entry 1). When the reaction was repeated replacing CuO nanoparticle by Cu Nano powder, the yield of **3a** dwindled to 22% (Table 1, entry 2). On the contrary, copper powder proved to be profoundly ineffective since trace amount of **3a** only was obtained (Table 1, entry 3). Cu(I) salts such as CuI and CuCl also failed to make a pronounceable change in the efficacy of the reaction (Table 1, entry 4 and 5). Similarly, no product formation was detected when $CuSO_4.5H_2O$ was utilized (Table 1, entry 6). To our surprise, bulk CuO also stood ineffective since trace amount of product only was observed (Table 1, entry 7). In order to improve the yield, we attempted solvent variation fixing CNP as the catalyst. When the solvents such as DMSO, EtOH, MeOH, water, toluene and ethylacetate were examined, ethanol could excel as the better one since it furnishes 23% yield of **3a** and ethylacetate stood next to that giving 15% yield of **3a** (Table 1, entry 8 −13). Eventually, it was disappointing that no product was obtained even at neat condition Table 1, entry 14). Since DMF and CuO nanoparticles were proved to be the best among all the solvents and catalysts employed for this transformation, we changed the other conditions and monitored the outcome. While reducing the time duration of the reaction to 22 and 20 hours, we resolved to fix 22 h as the duration for this reaction as the yield of **3a** was slightly higher than the other one (Table 1, entry 15 and 16). When the quantity of the catalyst was gradually increased from 0.1 mmol to 0.4 mmol, we decided to use 0.3 mmol of catalyst for this transformation as we inferred from the yields of **3a** (Table 1, entry 17–19). When the reaction time was increased to 48 h, no significant difference was noticed in the yield (Table 1, entry 20). On the other hand, yield of **3a** dropped drastically to 32% when the duration of the reaction was shortened to 12 h (Table 1, entry 21). No pronounceable difference in the yield was observed when the reaction was performed at 150 °C and 120 °C (Table 1, entry 22–23). But the yield of **3a** was reduced to 63% and 62% when the temperature of the reaction was reduced to 100 °C and 80 °C (Table 1, entry 24–25). Hence, we resolved to carry out the reaction at 110 °C for 22 hours with 0.3 mmol of CNP (Table 1, entry 18). Having the condition optimized (Table 1, entry 18), we extended that condition to various olefins and azides as shown in Scheme 3. Initially deacylative azide-alkene cycloaddition was performed on benzyl azide (**2a**) with various benzylidene diketones.

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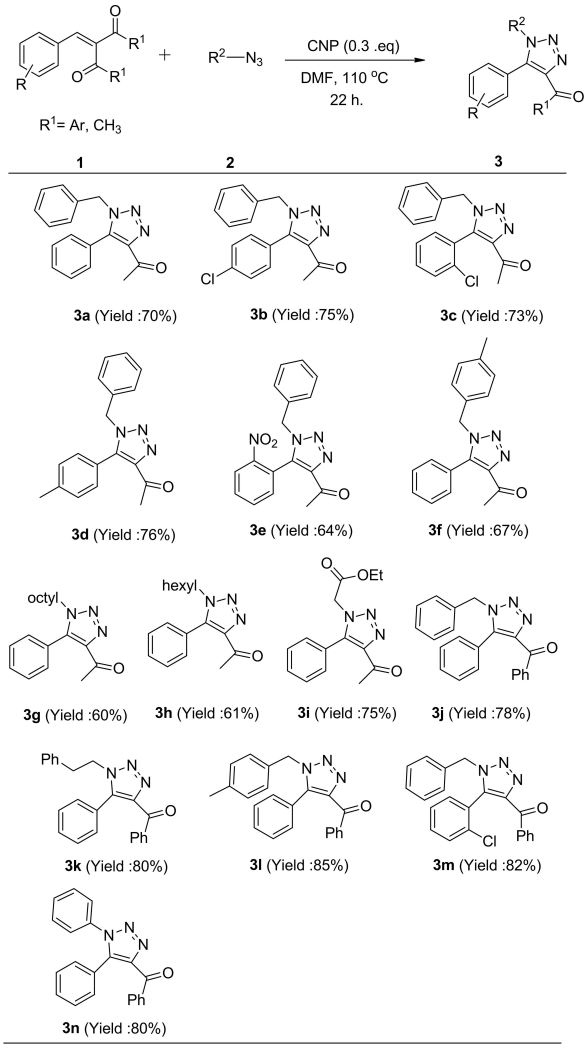


Scheme 3. Deacylative azide-alkene cycloaddition of benzylidene diketones and organic azides.

