SYNTHESIS OF 1,2,4 TRIAZOLE COMPOUNDS

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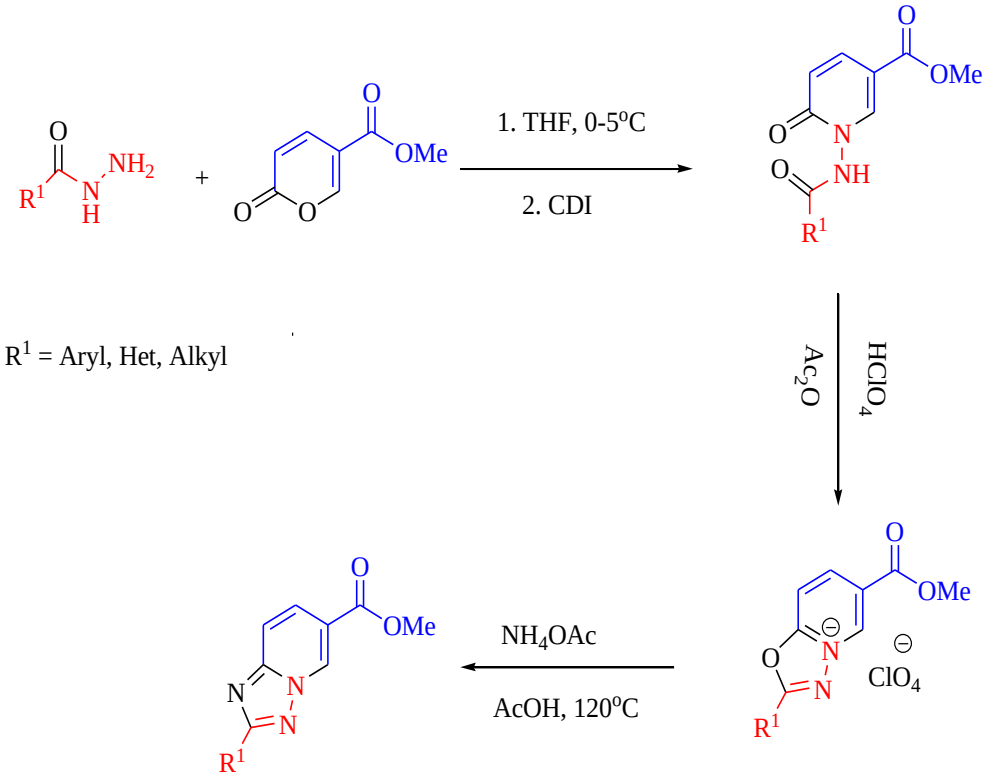
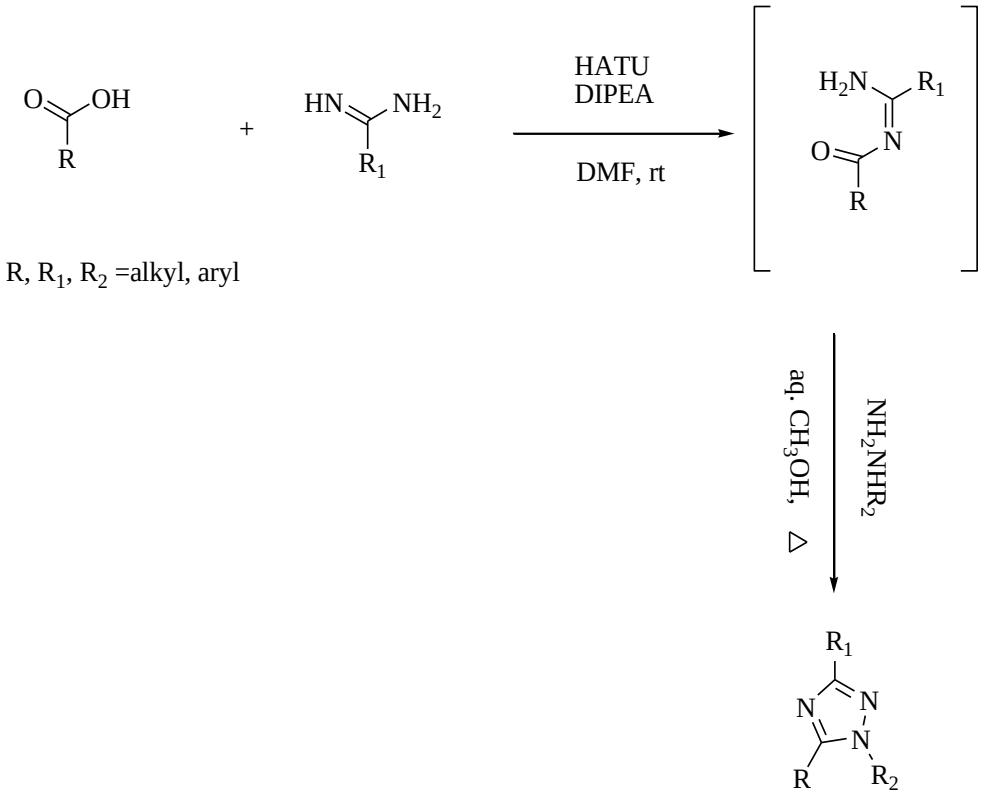
As highly privileged heterocyclic scaffolds, 1,2,4-triazoles have many uses in the fields of biology, pharmacology, and materials science (Gulyaev et al., 2021; Brandt et al., 2007; Cai et al., 2022; Cetin et al., 2018; Chawla et al., 2022; Kotan et al., 2020; Li et al., 2018; Matsuzaki et al., 2021; Medetalibeyoglu, 2022; Medetalibeyoğlu et al., 2022; Medetalibeyoğlu & Yüksek, 2021; Mermer & Boulebd, 2023; Mucha et al., 2023; Bogdan & Wang, 2015; Sanina et al., 2022; Todoulou et al., 1994; Sedash et al., 2012; Wang & Wudl, 2010; Yin et al., 2023; Yunusova et al., 2018; Zhang et al., 2020; Zhang et al., 2008; Zhang et al., 2017). Among medicinal chemists, there is a lot of interest in compounds with significant biological activity, including antihypertensive, antibacterial, and antifungal properties (Abuelizz et al., 2019; Bekircan et al., 2022; Chawla et al., 2022; Chen et al., 2019; Erensoy et al., 2023; Gavara et al., 2022; Liu et al., 2013; Madhu Sekhar et al., 2018; Mazur et al., 2019; Mohassab et al., 2017; Muzaffar et al., 2021; Sadeghian et al., 2023; Siddiqui et al., 2011). There were 1,2,4-triazole scaffolds in valuable drugs like maraviroc, sitagliptin, triazolam, and deferasirox. Furthermore, 1,2,4-triazoles, which have many possible uses, have been investigated as adaptable ligands for metal coordination (Bahemmat et al., 2015; Bazhina et al., 2022; Dong et al., 2012; Geetha et al., 2020; Haasnoot, 2000; Heidari et al., 2021; Kumari et al., 2022; Lässig et al., 2010; Liu et al., 2017; Prozorova et al., 2020; Tahli et al., 2011; Wang et al., 2012; Wang et al., 2014; Yu et al., 2022; Zha et al., 2022; Zhang et al., 2017).

