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Synthesis of Diverse Nitrogen Heterocycles Explored in Denitrogenative Transformations

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1.1 Introduction

Nitrogen heterocycles are extensively present in numerous drug molecules which manifest potent therapeutic activities such as antibacterial, anticancer, antiallergic, potassium-channel activator, antiplatelet, glucosidase, and HIV-1 reverse transcriptase inhibitory activities (Figure 1.1) [1].

Beside living in the core of biologically active molecules, N-heterocycles can act as ligands as well as directing groups in various transition metal catalysis. Importantly, polynitrogen heterocycles can participate in various fruitful transformations that pave the way to access structurally complex molecules of biological importance (Figure 1.2). In this context, *N*-sulfonyl-1,2,3-triazole and its analogs have been exclusively exploited as safe-to-handle diazo surrogates in various denitrogenative transformations. These methods yield a diverse range of structural motifs to facilitate structural modification and total synthesis of natural products and drug molecules [2–4]. Over a period of time, denitrogenative transformations of some related heterocycles such as 5-iodotriazoles [5], F-containing triazoles [6–8], tetrazoles [9, 10], pyridotetrazoles [11], and aminoindazoles [12] have also been explored and established as efficient synthetic tools.

Consequently, easily accessible, atom-economical, and widely compatible synthetic methodologies to access these diverse N-heterocycles are highly desirable. This chapter briefly showcases the development of such primitive to advanced synthetic methodologies to serve the aforementioned purposes.

1.2 Synthesis of 1,2,3-Triazoles

1.2.1 Synthesis of *NH*-Triazoles

NH-triazole is one of the polynitrogen heterocycles that undergoes denitrogenative transformation and their recent development emphasized its importance as a

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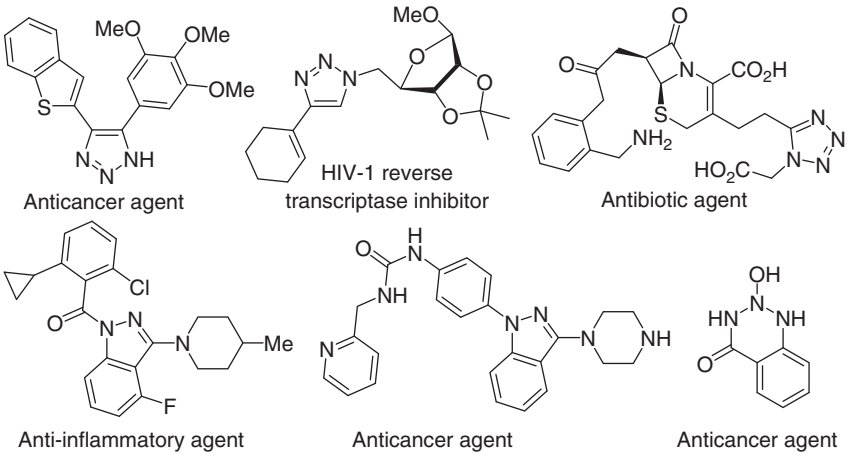


Figure 1.1 Representative drug molecules containing N-heterocycles.

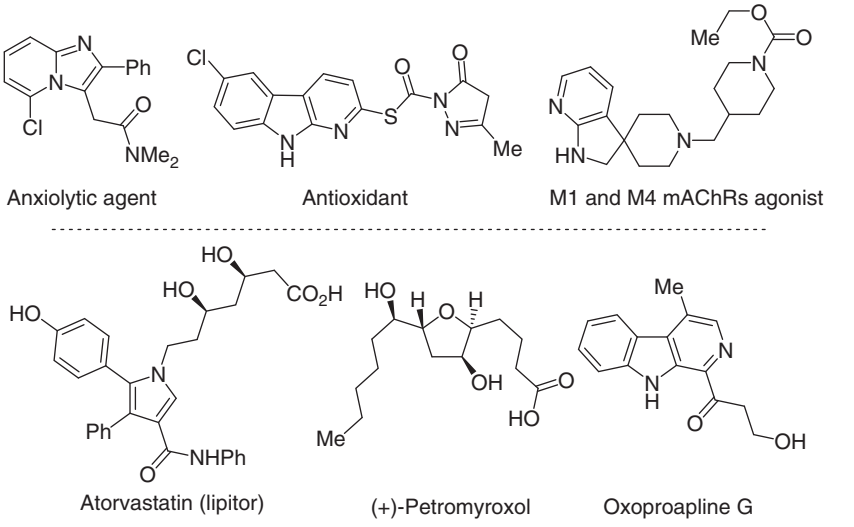
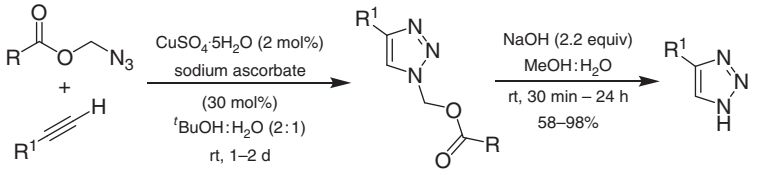


Figure 1.2 Representative drug molecules and natural products synthesized through denitrogenative transformations.

building block and their elegant synthesis. Initially, *NH*-triazoles were prepared *via* the deprotection of various N-protected triazoles. In this context, various organic azides with removable protecting groups such as benzyl [13], tropylium [14], trimethylsilyl [15, 16], tosyl [17, 18], (trimethylsilyl)ethoxymethyl (SEM) [19], and *p*-methoxybenzyl [20] azides have been explored along with sodium azide [21, 22]. Later, Sharpless and co-workers [23] introduced three more organic azides, azidomethyl pivalate, azidomethyl morpholine-4-carboxylate, and azidomethyl *N,N*-diethylcarbamate, which deliver a base-labile N-protected triazole (Scheme 1.1).

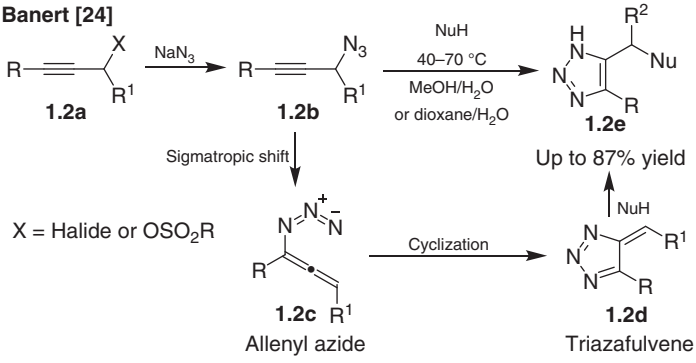
Sharpless [23]



Scheme 1.1 Synthesis of *NH*-triazoles *via* N-protected triazoles. Source: Adapted from Sharpless [23].

In 1989, Banert [24] demonstrated an efficient strategy to synthesize *NH*-triazoles from propargyl azides under mild conditions (Scheme 1.2). Mechanistically, propargyl azide **1.2b** is obtained by treatment of propargyl halide **1.2a** with sodium azide, which undergoes a [3, 3]-sigmatropic rearrangement to generate the reactive allenyl azides **1.2c** that readily cyclizes to triazafulvene intermediate **1.2d**. Finally, the intermediate **1.2d** is trapped by various nucleophiles to afford corresponding triazole **1.2e**.