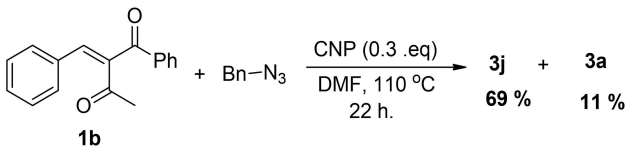
As stated in the optimization table, diacetyl benzylidene (**1a**) gives 70% yield of 1,2,3-triazoles (Scheme 3, compound **3a**). 4-Chlorosubstitution in the olefin increases the yield of the product (**3b**) into 75%. while 2-chloro substitution slightly reduces the yield of **3c** to 73%. On the other hand, 4-methyl substitution increases the yield of **3d** to 76%. To our anticipation, electron withdrawing nitro group at the second position, significantly reduces the yield of the triazole **3e**. It is noteworthy that no deacylative azide-alkene cycloaddition takes place when the alkyl substituted alkene-dione such as 3-propylidenepentane-2,4-dione was treated with benzyl azide. Moreover, decomposition of the starting material was detected. Subsequently, azide variation was examined on the olefin **1a**. 4-Methyl benzyl azide on reaction with **1a** furnished substantially good yield of the product **3f**. Aliphatic azides such as *n*-octyl azide and *n*-hexyl azide displayed same efficiency as shown from the yields of the products **3g** and **3h**. On the other hand, when ethyl 2-azidoacetate was used, the yield of **3i** was substantially improved than **3g** and **3h**. In the place of **1a**, 2-benzylidene-1,3-diphenylpropane-1,3-dione was used against different azides and monitored the outcome.

With benzyl azide (**2a**) 78% of triazole **3j** was obtained whose yield is comparatively higher than that of **3a**. Better results were obtained in the case of phenethyl azide and 4-methyl benzyl azides as inferred from the yields of **3k** and **3l**. 2-Chloro substitution on the olefin also furnished good amount of triazole **3m** with benzyl azide (**2a**). Similarly, the reaction with phenyl azide also furnished the corresponding triazole (**3n**) in good yield. When the same reaction was performed with alkene bearing unsymmetrical diketone (**1b**), acetyl group was predominantly eliminated instead of benzoyl group (Scheme 4).

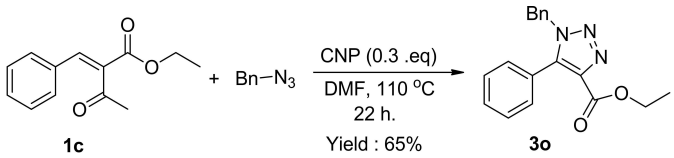
Similarly, in the case of the alkene connected with ester and ketone (**1c**), acetyl group was eliminated while ester group was remaining intact (Scheme 5).

In order to study the recyclability of the heterogeneous CuO nanoparticles, it was recovered after each cycle from the reaction mixture by simple centrifugation followed by washing with ethyl acetate and drying in vacuo (Table 2).

Similarly, when deacylative azide-alkene cycloaddition was attempted in diethyl benzylidene malonate **(1d)**, enamine **(3p)** was obtained (Scheme 6). After meticulous optimization (refer the supporting information) on this reaction, a collection of enamines was accomplished in excellent yields by stirring olefin (1.0 mmol) and azide (2.5 mmol) at 110 °C for 16 h at neat condition (Scheme 6). Our literature perusal revealed that



Scheme 4. Deacylative azide-alkene cycloaddition of benzylidene bearing unsymmetrical diketone and organic azides.