Moloney et al. produced a feasible three-step synthesis of a series of fused bicyclic s-[1,2,4]triazolo[1,5-a]pyridines one utilizing unique intermediates derived from inexpensive, commercially accessible hydrazides and methyl cumulate. This approach was noteworthy in

forming dihydrazide intermediates without the need for oxidative N-N bond formation during 1,2,4-triazole synthesis. Because the crystalline oxadiazolium salts remove impurities, further purification of the dihydrazides was found to be unnecessary beyond simple separation. The oxadiazolium perchlorate salts demonstrated outstanding moisture stability which is unusual for these compounds (Moloney et al., 2017).

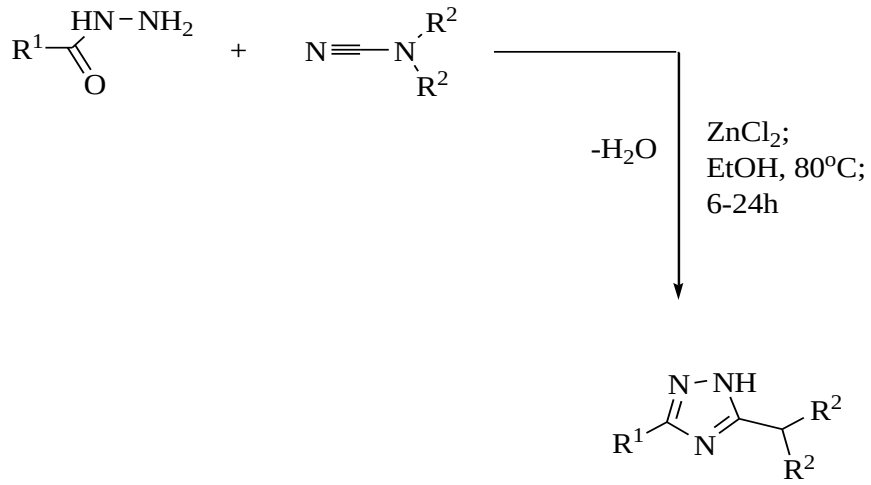


Castanedo and his colleagues demonstrated rapid and highly regioselective access to a wide range of 1,3,5-trisubstituted 1,2,4-triazoles. The components of this convenient one-pot reaction are carboxylic acids, monosubstituted hydrazines, and primary amidines. HATU is an essential component of the reaction for the coupling of peptide reagents to form acylamide intermediates with diisopropylethylamine (DIPEA) as a base in DMF. The final 1,2,4-triazole molecule might comprise a variety of substituents at position 5 (Castanedo et al., 2011).