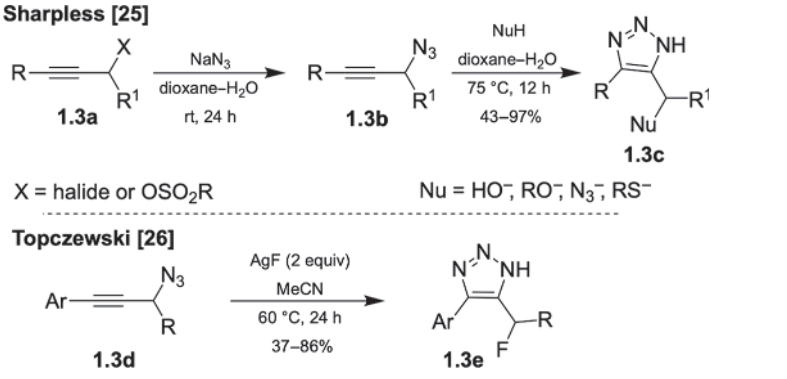
Banert [24]



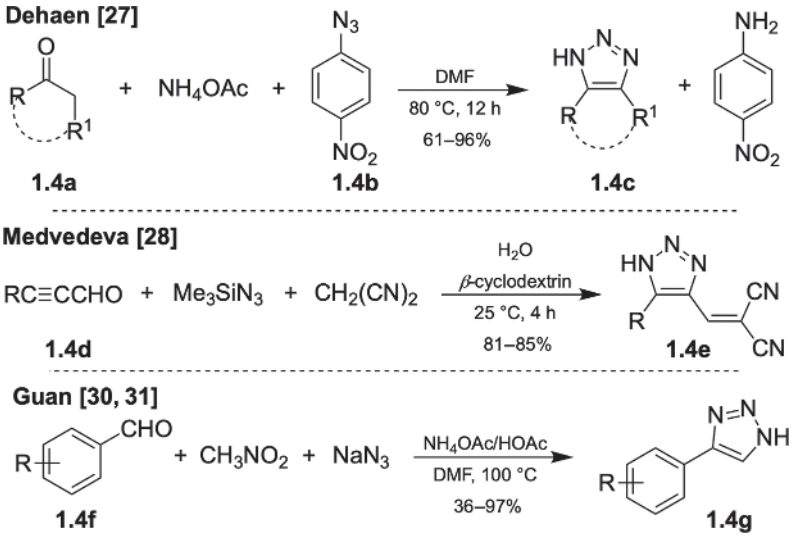
Scheme 1.2 Synthesis of *NH*-triazoles by using Banert cascade. Source: Adapted from Banert [24].

Despite its high reliability and wide substrate scope, its synthetic utility was hardly explored. In 2005, Sharpless and co-workers [25] exclusively studied this pathway to access diverse *NH*-triazoles and expanded the scope of nucleophiles involved in the process (Scheme 1.3). Recently, Topczewski and co-workers [26] exploited silver(I) fluoride as nucleophile, which facilitated access to α-fluorinated *NH*-1,2,3-triazoles **1.3e** in excellent yields.

In 2016, Dehaen and co-workers [27] disclosed the synthesis of various mono-, di-, and tri-substituted triazoles **1.4c** from the reaction of enolizable ketones **1.4a**, NH_4OAc, and nitrophenyl azide **1.4b** under mild acidic condition (Scheme 1.4). Simultaneously, a β-cyclodextrin-mediated multicomponent synthesis of *NH*-triazoles **1.4e** from propynals **1.4d**, trimethylsilyl azide, and malononitrile in water was reported by Medvedeva and co-workers [28]. Besides, the use of amine in place of malononitrile under microwave irradiation furnished the imine-substituted



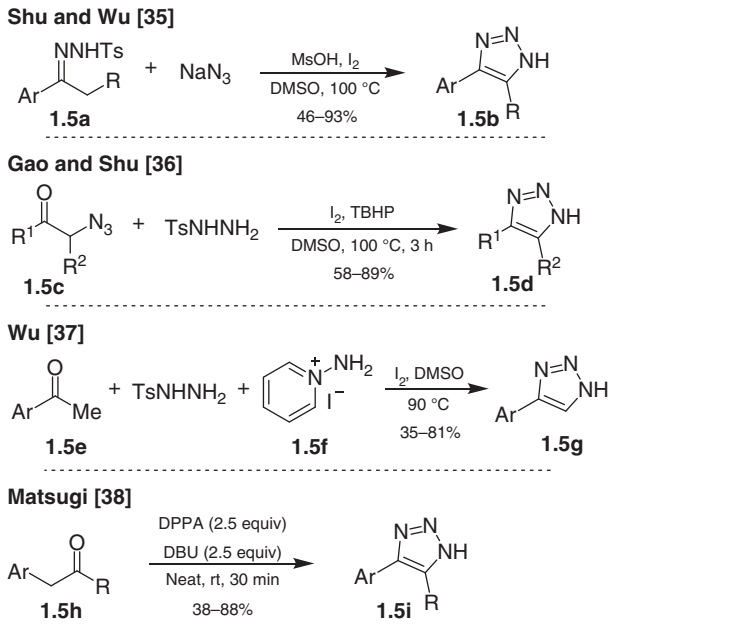
Scheme 1.3 Synthesis of diverse *NH*-triazoles.



Scheme 1.4 Synthesis of *NH*-triazoles through three-component reactions.

triazole with a shorter reaction time [29]. Subsequently, Guan and co-workers [30–33] accomplished the synthesis of various 4-aryl-*NH*-1,2,3-triazoles **1.4g** through three-component reaction of aldehydes **1.4f**, nitromethane, and NaN_3. Later, Negrón-Silva and co-workers [34] developed a heterogeneous catalytic system consisting of Al-MCM-41 and sulfated zirconia to accomplish the same synthesis.

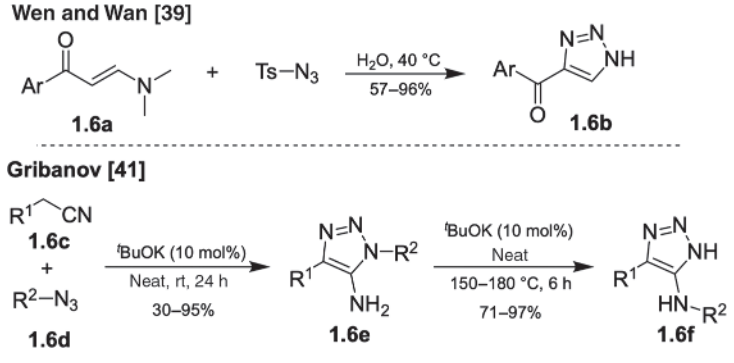
In 2019, Shu and Wu reported a molecular iodine-mediated cascade [4 + 1] cyclization of *N*-tosylhydrazones **1.5a** and sodium azide in presence of MsOH to access 4-aryl-*NH*-1,2,3-triazoles **1.5b** (Scheme 1.5) [35]. Subsequently, the group of Gao and Shu achieved the synthesis of 4-aryl-*NH*-1,2,3-triazoles **1.5d** *via* an iodine-mediated condensation-cyclization of α-azido ketones **1.5c** with *p*-toluenesulfonyl hydrazide



Scheme 1.5 Synthesis of 4-aryl-*NH*-1,2,3-triazoles.

[36]. Recently, Wu and co-workers demonstrated the synthesis of *NH*-triazole under azide-free conditions *via* an iodine-mediated [2 + 2 + 1] cyclization of methyl ketones **1.5e**, *p*-toluenesulfonyl hydrazide, and 1-aminopyridinium iodide **1.5f** [37]. Solvent-free synthesis of 4-aryl-*NH*-1,2,3-triazoles **1.5i** has been demonstrated by Matsugi and co-workers [38] from benzyl ketones **1.5h** exploiting diphenyl phosphorazidate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Catalyst-free synthesis of 4-acyl-*NH*-1,2,3-triazoles **1.6b** was reported by Wen and Wan, which involves water-mediated cycloaddition reactions of enaminones **1.6a** and tosyl azide (Scheme 1.6) [39, 40]. Instead of enaminones, Gribanov et al. [41] employed alkylnitriles **1.6c** and azide **1.6d** in the presence of KO^{t}Bu

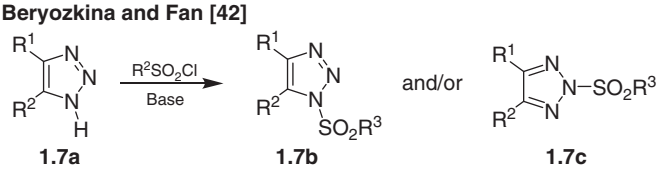


Scheme 1.6 Synthesis of various *NH*-triazoles.

for the synthesis of 5-amino-1,2,3-triazoles **1.6e**, which on subsequent Dimroth rearrangement affords **1.6f** at elevated temperature under solvent-free conditions in one pot.