Scheme 5. Deacylative azide-alkene cycloaddition of benzylidene bearing ester and ketone with organic azides.

Table 2. Recycling of CuO nanoparticles.

Entry	Catalyst recovery [%]	Cycle	Yield[c] [%]
1[a]	93	1	70
2[b]	87	2	66
3[b]	83	3	60
4[b]	75	4	56

[a] Reaction condition: **1a** (4.0 mmol), 2a (6.0 mmol) and CuO nanoparticles (1.2 mmol) were heated at 110 °C for 22 h. [b] Recovery catalyst was used under the same reaction conditions to those of the initial run. [c] All are isolated yields.

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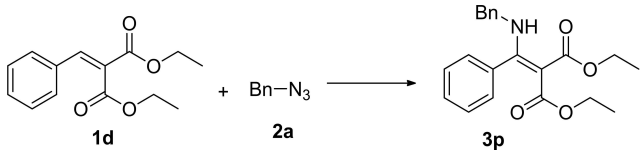
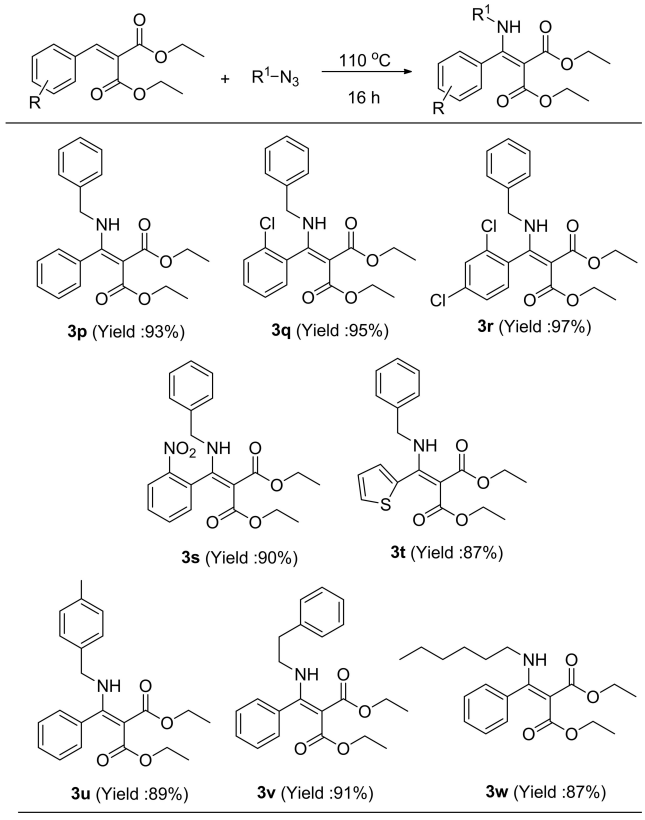


Scheme 6. Azide-alkene cycloaddition on benzylidene diester.

Prager *et al.* have reported a two-stage synthesis of enamine in which the triazoline prepared from diethyl benzylidene malonate and benzyl azide was treated with potassium tertiary butoxide followed by trifluoro acetic acid to achieve the diethyl benzyl amino benzylidene malonate.[19] In spite of the usage of vigorous condition in this method, the enamine was obtained in poor yield along with 1,2,3-triazole.

When benzyl azide was treated with various benzylidene diesters, excellent yields of the corresponding enamines were obtained and the results are displayed in Scheme 7. Alkene **1 d** furnished 93% of enamine (**3 p**) while 2-chloro substitution on the alkene led to 95% of enamine (**3 q**). 2,4-Dichloro substitution on the olefin could achieve the highest yield of 97% of the corresponding enamine (**3 r**). In the case of 2-nitro substitution on the olefin, efficacy decreased slightly and rendered 90% yield of the product (**3 s**). On the contrary, mild decrement in the efficiency of this protocol was noticed in the case of thiophene substituted olefin as shown from the yield of **3 t**.



Scheme 7. Enamine synthesis through azide-alkene cycloaddition of diethyl benzylidene malonates and organic azides.

