

Synthesis of 2*H*-1,2,3-Triazoles

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Abstract This chapter gives an overview of methods for the synthesis of NH- and N(2)-substituted 1,2,3-triazoles, their advantages, lacks, scope, and limitations. Moreover, it will give some insights on the reaction mechanisms and will explain how different conditions and structure substrates can influence the direction for reactions. An extensive analysis for the last 20 years (starting at 1990) of NH-1,2,3-triazoles chemistry is presented. Some older data with high importance are also included.

Keywords Alkylation · Arylation · Azide · Cycloaddition · Oxidative cyclization · Rearrangement · Regioselectivity

Contents

1	Introduction	53
2	Thermal 1,3-Dipolar Cycloaddition of Azides to Alkynes	56
2.1	Cycloaddition of Alkynes to Hydrazoic Acid and Sodium Azide	56
2.2	Cycloaddition of Alkynes to Azidotrimethylsilane and Azidotributylstannane	58
2.3	Cycloaddition of Alkynes to Organic Azide	59
2.4	Cycloaddition of Alkynes with Metal-Coordinated Azide Ligands	60
2.5	Cycloaddition of Activated Alkenes to Azides	61
2.6	Cycloaddition of Enamines to Azides	64
2.7	Cycloaddition of Alkenes to Metal Azides	65
2.8	Microwave-Assisted and One-Pot Reactions	66
2.9	Solid-Phase Techniques for [3+2]-Cycloaddition of Azides to Alkenes	68
3	Catalysis in Synthesis of 2 <i>H</i> -1,2,3-Triazoles by 1,3-Dipolar Cycloaddition Reactions ...	70
4	Synthesis of 2-Substituted 1,2,3-Triazoles by Reactions of NH-1,2,3-Triazoles with Electrophiles	77
4.1	<i>N</i> -Alkylation of NH-1,2,3-Triazoles with Alkylhalides	78
4.2	Alkylation of NH-1,2,3-Triazoles with Alkyl Carboxylates and Sulf(on)ates	82

4.3	Mitsunobu Reaction of NH-1,2,3-Triazoles	83
4.4	Michael Addition	84
4.5	<i>N</i> -Arylation (<i>N</i> -Heteroarylation) of NH-1,2,3-Triazoles	87
4.6	<i>N</i> -Acylation, <i>N</i> -Sulfonation, and <i>N</i> -Carbamoylation of NH-1,2,3-Triazoles	90
5	Synthesis of 2 <i>H</i> -1,2,3-Triazoles by Transformations of Functionalized Hydrazones	91
5.1	Oxidation of Mono- and Bis(arylhydrazones)	91
5.2	Oxidative Cyclization of Arylhydrazonoacetamidoximes and α -Hydrazono-Oximes	94
5.3	Oxidative Cyclization of Arylhydrazonoacetamidines	95
5.4	Intramolecular Cyclization of Bis(hydrazones) and Hydrazonoamidoximes	96
5.5	Boulton–Katritzky Rearrangement of 3-Hydrazono Oxadiazoles, -Furoxans and -Isoxazoles	98
6	Intra- and Intermolecular Reactions of Diazocompounds	102
7	Heterocycle Transformations in the Synthesis of 2 <i>H</i> -1,2,3-Triazoles	104
8	Conclusion	105
	References	106

Abbreviation

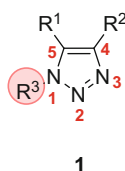
Ac	Acetyl
anhyd	Anhydrous
Ar	Aryl
B3LYP	Becke three-parameter, Lee–Yang–Parr
Bn	Benzyl
Bu	Butyl
cat	Catalyst
COSMO	Conductor-like Screening MOdel
Cy	Cyclohexyl
d	Day(s)
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIPA	Diisopropyl amine
DMA	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
EDG	Electron-donating group
equiv	Equivalent(s)
EWG	Electron-withdrawing group
Fc	Ferrocenyl
GIAO	Gauge Independent Atomic Orbital
h	Hour(s)

Hex	Hexyl
HMBC	Heteronuclear Multiple Bond Coherence
<i>i</i> -Pr	<i>Iso</i> -propyl
KHMDS	Potassium hexamethyldisilazide potassium bis(trimethylsilyl)amide
LHMDS	Lithium hexamethyldisilazide lithium bis(trimethylsilyl)amide
min	Minute(s)
mol	Mole(s)
MW	Microwave irradiation
NICS	Nucleus Independent Chemical Shifts
NMP	<i>N</i> -methylpyridine
NOE	Nuclear Overhauser effect
Ph	Phenyl
Pr	Propyl
Pv	Pivaloyl
py	Pyridine
rt	Room temperature
SFC	Solvent free condition
SPS	Solid-phase synthesis
TBAF	Tetrabutylammonium fluoride
<i>t</i> -Bu	<i>Tert</i> -butyl
Tf	Trifluoromethanesulfonyl (triflyl)
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TMS	Trimethylsilyl
Tp	Tetrazole
Ts	Tosyl 4-toluenesulfonyl
XRD	X-ray diffraction

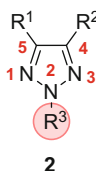
1 Introduction

1,2,3-Triazoles can be divided into three groups depending on the position of substituent at nitrogen atom [1–6]:

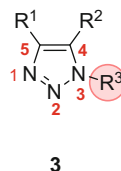
1*H*-1,2,3-Triazole



2*H*-1,2,3-Triazole

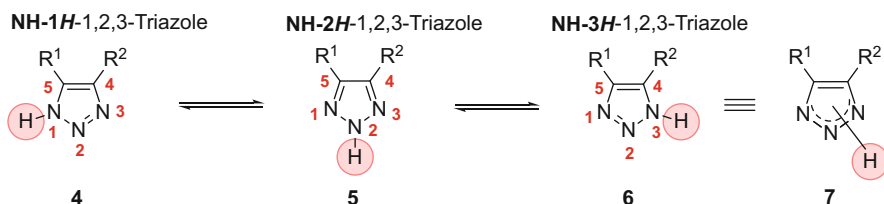


3(1)*H*-1,2,3-Triazole



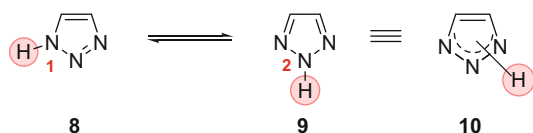
The third isomer **3**, which formally may be named as 3(1)*H*-1,2,3-triazole, was obtained in rare cases (see paragraph 4).

Triazoles **4–6** with unsubstituted ring nitrogen atom have special interest due to their importance for the synthesis of new derivatives. NH-triazoles **4–6** are thermodynamically stable tautomers. They exist in equilibrium in solutions and have very close values of Gibbs energy [1, 2, 6–12]. The ratio of tautomeric forms **4–6** can be determined by spectral methods, although it is impossible to separate them. In modern books it is a common practice not to put a certain form of tautomer to represent NH-1,2,3-triazoles, but rather to use generalized formulas, for example **7** or **10**.



Theoretical calculations of magnetic properties of NH-1,2,3-triazoles performed at B3LYP/6-311++G(d,p) level within GIAO approach confirmed the aromatic character of these *6e*-heterocycles. Nucleus independent chemical shifts (NICS) (1) calculated above the ring centers were -13.51 ppm for tautomers **8** and -13.61 ppm for **9** [7].

Experimental and theoretical studies indicated that the tautomer **8** is more stable in solution, while *2H*-isomer **9** is more stable in gas phase (~ 4.0 kcal mol $^{-1}$) [7–12].

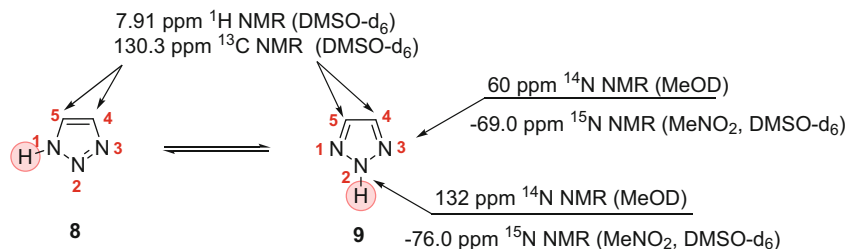
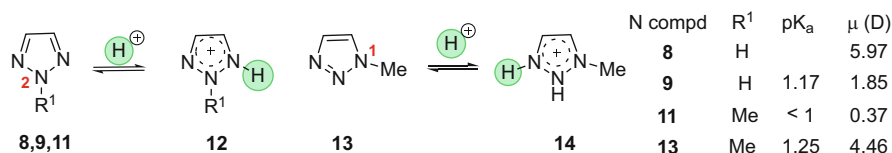
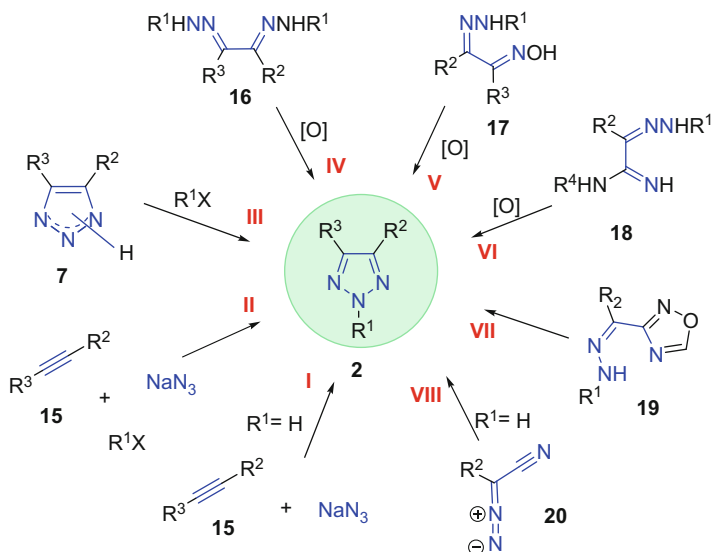


Spectroscopic ^{14}N and ^{15}N NMR data revealed that unsymmetrical 1,2,3-triazoles **4–5** exist in the *2H*-tautomer form (70–100%) [13, 14]. ^1H , ^{13}C , ^{15}N and ^{14}N NMR shifts were identical for the two hydrogen and carbon atoms in positions 4 and 5 and nitrogen atoms at positions 1, 2 and 3 of 1,2,3-triazoles for both tautomers (Scheme 1) [1, 2, 6, 9].

N-Substituted isomers of *1H* and *2H*-1,2,3-triazoles can be differentiated based on their polarity. Indeed, the dipole moment of the *1H*-isomer is substantially higher than for *2H*-1,2,3-triazoles (Scheme 2) [1, 2, 6].

1,2,3-Triazoles demonstrate amphoteric properties and can behave as a weak base or a weak acid similar to phenol. 2-Methyltriazole **11** shows a much weaker basicity in comparison with 1-methyl-1,2,3-triazole **13** (Scheme 2) [1, 3, 6, 9–14].

1,3-Dipolar cycloaddition of substituted azides to alkynes is a common approach to obtain various N(1)-derivatives of 1,2,3-triazoles. Huisgen was the first one to establish mechanistic details underlying this reaction [15]. The groups of Sharpless et al. [16] and Meldal et al. [17] modified this method. They performed it as a highly

**Scheme 1** NMR spectra data for NH-1,2,3-triazoles**Scheme 2** Polarity and acidity of 1*H*- and 2*H*-1,2,3-triazoles**Scheme 3** General methods for the synthesis of 2*H*-1,2,3-triazoles

regioselective process catalyzed by Cu(I) and Ru(II) salts taking place under mild conditions and giving desired products with exceptionally high yields [3].

It should be stressed that in opposite to 1*H*-1,2,3-triazoles, there is no universal approach to obtain 2*H*-1,2,3-triazoles, although numerous synthetic methods have been developed (Scheme 3) [1–6]. The most known one among them are: the cycloaddition of azides to acetylenes **15** (I), one-pot three-component cyclization

(II), reaction of 2*H*-1,2,3-triazoles **7** with electrophilic agents (III), the various cyclizations of hydrazones **16–18** (IV–VI), Boulton–Katritzky rearrangement of (*Z*)-3-arylhydrazones of 3-acyl-1,2,4-oxadiazoles **19** (VII), and intra- and intermolecular cyclization of diazocompounds **20** (VIII).

Currently, 2*H*-1,2,3-triazoles are being applied into various fields [18, 19] including their diverse biological activity and unique photonic properties. In that respect, the development of versatile methods for their synthesis became an important direction of triazole chemistry. In the following part of this critical review, we will describe the current state of the art of synthetic approaches listed above in Scheme 3.

2 Thermal 1,3-Dipolar Cycloaddition of Azides to Alkynes

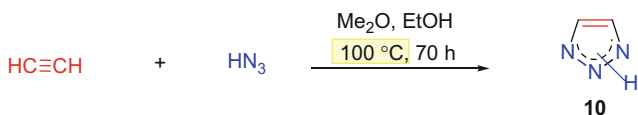
2.1 Cycloaddition of Alkynes to Hydrazoic Acid and Sodium Azide

Dimroth and Fester were first to propose the direct construction of unsubstituted NH-1,2,3-triazole ring by the interaction of hydrogen azide with acetylene [20]. The reaction was carried out by prolonged heating in a sealed tube (Scheme 4). The analogous transformation of phenyl azide with acetylene proceeded faster, in 40 h.

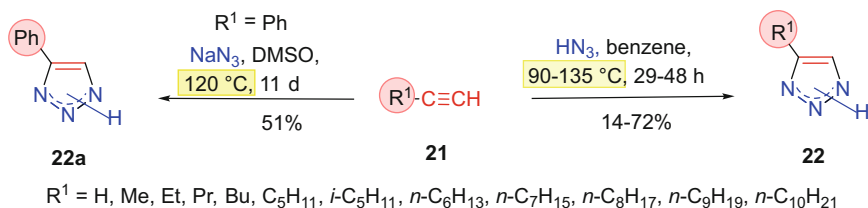
The dipolarophilic substrates used in 1,3-dipolar cycloaddition with azides were acetylenes bearing alkyl [21], aryl [22–27], heterocyclic [28–34], carboxy, formyl, cyano, nitro, phosphonyl, benzoyl [26, 35–44] substituents, and nucleoside residues [45]. Although the cycloaddition of alkynes to azides was characterized by a substantial exothermic effect, its high activation barrier implies that the reaction should be performed at increased temperatures. A general procedure is to heat the reactants at reflux in toluene, benzene, or alcohols, or to heat them in DMF/DMSO. For example, monoalkyl- or monophenylacetylenes **21** can interact with azides in benzene in closed vessels or after heating in DMSO [21, 22, 25] (Scheme 5).

A disadvantage of this protocol is that higher temperatures shift the thermodynamic equilibrium toward the side products and the yield of the desired product can be decreased [38]. The efficiency of the process strongly depends on spatial and electronic factors of the substituents on the alkyne. It was established that introduction of electron-withdrawing groups (EWGs) enhanced the 1,2,3-triazole yields. Conversely increasing the electron-donating properties of the substituent or the presence of several electron-donating groups (EDGs) at the same time on phenylpropionitriles **23** led to decreased yields of triazoles **24** down to 54–60% even though a high temperature was employed (Scheme 6) [38].

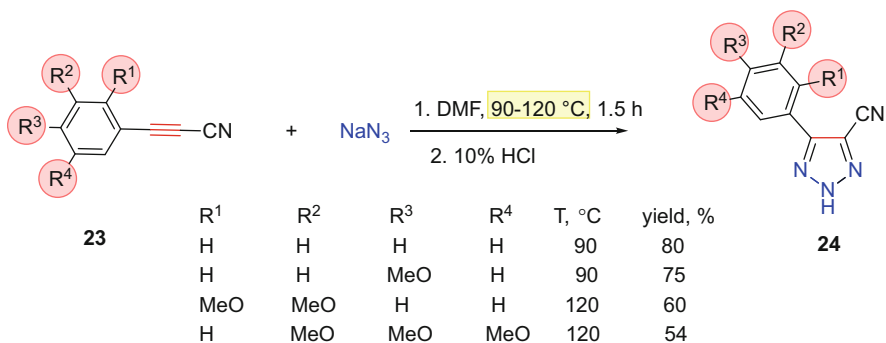
Ethyne-bisdiphenylphosphine oxide and sulfide **25** reacted exothermally with NaN_3 in methanol to produce the sodium 1,2,3-triazolide salt **26** ($\text{X}=\text{O}$, S) (Scheme 7) [40–42]. It should be noted that the reaction with ethyne-bisdiphenylphosphine selenide **25** ($\text{X}=\text{Se}$) required longer heating. The reactivity of ethynes in this reaction decreases in the series: $-\text{PPh}_2=\text{O}>-\text{PPh}_2=\text{S}>-\text{PPh}_2=\text{Se}$



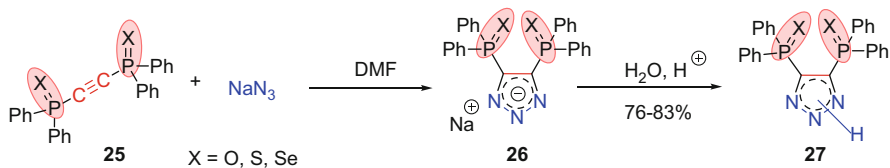
Scheme 4 The first example of the reaction of 1,3-dipolar cycloaddition acetylene to hydrazoic acid



Scheme 5 Reaction of 4-alkyl(phenyl) acetylenes **21** with hydrazoic acids and sodium azide



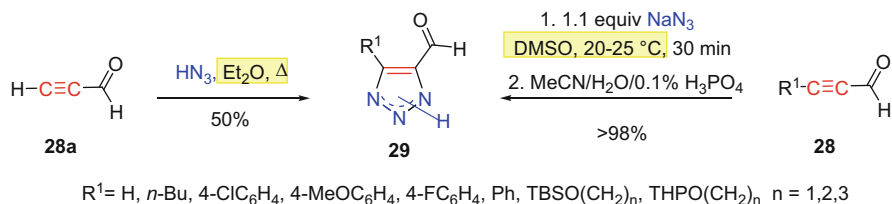
Scheme 6 Electronic substituent effect on the cycloaddition phenylpropiol nitriles **23** to sodium azide



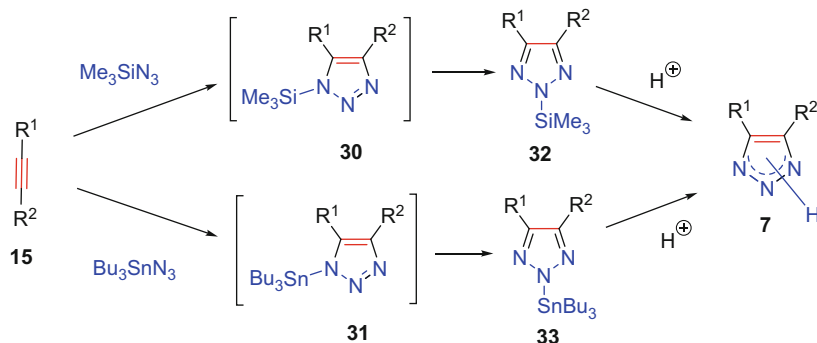
Scheme 7 Reaction of ethyne-bisdiphenylphosphine oxide, sulfide, and selenide **25** with sodium azide

and, consequently, the activity of the triple bond decreased in the same order. Acidification of 1,2,3-triazolides **26** yielded free acid **27** (Scheme 7).

The choice of a solvent is a crucial point for the cycloaddition reaction. Sodium azide reacted with propiolic aldehyde **28a** or its derivatives **28** in DMSO at room temperature and 4-formyl-1,2,3-triazoles **29** were obtained in quantitative yields.



Scheme 8 Synthetic routines to 2H-1,2,3-triazole-4-carbaldehydes



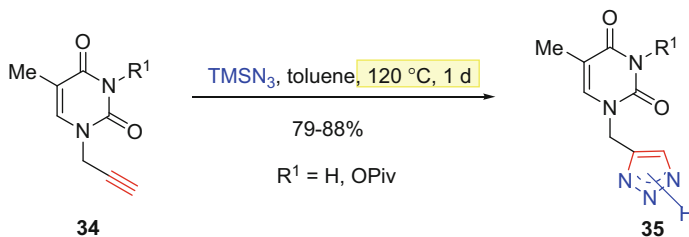
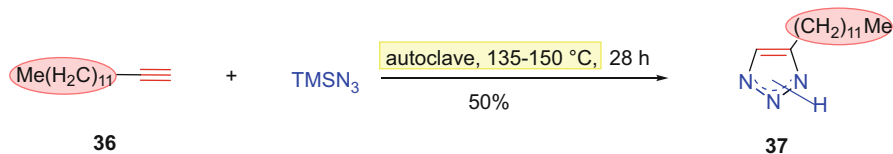
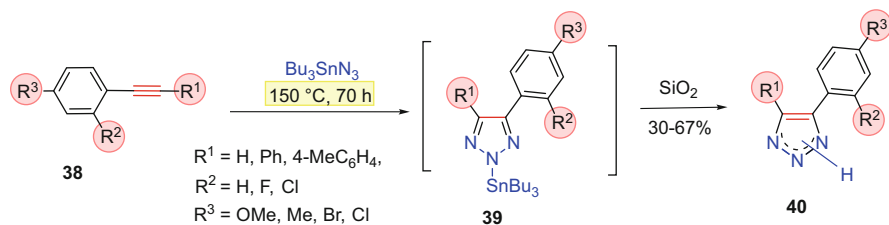
Scheme 9 1,3-Dipolar cycloaddition of alkynes with trimethylsilyl-/tri-*n*-butylstannylazides

Only moderate yields were obtained by reflux of the same components in ether (Scheme 8) [35–37].

