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RECENT ADVANCES IN 1,2,4-TRIAZOLE RING CONSTRUCTION VIA CYCLOADDITION REACTIONS

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Abstract – The sources, describing cycloaddition reactions that lead to obtaining of substituted 1,2,4-triazoles and their fused derivatives were reviewed. The review article covers the literature data published in the period 2011-2021. Synthetic particularities of cycloaddition products, the optimization of reaction conditions, factors that influence on the direction of the reaction are reasonably mentioned. Cycloaddition reactions are presented as convenient method for obtaining of as functional 1,2,4-triazoles, as well as their fused derivatives.

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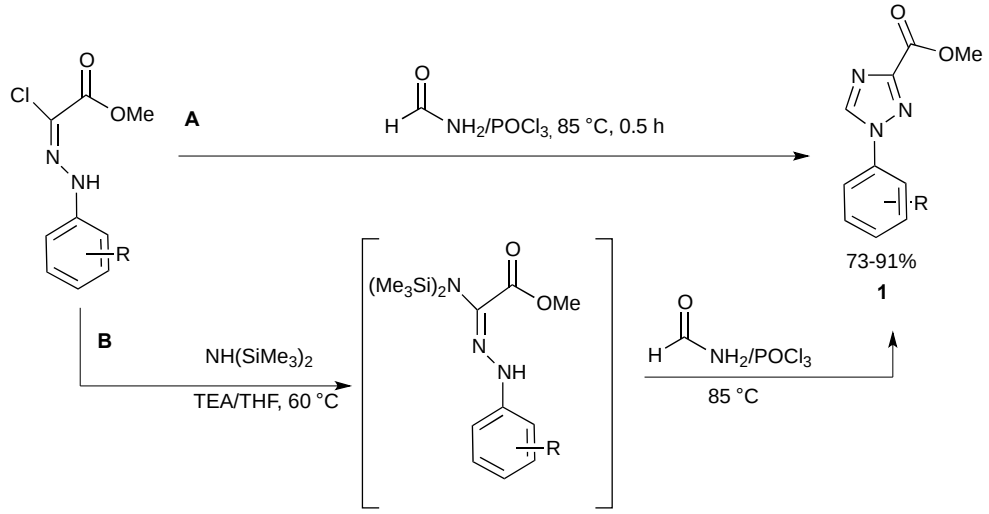
1. INTRODUCTION

Currently, the chemistry of 1,2,4-triazoles and their condensed heterocyclic derivatives have received considerable attention due to their synthetic and biological significance. The chemical industry is actively involved in the elaboration of simple and affordable synthetic procedures for production of as functional, as well as condensed 1,2,4-triazole systems,[1-7] especially after recent discovering that certain triazoles are effective photoemulsion stabilizers,[8] and some others are effective herbicides.[9] A large number of representatives of the 1,2,4-triazole-containing system have been involved into a wide range of therapeutic drugs, which include anti-inflammatory, sedative, antimicrobial and antifungal agents.[10-18] At the same time cycloaddition process is one the most powerful and usable approach for construction of new heterocyclic systems.[19,20] The family of 1,2,4-triazole isn't an exception and it might be obtained via cycloaddition reactions by various ways. This review covers the most recent research articles dedicated to investigation the different cycloaddition reactions which lead to obtaining both functional and fused

derivatives of 1,2,4-triazole. The synthetic particularities, influence of substituents nature and using of catalysts are also discussed.

2. CYCLOADDITION REACTIONS LEADING TO FORMATION OF 1,2,4-TRIAZOLE DERIVATIVES

The convenient one-pot procedure has been developed to synthesize of methyl 1-aryl-1*H*-1,2,4-triazole-1-3-carboxylates **1** by using of hydrazonoyl hydrochlorides (nitrilimines) with Vilsmeier reagent (Scheme 1). The direct one-pot method **A** involved the interaction between nitrilimines and Vilsmeier reagent during 0.5 h at 85 °C. Another one-pot two-step cascade method **B** proceeded via nucleophilic substitution with bis(trimethylsilyl)amine [$NH(SiMe_3)_2$] and subsequent intramolecular cycloaddition reaction with Vilsmeier reagent. Substrate scope, multicomponent examples, and mechanistic insights are clearly discussed in the source.[21] Mechanistic insights on method **A** involve the interaction of methyl 2-chloro-2-(2-phenylhydrazono)acetate and Vilsmeier reagent in the acidic species and they can be simultaneously reacted at ~85 °C to give imine intermediate. Subsequently, intramolecular cycloaddition reaction happened effectively under heating condition. The expected product **1** was smoothly provided in good yields. For two-step cascade method **B**, methyl 2-chloro-2-(2-phenylhydrazono)acetate in THF solution was reacted with bis(trimethylsilyl)amine [$NH(SiMe_3)_2$] in presence of excess amount of TEA.