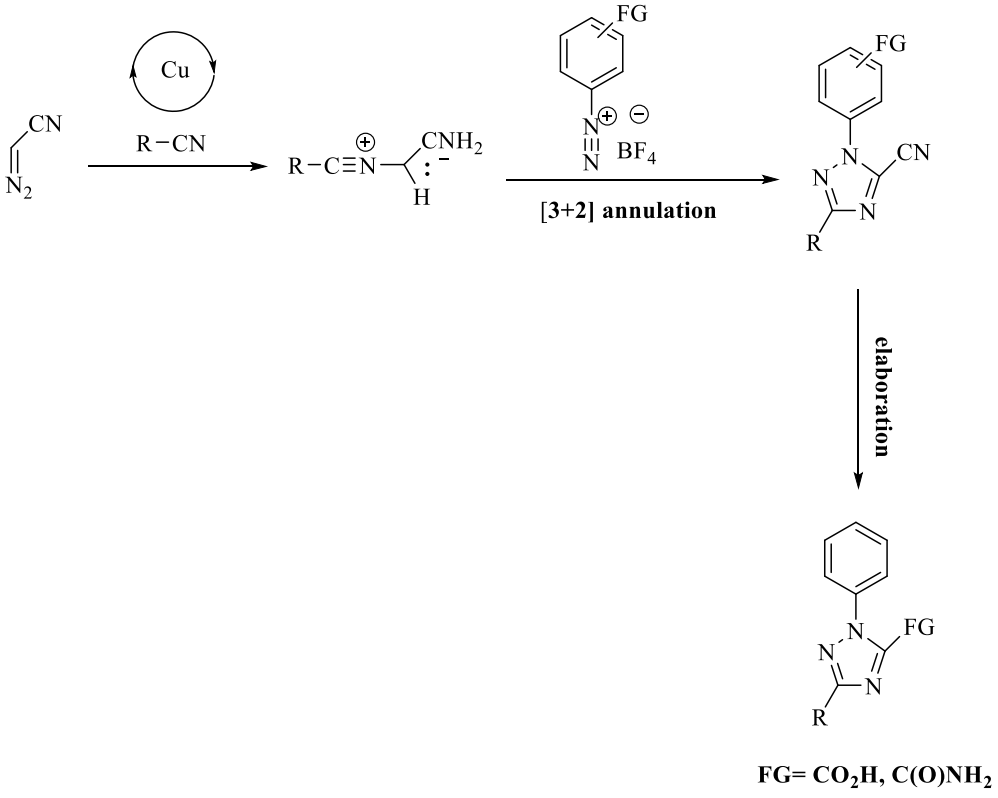


R, R_1, R_2 =alkyl, aryl

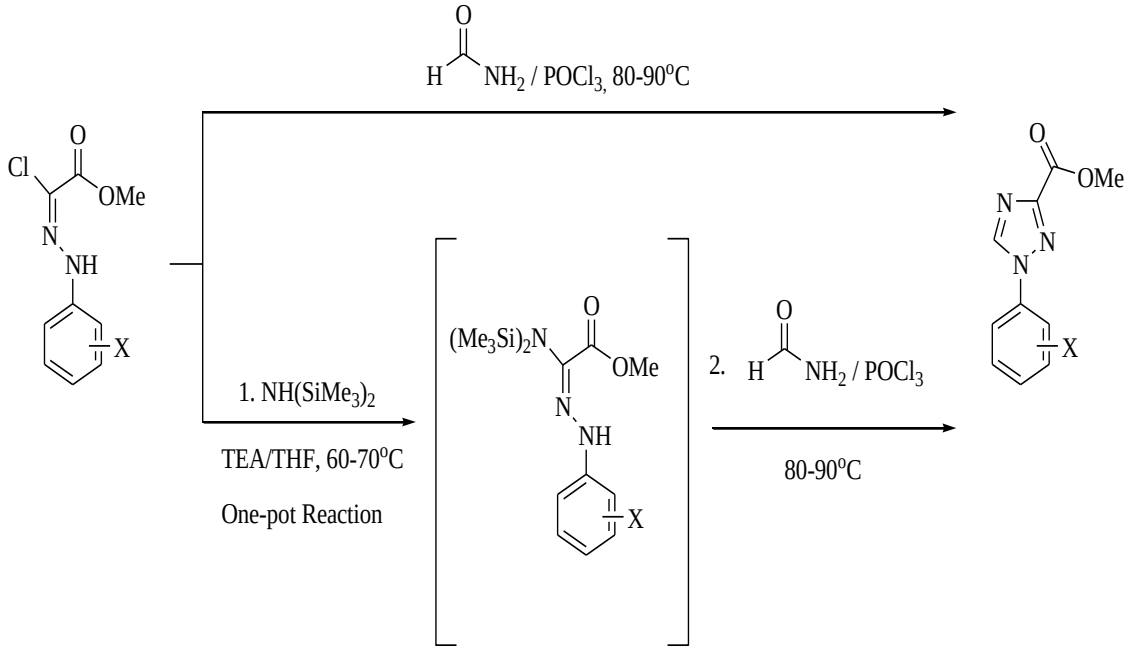
Yunusova et al. report a unique and very effective synthetic approach for producing 3-dialkylamino-1,2,4-triazoles formed from dialkylcyanamide coupling and Zn^{II}-catalyzed acyl hydrazide. The Zn^{II}-catalyzed process starts with the formation of $[Zn\{RC(=O)NHNH_2\}_3](ZnCl_4)$ complexes. It was discovered that the electronic effects of the acyl hydrazide unit substituents did not influence the reaction rate or yield of the target triazoles, while steric hindrances reduced the reaction rate without altering the yield of the heterocycles (Yunusova et al., 2018).



Zhou et al. have discovered an approach for the regioselective synthesis of 1-aryl-5-cyano-1,2,4-triazoles that is Cu-enabled and makes use of the tricomponent, [3+2] annulation reaction that combines nitriles and 2-diazoacetonitriles with aryldiazonium salts. Novel bidentate ligands for asymmetric catalysis and structurally various bioactive compounds may be synthesized using this procedure due to its versatility in gram-scale synthesis, chemical modifications to the nitrile moieties, and access to chiral bis(cyano-triazole)-1,1′-naphthalene (Zhou et al., 2021).

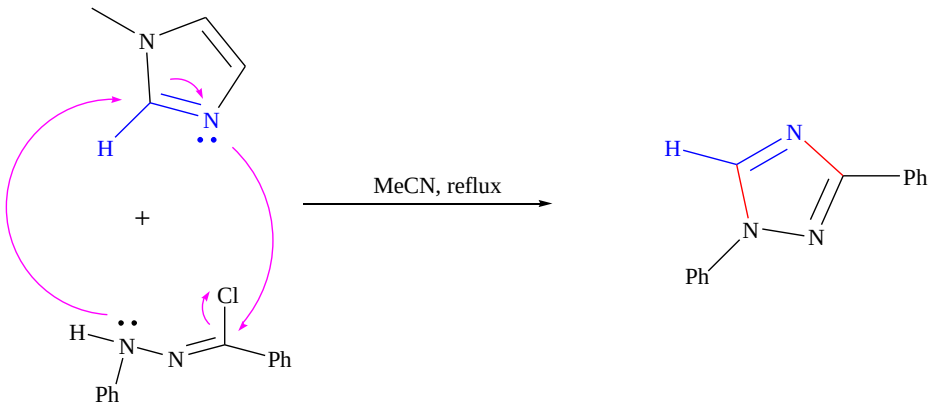


Tsai et al. have devised two straightforward one-pot procedures for synthesizing methyl 3-carboxylate-1-aryl-1H-1,2,4-triazoles, including the two-stage stepwise cascade synthetic procedure and the direct one-pot reaction. In the presence of nitrilimines and Vilsmeier reagent, methyl 3-carboxylate-1-aryl-1H-1,2,4-triazoles were successfully obtained at normal heating conditions (Tsai et al., 2019).