2.2 Cycloaddition of Alkynes to Azidotrimethylsilane and Azidotributylstannane

Further methodological development for the synthesis of 2H-1,2,3-triazoles via [3+2]-cycloaddition involved the use of trimethylsilyl or tributylstannyl azides as 1,3-dipoles (Scheme 9) [15, 22, 31, 34, 43, 46–58]. Thus, NH-1,2,3-triazoles **7** were obtained via rearrangement followed by hydrolysis of initially formed 1-trimethylsilyl- or 1-tri-*n*-butylstannyl-1,2,3-triazoles **30** and **31** (Scheme 9) in good yields.

Unlike hydrazoic acid, these azides were thermodynamically stable. Therefore, they are very convenient and relatively safe substitutes for hydrazoic acid in many reactions with various alkynes. Nevertheless, to obtain triazoles by reaction of these stable azides with acceptable yields, a prolonged heating of substrates in different high boiling solvents (usually DMF, DMA, toluene, xylene) is required. For example, to produce thymine-substituted NH-1,2,3-triazoles **35**, 1-propargyl-thymine **34** and trimethylsilylazide were continuously heated for 1 day in toluene (Scheme 10) [50].

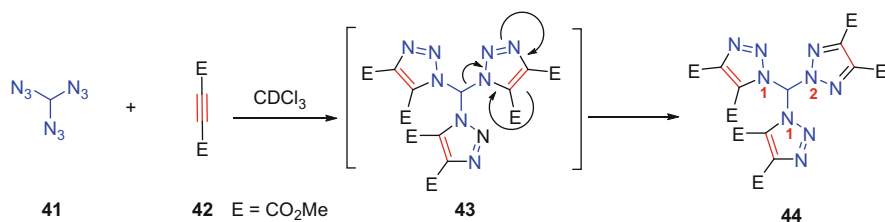
**Scheme 10** Synthesis of NH-1,2,3-triazoles **35** with thymine residue**Scheme 11** Reaction of hexacos-13-yne **36** with trimethylsilyl azide**Scheme 12** Synthesis of 4,5-disubstituted NH-1,2,3-triazoles **40** by reaction of alkynes with tri-*n*-butylstannyl azide

In several cases not only a higher temperature but also a higher pressure was involved [34, 56, 57]. 4-Dodecyl-1,2,3-triazole **37** was obtained by heating of tetradec-1-yne **36** in neat trimethylsilyl azide in autoclave (Scheme 11) [57]. Thus, this method has an expanded scope of dipolarophiles by including inactivated alkynes with electron-donating alkyl substituents (Scheme 11).

Further examples of this cycloaddition yielding 4,5-disubstituted NH-1,2,3-triazole **40** in moderate amounts (30–67%) were described [43, 54]. The reaction of tri-*n*-butylstannyl azide with mono- and disubstituted alkynes was performed by heating the reaction mixture in a sealed tube (Scheme 12) [43, 54].

2.3 Cycloaddition of Alkynes to Organic Azide

2*H*-1,2,3-triazole can be obtained by the reaction of alkynes with selected organic azides, if they have a leaving group in their structure. Such groups facilitate the hydrolysis or N-N/N-C rearrangements taking place in the next step [54–56,



Scheme 13 Cycloaddition of triazidomethane **41** with DMAD followed by rearrangement

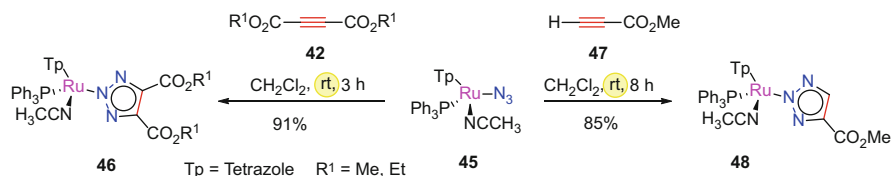
59–72]. It has been shown that 3-nitrobenzoyl, pivaloyloxymethyl, perfluoro-alkylvinyl, or trifluoromethansulfonyl azides reacted with alkynes to form NH-1,2,3-triazole [50, 54, 59–63], while (azidomethanetriyl)tribenzene, 7-azidocyclohepta-1,3,5-triene, ethyl 3-azidoacrylate, 3-azido-1,2,3-tri-*tert*-butylcycloprop-1-ene, diethyl azido(benzamido)methylphosphonate, alkyl 3-azido-2-alkenoates, and azidomethylamines produced a mixture of 2-R-1,2,3-triazole and NH-triazole, or 1- and 2-substituted 1,2,3-triazoles with an excess of the latter isomer [56, 64–71].

An interesting example of tri(1,2,3-triazole) **44** involved a step of N(1)-N(2) rearrangement occurring during the reaction of triazidomethane **41** with DMAD (Scheme 13) [71].

¹H and ¹³C NMR spectroscopy and single-crystal X-ray diffraction experiments revealed that the 3:1 adduct exists in the structure **44** consisting of one 2-substituted and two 1-substituted triazole units. One of the three initially formed symmetrical triazole rings in **43** underwent a 1,5-sigmatropic alkyl rearrangement to yield **44**. The driving force behind this rearrangement was the demand from the molecular system to relieve the inner steric strain. Elimination of the triazole unit from the symmetrical adduct **43** followed by its re-addition led to the compound **44**.

2.4 Cycloaddition of Alkynes with Metal-Coordinated Azide Ligands

Metal-coordinated azido ligands can undergo 1,3-dipolar cycloaddition reactions. Co(III)-, Ru(IV)-, Pd(II)-, Pt(II)-, In(III)-, Ir(III)-, Mo(II)-, Os(IV)-, and Ta(V)-coordinated examples of such complexes were described [73–84]. Usually, metal-azido complexes react with alkynes to produce *Stable 2H*-1,2,3-triazolates at lower temperatures and in shorter reaction time when compared to reactions of NaN₃ and HN₃ with alkynes. It should also be mentioned that the mechanism for the reaction of metal-azide complexes with dipolarophiles is similar to the one for the reaction of TMSN₃ and BuSnN₃ described above (Scheme 9). However, the complex containing the N(1)-bound triazolate ligand immediately converts into the thermodynamically more *Stable* N(2)-bound isomer.



Scheme 14 Synthesis of complexes (CH₃CN)[Ru]-N₃C₂(CO₂R)₂ **46** and (CH₃CN)[Ru]-N₃C₂(CO₂CH₃) **48**

Treatment of ruthenium-coordinated azide **45** with an excess of DMAD, DEAD **42**, or methylpropiolate **47** at room temperature afforded N(2)-bound 4,5-bis(methoxycarbonyl)-1,2,3-triazolate (CH₃CN)[Ru]-N₃C₂(CO₂Me)₂ **46** and 4-(methoxycarbonyl)-1,2,3-triazolate (CH₃CN)[Ru]-N₃C₂HCO₂Me **48** in high isolated yields. The formation of these complexes was undoubtedly confirmed by the disappearance of the characteristic absorption band of the azide group in the IR spectra. The ¹H NMR-assigned structure for **46** was the N(2)-isomeric form, since its spectrum exhibited a singlet at δ 3.63 ppm for six protons of the methoxycarbonyl group (Scheme 14) [80].

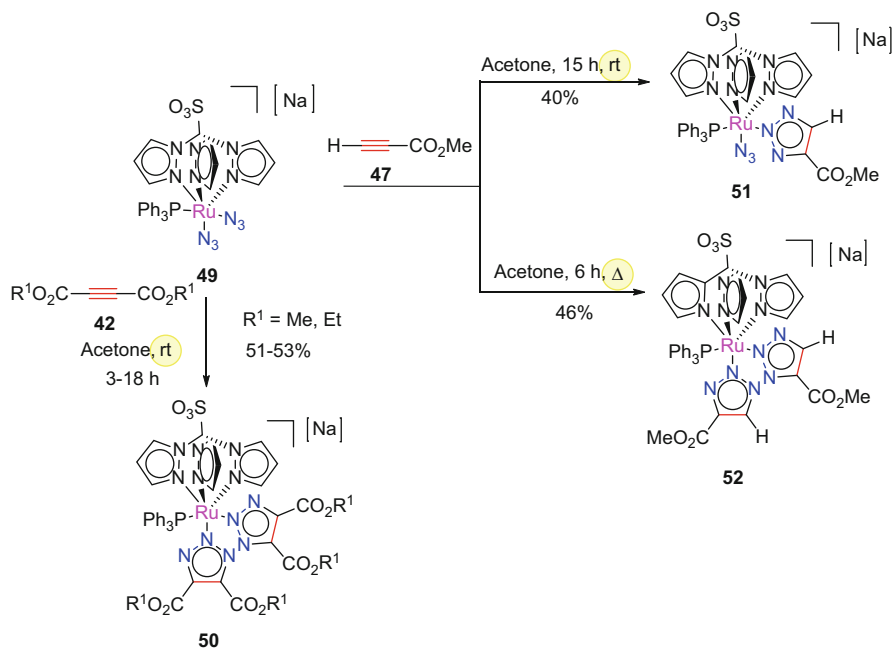
Two singlet resonances were registered at the beginning of the reaction while monitoring the reaction of azide complex **45** with DMAD, DEAD, and methylpropiolate by ³¹P NMR spectroscopy. Those signals were attributed to the N(1)- and N(2)-isomers observed. The N(1)-isomer completely transformed into the N(2)-isomer at room temperature within ~1–2 h.

Diazido ruthenium complex **49** reacted with alkynes in a 1,3-dipolar cycloaddition fashion. Depending on the alkyne structure and reaction conditions, the cycloaddition occurred through the involvement of one or two azido groups and led to ruthenium coordinated by triazolate ligands through the N(2)-atom as in compounds **50–51** (Scheme 15) [81].

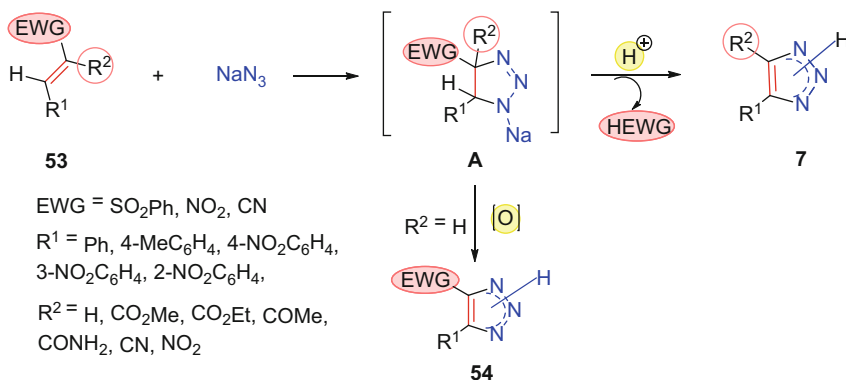
Complexes **50**, **51**, and **52** have been characterized by analytical and spectroscopic methods and X-ray diffraction crystallography.

2.5 Cycloaddition of Activated Alkenes to Azides

Other dipolarophiles that have the ability to react with azides via [3+2]-cycloaddition are activated alkenes. Their [3+2]-cycloaddition proceeds similarly to the cycloaddition of alkyne, but leads to 1,2,3-triazolines initially (**A**, Scheme 16), which was then followed by aromatization. Aromatization was achieved through the elimination of a leaving group (at the same time an EWG) or by oxidation [28, 43, 54, 85–104] (Scheme 16), resulting in two products **7** and **54**. The most convenient approach to perform this transformation was to combine cycloaddition and elimination processes, but not cycloaddition and oxidation.

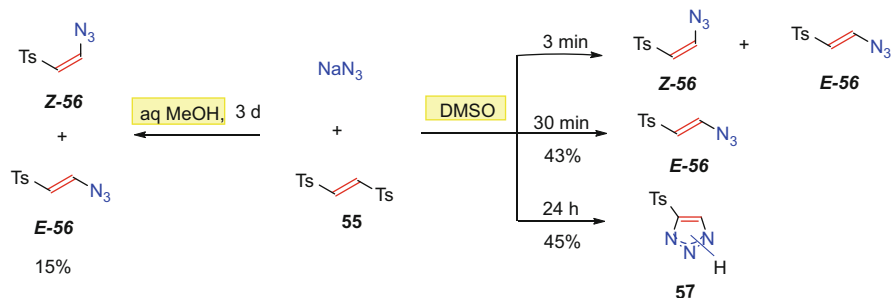


Scheme 15 Synthesis of complexes $[\text{Na}]\{\text{Ru}\{k(N^2)\text{N}_3\text{C}_2(\text{CO}_2\text{R}^1)_2\}\{k^3(N,N,N)\text{-Tpms}\}(\text{PPh}_3)\}$ **50**, $[\text{Na}]\{\text{Ru}(\text{N}_3)\{\text{N}_3\text{C}_2\text{H}(\text{CO}_2\text{Me})\}\{k^3(N,N,N)\text{-Tpms}\}(\text{PPh}_3)\}$ **51**, $[\text{Na}]\{\text{Ru}\{\text{N}_3\text{C}_2\text{H}(\text{CO}_2\text{Me})\}_2\{k^3(N,N,N)\text{-Tpms}\}(\text{PPh}_3)\}$ **52**

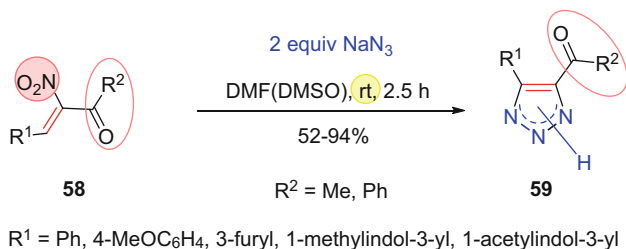


Scheme 16 [3+2]-Cycloaddition of activated alkenes **53** to sodium azide

The yields of cycloadduct were substantially increased if the reaction of alkene with azides was carried out in aprotic solvents [86, 87]. It was observed that the reaction of sodium azide with 1,2-di-*p*-toluenesulfonylene **55** in aqueous methanol produced azidovinyl *p*-tolyl sulfone **56** as a mixture of *Z*- and *E*-isomers. On the other hand, in DMSO three products, namely *E*-**56**, *Z*-**56**, and NH-1,2,3-triazole **57**,



Scheme 17 Reaction of 1,2-di-*p*-toluenesulfonylethene **55** with NaN_3 in different solvents



Scheme 18 Reaction of β -acetyl(benzoyl)- β -nitroethenes **58** with sodium azide

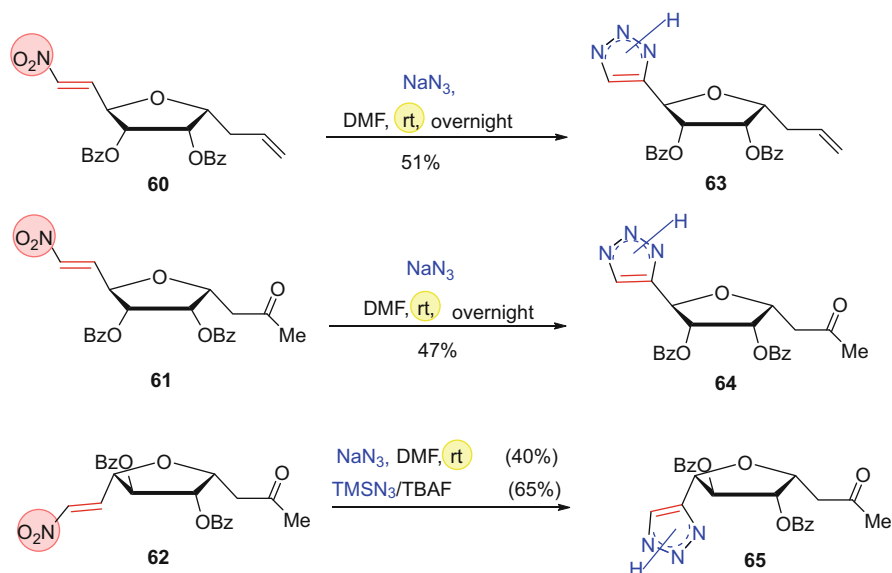
were obtained and their amounts depended on the reaction time. This observation questions the mechanism of reaction as to be simultaneous synchronic [3+2]-cycloaddition and suggests that a two-step formation for azole **57** takes place (Scheme 17).

Due to weaker reactivity of alkenes, their reactions with azides required stronger conditions. Usually, electron-deficient alkenes are utilized in order to improve the reactivity. Experimentally established elimination abilities of electron-deficient substituents on alkenes decreased in the row: benzenesulfonyl > nitro > cyano. Rare examples of halogen or thiol elimination were described as a supportive process for the transformation of 1,2,3-triazolines to 1,2,3-triazoles [99–102].

Alkenes with two geminal electron-withdrawing groups were better substrates for the [3+2]-cycloaddition with azide. The reaction of β -acetyl(benzoyl)- β -nitroethenes **58** with sodium azide proceeded in comparatively mild conditions and gave 4,5-disubstituted-NH-1,2,3-triazoles in moderate to high yields (Scheme 18) [88–92].

Activated geminal nitroethenes containing a carbonyl group as an additional electron-withdrawing unit have high synthetic accessibility and attract a lot of interest due to the ability to introduce in triazole ring biologically active fragments and different heterocycles [28, 54, 89, 91, 98, 101].

Interaction of nitroalkene-containing glycosides **60–62** with sodium azide at room temperature led to ribavirin triazole-base analogous **63–65**, obtained in



Scheme 19 Reactions of nitroalkenyl-containing glycosides **60–62** with sodium azide and trimethylsilyl azide

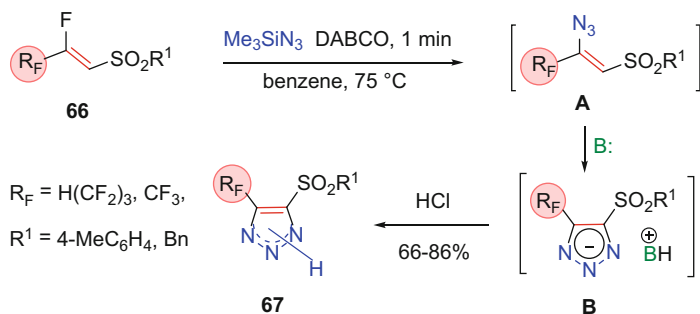
moderate yield (Scheme 19). Higher yields were achieved if the same alkene **62** reacted with TMSN_3 activated by *tert*-butyl ammonium fluoride (TBAF) added to the mixture (Scheme 19) [98].

This method was also convenient to synthesize fluorocontaining NH-1,2,3-triazoles [103–105]. The reaction of fluorinated sulfones **66** with trimethylsilyl azide in the presence of base reagent allowed to obtain 5-polyfluoroalkyl-4-arylsulfonyl-1,2,3-triazole **67** in good yields (Scheme 20) [103, 104].

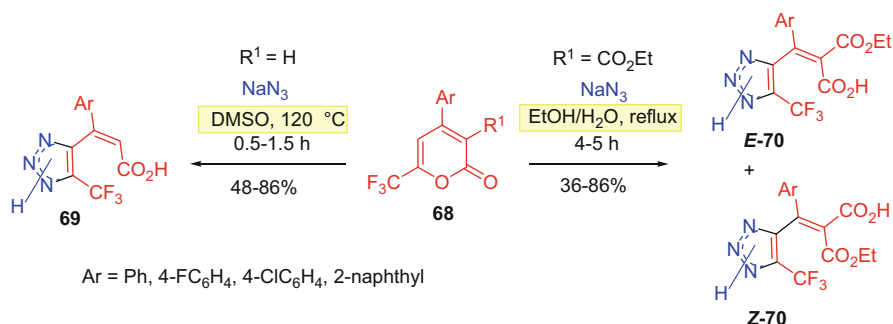
Cyclic alkenes – ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2H-pyran-3-carboxylates **68**, reacted with NaN_3 under mild condition, likely because an additional activating EWG substituent was introduced at the pyrone ring. As a result, highly functionalized trifluoromethyl-triazoles: 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl] cinnamic acids **69** and ethyl esters 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl] arylmethylidene malonic acids **70** were isolated (Scheme 21) [105].