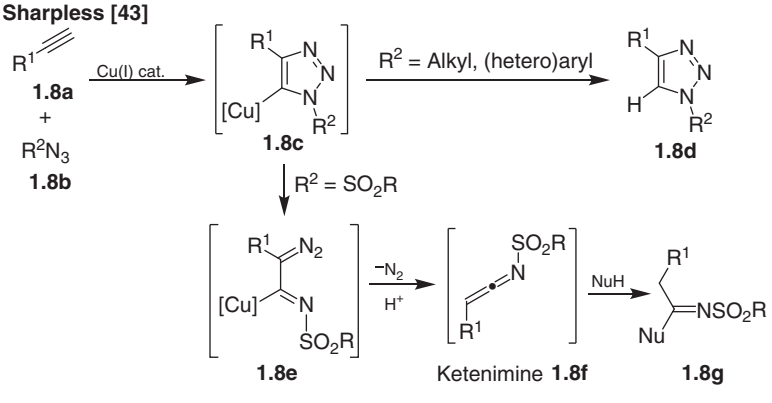
1.2.2 Synthesis of *N*-Sulfonyl-1,2,3-triazoles

For years, a large number of *N*-sulfonyl-1,2,3-triazoles have been extensively exploited as diazo surrogate in numerous denitrogenative transformations. In general, sulfonylation of *NH*-1,2,3-triazoles **1.7a** with sulfonyl chlorides could furnish the corresponding *N*-sulfonyl-1,2,3-triazoles **1.7b** (Scheme 1.7). But the major drawback of this strategy is the formation of a mixture of regioisomeric products **7.2** and **1.7c**, which significantly reduces its efficiency and applicability [42].



Scheme 1.7 Synthesis of *N*-sulfonyl-1,2,3-triazoles from *NH*-triazoles. Source: Adapted from Beryozkina and Fan [42].

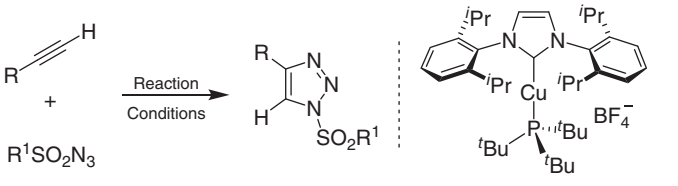
On the other hand, 1,2,3-triazoles **1.8d** were readily achieved through the copper-catalyzed azide-alkyne cycloaddition (CuAAC) as reported by Sharpless and co-workers in 2002 (Scheme 1.8) [43–45]. This reaction appeared to be the most effective click reaction over the traditional Huisgen cycloaddition due to its remarkably high regioselectivity and yields. Various 1,4-disubstituted triazoles **1.8d** could be synthesized from terminal alkynes **1.8a** and azides **1.8b** (Scheme 1.8). However, the use of sulfonyl azides led to the formation of various secondary products **1.8g** instead of the desired triazoles **1.8d** *via* the generation of ketenimine



Scheme 1.8 Synthesis of *N*-sulfonyl-1,2,3-triazoles through CuAAC. Source: Adapted from Sharpless [43].

intermediate **1.8f** [46, 47]. The formation of ketenimine was due to the poor stability of the copper-triazole species **1.8c**.

To increase the stability of sulfonyl substituted **1.8c** and for the synthesis of sulfonyltriazoles, in 2007, for the first time, Chang, Fokin and co-workers utilized stoichiometric amount of base, 2,6-dimethylpyridine in the CuI-catalyzed selective synthesis of 4-substituted *N*-sulfonyl-1,2,3-triazoles from the corresponding terminal alkynes and sulfonyl azides (Scheme 1.9) [48, 49]. Subsequently, Fu and co-workers [50] reported an inexpensive catalytic system by exploiting the thioanisole as ligand in combination with CuBr in water medium at room temperature. It was emphasized that the addition of sulfur-containing ligands could inhibit cleavage of N1—N2 bond and stabilize the 5-cuprated triazole species. Two years later, Pérez and co-workers [51] demonstrated the synthesis of *N*-sulfonyl-1,2,3-triazoles using well-defined copper complex, $[Tpm^{*,Br}Cu(NCCH_3)]BF_4$. On the other hand, Raushel and Fokin [52] employed Cu(I)-thiophene-2-carboxylate (CuTC) complex, in the absence of external ligand, under mild conditions for more efficient and general synthesis of *N*-sulfonyltriazoles (Scheme 1.9).



Cu(I)–NHC complex *(Cazin)*

Reaction conditions:

Chang and Fokin [48]: CuI, 2,6-dimethylpyridine, $CHCl_3$, 0 °C

Fu [50]: CuBr, PhSMe, H_2O, rt, 16 h

Pérez [51]: $[Tpm^{*,Br}Cu(NCCH_3)]BF_4$, $CHCl_3$, 40 °C

Raushel and Fokin [52]: CuTC, toluene or H_2O, rt, 15 h

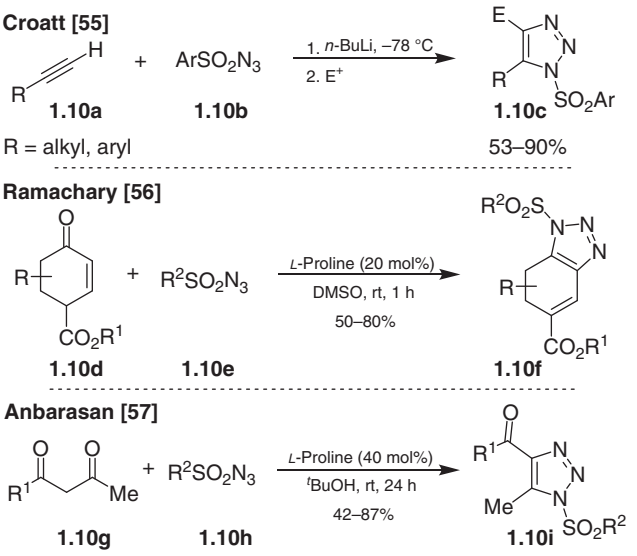
Hu [53]: $Cu(OAc)_2{\cdot}H_2O$, 2-aminophenol, CH_3CN, rt, 20–50 min

Cazin [54]: Cu(I)-NHC complex, toluene, rt, 15 h

Scheme 1.9 Cu-catalyzed synthesis of *N*-sulfonyl-1,2,3-triazoles.

In 2011, Hu and co-workers [53] reported 2-aminophenol as a suitable ligand in copper-catalyzed highly selective synthesis of *N*-sulfonyltriazoles. Herein, it was proposed that 2-aminophenol plays a dual role as a reductant and ligand. Importantly, the first triazole possessing two electron-withdrawing groups was synthesized successfully by using this strategy. In 2018, Cazin and co-workers [54] employed Cu(I)-NHC complexes for the selective synthesis of 4-substituted 1,2,3-triazoles through click reaction.