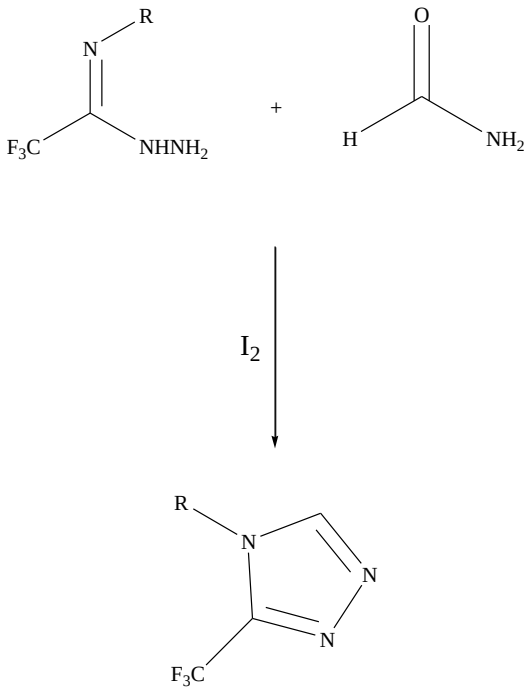


X= H, *o*-, *m*-, *p*-F, *o*-, *m*-, *p*-CF_3, *m*-, *p*-Cl, *m*-, *p*-Me, *p*-Br, *p*-OMe, and 3,4-di-Cl

Yavari and Khaledian have developed an easy-to-use one-pot, two-component method for synthesizing 1,3-disubstituted 1,2,4-triazoles utilizing easily accessible *N*-Methylimidazole (NMI) and hydrazonoyl chlorides. Nucleophilic substitution of hydrazonoyl chloride with NMI (*N*-Methylimidazole) was observed as the first step of the process. This unusual formal [3+2] cycloaddition, followed via two C-N bond cleavage, resulted in a variety of structurally different 1,3-disubstituted-1H-1,2,4-triazoles. Transformations proceeded without significant sensitivity to steric or electronic hindrance factors, and five-membered 1,2,4-triazole rings were obtained in yields ranging from 71% to 96% (Yavari & Khaledian, 2020).

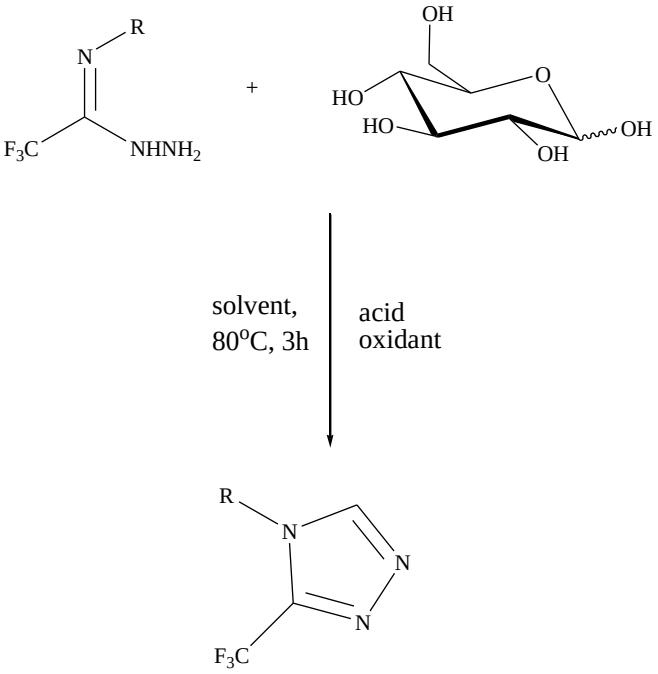


Lu et al. have developed a metal-free approach for synthesizing 3-trifluoromethyl-1,2,4-triazoles via I_2-mediated oxidative cyclization of trifluoroacetimidohydrazides by utilizing DMF, a common solvent, as the carbon source. It is observed that the desired 1,2,4-triazole products' methine units are obtained from both the *N*-methyl and *N*-acyl forms of DMF. Lu et al. stated that this method's benefits include easy access to reagents, simple operation, a wide range of substrates, and insensitivity to air and moisture (Lu et al., 2022).



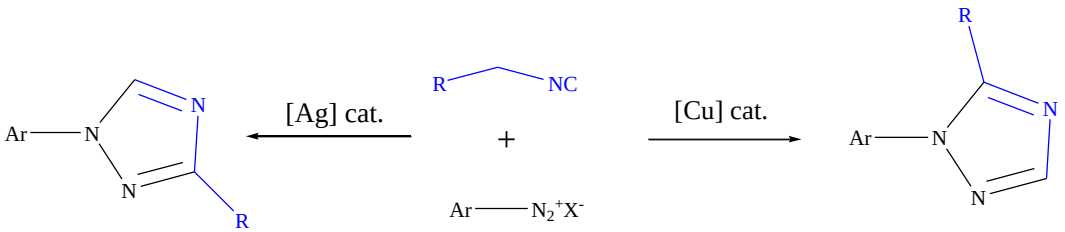
A straightforward and facile method for synthesizing 3-trifluoromethyl-1,2,4-triazoles via metal-free oxidative cyclization of trifluoroacetimidohydrazides utilizing D-glucose has been described by Lu et al. It was observed that the protocol could be used with the easy-to-find and renewable D-glucose as the C1 synthon, which has a wide range of substrates, and mild reaction

conditions and can be scaled up. They stated that the current study broadens the applications for compounds obtained from biomass in creating functionalized heterocycles (Lu et al., 2021).