2.6 Cycloaddition of Enamines to Azides

Several published examples of reaction of azides with electron-rich dipolarophiles, such as enamines, have been described [106–110]. Depending on the structure of the substrates different transformations may occur with initially formed 1,2,3-triazolines. Sodium azide reacted with β -monosubstituted- α -chloroenamines **72** (generated from tertiary amides **71**) in mild conditions and, as a result, 5-methyl



Scheme 20 Reaction of 1,1-polyfluoroalkyl alkenylsulfones **66** with trimethylsilyl azide



Scheme 21 Synthesis of CF_3 -triazoles **69** and **70** from pyrones **68** and NaN_3

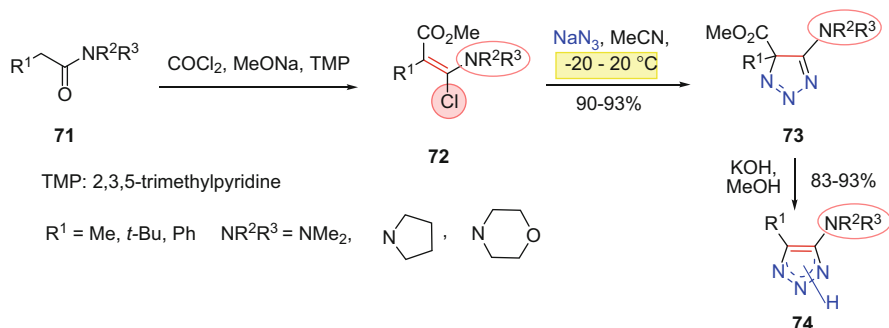
(phenyl)-2*H*-1,2,3-triazol-4-amines **74** were synthesized via 5-amino-4*H*-1,2,3-triazole-4-carboxylate intermediate **73** after saponification and decarboxylation with an excellent yield (Scheme 22) [106, 107].

1,3-Dipolar cycloaddition of heteroaroyl azides **75** to methyl 3-pyrrolidinoacrylate **76** occurred smoothly to produce 1,2,3-triazole **79** by the displacement of the pyrrolidine moiety from the 1,2,3-triazoline ring (Scheme 23) [110].

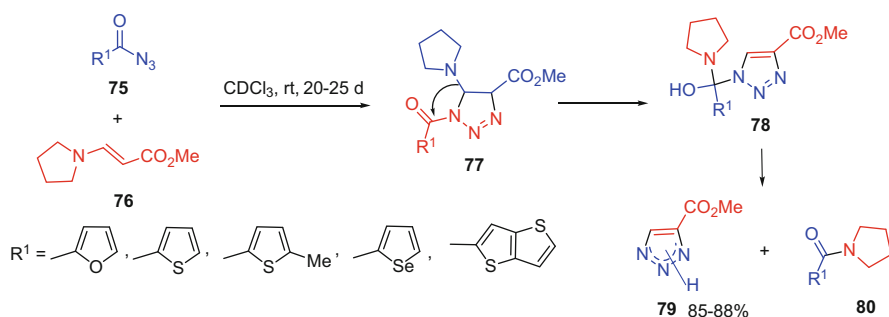
An analogous rearrangement-elimination sequence was observed in the reaction of tosyl azide with nitro- and sulfonyl enamines [108, 109].

2.7 Cycloaddition of Alkenes to Metal Azides

As it was mentioned above, the reaction of hydrazoic acid and azide ions with alkenes yields a linear product in the first place existing in dynamic equilibrium with 1,2,3-triazoline cyclic intermediates that may be transformed in several ways affording various by-products. However, when α,β -unsaturated aminoketone **81** reacted with diethylaluminium azide, obtained from diethylaluminium chloride and sodium azide in situ, no linear adduct was detected [111]. Triazole yields strongly depended on the nature of substituents R^1 and R^2 in aminoketone **81**.



Scheme 22 Reaction of sodium azide with β -monosubstituted- α -chloroenamines **72**



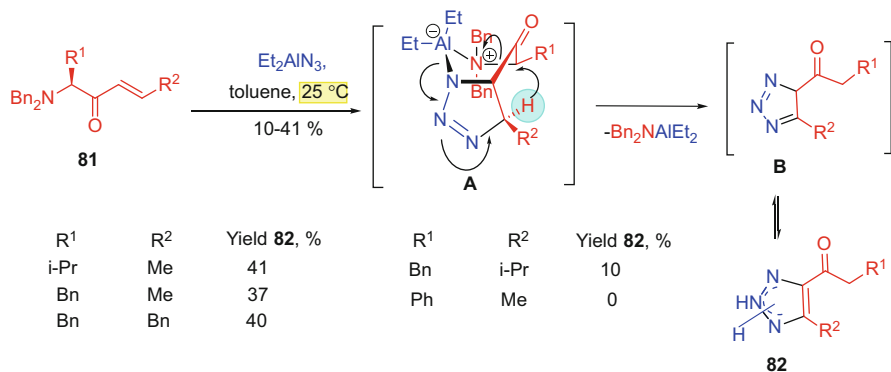
Scheme 23 Reaction of azido(2-heteroaryl)methanones **75** with methyl 3-pyrrolidinoacrylate **76**

Cycloaddition of alkenes **81**, containing electron-withdrawing groups proceeded via the intermediate **A** where two rings were optimally aligned for intramolecular migration of a hydride from the triazoline C(4) atom to the α -carbon atom with a displacement of *N,N*-dibenzylamino group, activated by complexation with aluminium (Scheme 24).

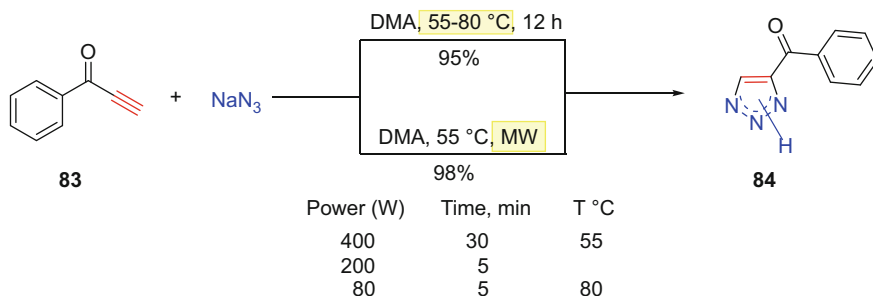
The mechanism shown in Scheme 24 was confirmed by isolation of dibenzylamine. Involvement of alkenes bearing electron-donating substituents allowed to expand the scope of the described method of synthesis of 1,2,3-triazoles via [3+2]-cycloaddition with azides.

2.8 Microwave-Assisted and One-Pot Reactions

In addition to being energy saving, the microwave irradiation also causes a striking reduction of reaction times. To surpass the efficiency of conventional protocols for cycloadditions, microwave-assisted processes were introduced in some cases [23, 51, 112, 113].



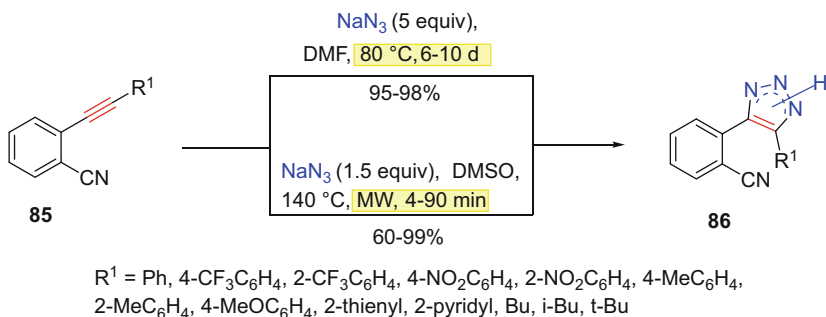
Scheme 24 Diethylaluminum azide addition to α,β -unsaturated aminoketones **81**



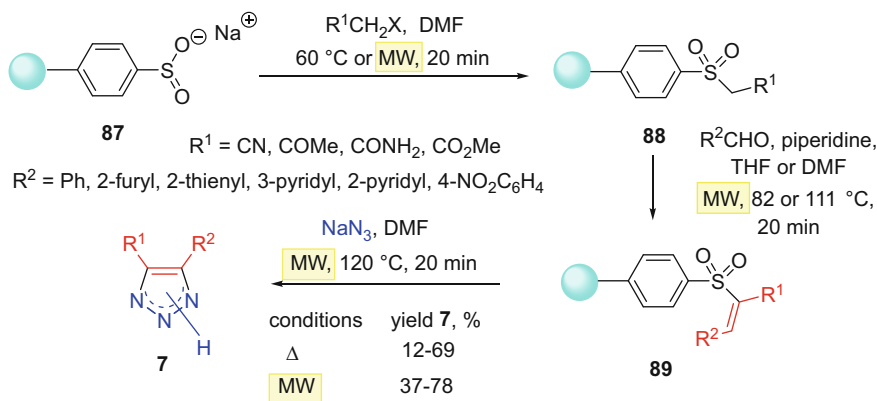
Scheme 25 Reaction of phenyl ethynyl ketone **83** with NaN_3 under conventional condition and microwave assistance

Conventional and microwave heating of the reaction of phenyl ethynyl ketone **83** with NaN_3 in anhydrous dimethylacetamide (DMA) were performed. It was shown that the procedure including microwave heating allowed the authors to achieve the desired compound **84** faster and in better yields compared to the conventional method (Scheme 25) [51].

Cycloaddition of internal alkynes **85** to an excess of sodium azide in DMF required 6 days to be completed and, even increase of sodium azide amounts (up to 10 eq) did not accelerate it (Scheme 26). Indeed, microwave irradiation noticeably improved reaction rates. The process was finished within 10 min, and triazole adduct **86** was obtained in high yield. The reaction was completed in 4–90 min for phenyl alkynes with electron-donating groups on the aromatic ring (Scheme 26) [112].



Scheme 26 Comparative study of conventional and microwave-assisted procedures on the reaction of internal alkynes with NaN_3

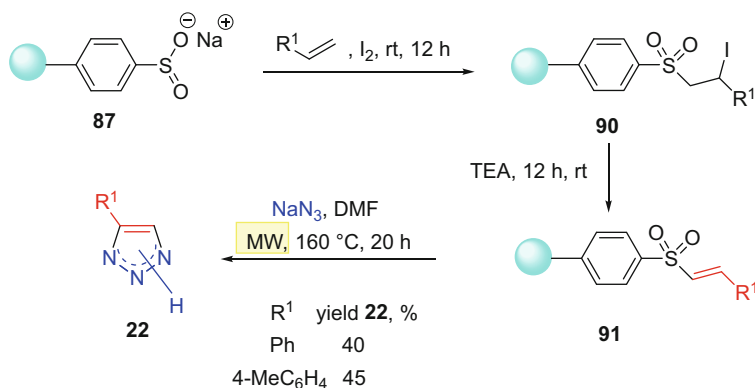


Scheme 27 Sulfonate solid-phase synthesis of 4,5-disubstituted 1,2,3-triazoles **7**

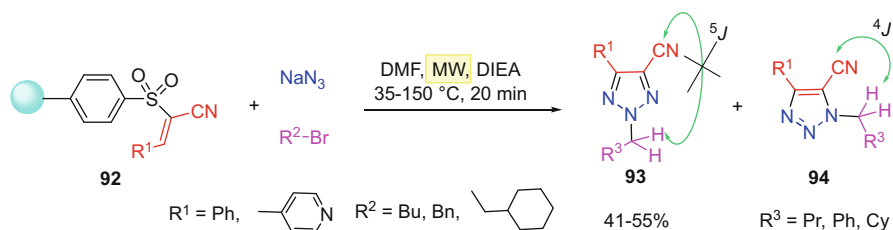
2.9 Solid-Phase Techniques for [3+2]-Cycloaddition of Azides to Alkenes

It should be mentioned that [3+2]-cycloaddition of azides to electron-deficient alkenes has received only a little attention because a poor reactivity of substrates requires applying harsh conditions. To overcome this issue solid-phase synthesis (SPS) was introduced.

A convenient solid-phase procedure for regioselective and traceless synthesis of di- and trisubstituted 1,2,3-triazoles **7** was found based on [3+2]-cycloaddition of polymer-bound vinyl sulfone to sodium azide, giving different yields (Scheme 27). Disubstituted vinyl sulfone dipolarophiles **89** were generated via Knoevenagel condensation of **88** with aldehydes. Microwave-assisted procedure in combination with solid-phase technique led to higher conversion rates and higher purity of the product **7** [113].



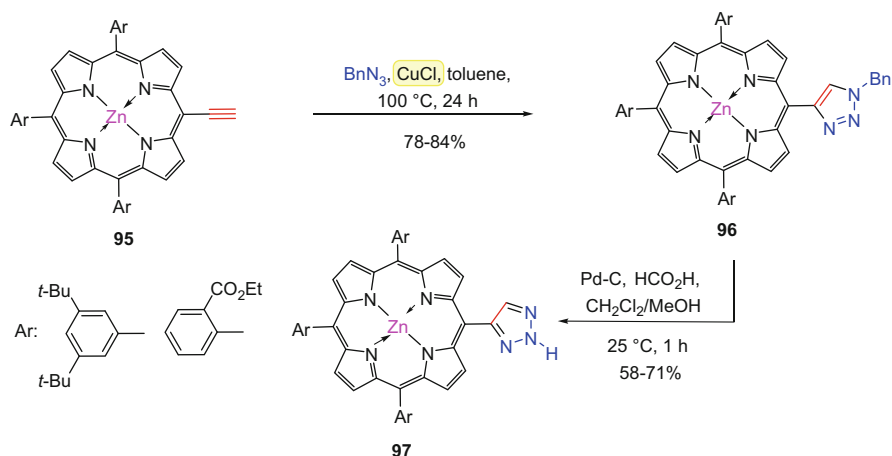
Scheme 28 Sulfonate solid-phase synthesis of monosubstituted 1,2,3-triazoles **22**



Scheme 29 Reaction of resin **92**, sodium azide, and alkyl bromide led to 2-alkyl-1,2,3-triazole **93**

Monosubstituted vinylsulfones **91** were obtained via ionic addition of **87** to alkenes (Scheme 28). Microwave-assisted cycloaddition of vinylsulfones **91** to sodium azide was carried out at high temperature in DMF and resulted in moderate yields of 4-aryl-1,2,3-triazoles **22** [113].

Convenient regioselective one-pot coupling procedure of resin **92** with sodium azide and alkyl halides yielding 2-alkyl-1,2,3-triazoles **93** as major isomer was described (Scheme 29) [113]. The ratio of isomers **93** and **94** in crude mixture was approximately 10:1. Their structures were confirmed by proton–carbon correlation between methylene proton and nitrile carbon in ¹³C HMBC spectra (Scheme 29). X-ray crystallography also confirmed that the major isomers were 2-substituted 1,2,3-triazoles **93**.



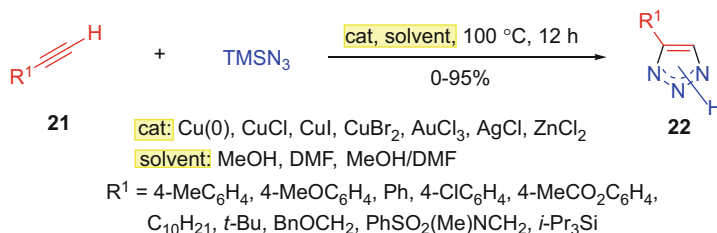
Scheme 30 Synthesis of NH-1,2,3-triazolylporphyrins **97**

3 Catalysis in Synthesis of 2*H*-1,2,3-Triazoles by 1,3-Dipolar Cycloaddition Reactions

Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) offers an efficient method for synthesis of 1,4-disubstituted-1,2,3-triazoles [2–4, 6, 16, 17]. On the other hand, Ru-catalyzed reaction of terminal alkynes with alkyl azides can serve a unique routine towards 1,5-disubstituted-1,2,3-triazoles [2, 6]. In these methods the activity of inorganic azides is suppressed in mild conditions and preparation of 4,5-disubstituted NH-1,2,3-triazoles by 1,3-dipolar cycloaddition reaction is considered being useless. Conversely, there are examples of metal-catalyzed synthesis of NH-1,2,3-triazole based on sodium or lithium azide [23, 27, 114–116]. Other described examples of 1,3-dipoles for this reaction were trimethylsilyl azide [117–119] and organic azides [39, 50, 120–126]. In this case, the reaction with organic azides was followed by a rearrangement or an elimination of organic residue and lead to NH- or 2-R-1,2,3-triazoles.

Using metal salts to catalyze the reaction of organic azides with alkynes resulted in linking the NH-1,2,3-triazole moiety to porphyrinic supramolecular assemblies. *meso*-1,2,3-Triazolyl Zn(II) porphyrins **97** were synthesized via Cu(I)-catalyzed 1,3-dipolar cycloaddition of *meso*-ethynyl Zn(II) porphyrins **95** to benzyl azide [122]. The benzyl group was removed by treatment with Pd/C and formic acid (as hydrogen source) in the final step (Scheme 30).

The main problem of regioselectivity for unsymmetrical 4- or 5-monosubstituted and 4,5-disubstituted 1*H*-triazoles is managed by utilization of well-known ‘click chemistry’ approaches. This problem becomes insignificant in case of NH-1,2,3-triazoles and their 2-substituted derivatives due to their tautomerism or symmetry caused by the 2-substituents position. Introduction of the catalyst facilitates the cycloaddition and gives the opportunity to expand the scope of this



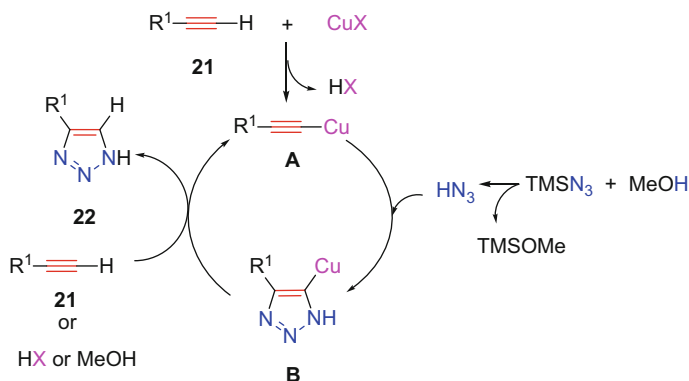
Scheme 31 Synthesis of *N*-unsubstituted 1,2,3-triazoles **22** by catalyzed [3+2]-cycloaddition reaction of nonactivated terminal alkynes **21** and TMSiN₃

reaction. This explains why metal-catalyzed syntheses currently are being very popular in triazole chemistry.

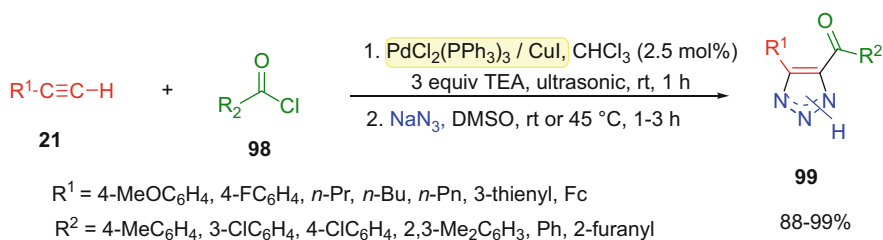
For example, the [3+2]-cycloaddition of nonactivated terminal alkynes **21** and trimethylsilyl azide proceeded smoothly in the presence of Cu(I) catalyst (CuI, CuCl, etc.) to give the corresponding NH-1,2,3-triazoles **22** in good to excellent yields (Scheme 31) [119]. Among all tested solvents, the protic ones had a larger effect on this reaction. A mixture of DMF and MeOH improved the yield of 1,2,3-triazoles **22** up to 59–69% as compared to 14–55% obtained in other cases. Other copper catalysts, such as Cu(II)Br₂ and Cu(0) powder, were also effective [119]. The reaction without a copper catalyst was characterized by a lower yield (13%). Non-copper metal catalysts (AuCl₃, AgCl and ZnCl₂) were not effective at all.

A mechanism for catalyst-activated cycloaddition, performed via multi-component one-pot synthesis technique, was proposed [115, 119, 127–131]. At the very beginning of this reaction CuX interacts with terminal alkynes **21** which result in the copper acetylide **A** [119]. Simultaneously, the formation of HN₃ occurs in situ by the reaction of TMSN₃ with MeOH. Since a C–C triple bond in a copper acetylide **A** is already activated the [3+2]-cycloaddition process immediately takes place. Protolysis of the C–Cu bond, initiated by terminal alkynes **21**, HX or MeOH occurred with intermediate **B**, affording NH-1,2,3-triazoles **22** in the final step (Scheme 32) [119].