Subsequently, olefin **1 d** was treated with 4-methyl benzyl azide, phenethyl azide and *n*-hexyl azide. In the case of *n*-hexyl azide, the efficiency was slightly diminished while the other two showcased similar efficiency as shown from the yields of **3 u**, **3 v** and **3 w**.

Conclusion

A novel approach has been developed to achieve the 1,2,3-triazoles by deacylative azide-alkene cycloaddition. To the best of our knowledge, synthesis of 1,2,3-triazoles through deacylative azide-alkene cycloaddition is unknown. By this approach, various 1,2,3-triazoles bearing electron withdrawing groups such as ketones and esters are obtained simply from the benzylidenes bearing an acyl group. Easy accessibility of these alkenes and recyclability of the heterogeneous CuO nanoparticles are additional advantages of this protocol. Moreover, preparation of enamines from the azide alkene cycloaddition of benzylidene malonates also has been demonstrated. Excellent yields, solvent-free and catalyst-free conditions foster this method to stand unique from the precedent approach for the synthesis of enamines. At present, our group is engaged in extending the scope of these findings to the synthesis of 1,2,3-triazole fused oxygen and nitrogen heterocycles.

Experimental Section

General Procedure for the Synthesis of 1,4,5-trisubstituted 1,2,3-triazole: A mixture of 3-benzylidenepentane-2,4-dione (**1 a**, 1.0 mmol), organic azides (**2 a**, 1.5 mmol) and CuO nanoparticles (0.3 mmol) were heated at 110 °C for 22 h in DMF (1.0 ml). When the completion of the reaction was ensured by TLC, the reaction mixture was cooled to room temperature and poured to water. The organic layer was extracted with ethyl acetate and the organic layer was dried with Na_2SO_4. The resulting crude product was purified by column chromatography.

General Procedure for the synthesis of enamine: A mixture of diethyl benzylidene malonate (**1 d**, 1.0 mmol) and organic azide (**2 a**, 2.5 mmol) were stirred at 110 °C for 16 h under neat condition. When the completion of the reaction was ensured by TLC, the reaction mixture was cooled to room temperature and purified by the column chromatography.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Azide-alkene cycloaddition · Cycloaddition · Deacylative azide-alkene cycloaddition · Nitrogen heterocycles · 1,2,3-Triazoles

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A novel route to 1,4-disubstituted-1,2,3-triazoles through metal-free decarboxylative azide-alkene cycloaddition

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ABSTRACT

A collection of 1,4-disubstituted 1,2,3-triazoles was achieved by decarboxylative [3 + 2] cycloaddition of organic azides and cinnamic acids. Metal-free condition, high regioselectivity and easy accessibility of starting materials are the salient attributes of this protocol.

Introduction

Despite being devoid of natural origins,[1] 1,2–3-trizoles have drawn great deal of attention for the past two decades owing to their formidable role in diverse fields such as organic synthesis, [2] supramolecules,[3] drug discovery,[4] polymers [5] and materials [6]. In spite of the conventional Huisgen cycloaddition,[7] a major breakthrough was achieved in the synthesis of 1,2,3-triazoles by copper-catalyzed azide-alkyne cycloaddition (CuAAC)[8] whose mettle is to furnish 1,4-disubstituted 1,2,3-triazoles selectively. Subsequently, the complementary regio isomer (1,5-disubstituted 1,2,3-triazole) was achieved by ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC).[9] As alternative to azide-alkyne cycloaddition, azide-alkene cycloaddition was developed since the alkenes have better synthetic and commercial viability than alkynes. This idea was ingeniously executed by oxidative azide-olefin cycloaddition (OAOC)[10] and eliminative azide-olefin cycloaddition (EAOC).[11] In OAOC, 1,2,3-triazole was achieved through cycloaddition-oxidation route while EAOC follows cycloaddition-elimination route. Recent years, our research group also has substantially contributed in the field of OAOC and EAOC. [12] Another interesting class of reactions called "organo-click" reactions were also developed in which metal catalysts were replaced by organocatalysts to achieve the triazoles. [13] As an alternative to OAOC and EAOC, decarboxylative azide-alkene cycloaddition was introduced by Atul Kumar and co-workers in which 1,5-disubstituted 1,2,3-triazoles were prepared by employing Cu (II) catalyst (Scheme 1, Equation 1).[14] Herein we report a metal-free decarboxylative azide-alkene cycloaddition of cinnamic acid and organic azide (Scheme 1, Equation 2) to achieve the complementary regioiosomer (1,4-triazole).