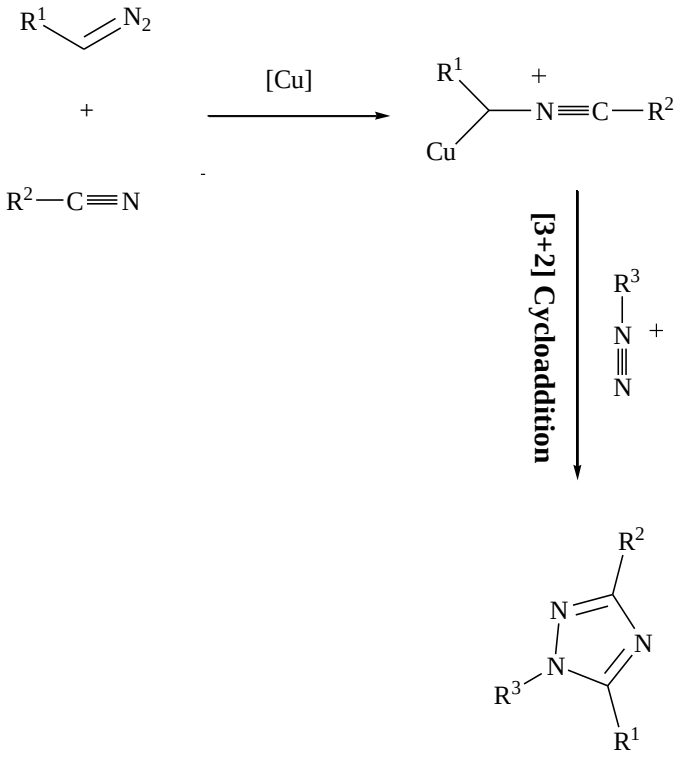


R= 4-*t*-BuPh

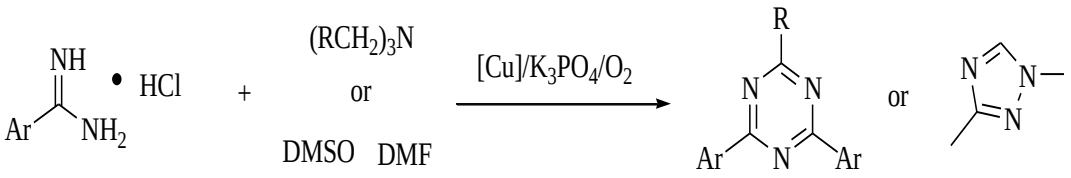
Liu et al. have reported the first catalyst-controlled methodology for the regioselective [3+2] cycloaddition of isocyanides with diazonium salts, which, under mild conditions, provides a practical method for the design of 1,2,4- triazoles in high yield from a variety of functionally diverse substrates. Under Ag(I) catalysis, 1,3-disubstituted 1,2,4-triazoles were synthesized selectively and in high yield, while 1,5-disubstituted 1,2,4-triazoles were produced by Cu(II) catalysis. Liu et al. developed these catalytic methods that give controlled, modular, and easy access to 1,2,4-triazole moieties with good efficiency, a wide range of substrates, and good compatibility with functional groups (Liu et al., 2018).



Li et al. have demonstrated a copper-catalyzed intermolecular [3+2] cycloaddition that affords 1,2,4-triazoles in medium to high yields by trapping an intermediate nitriles ylides species via the diazonium salt. They showed that this methodology offers a facile and effective strategy to generate structurally diverse 1,2,4-triazoles from readily available starting materials in a one-step manner under mild conditions. Their preliminary results have displayed that diazonium salts were the source of two N atoms for the target 1,2,4-triazoles scaffolds. Mild conditions, operational simplicity, and ready accessibility have characterized this copper-catalyzed three-component reaction, providing access to 1,2,4-triazoles with various substitution patterns (Li et al., 2018).

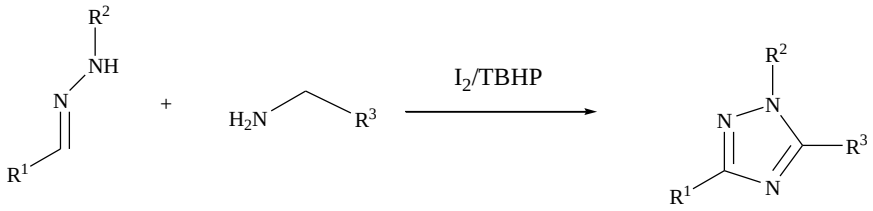


Huang et al. have described a very effective catalytic [Cu]/O2 system for obtaining 1,2,4-triazoles from amidines through oxidative functionalization of the C(sp^3)-H. To efficiently synthesize 1,3-disubstituted 1,2,4-triazoles obtained from amidines with trialkylamines, DMF, and DMSO as the reaction members, a simple and adaptable catalytic system involving copper catalyst, O_2 as the oxidant, and K_3PO_4 as the base have been devised. The method has been reported to provide significant synthetic bias and flexibility for synthesizing multi-nitrogen heterocycles from amidines. All of these have been observed to make the synthesis procedure attractive and fascinating (Huang et al., 2015).

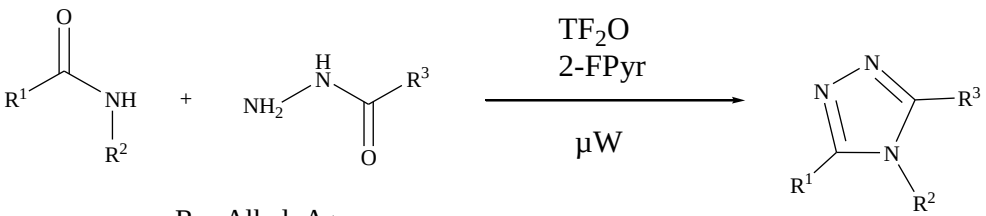


(R=H, aryl, alkyl)

Chen et al. have devised a very appealing approach for the quick and effective synthesis of compounds with 1,2,4-triazole scaffolds from hydrazones and amines via a metal-free intermolecular mechanism under aerobic oxidative conditions. It has been noted that the reaction proceeds via a cascading process of C−H functionalization, the formation of double C-N bonds, and oxidative aromatization. The methodology is reported to have easily accessible starting reagents, general and favorable operating conditions, a wide substrate coverage, and high yields (Chen et al., 2016).