But the limitation of all these above-mentioned methods remains in the selective synthesis of 1,4-disubstituted triazoles. Croatt and co-workers [55] documented the synthesis of 5-substituted *N*-sulfonyl-1,2,3-triazoles **1.10c** from corresponding terminal alkynes **1.10a** and sulfonyl azides **1.10b** using a strong base, such as



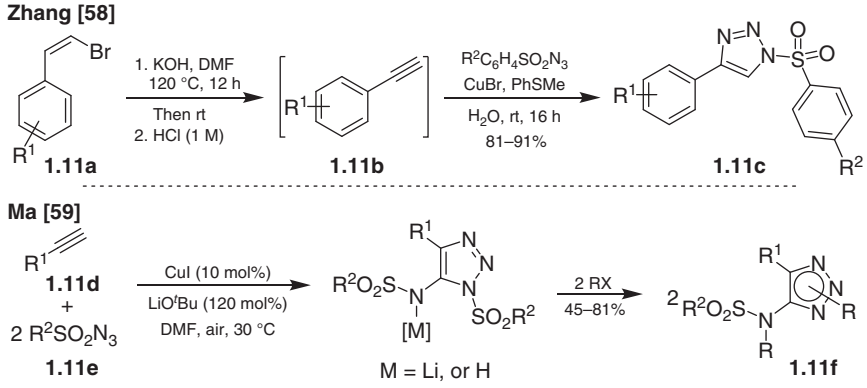
Scheme 1.10 Synthesis of multisubstituted *N*-sulfonyl-1,2,3-triazoles.

n-BuLi (Scheme 1.10). Interestingly, the synthesis of various 1,4,5-trisubstituted triazoles was also achieved by trapping the 4-lithio-1,5-disubstituted triazole in the reaction mixture with suitable electrophiles. In 2008, Ramachary and co-workers reported the first proline-catalyzed synthesis of 4,5-disubstituted triazoles **1.10f** from Hagemann's ester **1.10d** and tosyl azides **1.10e** [56]. Later, Anbarasan and co-workers [57] accomplished a general proline-mediated synthesis of a diverse range of 4,5-disubstituted 1,2,3-triazoles **1.10i** with excellent regioselectivity from substituted 1,3-dicarbonyl compounds **1.10g** and sulfonyl azides **1.10h** through enamine-azide cycloaddition.

In 2016, Zhang and co-worker [58] achieved the synthesis of 4-substituted 1,2,3-triazoles **1.11c** from (*Z*)-arylvinyl bromides **1.11a** and sulfonyl azides through the generation of arylacetylene (Scheme 1.11). This strategy involves KOH-promoted HBr elimination from the vinylbromide **1.11a** followed by a copper-catalyzed [3 + 2] cycloaddition of the resulted alkyne **1.11b** with azide. Subsequently, Ma and co-workers [59] reported a regioselective synthesis of 5-sulfamido-*N*-sulfonyl-1,2,3-triazoles **1.11f** in high yields through a Cu-catalyzed cycloaddition of terminal alkynes **1.11d** and sulfonyl azides **1.11e** using 1.2 equivalents of LiO^tBu. Most recently, Kim and co-workers [60] reported the first continuous flow synthesis of *N*-sulfonyl-1,2,3-triazoles.

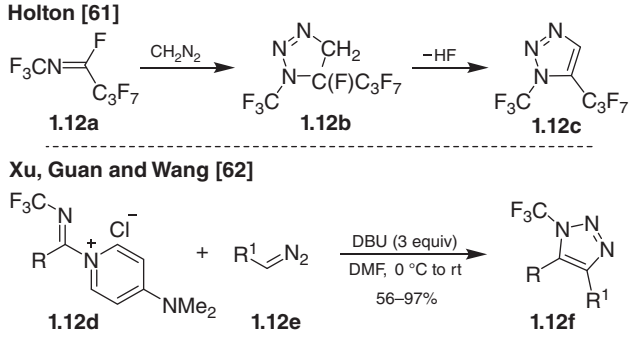
1.2.3 Synthesis of *N*-Trifluoromethyl-1,2,3-triazoles

N-trifluoromethyl-1,2,3-triazoles also have been explored in the denitrogenative transformations owing to the unique physicochemical properties of F-containing organic moieties. But, unlike the synthesis of other *N*-sulfonyl-1,2,3-triazoles, the



Scheme 1.11 Synthesis of diverse *N*-sulfonyl-1,2,3-triazoles.

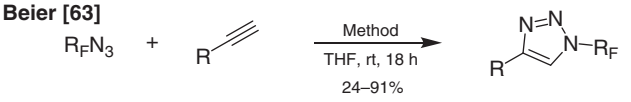
synthesis of *N*-fluoroalkyl-1,2,3-triazoles was not achieved following conventional alkyne-azide cycloaddition strategy. In 1977, Holton and co-workers [61] studied various 1,3-dipolar cycloaddition across the C=N bond of polyfluoroazaolefins with diazomethane (Scheme 1.12). A mixture of products was obtained in the reaction of perfluoro-*N*-(trifluoromethyl)butanimidoyl fluoride **1.12a** with excess diazomethane, in which, the l-(trifluoromethyl)-5-(heptafluoropropyl)-1,2,3-triazole **1.12c** was present as a major product. Recently, Xu, Guan, and Wang demonstrated the synthesis of *N*-trifluoromethyl-1,2,3-triazoles **1.12f** *via* a similar [3 + 2] cyclization of DMAP-stabilized *N*-CF_3 nitrilium salts **1.12d** with diazo compounds **1.12e** [62].



Scheme 1.12 Synthesis of *N*-trifluoromethyl-1,2,3-triazoles.

In 2017, Beier and co-workers [63] developed an efficient strategy to synthesize perfluoroalkyl azides (Scheme 1.13). Subsequently, the reactivity of perfluoroalkyl azide was explored in azide-alkyne cycloaddition reaction to access *N*-perfluoroalkyl triazoles.

Additionally, a one-pot synthesis of such triazoles has also been demonstrated directly starting from trifluoromethylsilane in good yield and regioselectivity.

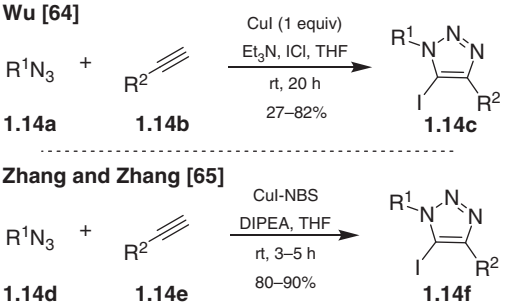


Method A: [$CuSO_4 \cdot 5H_2O$] (10 mol%), sodium L-ascorbate (10 mol%), H_2O
Method B: [CuMeSal] (1–5 mol%), THF

Scheme 1.13 Synthesis of *N*-perfluoroalkyl-1,2,3-triazoles. Source: Adapted from Beier [63].

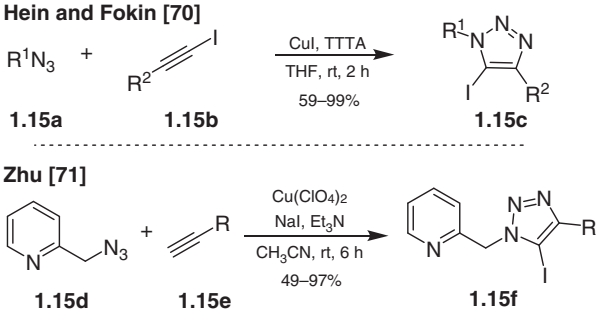
1.2.4 Synthesis of 5-Iodo-1,2,3-triazoles

Similar to electron withdrawing group-substituted triazoles, 5-iodo-1,2,3-triazoles having a tethered nucleophile are shown to undergo denitrogenative transformations. These triazoles were also synthesized through azide-alkyne cycloaddition. In this context, in 2005, Wu et al. [64] developed a strategy to access 5-iodo-1,2,3-triazoles **1.14c** in one-pot *via* Cu(I)-catalyzed reaction of organo-azides **1.14a** with terminal alkynes **1.14b** in presence of iodine as an electrophilic trapping reagent (Scheme 1.14). It was proposed that the reaction involves the formation of an intermediate of Cu(I) salt of triazole. Interestingly, yield was increased drastically when ICl was used instead of I_2. Subsequently, Zhang and Zhang [65] reported a CuI-NBS-mediated multicomponent reaction of azides **1.14d** and alkynes **1.14e**, which also facilitated access to 5-iodo-1,4-disubstituted-1,2,3-triazoles **1.14f** [66, 67]. To improve the reactivity and chemoselectivity, ICl was *in situ* generated from the combination of CuI and NCS and used as an effective iodonium source. Recently, these strategies were further modified to accomplish the synthesis in aqueous medium [68, 69].