Metal-catalyzed one-pot synthetic approaches to 1,2,3-triazoles can be classified into two types. The first one takes place as two consequent reactions of coupling and cycloaddition and leads to 4,5-disubstituted NH-1,2,3-triazoles. Sonogashira coupling reaction allows to construct acetylene dipolarophiles participating in the following step in the 1,3-dipolar cycloaddition [113, 114, 132–134]. The sequence of palladium-catalyzed Sonogashira coupling and the 1,3-dipolar cycloaddition of acyl chlorides, terminal acetylenes, and sodium azide was performed in a one-pot ultrasonic-promoted mode and led to 4,5-disubstituted-2*H*-1,2,3-triazoles **99** (Scheme 33) [132]. Reaction parameters (reaction time, yield, etc.) did not depend on the electronic properties of the substituents in the aryl terminal acetylenes and acyl chlorides. Reaction of aliphatic terminal acetylenes proceeded much slower



Scheme 32 Proposed mechanism for the formation of *N*-unsubstituted triazoles **22**



Scheme 33 One-pot synthesis of 4,5-disubstituted 1,2,3-triazoles **98** through Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide

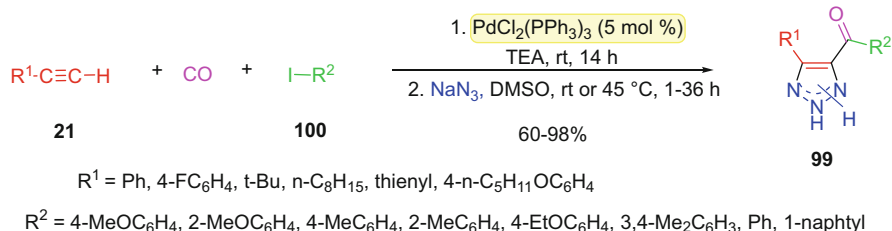
comparing to aryl acetylenes. The length of aliphatic chain was not a crucial factor affecting the yields of this process.

One-pot four-component synthesis of 4,5-disubstituted triazole **99** by Pd-catalyzed reaction of terminal acetylenes **21** with carbon monoxide, aryl iodide **100**, and sodium azide took place in mild conditions (Scheme 34) [133].

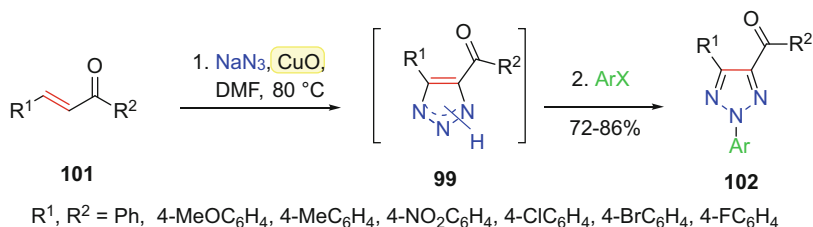
This class of one-pot reactions represents an atom economic approach, which can be easily propagated to industrial scale and is not strictly limited by the chemical diversity of substrates (Schemes 33, 34).

One-pot catalytic reactions of a second type occur when the cycloaddition is followed by nucleophilic substitution (arylation, alkylation, etc.) of the initially formed NH-triazoles, leading to 2-aryl- or 2-alkyl-1,2,3-triazoles [99, 114, 127–131]. A series of 2-aryl-1,2,3-triazoles **102** were obtained in mild conditions and with a high yield by three-component reaction proceeding via an azide-chalcone oxidative cycloaddition and post-arylation of triazoles (Scheme 35) [114]. Opting for chalcones with stronger electron-withdrawing R^1 and R^2 substituents leads to improved reaction yields.

The reaction described above was susceptible to the type of catalyst. The catalytic activity of different copper species, such as $\text{Cu}(\text{OAc})_2$, $\text{Cu}(\text{acac})_2$, CuI ,



Scheme 34 One-pot synthesis of 4,5-disubstituted 1,2,3-triazoles **99** using terminal acetylenes **21**, carbon monoxide, aryl iodides **100**, and sodium azide

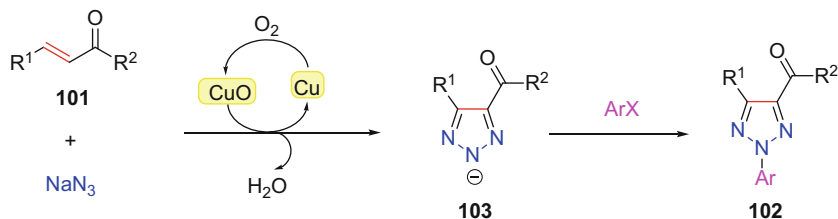


Scheme 35 Three-component reaction azide-chalcone oxidative cycloaddition and post-arylation triazole

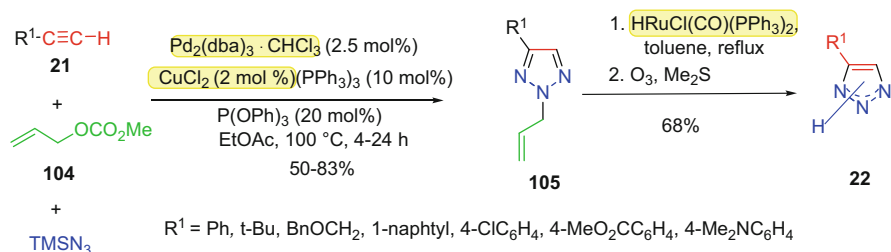
and CuO, was tested. It was found that CuO was superior and its utilization resulted in higher yields. Experimentally observed trends were in line with the proposed mechanism, involving the assumption that CuO acted not only as an oxidant for “triazoline–triazole” transformation (Scheme 16) but also as a trigger of the total catalytic process. The catalytic cycle is closed when Cu(0) is oxidized to Cu(II)O by air oxygen (Scheme 36) [114].

Regioselective formation of 2-allyl triazole **105** via three-component coupling reaction between allylmethylcarbonate **104**, TMSN₃ and alkynes in the presence of a catalytic amount of Pd₂(dba)₃ · CHCl₃ and 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 37) was reported in several publications [127–130].

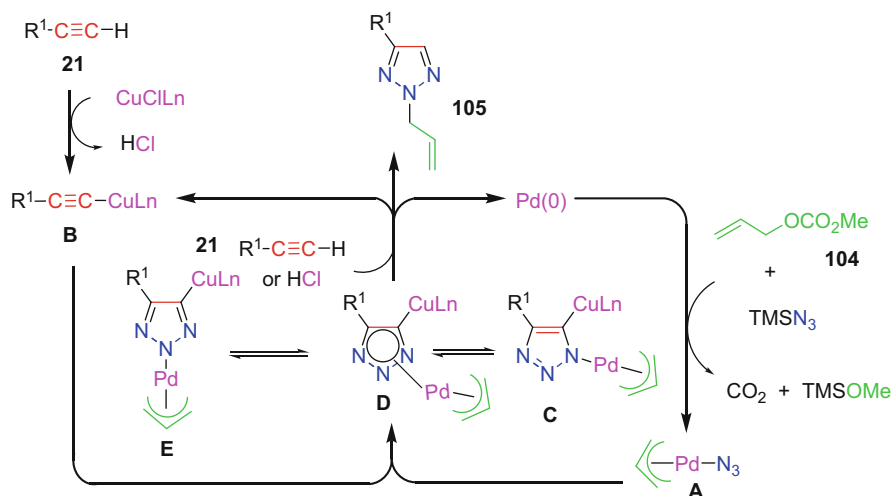
The structures of allyl triazoles **105** were determined by detailed analyses of spectroscopic data: according to ¹H and ¹³C NMR allyl triazole **105** had a symmetrical structure. The location of allyl group on the triazole ring was confirmed by NOE experiments. The mechanism for this bimetallic catalysis is shown in Scheme 38 [128]. Firstly, allylmethyl carbonate, trimethylsilyl azide, and Pd(0) reacted to yield π-allylpalladium azide complex **A**. This step of the catalytic cycle was accompanied with concomitant evolution of CO₂ and trimethylsilyl methoxide. At the same time, the copper-acetylide **B** would be formed along with the generation of HCl via the reaction of alkynes **21** and CuClLn. Then, 1,3-dipolar cycloaddition between the azide moiety of the complex **A** with copper-acetylide **B** takes place and leads to 1-(η³-allyl)(η⁵-triazoyl)palladium complex **C**. The intermediate complex **C** was suggested to exist in an equilibrium with 2-(η³-allyl)(η⁵-triazoyl)palladium complex



Scheme 36 Proposed mechanism of the catalysis of the azide-chalcone oxidative cycloaddition by the CuO

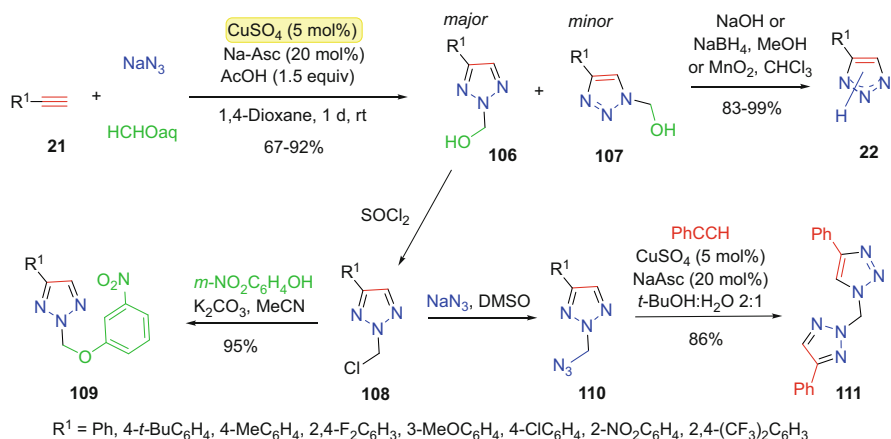


Scheme 37 Catalytic three-component coupling reaction between activated alkynes, allylmethyl-carbonate, and TMSN_3



Scheme 38 Proposed mechanism for the formation of 2-allyl-1,2,3-triazoles **105** under the $\text{Pd}(0)$ - $\text{Cu}(\text{I})$ bimetallic catalyst

E through intervention of the palladium complex **D**. Regeneration of $\text{Pd}(0)$ catalyst by reductive elimination of complex **E** results in 2-allyl-1,2,3-triazole **105**. Cu would activate the $\text{C}-\text{C}$ triple bond by forming a copper-acetylide species. One of the



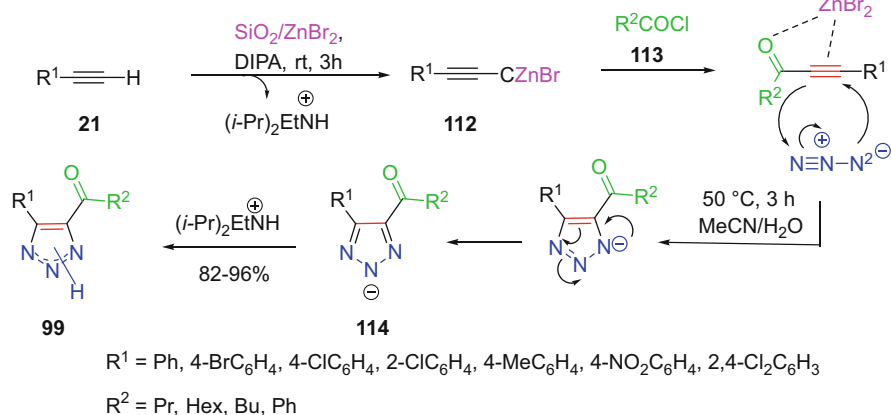
Scheme 39 One-pot two-step synthesis of *N*-hydroxymethyl-1,2,3-triazoles **106**

main particularities of this reaction was the extremely high regioselectivity since no other isomer was registered. The structure of the final product was controlled by the composition of complex catalyst.

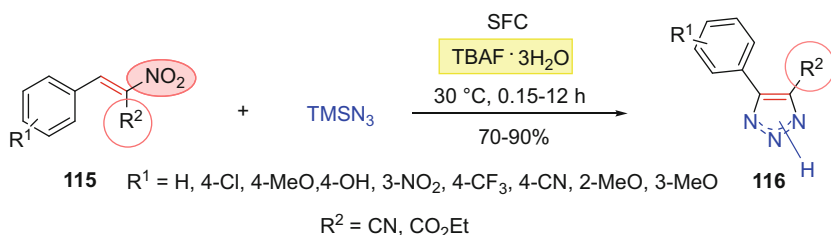
Several examples of the synthesis of 2-hydroxymethyl-2*H*-1,2,3-triazoles **106** were presented in literature [39, 131]. A one-pot stepwise reaction of formaldehyde, sodium azide, and a terminal alkyne **21** took place under slightly acidic (pH 6.5) conditions, representing another example of the synthesis of 2-substituted triazoles by catalytic cycloaddition [131] (Scheme 39).

For all tested alkynes, a mixture of 1- and 2-hydroxymethyl triazoles **106** and **107** was obtained. 2-Substituted triazoles were the major products and this fact was confirmed by the appearance of a characteristic chemical shift of the hydroxymethylene carbon atom in the ^{13}C NMR spectra and by X-ray crystallographic analysis. The identity of the minor product **107** was revealed by the heteronuclear correlation experiments. *N*-Hydroxymethyltriazoles **106** are attractive precursors due to their versatility. The described approach can be very convenient to obtain a broad variety of 2*H*-substituted 1,2,3-triazoles **109–111**, as well as NH-triazoles **22**. The authors also have evaluated the applicability of this method for gram-scale synthesis [131].

4,5-Disubstituted 1,2,3-triazoles **99** were obtained via an efficient one-pot procedure performed as a cross coupling/1,3-dipolar cycloaddition between acyl chlorides **113**, terminal alkynes **21**, and sodium azide [133, 134]. The reaction was performed in the presence of silica-supported zinc bromide (Scheme 40) [134]. When all substrates, ZnBr_2 as a catalyst and a base (DIPA or TEA) were dissolved in various solvents (MeCN, dioxane, THF, DMF) a poor yield of the desired 1,2,3-triazole **99** was obtained. However, if the reaction was performed in a sequential mode (the reaction between acyl chloride **113** and acetylene in first place and reaction with added azide afterwards) 62–96% of product was achieved. The reaction was carried out in different solvents or in solvent-free conditions (SFC),



Scheme 40 Synthesis of 4,5-disubstituted 1,2,3-triazoles **99** in the presence of silica supported-zinc bromide

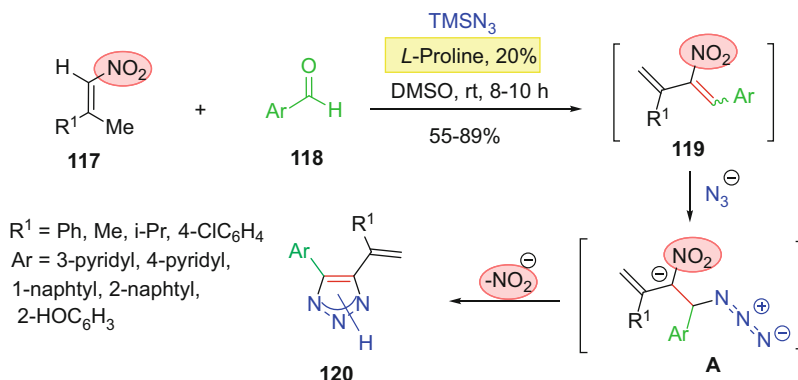


Scheme 41 Synthesis of 4-aryl-1,2,3-triazoles **116** through TBAF-catalyzed [3+2]-cycloaddition of 2-aryl-1-nitroethenes with TMSN_3 in SFC

adding ZnBr_2 or $\text{ZnBr}_2/\text{SiO}_2$ (10%) to the acyl chloride/acetylene mixture at initial step. The addition of sodium azide was postponed and 1,3-dipolar cycloaddition via ynone intermediate **112** was then yielding 2*H*-1,2,3-triazole **99** (Scheme 40).

A new chemically efficient, solvent-free, preparative procedure for 4,5-disubstituted NH-1,2,3-triazoles was described and proceeded as TBAF- or TBAB-catalyzed [3+2]-cycloaddition [98, 134, 135]. 2-Aryl-1-cyano- or 2-aryl-1-carboxy-1-nitroethenes **115** did not interact with TMSN_3 [98] in SFC and in an absence of any additives, even after 24 h. Addition of tetrabutylammonium bromide (TBABr) acting as catalyst allowed to obtain a triazole **116** (SFC, 30 °C). Best results were achieved if 0.1 equiv TBAF was applied. The proposed protocol was simple to perform: no dried glassware or inert atmosphere was required (Scheme 41).

Along with the metals and TBAF, TBAB, proline can catalyze the cycloaddition reaction. A convenient atom-efficient protocol for the preparation of 4,5-substituted NH-triazole **120** was developed as a one-step cascade reaction between nitroalkene,



Scheme 42 One-pot cascade synthesis of 4,5-disubstituted-(NH)-1,2,3-triazole **120**

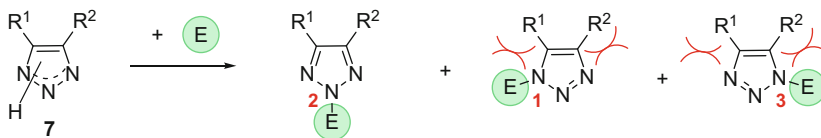
aldehyde, and NaN_3 catalyzed by proline [136, 137]. A variety of aryl aldehydes **118** and β -alkyl nitroalkenes **117** were suitable for this transformation. The reaction performance was controlled by the character of the aromatic substituent on the aldehyde and by the reaction temperature. Non-substituted and electron-deficient aromatic aldehydes worked well in this cascade transformation. The reaction with aryl aldehydes, bearing electron-donating groups, had poorer yields at room temperatures. Improved yields of 1,2,3-triazoles were achieved by increasing the temperature up to 80°C (Scheme 42) [137].

The mechanism for this reaction is shown in Scheme 42. It involves a step of in situ formation of highly reactive intermediate, 2-nitrobuta-1,3-diene **119**. Comparing to conventional procedure for 1,3-dipolar cycloaddition, the cascade approach avoids the difficulties of synthesis of α -nitroalkene dipolarophiles, and, therefore, significantly extends the scope of substrates suitable for this reaction.

The analysis of the literature on this topic has shown that a variety of diverse approaches to synthesize 2*H*-1,2,3-triazoles via a 1,3-dipolar cycloaddition of azides with alkynes/alkenes exist and includes conventional, catalytic, one-pot multi-step, and solid-phase synthetic procedures. There are obvious advantages of using them at larger scales. However, a main challenge to propagate them to industrial scales is the availability and the cost for alkynes/alkenes. In addition, the explosive character of organic/inorganic azides substantially limits their use for industrial synthesis.

4 Synthesis of 2-Substituted 1,2,3-Triazoles by Reactions of NH-1,2,3-Triazoles with Electrophiles

The vast majority of N(1) substituted 1,2,3-triazoles were obtained by the cycloaddition reaction of organic azides to alkynes and alkenes. Nonetheless, these reactions do not allow to obtain 2-substituted triazoles directly. To overcome



Scheme 43 Proposal products of the reaction of NH-triazoles with electrophilic agents

this restriction several approaches have been developed. N(2)-Substituted triazoles were synthesized by rearrangement of 1-substituted triazoles initially formed in cycloaddition of unsaturated C–C bonds to organic azides (paragraph 2.3 and 3), metal-catalyzed three-component cycloaddition (paragraph 3) metal-free solid phase synthesis (paragraph 2.9). These examples were limited to N(2)-hydroxymethyl-, N(2)-allyl, N(2)-aryl-1,2,3-triazoles (Schemes 29, 35, 36, 37, and 39).

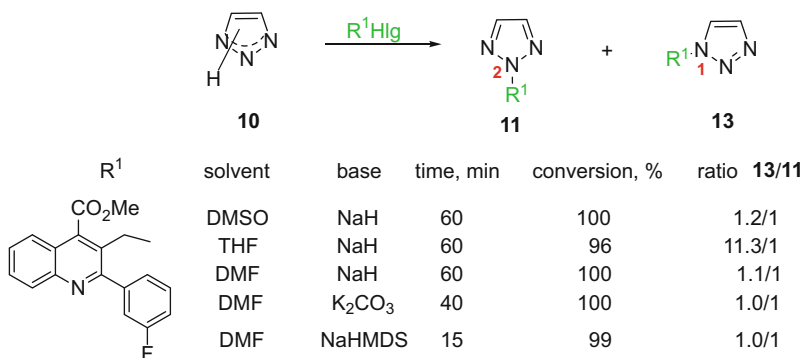
The main route to synthesize N(2)-substituted 1,2,3-triazoles is the reaction of NH-triazoles with electrophiles: alkylation, arylation, acylation, carbamoylation. Synthetic procedures for this type of reactions are well documented [1, 2, 6, 13, 18, 25, 27, 29, 31–34, 47, 49–53, 57, 59, 61, 62, 72, 83, 96, 104, 117, 118, 128, 131, 132, 136–234].

In general, all three nitrogen atoms in triazole cycle can participate in electrophilic substitution [1–6]. Most of the publications describing the transformations occurring in NH-1,2,3-triazoles pointed out that in first place a substitution at the N (1)- or N(3)-nitrogen atoms proceeds, resulting from a higher electronic density on the N(1) or N(3) atoms compared to the one at the N(2) atom (Scheme 43).

However, the thermodynamic stability of N(2)-substituted triazoles is much higher. Furthermore, the steric hindrance, caused by the presence of substituents at C(4)- and C(5)- atoms at the heterocycle, increases the predisposition for the central nitrogen atom to react with electrophiles. All listed factors can easily explain the formation of a mixture of products in the reaction of NH-1,2,3-triazoles with electrophilic agents. As a result, research for routes to increase the selectivity of the synthesis or the development of separation processes (liquid column chromatography, flash chromatography) becomes an integral part for the synthetic approach described above. Due to these reasons a selective N(2)-substitution remains a big challenge for the chemistry of triazole functionalization.