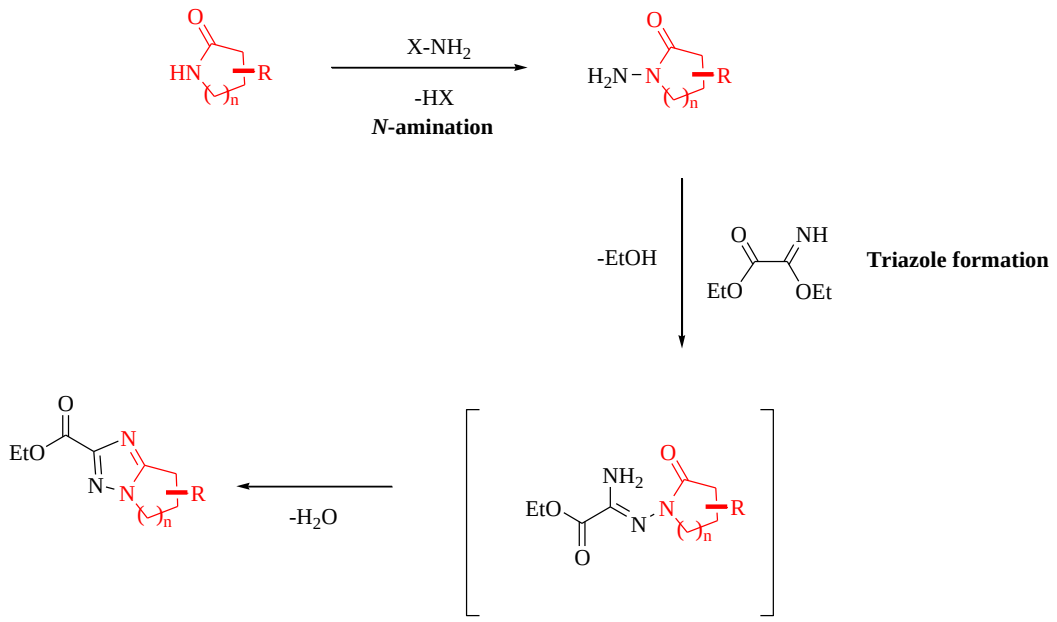


Bechara et al. have devised a general method for synthesizing 3,4,5-trisubstituted 1,2,4-triazoles from hydrazides and secondary amides via trifluoroanhydride activation followed by microwave-induced cyclodehydration. The procedure has been utilized to synthesize a range of 3,4,5-trisubstituted 1,2,4-triazoles with distinct alkyl/aryl substitution sequences (Bechara et al., 2015).

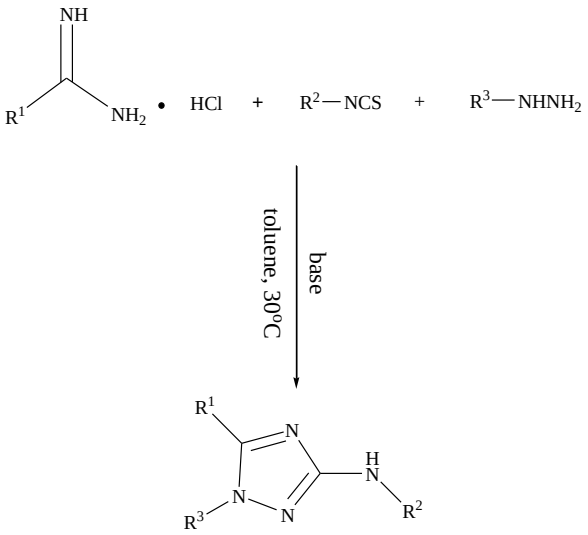


R = Alkyl, Ar

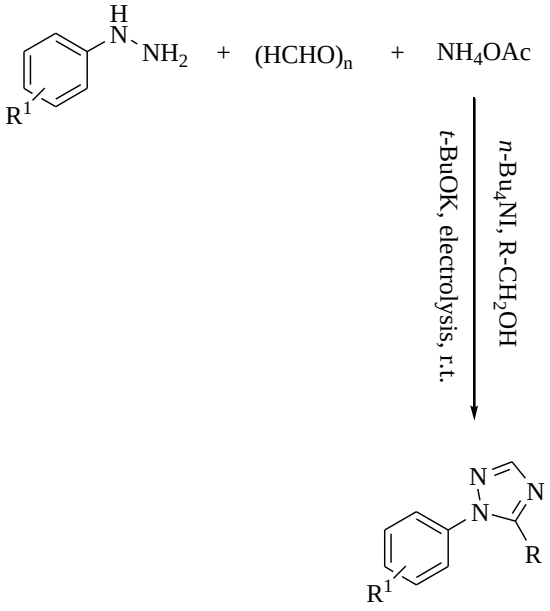
Nguyen and Hong discovered a two-step approach for synthesizing polycyclic 1,2,4-triazoles from lactams. This method involves an N-amination with HOSA, which was then followed by a cyclocondensation with ethyl 2-ethoxy-2-iminoacetate that was available for purchase. Semi-saturated triazoles with various functional groups and ring diameters have been produced utilizing this approach (Nguyen & Hong, 2021).



Guo et al. proposed an oxidant- and metal-free three-component desulfurization and deamination condensation of isothiocyanates, amidines, and hydrazines to synthesize structurally different completely substituted 1H-1,2,4-triazol-3-amines. The reaction is designed without the use of external catalysts, ligands, oxidants, or metals. This cyclization process [2+1+2] involves C–S and C–N bond cleavage, forming new C–N bonds in one pot. This study reported the synthesis of some fully substituted 1H-1,2,4-triazole-3-amines with this transformation, which has advantages such as a wide variety of substrates, environmental friendliness, mild reaction conditions, and applications in gram scale (Guo et al., 2021).

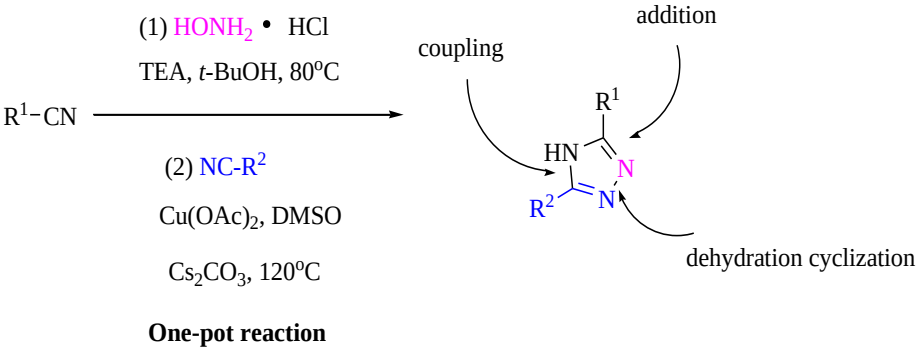


Yang and Yuan discovered a facile electrochemical approach for synthesizing 1-aryl and 1,5-disubstituted 1,2,4-triazoles, which were obtained from NH_4OAc, aryl hydrazines, alcohols, and paraformaldehyde. Employing a reactive iodide radical or I_2 and NH_3 electrogenerated in situ, it was possible to create a broad range of 1,2,4-triazole derivatives in excellent to good yields without the need of solid oxidants and transition-metal catalysts, and with little effort at room temperature (Yang & Yuan, 2018).