The preliminary optimization was initiated with cinnamic acid (**1a**) and benzyl azide (**2a**) as model substrates to fix the appropriate condition. We started with copper iodide as catalyst (0.1 eq.), potassium carbonate as base (1.0 eq.) and DMSO (2.0 mL) as the solvent at 110 °C. When the reaction was prolonged for 24 h, the required 1,2,3-triazole (**3a**) was obtained in 20% yield (Table 1, entry 1). Subsequently, other Cu species including CuCl, Cu powder, CuO nano particles and $Cu(OTf)_2$ were also examined for improving the conversion (Table 1, entries 2–5).

Among all of these catalysts, CuCl was found to be convincing since it showed slight improvement in the yield of the product (Table 1, entry 2). Hence, fixing CuCl as catalyst, we tested the other solvents such as DMF, toluene, THF and water and monitored the outcome (Table 1, entry 6–9). To our disappointment, none of these solvents could impose any pronounceable change in the conversion.

On the other hand, substantial improvement was noticed when the reaction was performed under solvent-free condition (Table 1, entry 10). Spurred by this, we varied the bases such as Potassium *tert*-butoxide, sodium bicarbonate, DABCO, DBU, pyridine and piperidine under solvent-free condition and monitored the

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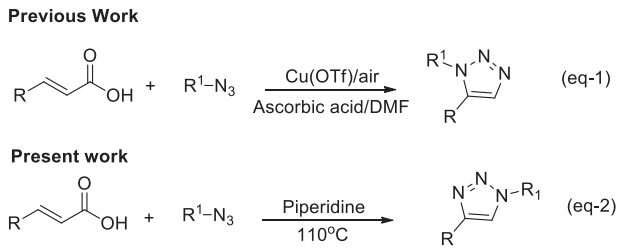
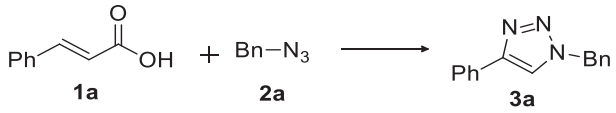


Scheme 1. Decarboxylative azide-alkene cycloaddition of cinnamic acids and organic azides.

outcome (Table 1, entries 11–16). To our surprise, the reaction performed in the presence of piperidine managed to furnish the corresponding product **3a** in 68% (Table 1, entry 16). Hence, fixing piperidine as base, when we tested the reaction in the absence of catalyst, we observed an unexpected spike in the efficiency of this protocol registering 92 % yield of the product (Table 1, entry 17). When we reduced the duration of the reaction from 24 h to 16 h, 14 h and 12 h, we resolved to fix 14 h as the suitable time duration to carry out this reaction (Table 1, entries 18 to 20). While reduced the amount of the base further, 0.5 equivalent and 0.25 equivalent, 93% yield of **3a** was obtained in the case of 0.5 equivalent of piperidine. (Table 1, entry 21 and entry 22). Fixing the quantity of base (0.5 eq) and time (14 h), we varied the temperature and monitored the outcome. While raising the temperature to 120 °C, there was no pronounceable change in the yield (Table 1, entry 23), while reducing the temperature to 100 °C, the yield dropped apparently (Table 1, entry 24). Hence, we resolved to perform the reaction in the presence of 0.5 equivalent of piperidine for a duration of 14 h at 110 °C (Table 1, entry 21).