Scheme 1.14 Synthesis of 5-iodo-1,2,3-triazoles.

In 2009, Hein, Fokin, and co-workers [70] reported the synthesis of 5-iodotriazoles from the CuI-catalyzed cycloaddition of 1-iodoalkynes **1.15b** and organic azides **1.15a** (Scheme 1.15). Various ligands such as TBTA or TTTA were screened to furnish the desired products in good yields with low catalyst loadings and shorter reaction times. Zhu and co-workers [71] reported an assisting ligand-free strategy to access various 5-iodo-triazoles **1.15f** (Scheme 1.15). Subsequently, the effect of ligand [72] as well as mechanism [73] involved in the reaction were

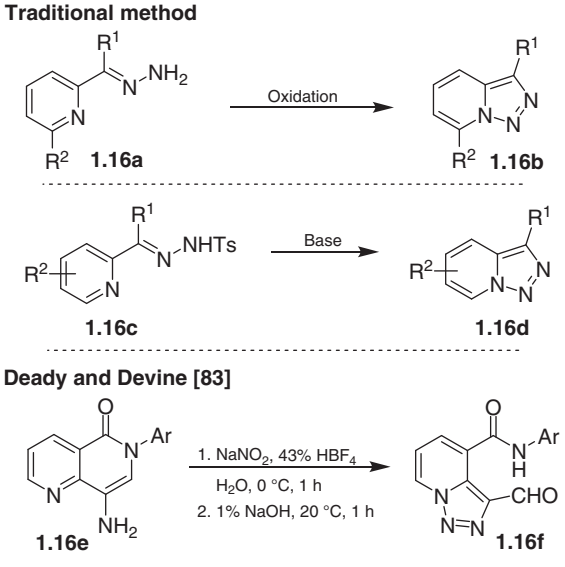


Scheme 1.15 Cu-catalyzed synthesis of 5-iodo-1,2,3-triazoles.

established. Besides, several other groups have also accomplished the synthesis of 5-iodotriazoles [74–80].

1.2.5 Synthesis of Pyridotriazoles

Pyridotriazoles being analogous to triazoles are highly compatible in denitrogenative transformations, but only selected strategies are known for their synthesis. Traditionally, pyridotriazoles **1.16b** have been synthesized from the corresponding hydrazones **1.16a** of pyridine-2-carbaldehydes or 2-pyridylketones *via* oxidative cyclization (Scheme 1.16) [81, 82]. Although some of the hydrazones are just refluxed in methanol under air to afford the corresponding pyridotriazoles, suitable oxidizing agents such as nickel peroxide, air and a cupric salt, potassium ferrocyanide and bicarbonate, manganese dioxide or (diacetoxyiodo)benzene are

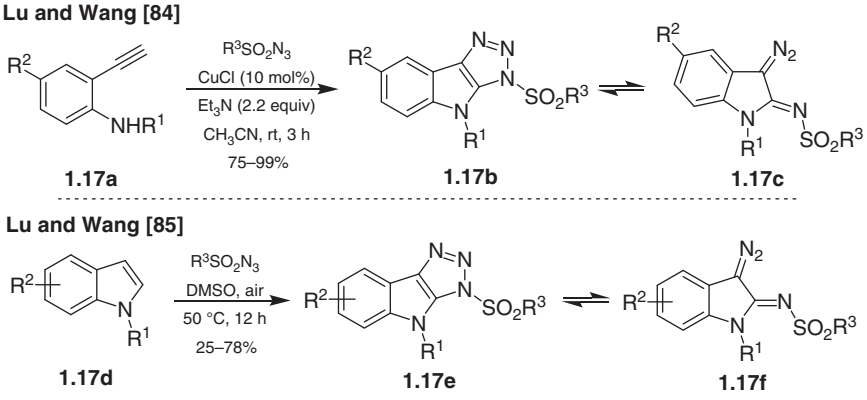


Scheme 1.16 Synthesis of pyridotriazoles. Source: Deady and Devine [83]/with permission of Elsevier.

necessary for most of the hydrazones. In the case of sensitive substrates, pyridotriazoles **1.16d** could be obtained from the reaction of tosyl hydrazones **1.16c** of pyridine-2-carbaldehydes or 2-pyridylketones with base, usually morpholine (Scheme 1.16). In 2006, Deady and Devine demonstrated an alternative strategy to access pyridotriazoles **1.16f** from an aminonaphthyridinone **1.16e** [83]. Compound **1.16e** could form a diazonium salt upon treatment with aqueous sodium nitrate and fluoroboric acid. Then triazolopyrido aldehyde **1.16f** is obtained as a white solid upon treatment of the salt with sodium hydroxide in water.

1.2.6 Synthesis of Triazoloindoles

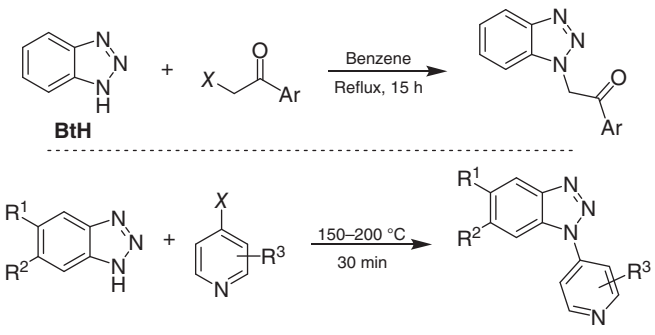
Due to the growing interest in the denitrogenative transformation of triazoles, in 2014, Lu and Wang accomplished the synthesis of diverse triazoloindoles **1.17b** from alkynes **1.17a** and sulfonylazides *via* a copper-catalyzed tandem process (Scheme 1.17), and demonstrated their reactivity [84]. This strategy involves a sequence of amine group-stabilized CuAAC and C—N coupling reactions. Further study on the triazoloindoles revealed its predominant existence as open-chain form, 3-diazoindolin-2-imines **1.17c**. Subsequently, the same group developed an efficient catalyst-free synthesis of 3-diazoindolin-2-imines **1.17f** from indole and sulfonyl azide [85]. Indoles bearing alkyl, allyl, and benzyl substituents at N1-position and electron-donating substituents in the aryl ring underwent the reaction smoothly and effectively. However, a significant loss in yields was witnessed in the presence of electron-withdrawing groups in aryl ring.



Scheme 1.17 Synthesis of triazoloindoles. Source: Adapted from Lu and Wang [84, 85].