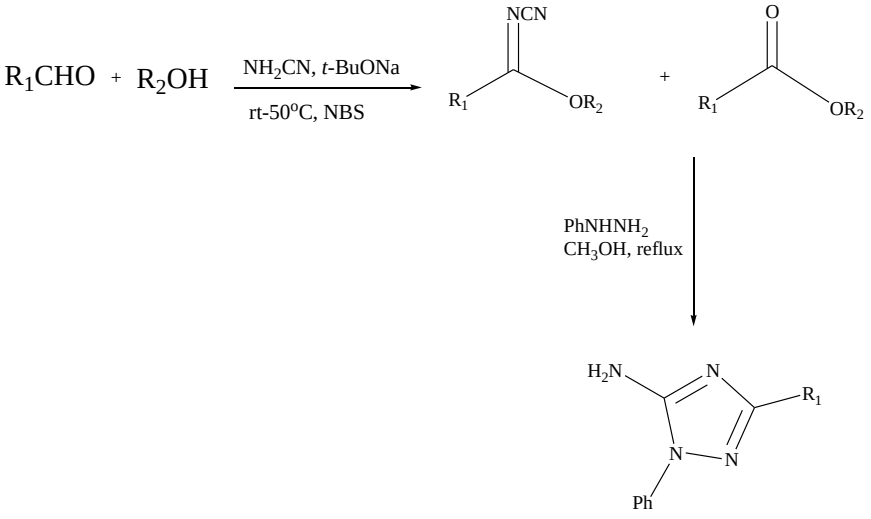


Xu et al. have devised a facile and efficient one-pot process catalyzed by copper to produce 1,2,4-triazole derivatives. In this procedure, nitriles and hydroxylamine hydrochloride, both easily accessible, are used as starting materials, while an affordable form of $Cu(OAc)_2$ is used as the catalyst. The catalytic cycle was completed without the need for an inert environment.

The corresponding 1,2,4-triazole derivatives were reportedly formed in medium to high yield in the one-pot reactions by sequentially intermolecular adding hydroxylamine to one nitrile to amidoxime, treating the amidoxime with another nitrile using a copper catalyst, and undergoing intramolecular dehydration cyclization without the addition of ligands or additives. It has been highlighted that the new strategy can tolerate a wide range of functional groups, including ether, C-Cl bonds, nitro, and N-heterocycles, and that it surpasses previous procedures economically and practically. Hence, it allows the design of a wide range of valuable compounds (Xu et al., 2015).

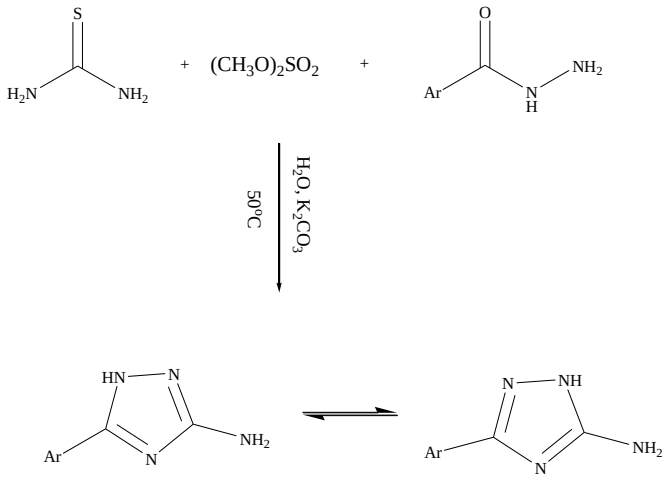


Yin et al. devised an efficient one-pot process for the cyanoimidation of aldehydes by utilizing cyanamide. The reaction took place with the NBS acting as an oxidant without the aid of a catalyst. In the next process, N-cyanobenimidate underwent cyclization reactions to produce 1,2,4-triazoles in high yields (Yin et al., 2009).

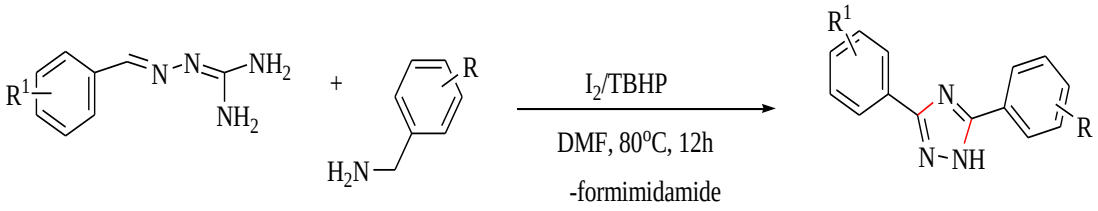


Beyzaei et al. proposed a method for efficiently synthesizing 3(5)-substituted 1,2,4-triazol-5(3)-amines in the presence of K_2CO_3 as an effective base through a one-pot synthesis involving

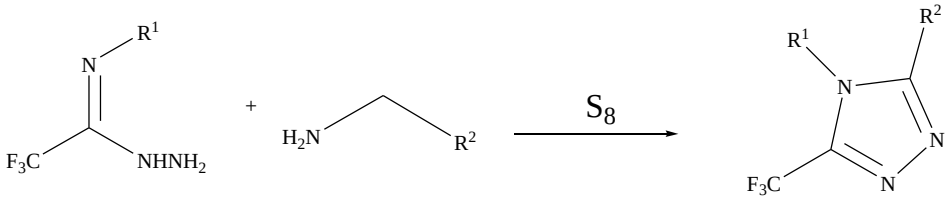
thiourea, dimethyl sulfate, and different hydrazides. It is noted that 1,2,4-triazole derivatives were produced under moderate circumstances and in accordance with certain green chemistry principles. Without additional purification, the products have been readily separated in 83-95% yields (Beyzaei et al., 2019).