Having fixed the optimized condition, we applied it to various substrates (Scheme 2). Fixing the benzyl azide (**2a**) we varied many substituted cinnamic acids and the results are reported in scheme 2. As stated in the optimization table, 93 % of product (**3a**) was obtained with cinnamic acid (**1a**). When 4-chlorocinnamic acid was used, yield of the corresponding triazole **3b** was improved little more. In the case of bromo substitution, remarkable decline of yield of the triazole (**3c**) was observed. In the case of 3-bromocinnamic acid, yield of the product (**3d**) plummeted furthermore. When 2,4-dichloro cinnamic acid was employed, a big surge in the yield of the product was observed than monochloro substitution (**3e**). On the other hand, electron donating substituents like methoxy group could achieve substantially good yield (81%) of product (**3f**). On the contrary, isopropyl group which is also an inductive electron donating group, pronounceably reduces the efficiency as depicted by the slump of yield of **3g**. Other acrylic acids such as 3-(2-naphthyl) acrylic acid and 3-(2-furyl) acrylic acid also could not show the same potential of cinnamic acid (**1a**) which is evident from the yields of **3h**, **3i** and **3a**. In continuation, various azides were examined with cinnamic acid (**1a**). 4-Methylbenzyl azide registers the highest yield of 99% whereas 4-methoxy benzyl azide could furnish only 89 % of the corresponding triazoles (**3j** and **3k**). When aliphatic azides such as phenethyl azide and *n*-octyl azide were studied, phenethyl azide managed to show substantially better efficiency than *n*-octyl azide as depicted from the yields of **3l** and **3m**. In the case of phenyl azide, similar efficiency reminiscent of the octyl azide was observed as the yields of **3m** and **3n** are very closer. When phenethyl azide was subjected to react with 4-chloro, 4-bromo and 4-methoxy cinnamic acids, chloro substitution led to a remarkably highier yiled of th prouct (**3o**) while bromo and methoxy substitutions furnish similar yields of products (**3p** and **3q**). Similarly, when 4-methylbenzyl azide was treated with different cinnamic acids such as 4-chloro, 3-bromo and 4-methoxy cinnamic acids, better result was observed in the case of 4-methoxy cinnamic acid as testified from the yields of the corresponding triazoles (**3r**, **3s** and **3t**). When octyl azide was treated with 4-chlorocinnamic acid, 91% of the triazole (**3u**) was obtained. This is remarkably different from the yield of **3m**. The