4.1 N-Alkylation of NH-1,2,3-Triazoles with Alkylhalides

N-Alkylation of NH-1,2,3-triazoles can be implemented as a nucleophilic substitution onto alkylhalides [25, 33, 50–53, 57, 61, 62, 72, 96, 118, 136, 138–171], diazoalkanes [32, 171], alkyl sulfonates or carboxylates [59, 62, 172–181], alcohols (Mitsunobu reaction) [131, 137, 182–186] or as a nucleophilic addition of alkenes and alkynes activated by EWG-groups (Michael addition) [50, 104, 187–197].



Scheme 44 N(1)/N(2)-Selectivity in the alkylation of unsubstituted NH-1,2,3 triazole **10** by alkyl halides

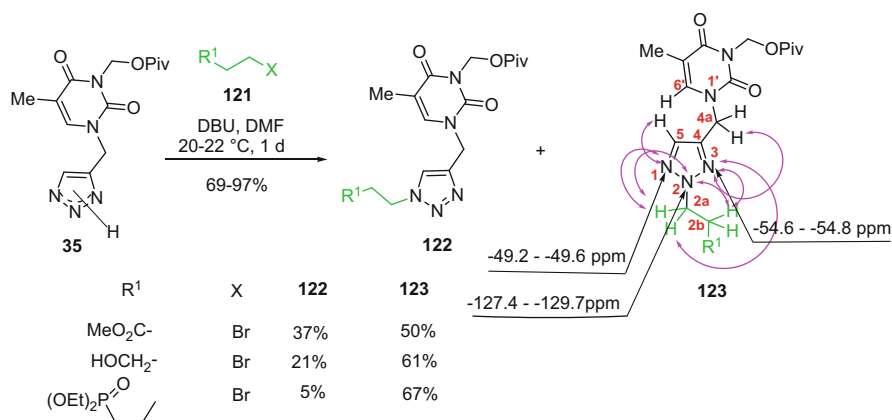
A significant drawback of this method is the formation of a mixture of regioisomeric *N*-alkyl-1,2,3-triazoles. Quite often the product ratio in this reaction is unfavorable for the N(2)-isomer, especially in the case of simple alkylating agents and unsubstituted, or monosubstituted NH-1,2,3-triazoles [149–153].

The *N*-alkylation of NH-triazoles was carried out in the usual manner in acetone, DMF, DMSO, acetonitrile, EtOH, EtOAc and in the presence of different bases (K₂CO₃, NaH, Na₂CO₃, Cs₂CO₃, EtONa, NaHMDS, LiHMDS, KHMDS, TEA, DBU) [25, 33, 50–53, 57, 61, 62, 72, 96, 117, 136, 138–171]. The application of base is necessary: the reaction was unsuccessful if the base was not added. Screening for optimal reaction conditions revealed that the choice of a solvent and a base was crucial for the kinetics and resulted in different reaction rates. However, the influence of these factors on the reaction regioselectivity is subtle. Stronger bases, such as NaH, caused the deprotonation of NH-proton and favored N(1)-substitution. On the other hand, the nature of electrophile mainly influenced the regioselectivity of the reaction [136].

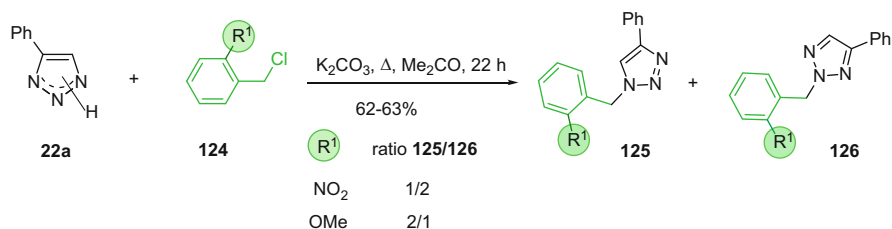
As a result, alkylation of NH-1,2,3-triazole **10** led to two isomers **11** and **13**, and their ratio depended on the electron-withdrawing nature of the substituents on the alkylation agent. The reaction was also sensitive to the type of solvent (Scheme 44) [33, 51, 118, 139–148, 157].

Variation by combination of different conditions (solvent, base and temperature) did not further improve the yield of N(2)-isomer. Despite considerable efforts being made to get a better ratio, a 1:1 mixture of 1*H*- (**13**) and 2*H*-isomers (**11**) was obtained in all circumstances.

The alkylation of C(4)-substituted triazoles may lead to different ratios of three regio-isomers, namely 1-, 2-, and 3-alkylated products, as described in several reports [25, 50, 53, 149–153]. Because of the spatial hindrance between the two neighboring groups, the thermodynamic stability of the latter isomer was decreased and some authors were able to detect this only in trace amounts and in selected cases. For example, 1-(2*H*-1,2,3-triazol-4-yl)pyrimidine-2,4-(1*H*,3*H*)-dione **35**



Scheme 45 *N*-Alkylation of 3-(pivaloyloxymethyl)-1-[(NH-1,2,3-triazol-4-yl)methyl]thymine **35**

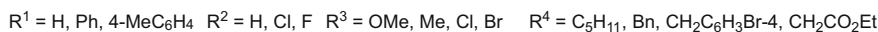
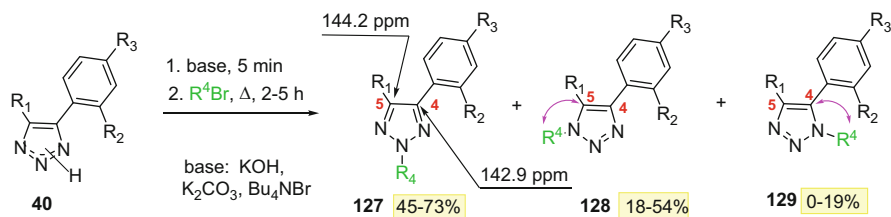


Scheme 46 Reaction of 4-phenyl-1,2,3-triazole **22a** with 2-nitro- and 2-methoxybenzyl chlorides **123**

reacted with methyl bromoacetate, 2-bromoethanol or diethyl 3-bromopropylphosphonate yielding 69–87% (combined) of **122/123** (Scheme 45) [50]. The N (2)/N(1) regioselectivity of the alkylation varied from 37:50 (methylbromoacetate) to 67:5 (diethyl 3-bromopropylphosphonate). Steric effects and the specific nature of the R-substituent on the electrophilic carbon in **121** were considered as factors to impact the course for the alkylation. The structure of 2-alkyl-2*H*-1,2,3-triazolo-nucleosides **123** was confirmed by ¹H-¹⁵N HMBC NMR spectra. The triazole nitrogen atoms were identified through their correlation with *exo*-cyclic protons of the side chain.

Alkylation of NH-1,2,3-triazole **22a** with benzyl chlorides **124** confirmed the previously established importance of electronic effects of the alkyl halide substituents R¹ for the direction of the reaction (Scheme 46) [25]: the ratio of obtained isomers **125** and **126** convincingly reflected this trend.

The problem of regioselectivity is present to the full extent for the alkylation of 4,5-disubstituted 1,2,3-triazoles [52, 53, 62, 72, 137, 154–171]. *N*-Alkylation of unsymmetrical 4,5-disubstituted-1,2,3-triazoles produced a mixture of three regioisomers: **127** N(2)-, **128** N(1)-, and **129** N(3) (Scheme 47) [52]. For this



Scheme 47 Alkylation of 4,5-disubstituted-1,2,3-triazoles **40**

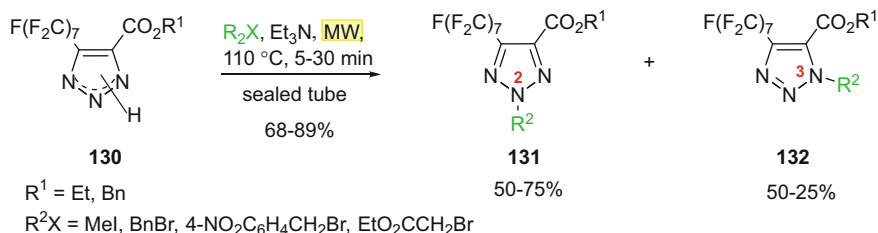
type of substrates, N(2)-isomers were the major products. N(3)-Substituted 1,2,3-triazole **129** was obtained in small proportion or could not be detected, possibly, as a consequence of steric effects.

The question of relative stability of isomers **127–129** was assessed by quantum chemical calculations. The stability of the N(1)-, N(2)-, and N(3)-isomers was evaluated at B3LYP/6-311++ G (d,p) level of theory was in line with experimentally observed ratios.

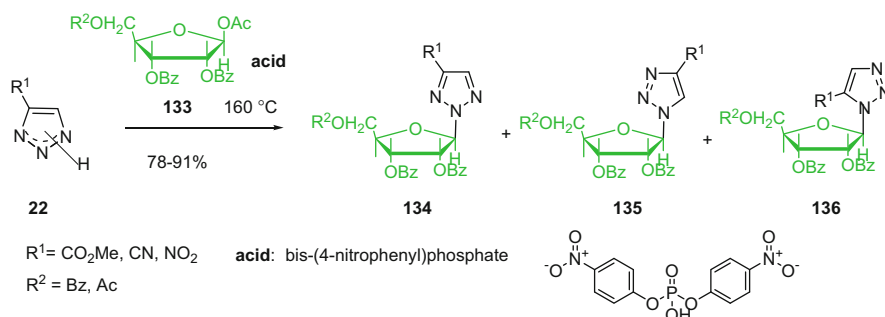
The structural assignment of compounds **127–128** was based on 2D ^1H - ^{13}C NMR experiments. While no correlation was observed for **127**, the spectra of **128** and **129** exhibited different types of correlations between the H-signal of the CH_2 -group in the alkyl chain (R^4) and the C(5)- or C(4)-signals for 1,2,3-triazole ring (Scheme 47).

Alkylation of NH-triazole can be performed by a microwave procedure [62, 136, 169, 170]. A series of fluoroalkylated 1,2,3-triazoles **131** and **132** were synthesized in significant yields. Nevertheless, it should be noted that two regioisomeric triazoles were formed. As it was expected, N(2)-isomer of the 4,5-substituted triazole was the major product and the ratio between the N(2)- and N(1)-isomers depended on the spatial effects of the substituents. The structure of the isomers was carefully analyzed by ^1H , ^{19}F , and ^{13}C NMR spectroscopy and X-ray diffraction [62].

It was shown that the selectivity of N(1)-alkylation of 1,2,3-triazole could be enhanced by introducing metal salts (Ag(I), Tl(III) or Hg(II)) [1]. Glycosylation of ethyl 1,2,3-triazole-4-carboxylate with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in the presence of mercuric cyanide gave N(1)-glycosylated product only [179], while acid-catalyzed fusion led to a mixture of N(1) and N(2)-triazoles [179]. The reaction of NH-1,2,3-triazole with β -bromostyrene resulted in the 2-isomer exclusively if CuI was added, in opposite to an analogous transformation described above (Scheme 48) [146].



Scheme 48 Microwave-assisted alkylation of NH-triazole **120**



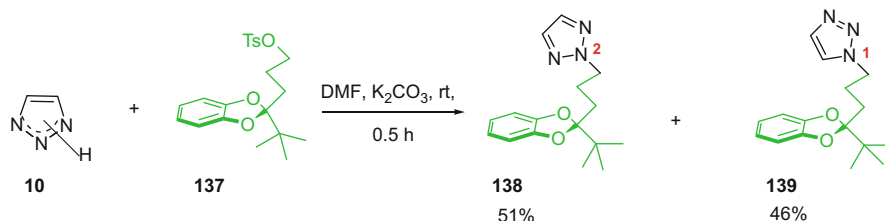
Scheme 49 Synthesis of 1,2,3-triazole nucleosides via procedure of acid-catalyzed fusion

4.2 Alkylation of NH-1,2,3-Triazoles with Alkyl Carboxylates and Sulf(on)ates

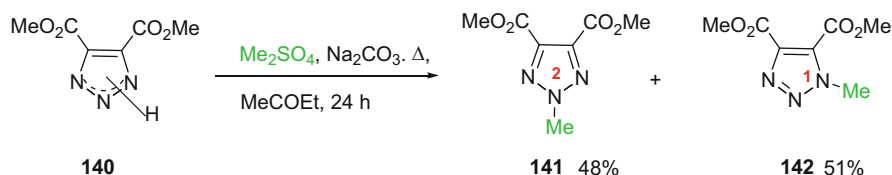
The regioselectivity factor was also very important for the alkylation of NH-1,2,3-triazoles by alkyl carboxylates and sulf(on)ates [59, 62, 172–181]. The fusion of methyl 1,2,3-triazole-4-carboxylate (**22**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (**133**) in the presence of an acidic catalyst provided a mixture of nucleosides **134** and **135**, and a third isomer **136**, in approximate ratio 60:30:10 ratio (Scheme 49). 1- and 3-glycosyl-4-substituted-1,2,3-triazoles **134** and **136** were identified by comparing them with the same compounds synthesized by alternative reaction via cycloaddition of methyl propiolate with 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl azide (Scheme 49) [177–181].

Reaction of unsubstituted NH-1,2,3-triazole **10** with tosylate catechol ketal **137** at room temperature with a base led to 1,2,3-triazole isomers **138** and **139** with good yields and in equal ratio (Scheme 50) [173].

Methyl 1,2,3-triazole 4,5-dicarboxylate **140** underwent a methylation with dimethyl sulfate in methyl ethyl ketone and anhydrous sodium carbonate (Scheme 51). A mixture of the *N*-methylsubstituted isomers **141** and **142** was isolated in quantitative yield. Isomers were separated by flash-chromatography through a silica-gel column [181] and were characterized by analytical and spectroscopic analyses. The results were in accordance with known data for the isomer **142**



Scheme 50 Reaction of NH-1,2,3-triazole **10** with tosylate catechol ketal **137**



Scheme 51 Reaction of NH-1,2,3-triazole 4,5-dicarboxylate **139** with dimethyl sulfate

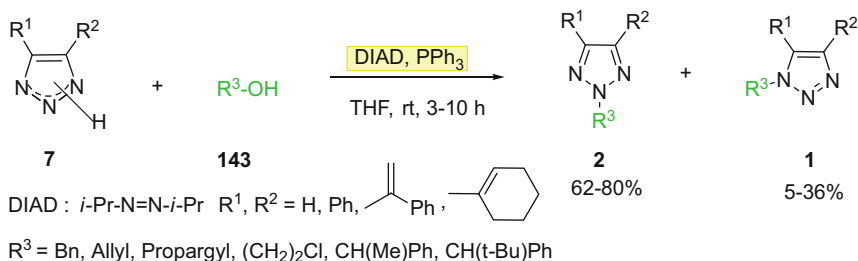
obtained from methyl azide (Scheme 51) [181]. The ratio of isomers **141/142** was 51:48, respectively, as determined by gas chromatography.

4.3 Mitsunobu Reaction of NH-1,2,3-Triazoles

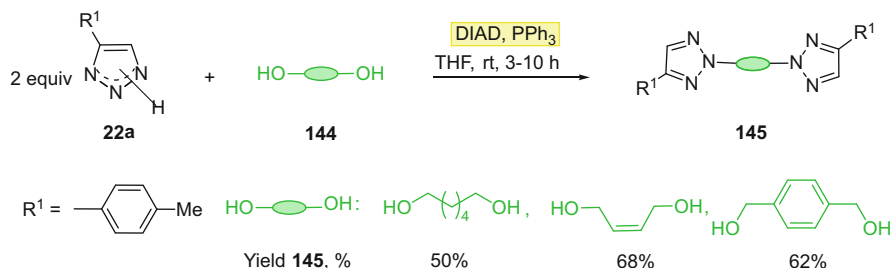
The relatively high acidity (pK_a 8–10) and strong nucleophilicity make NH-1,2,3-triazoles suitable partners of alcohols reacting in Mitsunobu reaction (DIAD, PPh_3 in THF) (Scheme 52) [131, 137, 182–186].

Compared to the above described examples of alkylation, significantly higher yields of N(2) products were observed for all cases of the Mitsunobu reaction. The reaction with secondary alcohols required longer times (8–12 h) and provided N(2)-isomers as the major products [184]. The significance of the choice of the alcohol for influencing the N(1)/N(2) selectivity was highlighted for the synthesis of bis-N(2)-triazole derivatives **145** (Scheme 53).

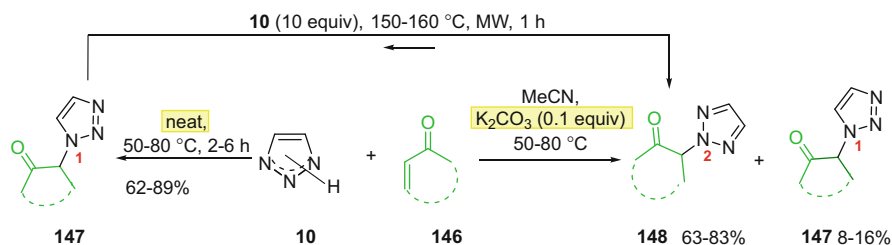
The conditions of the Mitsunobu reaction were suitable for a wide variety of alcohols and in general provided excellent yields of coupling products. Combined yields of N(1) and N(2)-isomers were more than 85%. This method can serve as a good alternative for N(2)-substitution involving no catalysts or sophisticated manipulation while altering the reactivity of the triazoles. Moreover, with the excellent stereochemical control, this method establishes the background for an asymmetric synthesis of pure 2*H*-1,2,3-triazole derivatives [184].



Scheme 52 Mitsunobu reaction of 4,5-disubstituted NH-1,2,3-triazoles **7**



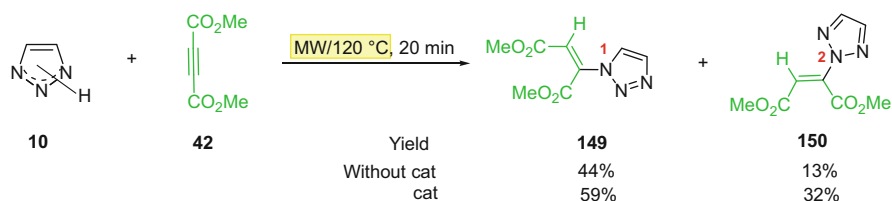
Scheme 53 Synthesis of bis(1,2,3-triazoles) **145** under Mitsunobu conditions



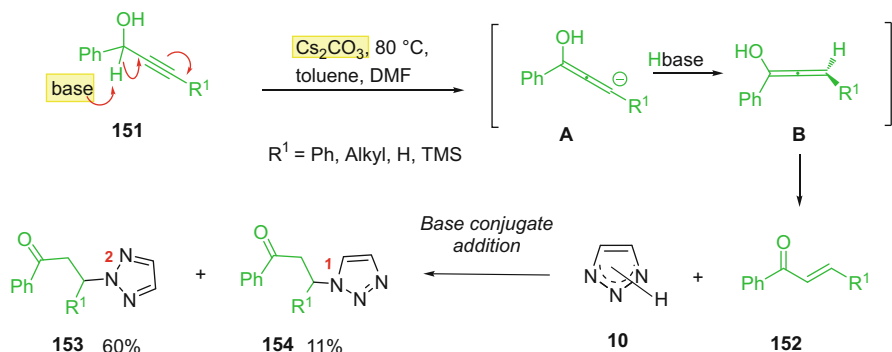
Scheme 54 Michael addition of NH-triazole **10** to α,β -unsaturated ketones **145**

4.4 Michael Addition

Ethyl propiolate, dimethyl acetylenedicarboxylate, phenyl propiolic aldehyde, and ethylphenylpropiolate reacted with triazole salts (triazolides) giving Michael adducts, with preference for the N(2)-isomers [50, 104, 187–197]. The selectivity depended on reaction conditions. Michael addition of neat triazoles with alkynones taking place upon heating led to N(1)-triazoles **147**. However, heating of reagents in aprotic solvents (acetonitrile was the best) and under basic conditions (K_2CO_3) yielded predominantly N(2)-substituted triazoles **148** (Scheme 54) [189].



Scheme 55 Reaction between NH-1,2,3-triazole **10** and DMAD



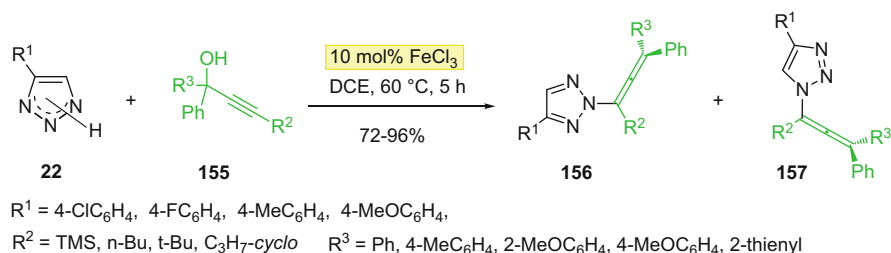
Scheme 56 Reaction of NH-1,2,3-triazole **10** and propargyl alcohols **150** in base condition

Michael addition of NH-1,2,3-triazole **10** and DMAD under microwave irradiation in the absence of catalyst led to a mixture of products **149** (as the *E*-stereoisomer) and **150** (as a of *Z/E* mixture in 7:3 ratio) (Scheme 55) [191]. The overall yields of **149** and **150** increased from 57 to 91% with little change in the isomers ratio when silica-bound AlCl_3 was used as the catalyst.