1.2.7 Synthesis of Benzotriazoles

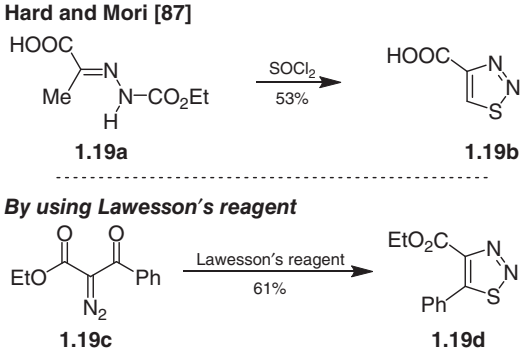
Denitrogenative transformations of benzotriazoles have also witnessed significant development in past years. Particularly, benzotriazoles containing aryl, aroyl, alkenyl, and alkyl substituents at N1-position have been explored well. In general, benzotriazole derivatives are obtained through the selective protection of readily available benzotriazoles (BtH) as shown in Scheme 1.18 [86].



Scheme 1.18 Synthesis of benzotriazole derivatives.

1.3 Synthesis of 1,2,3-Thiadiazoles

1,2,3-Thiadiazoles were also demonstrated to undergo denitrogenative transformation through the generation of thiavinyl carbenes. Their synthesis involves an interesting cyclization with the introduction of sulfur. In 1955, Hard and Mori reported an effective synthesis of 1,2,3-thiadiazoles from acylhydrazones and thionyl chloride (Scheme 1.19) [87]. This method is widely applicable for the synthesis of a variety of substituted thiadiazoles. Alternatively, thiadiazoles could be accessed *via* the reaction of diazo compound with Lawesson's reagent [88].



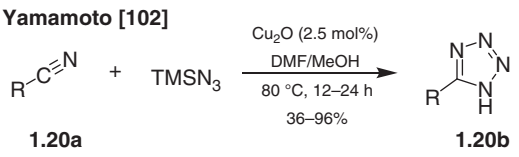
Scheme 1.19 Synthesis of 1,2,3-thiadiazoles. Source: Hurd and Mori [87]/American Chemical Society.

1.4 Synthesis of Tetrazoles

1.4.1 Synthesis of 1*H*-Tetrazoles

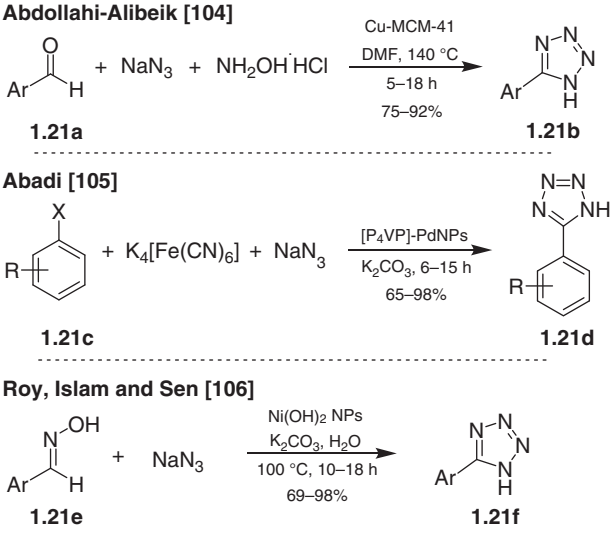
1*H*-tetrazole as a privileged scaffold has received significant attention from researchers in development of drugs as well as in the denitrogenative transformations. Initially, 1*H*-tetrazoles have been exclusively synthesized *via* the

[3 + 2]-cycloaddition reaction of nitriles with various azides such as alkylsilyl azides, alkyltin azides, or sodium azide [89–93]. Major drawbacks of these primitive strategies were use of expensive and toxic metals, water sensitivity, or the possible generation of volatile and explosive hydrazoic acid [94–101]. Consequently, an efficient catalytic synthetic route was highly desired. In 2008, Yamamoto and co-workers [102] developed an efficient Cu(I)-catalyzed synthesis of 5-substituted 1*H*-tetrazoles **1.20b** in good yields *via* the [3 + 2] cycloaddition of nitriles **1.20a** and trimethylsilyl azide (Scheme 1.20). Recently, Gholizadeh and co-workers [103] achieved the synthesis of tetrazole from nitrile using ionic liquid as a catalyst.



Scheme 1.20 Synthesis of 1*H*-tetrazoles. Source: Yamamoto [102]/with permission of Elsevier.

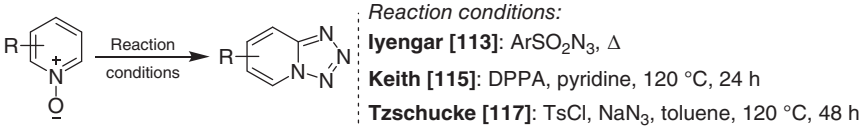
In 2015, Abdollahi-Alibeik et al. [104] reported a Cu-MCM-41 nanoparticles-catalyzed novel three-component reaction of aldehydes **1.21a**, hydroxylamine, and sodium azide for the synthesis of various tetrazoles **1.21b** (Scheme 1.21). Subsequently, polymer-supported palladium nanoparticles were exploited for the synthesis of tetrazole by Abadi and co-workers [105]. Roy, Islam, and Sen [106] developed a $Ni(OH)_2$ nanoparticles-catalyzed synthesis of 5-substituted 1*H*-tetrazoles **1.21f** from aldoximes **1.21e** and sodium azide in water under mild reaction conditions. Following this development, a remarkable advancement in the synthesis of 1*H*-tetrazole has recently been observed [9, 10, 107–112].



Scheme 1.21 Metal nanoparticles-catalyzed synthesis of 1*H*-tetrazoles.

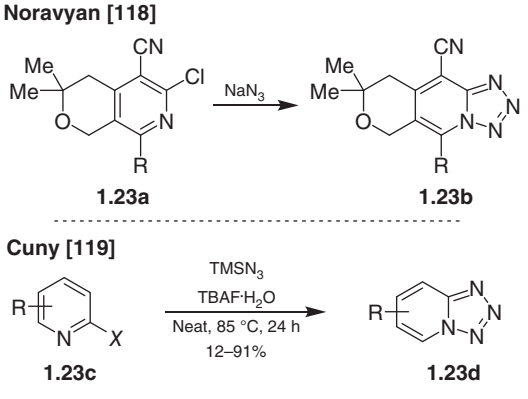
1.4.2 Synthesis of Pyridotetrazoles

Pyridotetrazoles analogous to tetrazoles also undergo various denitrogenative transformations facilitating access to structurally complex molecules. In 1983, Iyengar and co-workers [113] observed the unprecedented formation of tetrazolo[1,5-*a*]pyridine [114] upon reaction of pyridine-*N*-oxide with arenesulfonyl azide (Scheme 1.22). Later, Keith [115, 116] optimized the reaction conditions and explored the substrate scope extensively. Further, the reaction was modified by Tzschucke and co-workers [117] to achieve the synthesis from pyridine-*N*-oxides, *p*-toluenesulfonyl chloride, and sodium azide.



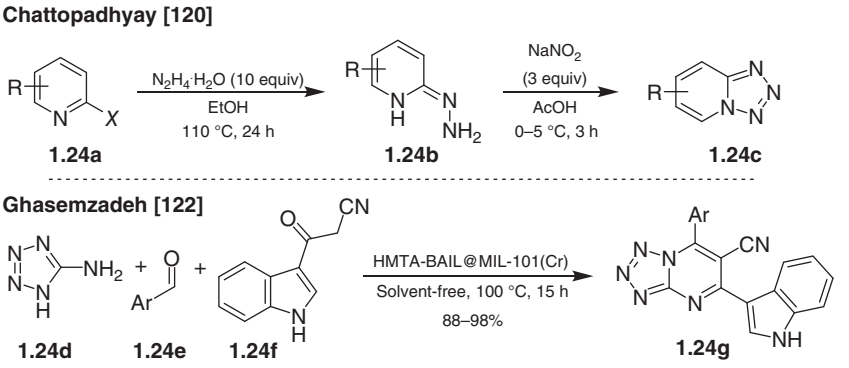
Scheme 1.22 Synthesis of pyridotetrazoles.