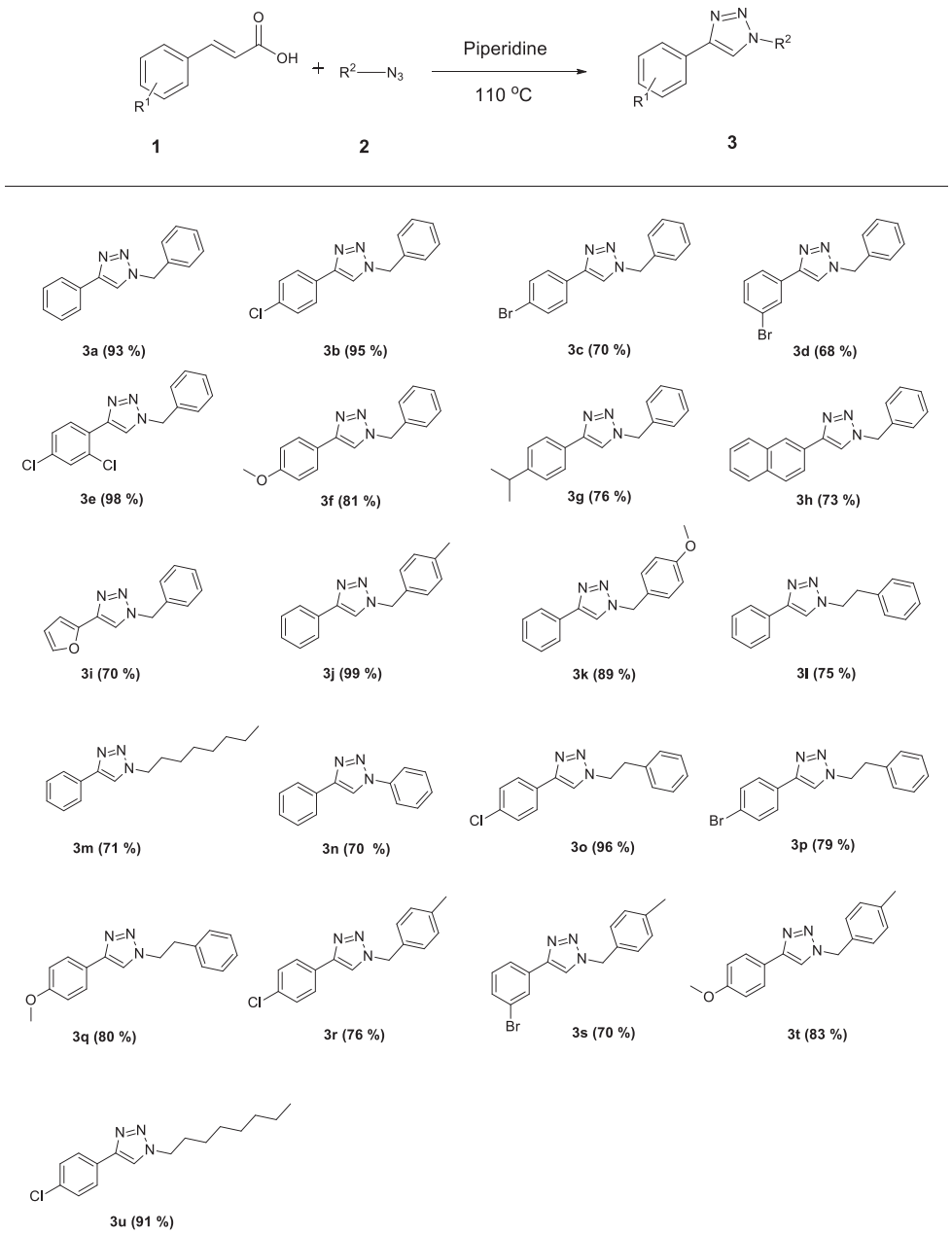
Table 1
Optimization of decarboxylative azide-alkene cycloaddition.[a]



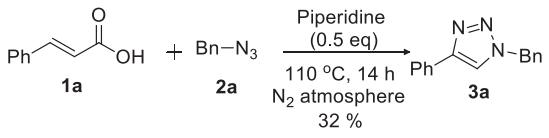
1a 2a 3a

Entry	Catalyst	Base	Solvent	Time (h)	Temperature (° C)	Yield (%) [b]
1	CuI	K_2CO_3	DMSO	24	110	20
2	CuCl	K_2CO_3	DMSO	24	110	30
3	Cu Powder	K_2CO_3	DMSO	24	110	26
4	CNP [c]	K_2CO_3	DMSO	24	110	23
5	$Cu(OTf)_2$	K_2CO_3	DMSO	24	110	Trace
6	CuCl	K_2CO_3	DMF	24	110	09
7	CuCl	K_2CO_3	Toluene	24	110	Trace
8	CuCl	K_2CO_3	THF[d]	24	110	08
9	CuCl	K_2CO_3	Water	24	110	Trace
10	CuCl	K_2CO_3	-	24	110	42
11	CuCl	K^tOBu	-	24	110	18
12	CuCl	$NaHCO_3$	-	24	110	Trace
13	CuCl	DABCO	-	24	110	Trace
14	CuCl	DBU	-	24	110	Trace
15	CuCl	Pyridine	-	24	110	25
16	CuCl	Piperidine	-	24	110	68
17	-	Piperidine	-	24	110	92
18	-	Piperidine	-	16	110	94
19	-	Piperidine	-	12	110	85
20	-	Piperidine	-	14	110	93
21	**-**	**Piperidine** [e]	**-**	**14**	**110**	**93**
22	-	Piperidine [f]	-	14	110	81
23	-	Piperidine [e]	-	14	120	91
24	-	Piperidine [e]	-	14	100	82

[a] A mixture of Cinnamic acid (1.0 mmol), benzyl azide (1.5 mmol), catalyst (0.1 mmol), base (1.0 mmol) and solvent (2.0 mL) were heated. [b] Isolated yields. [c] CNP = CuO Nanoparticles. [d] Reaction was performed in sealed tube. [e] 0.5 equivalent of base is used. [f] 0.25 equivalent of base is used.