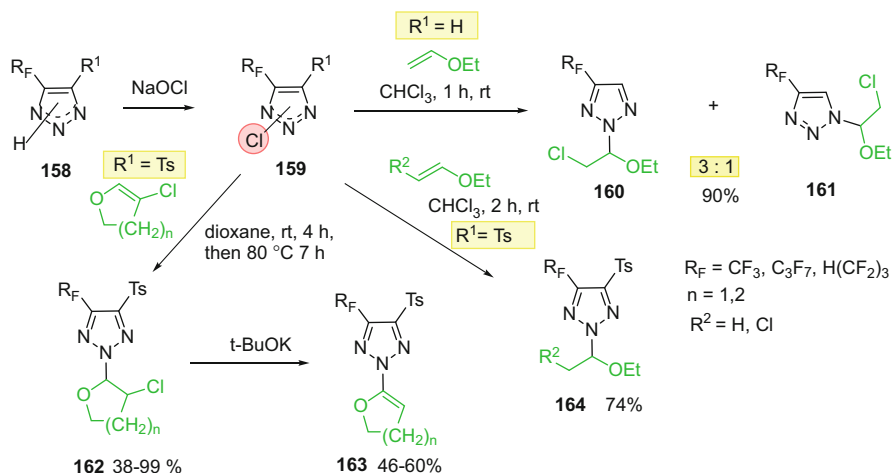
Conjugated addition of triazole to propargyl alcohols **151** in the presence of DBU was unsuccessful [191]. Heating of triazole **10** with propargyl alcohols **151** in toluene with DMF and DBU was sluggish. The corresponding triazoles **153** and **154** (6:1) were isolated in satisfying total yield. Redox-isomerization of accessible propargyl alcohols occurred via conjugated one-step addition of NH-azole **10** proceeded by nucleophilic attack of basic reagent. This reaction displayed a broad scope and tolerated a variety of reactive functional groups (Scheme 56) [187].

Triazole addition to tertiary propargyl alcohols occurred in a regioselective manner in the presence of iron catalyst and led to allene triazoles **156** and **157**. The reaction proceeded under mild conditions, giving a mixture of regioisomers **156** and **157** in good or excellent yields (Scheme 57) [188].

To improve further the regioselectivity of this reaction the screening of different metals ($\text{Cu}(\text{OAc})_2$, CuI , PdCl_2 , RuCl_3 , IrCl_3 , $\text{Fe}(\text{acac})_3$, LaCl_3 , CeCl_3 , $\text{Bi}(\text{OTf})_3$, AlCl_3 , SnCl_2 , LiCl) as catalyst and different solvents (MeCN , Me_2O , THF, Toluene, MeOH , MeNO_2 , DMSO, DMF, CHCl_3 , EtOAc , DCE) was performed. It was found that FeCl_3/DCE conditions were the best option [183, 188].



Scheme 57 Reaction of 1,2,3-triazole **22** addition to tertiary propargyl alcohols **155**



Scheme 58 Nucleophilic addition NH-1,2,3-triazole to electron-rich alkenes via *N*-halogenated derivative **158**

Regioselective addition at the N(2)-position of 1,2,3-triazoles should be achieved via their transformation into N(2)-halogen derivatives. N(2)-Chlorotriazoles **159** reacted with double bonds of vinyl ethers [104], 2,3-dihydro-2*H*-furan (DHF), and 3,4-dihydro-2*H*-pyran (DHP) [197] at room temperature (Scheme 58).

Monosubstituted 1,2,3-chlorotriazole **158** ($\text{R}^1 = \text{H}$) reacted with alkenes giving a mixture of 1- and 2-alkyl derivatives **160** and **161**. At the same time, 4,5-disubstituted triazole **159** led to 2-substituted derivatives **162–164** only. Compound **163** was obtained after elimination of HCl from adduct **162**.

Obviously, due to the formation of the product mixture observed for the most cases of described alkylation examples, the separation of products becomes an important task to be performed at the final step. Luckily, the lower polarity of the desired N(2)-isomers comparing to the N(1)/N(3) ones can substantially facilitate this process.

4.5 *N*-Arylation (*N*-Heteroarylation) of *NH*-1,2,3-Triazoles

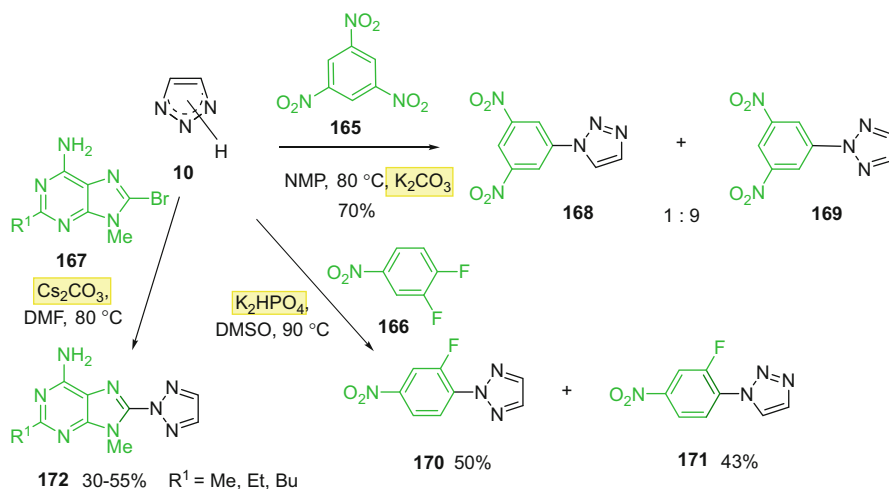
Theoretically, an ideal route to obtain *N*(2)-aryl(heteroaryl)-1,2,3-triazoles would be a direct *N*-arylation(heteroarylation) of *NH*-1,2,3-triazoles [18, 27, 29, 31, 34, 49, 117, 128, 132, 146, 149, 163, 198–223]. This reaction, occurring at higher temperatures (50–120 °C) in DMF, DMSO, MeCN, acetone, THF and catalyzed by bases (K₂CO₃, Cs₂CO₃, NaH, KOH, K₂HPO₄), could not provide an acceptable yield of desired product. It was because the reaction resulted in a mixture of two isomers in various ratios and with lower (20–50%) total yields [34, 49, 215, 217, 219]. An increase of the total yields, up to 60–70%, was observed only for *N*-arylation (heteroarylation) of *NH*-1,2,3-triazoles with activated electrophiles (1,3,5-trinitrobenzene or pentafluoropyridine) (Scheme 59) [18, 31, 132, 163, 200, 202, 210, 217, 219, 223].

To evaluate the regioselectivity for *N*-arylation/heteroarylation, the S_NAr substitution of various *NH*-1,2,3-triazoles was studied [18]. The product of arylation was stable and no C–N bond exchange occurred under the reaction conditions. This allows to evaluate directly the impact of C(4) and C(5) groups on the regioselectivity of this reaction. The introduction of phenyl group to the C(4)-atom of the 1,2,3-triazole **7** (R¹=Ph, R²=H) increased the selectivity and resulted in the major *N*(2)-arylation product, although with small ratio differences for all possible products. As reported previously, the selectivity of the reaction is controlled by both electronic and steric factors. A rise in the temperature leads to the strengthening of conformational factors and increases the steric effects of the C(4)- and C(5)-substituents. Indeed, *N*(2)-selectivity was noticeably improved with an increase of the reaction temperature (Scheme 60).

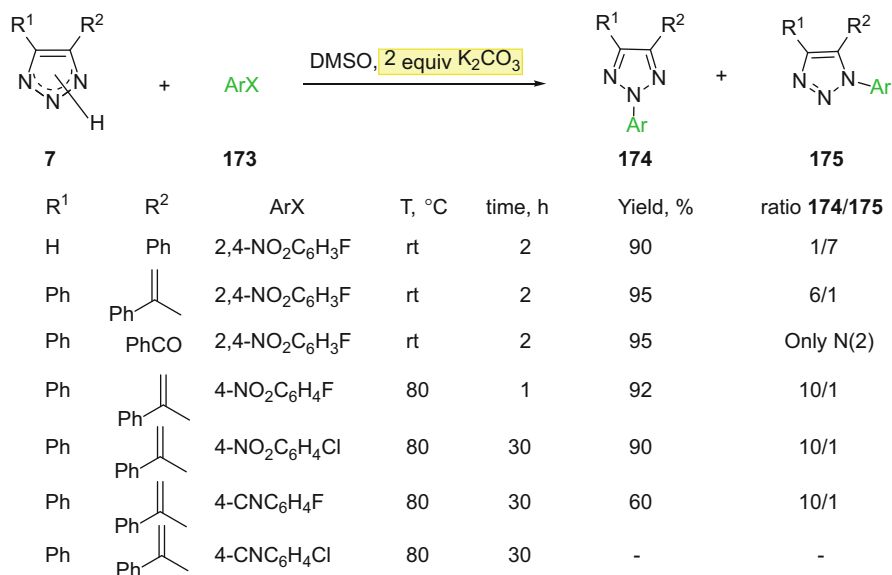
Arylation of *NH*-1,2,3-triazoles by different agents, including moderately active aryl halides was observed under Ullman conditions, e.g. in the presence of Cu(I,II) salts, and yielded *N*(2)-aryl-1,2,3-triazoles **176–178** (Scheme 61) [18, 198, 206, 221, 224–229].

The mechanism of this reaction was unresolved until now. Most likely, it involves the formation of Cu(III) intermediate followed by reductive elimination. It was established that the Cu(I) or Cu(II) oxidative addition to the carbon–halogen bond occurs via a catalytic cycle which is strongly dependable on the ligand type. Furthermore, a study of the reaction conditions established that *N*(2)-aryl-1,2,3-triazoles are formed exclusively if ligands were applied as co-catalysts. The best ligand among all co-catalysts tested (proline, glycine, Me-Gly, EDA, DMEDA, TMEDA, DACH) was proline [18].

Biarylphosphine palladium was found to be the most selective metal catalyst for the synthesis of 4,5-unsubstituted and 4-substituted *N*(2)-arylated 1,2,3-triazoles [207]. A variety of aryl bromides, chlorides, and triflates with ester, ketone, aldehyde, acetal, nitro, and cyano groups could be employed in this reaction. Slightly decreased *N*(2)-selectivity was observed for the reaction of aryl chlorides bearing an EWG at the *para*-position. For all other substrates an excellent *N*(2)-selectivity (>95%) was observed (Scheme 62).

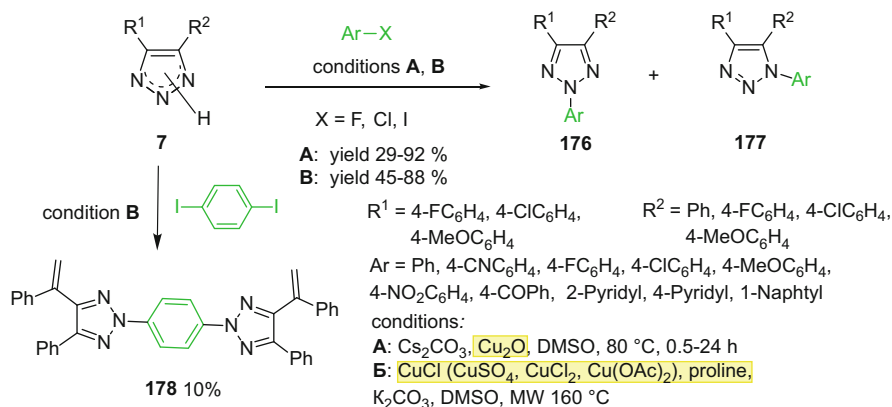
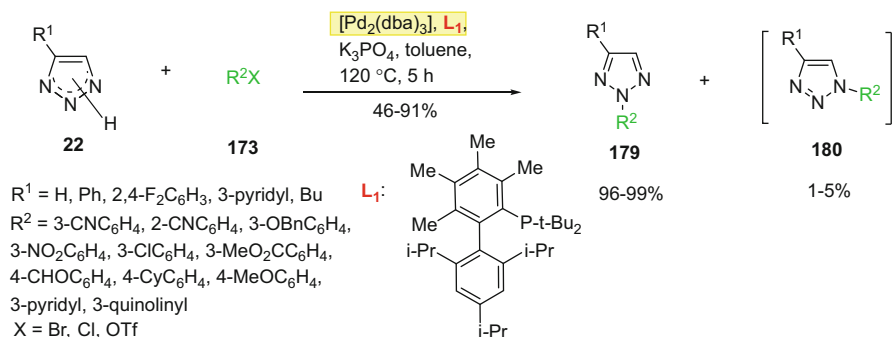
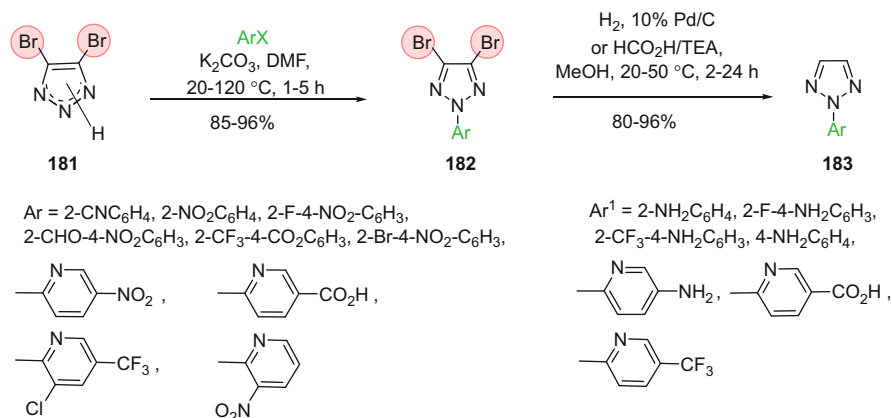


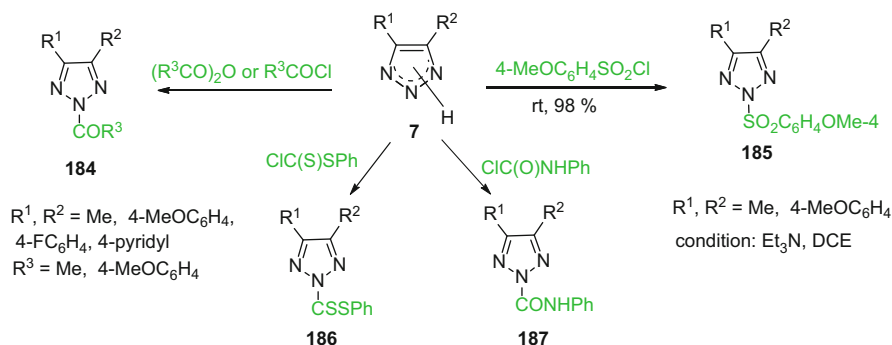
Scheme 59 Reactions of NH-1,2,3-triazole **10** with activated aryls **165**, **166** and 8-Br-purine **167**



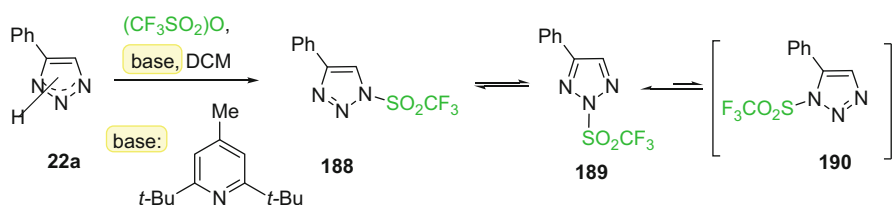
Scheme 60 4,5-Disubstituted triazole **7** arylation via S_NAr reaction

Another protocol for an efficient synthesis of N(2)-aryl-1,2,3-triazoles via highly regioselective N(2)-arylation of 4,5-dibromotriazole was executed (Scheme 63) [210]. Subsequent debromination of these triazoles via a hydrogenation efficiently furnishes 4,5-unsubstituted -2-aryltriazoles in excellent yields. Combination of steric hindrance and an electronic effects induced by 4,5-dibromo substituents

**Scheme 61** *N*-Arylation NH-1,2,3-triazole under the Ullman reaction condition**Scheme 62** N(2)-Selective arylation of 4,5-substituted and 4-substituted NH-1,2,3-triazole**Scheme 63** Selective aromatic substitution of 4,5-dibromo-2*H*-1,2,3-triazole



Scheme 64 Reaction of NH-1,2,3-triazole with acyl-, sulfonyl-, and carbamoyl chlorides



Scheme 65 Sulfonation of 4-phenyl-NH-1,2,3-triazole **22a**

contributed to the high regioselectivity observed for this reaction. Thus, the use of 4,5-dibromotriazole **181** as a nucleophile has a substantial practical value for the direct and specific N(2)-arylation of 1,2,3-triazoles.

4.6 N-Acylation, N-Sulfonation, and N-Carbamylation of NH-1,2,3-Triazoles

In contrast to *N*-alkylation and *N*-arylation, *N*-acylation, *N*-sulfonation, and *N*-carbamylation of NH-1,2,3-triazoles predominantly yielded 2-acyl-, 2-sulfonyl-, and 2-carbamoyl derivatives **184–187** (Scheme 64) [27, 29, 47, 97, 136, 185, 230–234] due to the lesser stability of N(1)-regioisomers.

2-Acyl-1,2,3-triazoles themselves are relatively stable only under anhydrous and neutral conditions. The treatment of them with an acid or a base causes the hydrolysis and results in NH-1,2,3-triazoles in high yield [136, 233].

Monitoring of the sulfonation of NH-1,2,3-triazole **22a** by 1H NMR spectroscopy allowed to register previously undetected isomer **190**, formed in negligible amounts [233]. Isomers **188** and **189** were formed in approximately 1:1 ratios (Scheme 65).

Nevertheless, all attempts to isolate the corresponding *N*-triflyl triazoles were unsuccessful due to their susceptibility to hydrolysis.

The lower stability of *N*-acyl/sulfonyl derivatives of 1,2,3-triazoles limits their synthetic potential.

5 Synthesis of 2*H*-1,2,3-Triazoles by Transformations of Functionalized Hydrazones

The next major group of methods for the synthesis of 2-substituted 1,2,3-triazoles is based on transformations of hydrazones (oxidative cyclizations, Boulton–Katritzky rearrangement and various types of condensations).

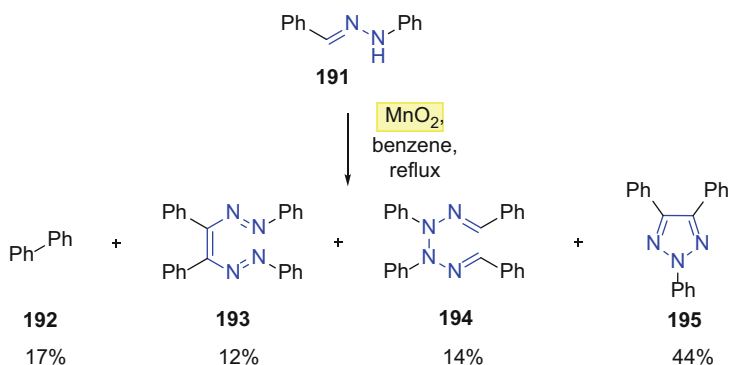
5.1 Oxidation of Mono- and Bis(arylhydrazones)

The first synthesis of a 1,2,3-triazole by the oxidation of bis(hydrazone) of 1,2-aldehydes was carried out by Pechmann [1]. Later this approach was thoroughly studied by other authors [1–6, 235–255]. Heating of ketone phenylhydrazones, bis(hydrazones), bis(arylhydrazones), or bis(semicarbazones) of 1,2-dicarbonyl compounds in the presence of MnO₂, HgO, Hg(OAc)₂, FeCl₃, NiO₂, Pb(OAc)₄ led to the formation of a mixture of products, including 1,2,3-triazole. Nevertheless, the yield of 1,2,3-triazole was quite low, 15–40%. It was shown that oxidation of arylaldehyde phenylhydrazone **191** with MnO₂ led to 1,4,5-triphenyl-1,2,3-triazole **195** mixed with by-products **192–193** (Scheme 66) [235–242].

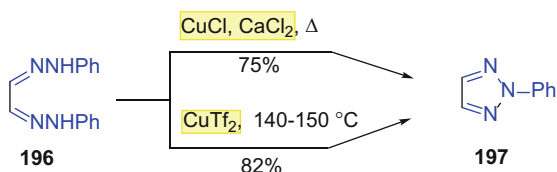
It was also found that oxidative cyclization of bis(hydrazone) **196** of glyoxal proceeded effectively in the presence of copper(I,II) salts (CuOAc, CuSO₄, CuTf₂, CuCl) (Scheme 67) [243–255].