In 1997, Noravyan and co-workers [118] synthesized tetrazolo[1,5-*a*]pyrano[3,4-*c*] pyridines **1.23b** from chloropyridines **1.23a** and sodium azide (Scheme 1.23). Later, Cuny and co-workers [119] employed trimethylsilyl azide and tetrabutylammonium fluoride hydrate for the synthesis of various pyridotetrazoles **1.23d** from 2-halopyridines **1.23c**.



Scheme 1.23 Synthesis of pyridotetrazoles from 2-halopyridines.

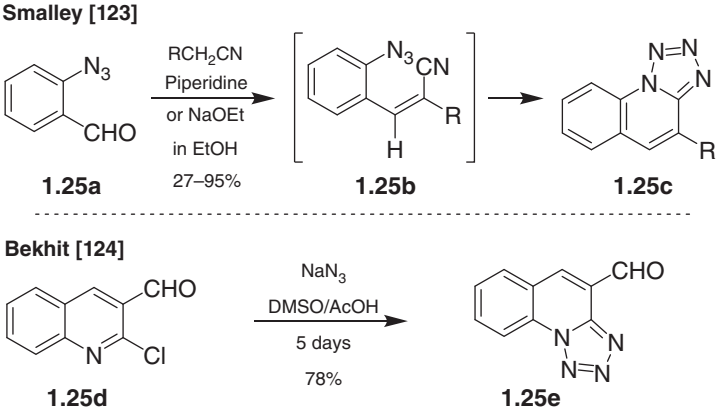
Recently, Chattopadhyay and co-workers [120, 121] synthesized various pyridotetrazoles **1.24c** in two steps starting from corresponding 2-halopyridines **1.24a** (Scheme 1.24), and explored their reactivity in denitrogenative transformations. Subsequently, Ghasemzadeh and co-workers [122] reported a three-component reaction of 1*H*-tetrazole-5-amine **1.24d**, benzaldehydes **1.24e**, and 3-cyanoacetyl indole **1.24f** in presence of hexamethylenetetramine-based ionic liquid/MIL-101(Cr) metal-organic framework as a recyclable catalyst, which facilitated access to diverse tetrazolo[1,5-*a*]pyrimidine-6-carbonitriles in excellent yields.



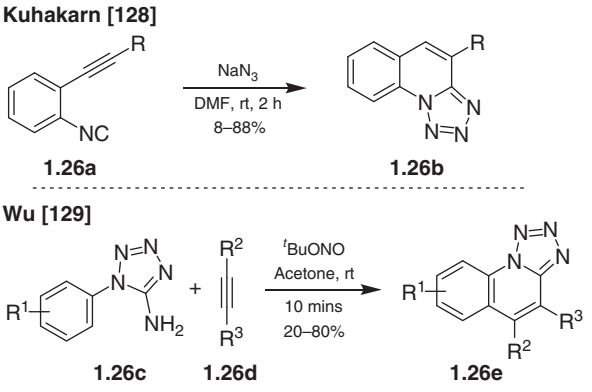
Scheme 1.24 Synthesis of diverse pyridotetrazoles.

1.4.3 Synthesis of Tetrazolo[1,5-*a*]quinolines

Tetrazolo[1,5-*a*]quinolines are largely found in natural products exhibiting biological activities. In 1997, Smalley and co-workers synthesized tetrazolo[1,5-*a*] quinolines **1.25c** by the reaction of 2-azidocarboxaldehyde **1.25a** with acetonitrile in the presence of piperidine or sodium ethoxide as base in ethanol (Scheme 1.25) [123]. The product formation could be rationalized through a Knoevenagel condensation of the acetonitrile with aldehyde **1.25a** followed by an intramolecular 1,3-dipolar cycloaddition reaction of azide with pendant cyano moiety present in **1.25b** intermediate. Later, Bekhit and co-workers reported the synthesis of tetrazolo[1,5-*a*]quinoline-4-carboxaldehyde **1.25e** from corresponding 2-chloroquinoline-3-carboxaldehyde **1.25d** by treating with sodium azide in DMSO/AcOH. [124–126] Recently, Chakroborty et al. modified the reaction conditions to attain a green and more efficient synthesis [127].



Scheme 1.25 Synthesis of tetrazolo[1,5-*a*]quinolines.



Scheme 1.26 Synthesis of various tetrazolo[1,5-*a*]quinolines.

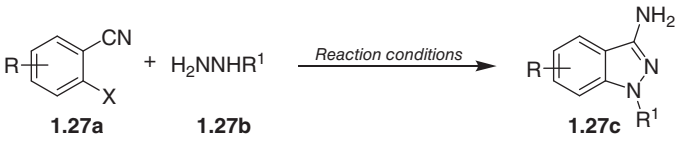
In 2019, Kuhakarn and co-workers [128] accomplished the synthesis of tetrazolo[1,5-*a*]quinolines **1.26b** from the reaction of *o*-alkynylisocyanobenzenes **1.26a** with sodium azide under metal- and base-free conditions (Scheme 1.26). This strategy involves nucleophilic addition of azide to isocyanide followed by 6-endo cyclization. On the other hand, Wu and co-workers [129] synthesized various tetrazolo[1,5-*a*]quinolines **1.26e** through *tert*-butylnitrite-mediated radical cyclization of 1*H*-tetrazol-5-amines **1.26c** with alkynes **1.26d**.

1.5 Synthesis of 3-Aminoindazoles

Interestingly, 3-aminoindazoles also has emerged as an efficient synthetic tool compatible with denitrogenative transformations. In 2002, Semple and co-workers [130–132] synthesized various 3-aminoindazoles from halobenzonitriles to access important non-covalent thrombin inhibitors. Later, the groups of Ma [133], Devkate [134], and Zhang and Hu [135] accomplished the synthesis of diverse 3-aminoindazoles **1.27c** from reaction of halobenzonitriles **1.27a** with hydrazines **1.27b** under the modified reaction conditions (Scheme 1.27). In 2010, Fabis and co-workers [136] reported a two-step synthesis of substituted 3-aminoindazoles **1.27g** from 2-bromobenzonitriles **1.27d** and hydrazones **1.27e**. This strategy involves *N*-arylation of hydrazone **1.27e** with *o*-bromobenzonitriles **1.27d** followed by deprotection of the hydrazone intermediate **1.27f** in methanol.

In 2011, Callot and co-workers [137] demonstrated a Buchwald–Hartwig C—N coupling reaction of various 3-haloindazoles **1.28a** to access 3-aminoindazoles **1.28b** in good to moderate yields (Scheme 1.28). Subsequently, Charrette and co-workers [138, 139] prepared 3-aminoindazoles from tertiary amides *via* the generation of aminohydrazones **1.28c** followed by intramolecular C—H amination.

Recently, Olmos and co-workers [140] reported the synthesis of 3-aminoindazoles **1.28g** from 3-(2-bromoaryl)-1,2,4-oxadiazol-5(4*H*)-ones **1.28e** and amines **1.28f** which involves an intramolecular N—N bond formation.