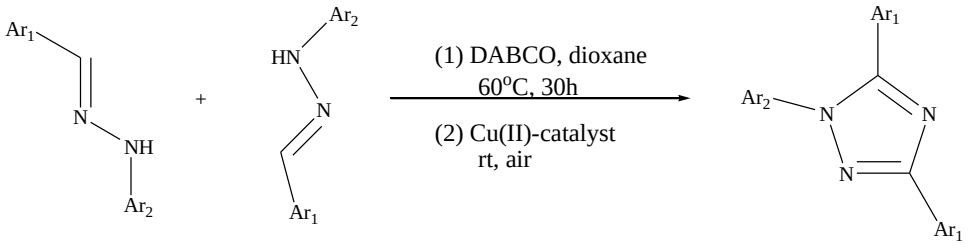
Wani et al. have discovered an effective approach for the straightforward, suitable, transition metal-free one-pot synthesis of 3,5-disubstituted-1,2,4-triazoles employing diaminoazines and benzylamines as substrates. This reaction has produced triazoles with symmetric and asymmetric substituents at moderate reaction conditions. In comparison to other approaches, it has been noted that this method offers products with a more extensive substrate range, faster production, and generally higher yields (Wani et al., 2021).



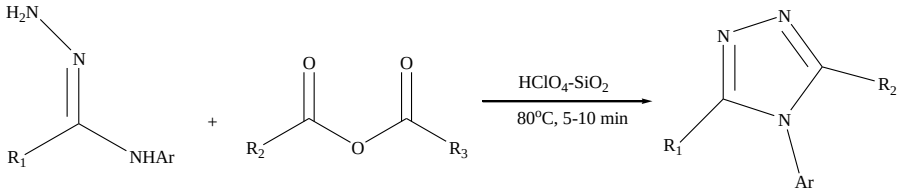
Lu et al. have developed a method for directly synthesizing 5-trifluoromethyl-1,2,4-triazoles in medium to good yields employing the elemental sulfur-mediated oxidative cyclization of aliphatic amines and trifluoroacetimidohydrazides. In this reaction, sulfur functions as a traceless oxidizer. It is noted that the metal-free procedure is distinguished by easily accessible reagents, a wide range of substrates, and promising applications (Lu et al., 2022).



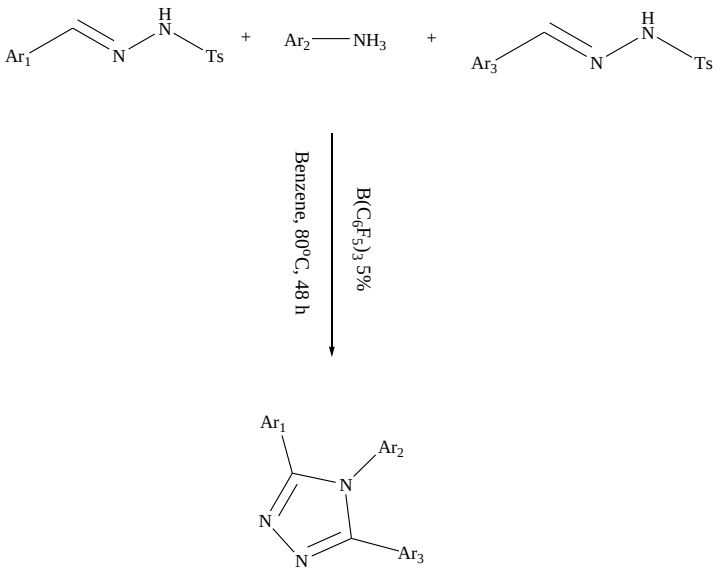
Tian et al. produced 1,2,4-triazole via decarboxylating and cyclizing 2-aryl-2-isocyanate from aryl diazonium salts. Using 1,4-diazocyclic [2,2,2]octane (DABCO) as a weak base was critical in this metal-free reaction (Tian et al., 2021).



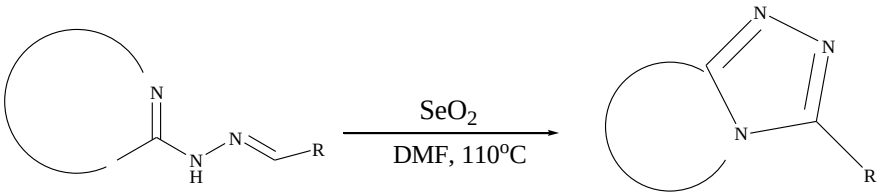
Siddaiah et al. discovered that using $HClO_4$-SiO_2 as a catalyst, 1,2,4-triazole compounds may be synthesized at 80°C with medium to high yields (55-95%). The amide hydrazone and anhydride substituents exhibit excellent tolerance under optimal conditions, and the $HClO_4$-SiO_2 catalyst was able to be recycled at least three times continuously (Siddaiah et al., 2011).



A metal-free catalytic approach for dehydrogenation cyclization based upon $B(C_6F_5)_3$ was disclosed by Guru et al. $B(C_6F_5)_3$ started a nucleophilic attack on the hydrazine part of the molecule, which was followed by amination, intramolecular cyclization, and dehydrogenation to make 3,4,5-trisubstituted-1,2,4-triazole with an 85% yield. This reaction pathway was characterized by its absence of oxidants, green economy, mild conditions, and selectivity providing a feasible platform for catalytic chemical transformation without the need for transition metals (Guru et al., 2019).



Zheng et al. described an effective and practical approach for generating 1,2,4-triazoles via the oxidative cyclization of hydrazones through the use of SeO_2. Through intramolecular oxidative cyclization between selenium dioxide and heterocyclic hydrazones, a series of fused 1,2,4-triazoles are formed. Based upon these compounds, which have a moderate to excellent yield of 1,2,4-triazolo [4,3-a] pyrimidines, 1,2,4-triazolo [4,3-a] pyridines, and 1,2,4-triazolo-[4,3-a] quinoxalines the straightforward application of this method was confirmed (Zheng et al., 2015).



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