Scheme 2. Decarboxylative azide-alkene cycloaddition of cinnamic acids and organic azides. In order to get the mechanistic insight, we performed the decarboxylative cycloaddition of 1a with 2a under nitrogen atmosphere. To our surprise only 32 % of the triazole (**3a**) was observed which emphasizes the pivotal role of oxygen in this transformation (Scheme 3).



Scheme 3. Decarboxylative azide-alkene cycloaddition under nitrogen atmosphere.

structure of the triazole prepared by this method was unambiguously ascertained by single crystal XRD (Fig 1).

No reaction took place when the reaction was performed on methyl cinnamate in the place of cinnamic acid (Scheme 4). Moreover, since only 0.5 equivalent of piperidine is used, it is inferred that the piperidine is consumed and regenerated in the course of the reaction. Another observation is, as soon as the reagents were added, heat was evolved which in indicates the neutralization reaction between the cinnamic acid and piperidine. From these above observations we propose the following mechanism (Scheme 5). The azide alkene cycloaddition takes place on the car-

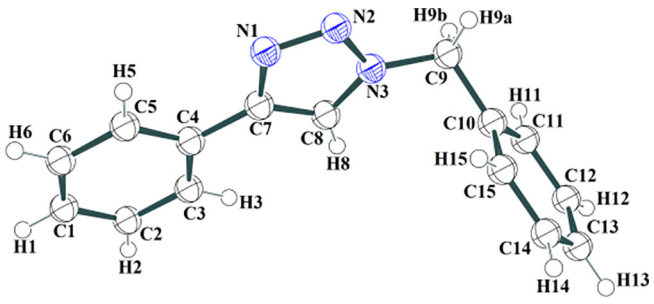
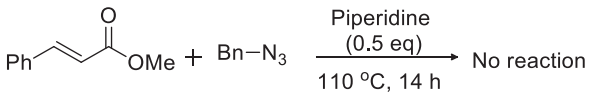
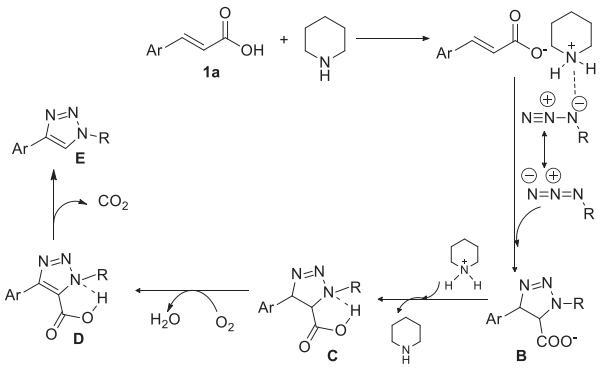


Fig. 1. ORTEP diagram of **3a**.[15]



Scheme 4. Decarboxylative azide-alkene cycloaddition on cinnamic ester.



Scheme 5. Proposed mechanism for the decarboxylative azide-alkene cycloaddition.

boxylate ion formed from the acid-base neutralization reaction and furnishes the triazoline **B**. Protonation on the carboxylate ion of **B** by the piperidinium ion leads to the triazoline **C**. We presume that the intramolecular hydrogen bonding between the carboxylic acid and the nitrogen of **C** is responsible for the regioselectivity of this cycloaddition. This idea was corroborated by the reaction of methyl cinnamate with benzyl azide (Scheme 4). In continuation, the concomitant oxidation and decarboxylation leads to the required 1,2,3-triazole (**E**).

In conclusion, we have developed a method to achieve a collection of 1,4-disubstituted 1,2,3-triazoles from decarboxylative azide-alkene cycloaddition of substituted cinnamic acids and organic azides. This method assures the complementary regioselectivity to the preceding method. Metal-free condition and easy accessibility of the starting materials are also the salient attributes of this protocol.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153440.

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[15] CCDC 2091252 (3a) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.