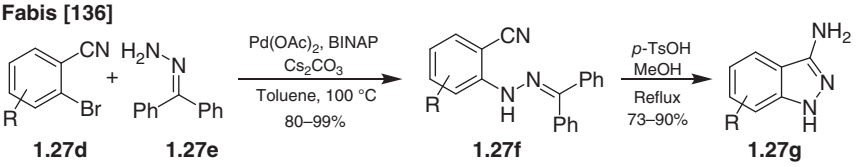
Reaction conditions:

Ma [133]: CuBr, K_2CO_3, DMSO, 80 °C [$R^1 = CO_2R^2$]

Devkate [134]: CAN, EtOH-H_2O,))))), 50–60 °C, 30–40 min

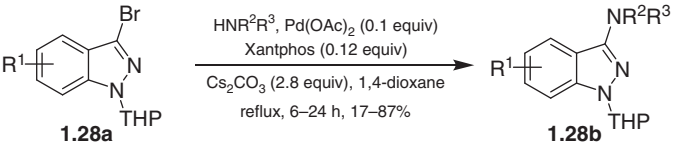
Zhang, Zhang and Wu [135]: ^{t}BuOK, diglyme

Fabis [136]

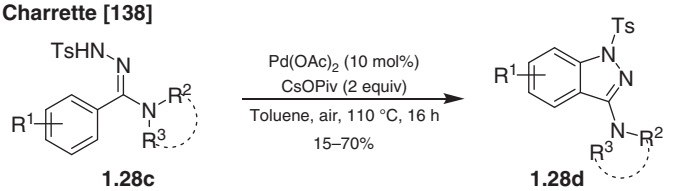


Scheme 1.27 Synthesis of 3-aminoindazoles from 2-halobenzonitriles.

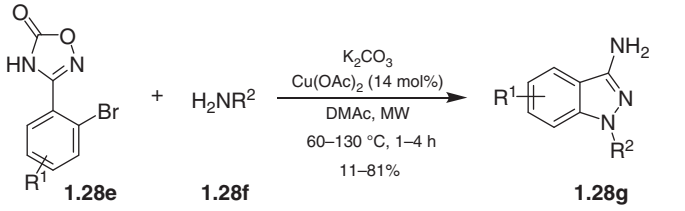
Callot [137]



Charrette [138]



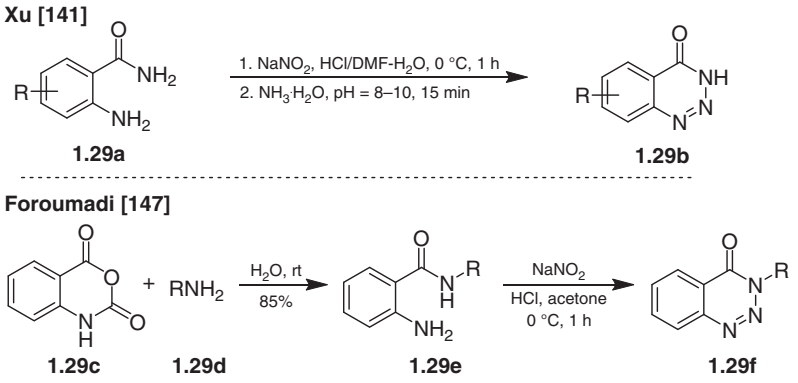
Olmos [140]



Scheme 1.28 Synthesis of various substituted 3-aminoindazoles.

1.6 Synthesis of Benzotriazinones

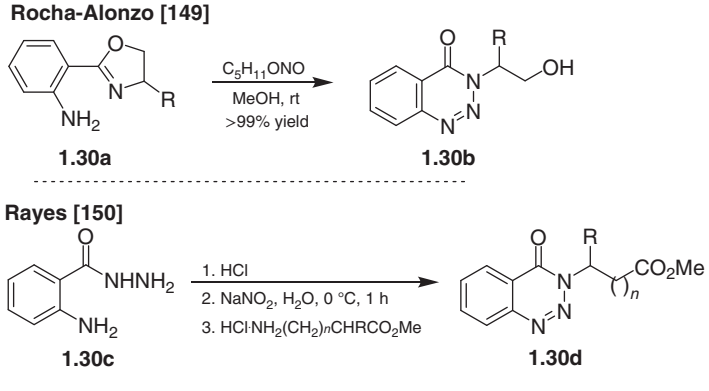
Another unique N-heterocycle, benzotriazinone, has been explored in several denitrogenative transformations. In 2015, Xu and co-workers [141–146] prepared several benzotriazinones **1.29b** from anthranilamides **1.29a** *via* diazotization, and cyclization reactions in one-pot (Scheme 1.29). They further derivatized these benzotriazinones by attaching spirocyclic indoline-2-one moieties, and studied



Scheme 1.29 Synthesis of benzotriazinones.

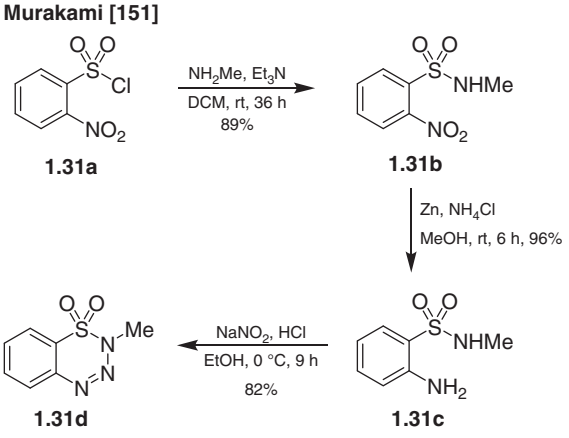
their nematicidal activities. Alternatively, the groups of Foroumadi [147], and Zhang and Li [148] prepared the benzotriazinones **1.29f** from isatoic anhydride **1.29c** and alkyl amines **1.29d** following the reaction sequence shown below. At first, isatoic anhydride **1.29c** and alkyl amines **1.29d** were stirred in water at room temperature to furnish 2-amino-*N*-(prop-2-yn-1-yl)benzamide **1.29e** as a white solid. Next, exposure of **1.29e** to acidic solution of sodium nitrite resulted in the formation of benzotriazinones **1.29f** *via* intramolecular nitrogen–nitrogen bond formation.

In 2017, Rocha-Alonzo and co-workers [149] developed a novel strategy to access 1,2,3-benzotriazinones **1.30b** from the reaction of 2-(*o*-aminophenyl)oxazolines **1.30a** with isoamyl nitrite in methanol (Scheme 1.30). Recently, Rayes and co-workers [150] reported the synthesis from anthranilhydrazide as well as methyl anthranilate.



Scheme 1.30 Synthesis of various N-substituted benzotriazinones.

In 2010, Murakami and co-workers reported a Ni-catalyzed annulation of 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxides **1.31d** with allenes (Scheme 1.31) [151]. Herein, benzothiazinone **1.31d** was synthesized from *ortho*-nitrobenzenesulfonyl chloride **1.31a**. Coupling of **1.31a** with methylamine followed by reduction of



Scheme 1.31 Synthesis of benzothiazinones. Source: Murakami [151]/John Wiley & Sons.

1.31b using Zn gives *ortho*-amino-*N*-methylbenzenesulfonamide **1.31c**. Finally, HONO-mediated ring closing of **1.31c** provides **1.31d** in 82% yield.

1.7 Summary and Outlook

Owing to the remarkable footprints left by various nitrogen heterocycles in the advancement of drugs, and total synthesis of natural products of biological importance, the development of methodologies to access such N-heterocycles has caught significant attention of synthetic chemists in past years. Wherein, atom and cost economy, green approach, and sustainability of the strategy were utmost priorities among other parameters. This chapter highlights the important modifications encountered over the years to accomplish the synthesis of diverse N-heterocycles, for example, triazoles, tetrazoles, 3-aminoindazoles, benzotriazinones, etc. with better yields and selectivity, specifically, which undergo various denitrogenative transformations. Delightfully, many synthetic routes have been developed in a metal-free manner and using milder conditions, some of which are even sustained in a water medium. In recent times, various metal nanoparticles have also been exploited in the advancement of synthesis of these N-heterocycles. Nonetheless, the synthesis of triazoloindoles, pyridotriazoles, thiadiazoles, and benzotriazinones has not received much attention. Hence, further development of synthetic methodologies to attain better accessibility is desirable due to the growing demand for these heterocycles as synthetic tools.

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