Oxidative cyclization of bis(hydrazones) is a useful method for the two-step synthesis of triazolyl sugars. For example, D-xylose, D-ribose, D-glucose, and D-galactose were converted into phenylosazones in the first step. The latter underwent an oxidative cyclization with 1% CuSO₄, yielding 43–54% of **200** (Scheme 68) [249–255].

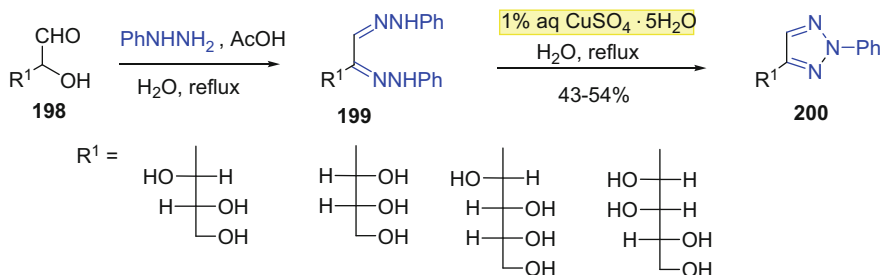
Detailed investigation on the oxidation of arylhydrazones led to the discovery of optimal conditions for the synthesis of 2,4,5-triaryl-1,2,3-triazoles and determined the mechanism of cyclization [244]. The reaction was successfully performed by heating in toluene under air with 20 mol% Cu(OAc)₂·2H₂O. In polar solvents, such as dioxane, DMSO, and THF, the yield of 2-aryl-1,2,3-triazoles **203** fluctuated from trace amounts to moderate values. The yields increased substantially when molecular oxygen was used. In contrast, the yields of target compounds **203** were reduced in a nitrogen atmosphere. The catalytic activity of different copper sources, such as Cu(OAc)₂, CuCl₂, Cu(OTf)₂, CuCl, and CuI was examined. The catalytic activity of Cu(II) salts was found to be superior to the activity of Cu(I) salts. Control experiments confirmed that no cyclization yielding compounds **203** was observed without a copper source (Scheme 69).



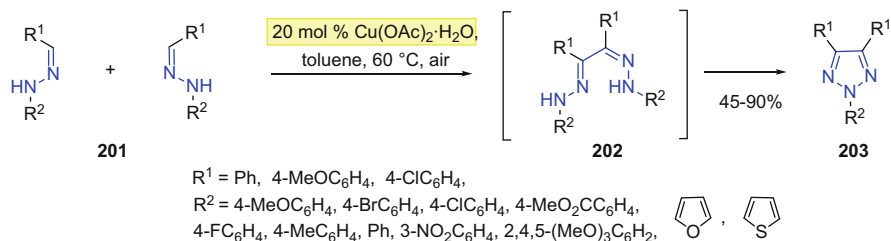
Scheme 66 Phenylhydrazone **191** oxidation in the presence of manganese(IV) oxide



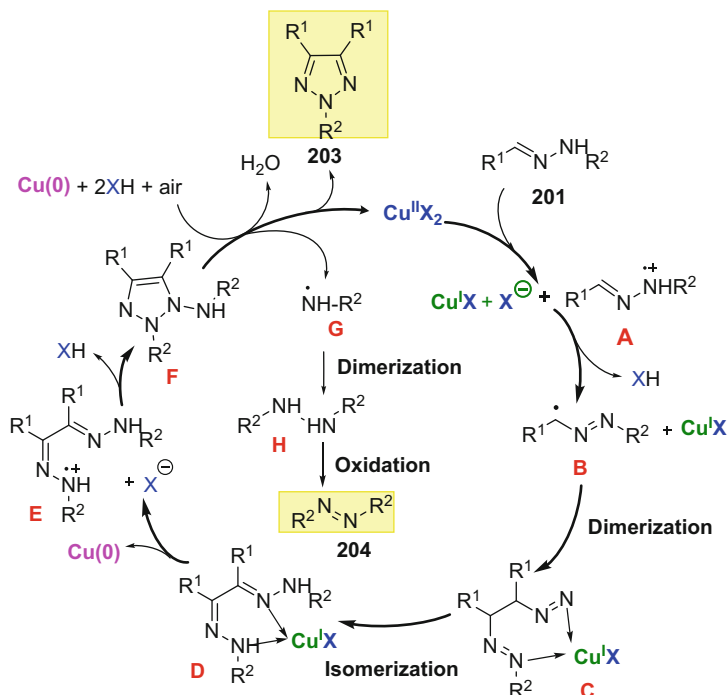
Scheme 67 Cu(I,II) salt catalyzed oxidative cyclization 1,2-bis(2-phenylhydrazono)ethane **196** to 2-phenyltriazole **197**



Scheme 68 Two-step synthesis of triazolyl sugars **200**



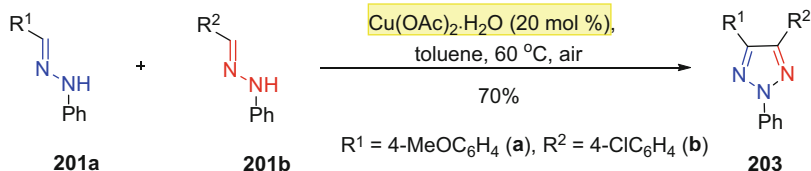
Scheme 69 Copper (II)-catalyzed synthesis of 2,4,5-triaryl-1,2,3-triazoles **201**



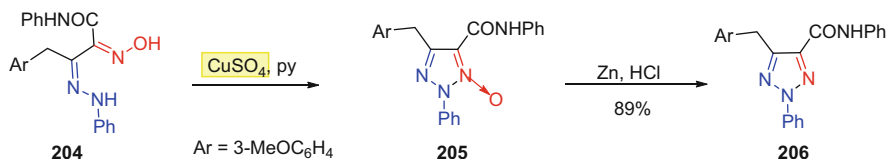
Scheme 70 Proposed catalytic cycle for the synthesis of substituted 2-aryl-1,2,3-triazoles **203** by oxidative cyclization of hydrazone **201**

It should be noted that during the oxidative cyclization of hydrazones **201** into 1,2,3-triazole **203**, intermediates **202** were isolated and their structure was confirmed by X-ray analysis. The result of the addition of TEMPO as an effective radical scavenger to the reaction mixture suggested that this transformation involved a radical intermediate. Analysis of experimental observations helped Guru and Punniyamurthy [244] to propose a plausible scheme for the synthesis of substituted 1,2,3-triazoles (Scheme 70). The generation of copper(0) was confirmed by the powder XRD analysis. Azo compounds **204** were also separated and identified by single-crystal X-ray analysis. The reaction was general, and a series of substrates underwent this cyclization to give target compounds in moderate to high yields.

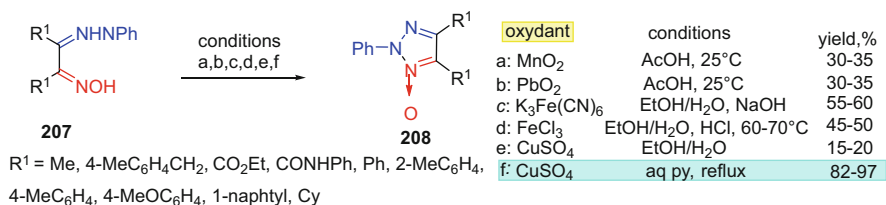
Moreover the reaction conditions were appropriate to obtain unsymmetrical 2,4,5-triaryl-1,2,3-triazoles **203** (Scheme 71) [244]. Finally, an optimal scale-up of the conditions for this reaction was developed to afford desired triazoles in 75–77% yields, but these updated conditions led to slightly extended reaction times.



Scheme 71 Copper(II)-catalyzed synthesis of unsymmetrically substituted 1,2,3-triazole **203**



Scheme 72 Synthesis of 2-phenyl-1,2,3-triazole **206** via the 2-phenyl-2H-1,2,3-triazolium 1-oxide **205**



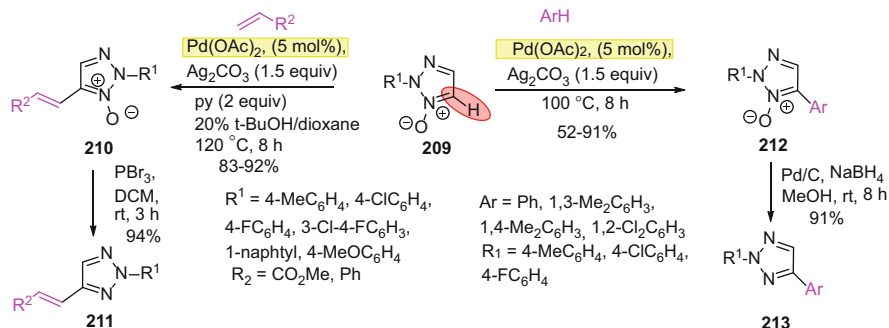
Scheme 73 The influence of various oxidative agent and solvents on the yield of 2-aryl-1,2,3-triazolium 1-oxide **208**

5.2 Oxidative Cyclization of Arylhydrazonoacetamidoximes and α -Hydrazono-Oximes

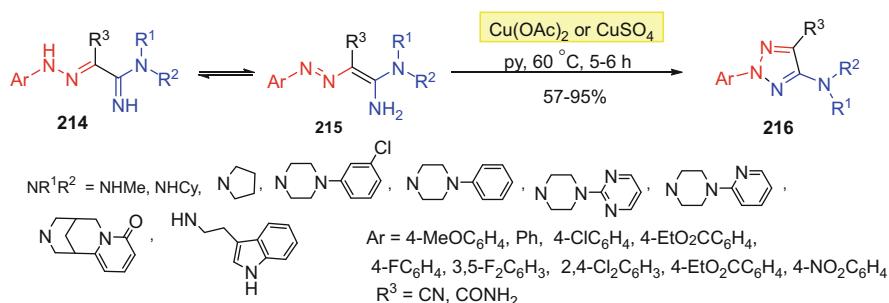
Oxidative cyclization of 2-(2-arylhydrazono)acetaldehyde led to 2-aryl-1,2,3-triazolium 1-oxides [256–268]. 1,2,3-Triazole derivatives **205** were easily transformed into 2-aryl-1,2,3-triazoles **206** by zinc reduction (Scheme 72) [259].

Various oxidative agents were applied for this reaction: $\text{K}_3\text{Fe(CN)}_6$, PbO_2 , MnO_2 , FeCl_3 , CuSO_4 , and *N*-iodosuccinimide. The heating of substrates in pyridine with copper(II) sulfate was the most effective method to reach an excellent yield (82–97%) (Scheme 73) [263].

This method used to construct the 1,2,3-triazole ring has an important synthetic application. The highly selective character of C–H bond activation occurring in triazolium 1-oxides **209** allowed them to interact with alkenes (site-selective alkenylation) and inactivated arenes (cross-coupling) in a regioselective manner in the presence of a Pd-catalyst (Scheme 74) [257].



Scheme 74 Reactions of 2-aryl-1,2,3-triazolium N-oxides **209** with alkenes and arenes

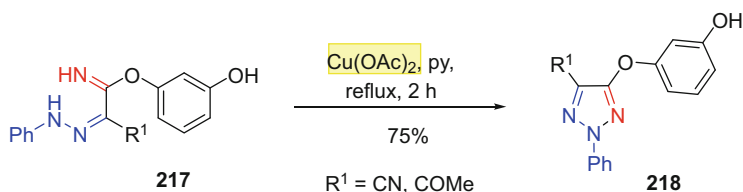


Scheme 75 Oxidative cyclization of hydrazonoacetamides **214** to 5-amino-2-aryl-2*H*-1,2,3-triazoles **216**

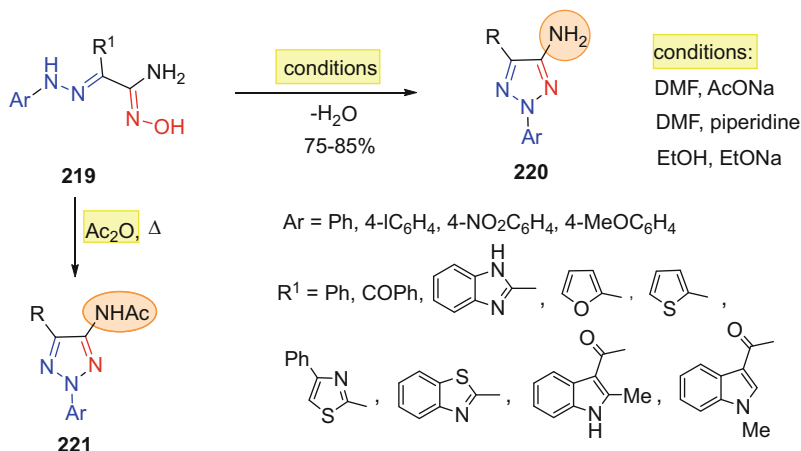
5.3 Oxidative Cyclization of Arylhydrazonoacetamides

A series of 5-amino-2-aryl-2*H*-1,2,3-triazoles were successfully prepared by oxidation of arylhydrazonoacetamides with copper(II) salt in pyridine [269–274]. The oxidative cyclization of 2-arylhydrazonoacetamides **214** was carried out with copper(II) acetate or sulfate in pyridine at 60°C under vigorous stirring and afforded aminotriazoles **216** in good yield (Scheme 75) [270–272, 274]. This synthetic approach allows to introduce amino, amide, and cyano groups in 1,2,3-triazoles, as well as various pharmacophores and fragments of natural products (e.g., tryptamine) and alkaloids (cytosine, piperazine) (Scheme 75).

3-Hydroxyphenyl 2-(2-phenylhydrazono)acetimidate **217** was transformed to 2-aryl-2*H*-1,2,3-triazoles **218** bearing an oxyphenolic group at the C(4) position by an oxidative cyclization occurring in the presence of copper(II) acetate (Scheme 76) [273].



Scheme 76 Oxidative cyclization of 3-hydroxyphenyl 2-(2-phenylhydrazono)acetimidate **217**



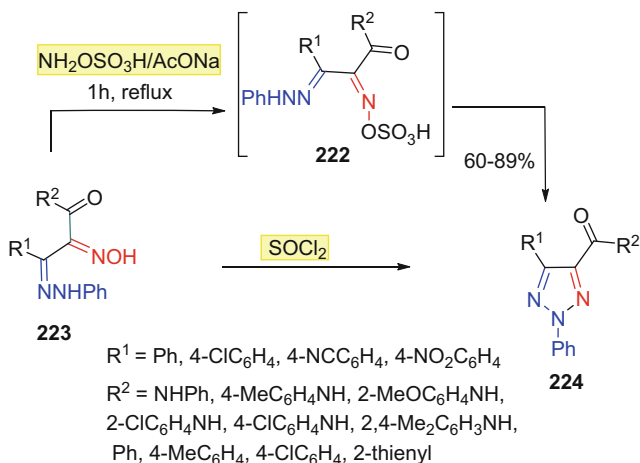
Scheme 77 Cyclization of arylhydrazonoamidoximes **219** to 5-amino- and 5-acylamino-2-aryl-2H-1,2,3-triazoles **220** and **221**

5.4 Intramolecular Cyclization of Bis(hydrazones) and Hydrazoneamidoximes

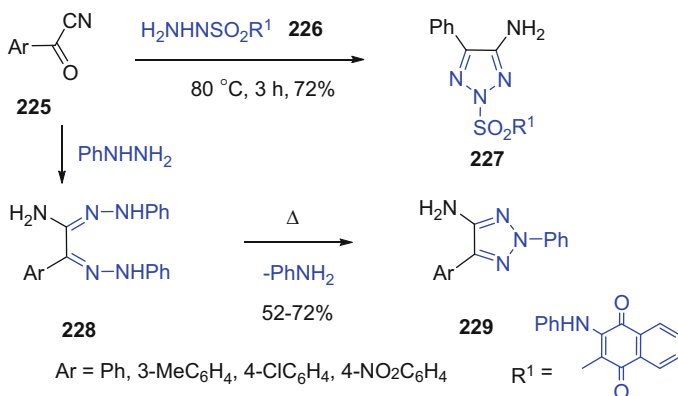
Another transformation of bis(hydrazones), hydrazoneamidoximes, and hydrazonehydrazides yielding 2-aryl-1,2,3-triazoles usually occurs under condensation conditions and is accomplished by the elimination of a leaving group [240, 275–294].

Arylhydrazonoacetamidoximes are widely accessible and can be easily transformed into 5-amino-1,2,3-triazoles by heating in DMF, EtOH with sodium acetate, EtONa, or piperidine, followed by treatment with POCl_3 , or by reflux in acetic anhydride, under microwave activation [275–281]. Refluxing hydrazones **219** with acetic anhydride causes the cyclization, which usually leads to mono- or diacetylated dehydration products (Scheme 77) [277–279].

It was shown that 1,2,3-triazole can be obtained directly from arylhydrazono-nitriles by heating them in DMF with hydroxylamine hydrochloride in the presence of sodium acetate [270].



Scheme 78 Cyclization of arylhydrazone α -oximes **222** to 2-aryl-2*H*-1,2,3-triazole-4-carboxamides **224**

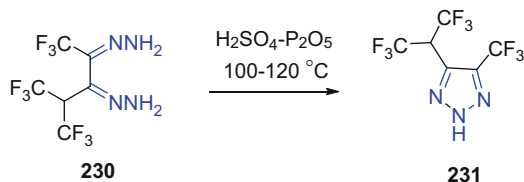


Scheme 79 Reaction of aryl nitriles **225** with the phenylhydrazine and sulfonylhydrazide **226**

Cyclization of arylhydrazone oximes **223** by dehydration agents (Ac_2O , SOCl_2 , hydroxylamine-*O*-sulfonic acid) led to 2-aryl-1,2,3-triazoles in the same manner (Scheme 78) [282–290].

Reaction of hydrazononitriles **225** with phenylhydrazine or sulfonylhydrazide **226** afforded 4-amino-1,2,3-triazoles **227** via intermediate bis(hydrazone) whose cyclization was accompanied with an elimination of aniline or sulfonamide. Bis(hydrazone) α -dicarbonyl compounds **228** were separated and identified (Scheme 79) [292–294].

Using arylhydrazone substrates with an ethoxycarbonyl group at the α -position provided a synthetic route to 5-hydroxy-2*H*-triazoles [294].



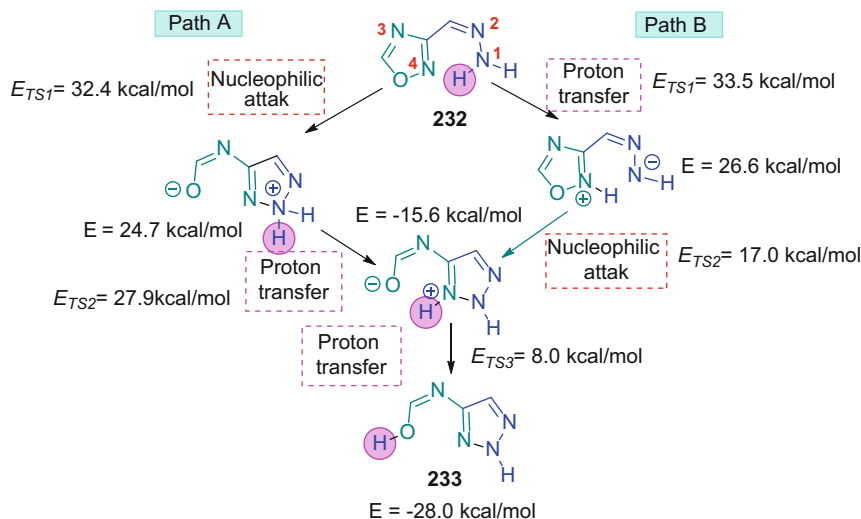
Scheme 80 Synthesis of fluorinated NH-1,2,3-triazole **231** by the cyclization of bis(hydrazono) **230**

The unsubstituted dihydrazono of α -diketone **230**, bearing two fluorinated alkyl substituents at C-hydrazono atom, underwent cyclization into (hexafluoropropan-2-yl)-5-(trifluoromethyl)-2H-1,2,3-triazole **231** by treatment with an $\text{H}_2\text{SO}_4\text{-P}_2\text{O}_5$ (3 : 1) mixture [240, 291]. It should be mentioned that α -hydrazono **230**, similarly to their nonfluorinated analogues, can be hydrolyzed exclusively into the α -ketohydrazono in the presence of concentrated H_2SO_4 (Scheme 80).

Intramolecular cyclization of bis(hydrazones) and hydrazones with the oxime groups proceeded selectively and provided novel 1,2,3-triazoles in good yield. Poor variability and availability of starting compounds (α -dicarbonyl substrates and hydrazines) limited greatly the applicability of this approach for the synthesis of new triazoles. Synthesis of 1,2,3-triazoles from bis(hydrazones) cannot be considered as an atom-economic process because aniline elimination is involved although theoretically aniline could be reconverted into phenylhydrazine. Using hydroxylamine derivatives is more useful in this case.

5.5 Boulton–Katritzky Rearrangement of 3-Hydrazono Oxadiazoles, -Furoxans and -Isoxazoles

It is well known that 1,2,4-oxadiazoles, 1,2,5-oxadiazoles (furoxans), and isoxazoles bearing a hydrazone group in the α -position of the side chain can be easily transformed into 2-aryl-1,2,3-triazoles via the Boulton–Katritzky monocyclic rearrangement [295–326]. This type of reaction represents an example of azole–azole interconversion. This peculiar case was also described as “monocyclic rearrangement of heterocycles” (MHR) recognized by Boulton and Katritzky as a general class of ring–ring rearrangements [327]. Besides its synthetic applications, this rearrangement gets a lot of attention due to the interesting aspects of its mechanism [295–304]. The process can be depicted as an internal (intramolecular) nucleophilic substitution (S_{Ni}), and therefore the reactivity of substrates can be related to the main factors affecting the reactivity towards S_{N} reactions, i.e.: (1) the nucleophilicity of the arylhydrazone α -nitrogen, (2) the electrophilic character of the N(2)-atom in the heterocycle, and (3) the strength of the N(2)/O(1) bond for the cleavage in the starting ring (1,2,4-oxadiazole, isoxazole, 1,2,5-oxadiazole) and, hence, the mobility of the O(1)-leaving group [295–304]. The last factor can be

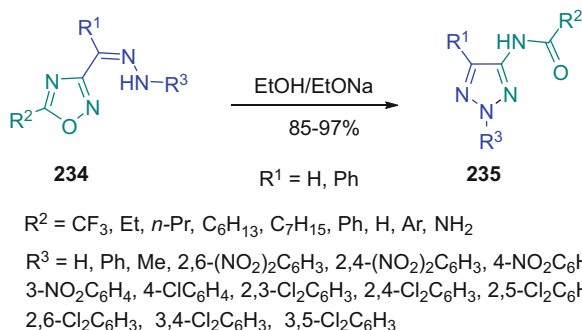


Scheme 81 Schematic representation of two pathways for intramolecular rearrangement of Z-hydrazone of 3-formyl-1,2,4-oxadiazole **232** to 1,2,3-triazole **233**

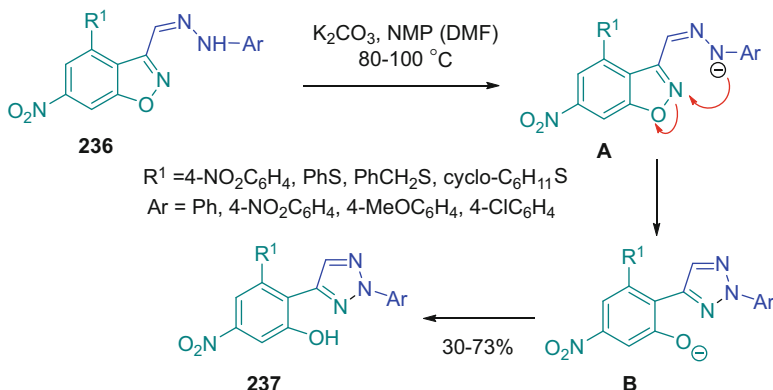
modulated by changing the type of azoles since in general the strength of N(2)–O (1) bond in general depends on the ability of the leaving group to accommodate the negative charge. It should be mentioned that the concentration of base is another crucial factor for the rearrangement process. Different pathways were confirmed to exist: a proton-concentration-independent or *uncatalyzed* pathway, and proton-concentration-dependent or *base-catalyzed* one, requiring either a general or a specific base catalyst [295–301].

Several investigations indicated the effect of the substituents on the arylhydrazone moiety on the electronic properties of the key atoms involved in the MHR, namely the hydrogen atom bound to the N(α)-atom, and the N(2) and C (5) atoms. Electron-withdrawing substituents were responsible for a decrease of reactivity of these atoms [298, 300, 304]. This S_N reaction was described in terms of push–pull shifts of electron density around the framework of broken/formed bonds. This phenomenon was accepted as an evidence for a concerted mechanism [300].

The mechanism for the uncatalyzed rearrangement of the Z-hydrazone of 3-formyl-1,2,4-oxadiazole was studied with DFT calculations. The study has shown that in vacuo the rearrangement occurs in a non-concerted mode along a stepwise pathway A with an activation barrier of 26.1 kcal/mol for the rate-determining step. Solvent effects (H₂O, DMSO), calculated via the COSMO continuum model, have a drastic influence on the activation barrier for the second step (this disappeared) while they slightly suppress the barrier for the first step. This suggests that under experimental conditions the reaction should proceed via an asynchronous concerted transition state where the nucleophilic attack and proton transfer occur in one kinetic step but not simultaneously (Scheme 81) [303].



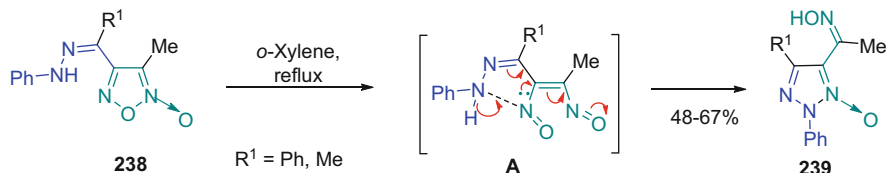
Scheme 82 Intramolecular rearrangement of the Z-arylhydrazones of 1,2,4-oxadiazole **234** to 5-acylamino-2-aryl-1,2,3-triazoles **235**



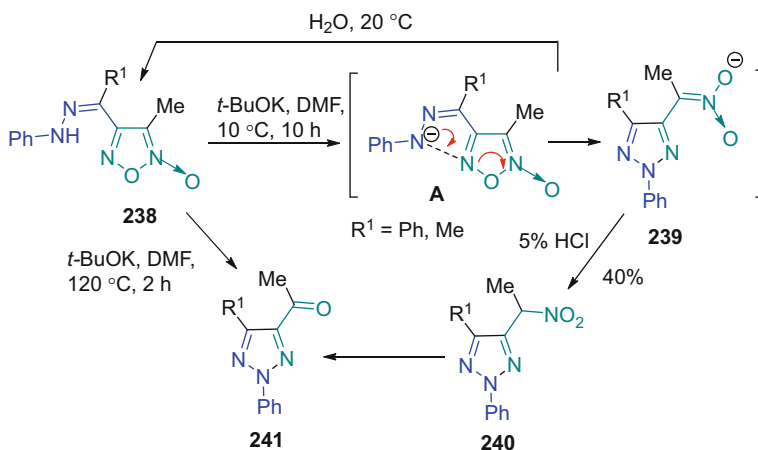
Scheme 83 Rearrangement of the hydrazone of benzo[d]isoxazole **236** to 2-aryl-2H-1,2,3-triazole **237**

Well-documented examples of this rearrangement include transformations of 1,2,4-oxadiazoles, bearing an arylhydrazone group [295–318]. They were observed at room and higher temperatures and in different solvents: dioxane/water system with buffers, in benzene and other organic solvents with various amines or activated by pyrolysis, copper catalysis, or photo- and microwave irradiation. The processes occurred faster in aprotic dipolar solvents, such as DMSO. Heating of substrates above their melting points could also trigger the rearrangement [300]. The availability of the substrates and the considerably convenient reaction conditions allowed to obtain a large series of 1,2,3-triazoles by this method (Scheme 82) [295–318].

Hydrazones of isoxazoles, benzoisoxazoles, and pyrazoloisoxazoles underwent ring-opening/recyclization when treated with K_2CO_3 in *N*-methylpyridine (NMP) or EtOH and gave 1,2,3-triazoles **237** with moderate yield (Scheme 83) [319–322].



Scheme 84 Thermally induced rearrangement of furoxanoketones phenylhydrazones **238**



Scheme 85 Base-induced rearrangement of furoxanylketone phenylhydrazones **238**

The study of rearrangements of noncondensed furoxan hydrazone derivatives **238** helped to identify two kinds of processes: rearrangement through dinitrosoethylene intermediate (1) (Scheme 84) and rearrangement resulting in 1-nitroalkylazoles (2) (Scheme 85). Reactions were initiated either thermally or by adding various bases. The thermally induced rearrangement leading to **239** was executed by refluxing a solution of furoxan phenylhydrazones in *o*-xylene [323–326].

The second variant of rearrangement for *Z*-phenylhydrazones was observed in basic conditions and at different temperatures. The best yield was achieved with a *t*-BuOK solution in DMF at 10 °C.

Rearrangement of *Z*-phenylhydrazones **238** occurred in the presence of base at different temperatures. In order to isolate the target compounds the reaction mixture was acidified in the final step. An attempt to isolate the product by slow dropwise addition of water to the reaction mixture resulted in the starting phenylhydrazones **238**. The reversible monocyclic rearrangement of the intermediate 1,2,3-triazole **239** into the corresponding furoxan was observed in aqueous alkaline media. The rearrangement of compounds **238** in the presence of *t*-BuOK at high temperature resulted in 3-acetyl-2,4-diphenyl-2*H*-1,2,3-triazoles **241** (Scheme 85). The formation

of compounds **241** may be explained by the participation of 5-(nitroethyl)-1,2,3-triazole **240** formed at the first stage in a Nef-type reaction. An insignificant amount of ketone **241** was also detected when the reaction was performed at 10°C (TLC monitoring) [323–326].

These examples of rearrangement of hydrazone derivatives were actively studied during the last decade. The attention was caused by the interest in the mechanistic details for this transformation. The main advantage for this method towards 1,2,3-triazoles consists of the possibility to introduce desired functional groups (cyano, amine, amide, ketone, etc.), while condensation of bis(hydrazones) and α -oxime hydrazones lacks this opportunity.

6 Intra- and Intermolecular Reactions of Diazocompounds

Dipolar cycloaddition of diazoalkanes **242** to nitriles **243** in the presence of base (*t*-BuOK) led to 4,5-disubstituted 2*H*-1,2,3-triazoles **7** (Scheme 86) [328–333]. In the reaction with diazomethane were obtained three regioisomers, namely **245–247**, as a result of alkylation of NH-triazoles **7**.

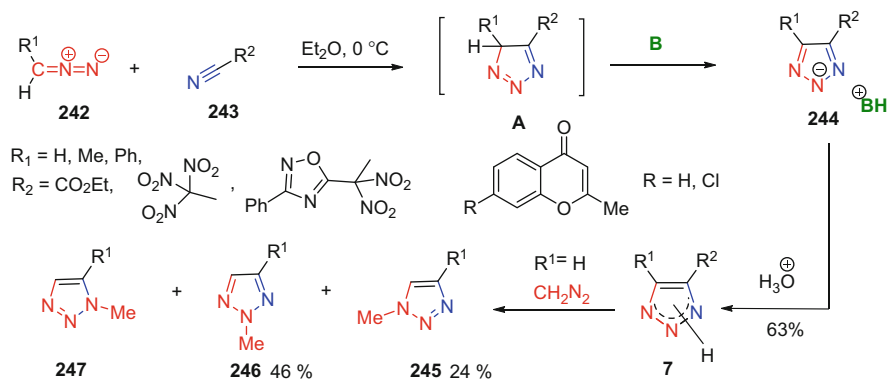
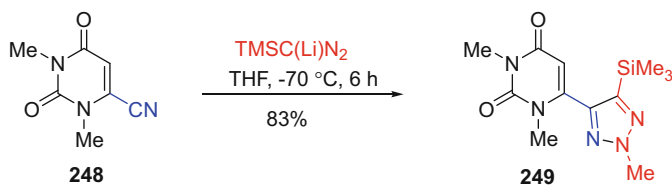
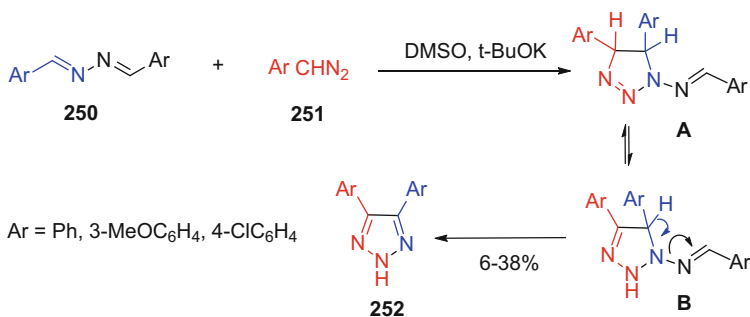
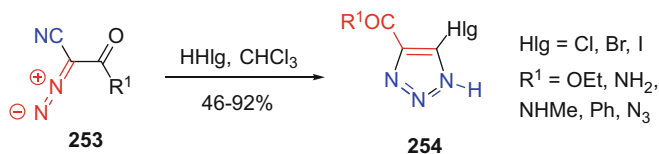
The high reactivity of exocyclic carbonitrile substituent at position 6 in uracil **248** caused it to interact with trimethylsilyldiazomethane (two equiv). Formed NH-1,2,3-triazole underwent in situ the methylation of N2 atom at the next step and derivative **249** was obtained (Scheme 87) [331].

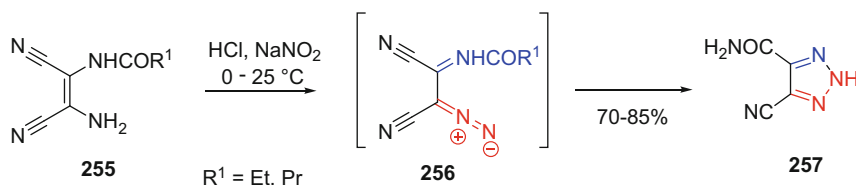
Other groups than nitriles can be involved in this type of reaction. Examples of azomethine double bonds reacting in 1,3-dipolar cycloaddition with diazomethane, yielding two or three isomers of *N*-alkylated triazoles, are also known [332, 333]. The reaction of 1,2-bis(arylmethylene)hydrazines **250** with (diazomethyl) benzene **251** led to symmetrical 4,5-diaryltriazoles **252** (Scheme 88). However, yields were significantly lower than the ones for the reaction shown in Scheme 87 [332].

The cyclization of diazo compounds containing cyano, amide, amidine, imidate groups at the α -position served as a convenient tool to obtain various derivatives of 1,2,3-triazole (Scheme 89) [334–337].

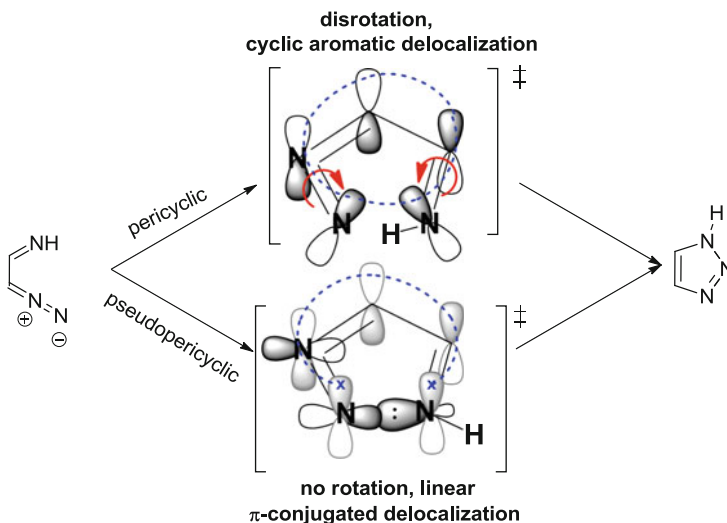
Intramolecular cyclization of diazo compounds, obtained by diazotization of *N*-(2-amino-1,2-dicyanovinyl)amides **255** in aqueous HCl, proceeded very fast and led to 5-cyano-2*H*-1,2,3-triazole-4-carboxylic acid amide **257** (Scheme 90) [334].

Besides the synthetic importance, diazo compounds are considered as attractive models to investigate the theoretical aspects of pericyclic/heteroelectrocyclic reactions frequently observed in heteroatomic π -conjugated compounds [337]. A spatial arrangement of frontier orbitals in the substrates induced them to react via symmetry-controlled pericyclic or symmetry-control-independent pseudopericyclic reactions (Scheme 91) [338]. The absence of electron–electron repulsion for the latter type of reaction substantially decreases the activation barriers and explains why this type of reaction can occur relatively easily.


Scheme 86 Reaction of diazomethanes **242** with nitriles **243**

Scheme 87 Reaction of 1,3,6-trimethyluracil **248** with TMSC(Li)N_2

Scheme 88 Reaction of 1,2-bis(arylmethylene)hydrazines **250** with (diazomethyl)benzene **251**

Scheme 89 Intramolecular cyclization of α -diazonitriles **254**



Scheme 90 Intramolecular cyclization of *N*-(2-amino-1,2-dicyanovinyl)propionamide **255**



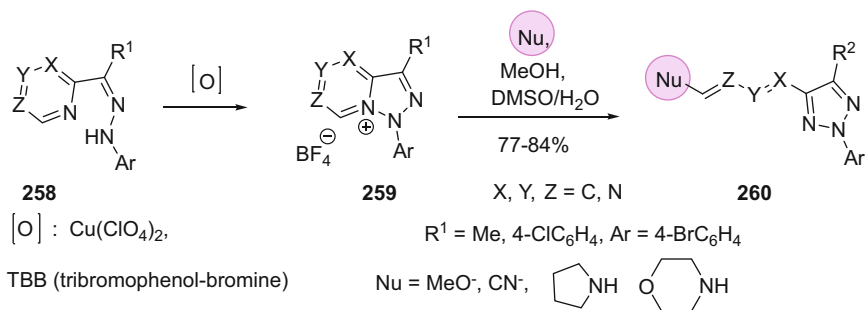
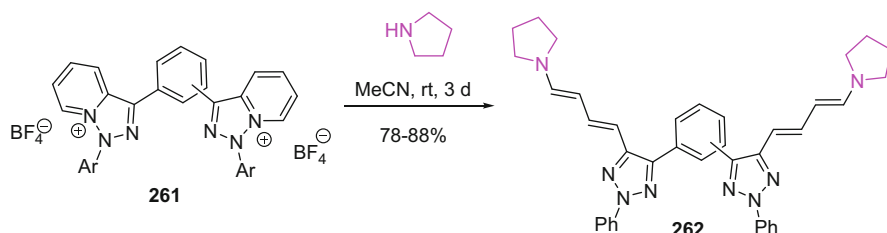
Scheme 91 Mechanism of intramolecular cyclization of 2-diazo-2-ethane imine

7 Heterocycle Transformations in the Synthesis of 2*H*-1,2,3-Triazoles

An interesting way to construct 2-aryl-1,2,3-triazoles was to use the ring-opening of bridgehead nitrogen-containing azoles yielding conjugated triazoles **260**. The starting heterocyclic salts were obtained by an oxidative cyclization of hydrazone precursor **258** (Scheme 92) [340–349].

The *m*- and *p*-phenylene-bridged bis(azolopyridinium)salts **261** were converted into the corresponding bis(dienamines) **262** by reaction with pyrrolidine (Scheme 93) [342].

A number of examples for rearrangement of 5-amino-1,2,3-thiadiazoles into 1,2,3-triazoles, also known as Dimroth rearrangement [350], have been described in detail in *Chapter 1*. In spite of the relative simplicity and the one-pot fashion of this rearrangements their preparative power to obtain various 1,2,3-triazoles is limited by the scope of the involved substrates (Schemes 92 and 93).

**Scheme 92** Ring-opening reaction of bridgehead nitrogen-containing azoles**Scheme 93** Ring-opening transformation of bis(triazolopyrimidinium) salts with pyrrolidine

8 Conclusion

This extensive review of synthetic approaches to obtain 2*H*-1,2,3-triazoles has shown that they can be classified into several distinct types.

NH-1,2,3-Triazoles and their 2-alkyl- and, rarer, 2-aryl substituted analogues can be synthesized by Huisgen azide-alkyne dipolar cycloaddition combined with postalkyl(aryl)ation or performed in a multicomponent and solid-phase fashion.

The nucleophilic substitution cannot be effectively used to obtain 2-substituted 1,2,3-triazoles since the regioselectivity of *N*-substitution is difficult to control kinetically and the N(1) atom becomes a preferred nucleophilic site under the reaction circumstances, especially for triazoles of a greater practical interest (e.g., 2-aryl and non-exchangeable N(2)-alkyl ones). It is also important to stress that acyl, sulfonyl, carbamoyl, and similar 2-substituted 1,2,3-triazoles are easily obtainable by nucleophilic substitution, but unfortunately unstable and thus did not find broad application.

Different types of cyclizations, such as oxidation, condensation, and rearrangement, occurring for arylhydrazones with an additional nitrogen-containing functional group (amidines, oximes, amidoximes) or heterocycles (1,2,4-oxadiazoles, 1,2,5-oxadiazoles, oxazoles), can also provide a convenient approach to 2-arylsubstituted 1,2,3-triazoles. Availability of substrates, convenient conditions, high yields, and regioselectivity are not the only features for this method

to be highlighted. This routine is also very useful because it provides the possibility to introduce various substituents and functional groups in order to design new materials with desired physical and biological properties.

The cumulative interest into methods of synthesis for 2*H*-1,2,3-triazoles is based on the need to develop a simple and effective synthetic approach to obtain them, as well as on the fundamental interest to the mechanistic aspects of these reactions.

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