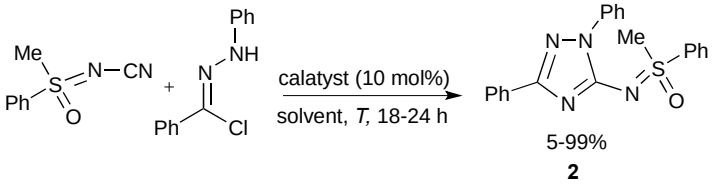


R = H, *o-*, *m-*, *p*-F, *o-*, *m-*, *p*-CF_3, *m-*, *p*-Cl, *m-*, *p*-Me, *p*-Br, *p*-OMe, 3,4-di-Cl

Scheme 1. Formation of methyl 1-aryl-1*H*-1,2,4-triazole-3-carboxylates **1**

Hydrazonoyl chlorides are known to undergo dehydrohalogenation reactions providing highly reactive nitrilimines - the 1,2,4-triazoles are resulted if the last react with nitriles via 1,3-dipolar cycloaddition.[22] In 2020, Krauskopf and co-workers developed this reaction with the using of sulfoximine and

hydrazonoyl chloride as representative starting materials. The keeping of a combination of the substrates with 10 mol% of $Yb(OTf)_3$ and 1.5 equiv of $NaHCO_3$ in benzene at 120 °C for 24 h together with the using a sealed tube in an aluminum heating block proved the optimal providing of target compound **2** in 99% yield. The usage of toluene as solvent under the same conditions gave **2** in 97% yield.



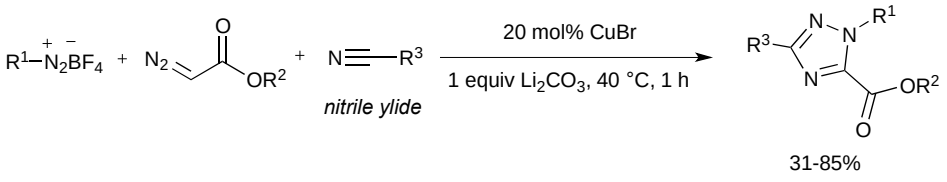
Scheme 2. Formation of *N*-triazolylsulfoximines **2**

A donor/acceptor diazoactivation strategy, processing via condensation using diazonium salts without the addition of any other catalysts or reagents was reported.[23] Thus the substituted 1,2,4-triazoles **3** were obtained in good to excellent yields in the presence of nitriles at room temperature (Scheme 3). This interesting diazenium route provides a new efficient approach to achieve complex heterocycle synthesis under mild conditions. Nitrile addition to the diazenium intermediate is dominant in acetonitrile solvent. Aryldiazonium salts containing electron-withdrawing substituents worked well in this transformation, providing the desired 1,2,4-triazoles **3** in good to excellent yields. On the other hand, aryldiazonium salts containing an electron-donating group on the aromatic ring did not promote the reaction due to rapid decomposition. The presence of both electron-withdrawing/-donating groups on the aromatic ring of the aryl diazoesters did not influence the reaction outcome, and target products **3** were formed in good yields. The employing of different nitriles, such as EtCN, *i*PrCN, and $TMSCH_2CN$, MeCN, furnished the substituted 1,2,4-triazoles **3** in moderate yields. However, less nucleophilic nitriles, such as PhCN, did not promote this reaction.

R^1 = C_6H_5, 4-F-C_6H_4, 3-F-C_6H_4, 2-F-C_6H_4, 4-Me-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4
R^2 = 4-F-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-CF_3-C_6H_4, 3-CF_3-C_6H_4, 2-CF_3-C_6H_4, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 2-NO_2-C_6H_4, 4-CN-C_6H_4, 2-Br-C_6H_4, 3,4-di-F-C_6H_3
R^3 = Me, Ph, Allyl

Scheme 3. Formation of 2,3,5-trisubstituted 1,2,4-triazoles **3**

A novel [3+2] cycloaddition between nitrile ylides and diazonium salts was well-discussed in the source.[24] The described copper catalyzed three-component reaction was distinguished by mild conditions, ready availability, and operational simplicity, thus opening access to 1,2,4-triazoles **4** with a diverse set of substitution patterns. The reaction mixture containing of nitrile ylide, diazonium salt, acetonitrile, catalytic amount of CuBr and Li_2CO_3 was placed in a test tube and stirred at 40 °C for 1 h under air (Scheme 4). Target 1,2,4-triazoles **4** was obtained in moderate to excellent yield.

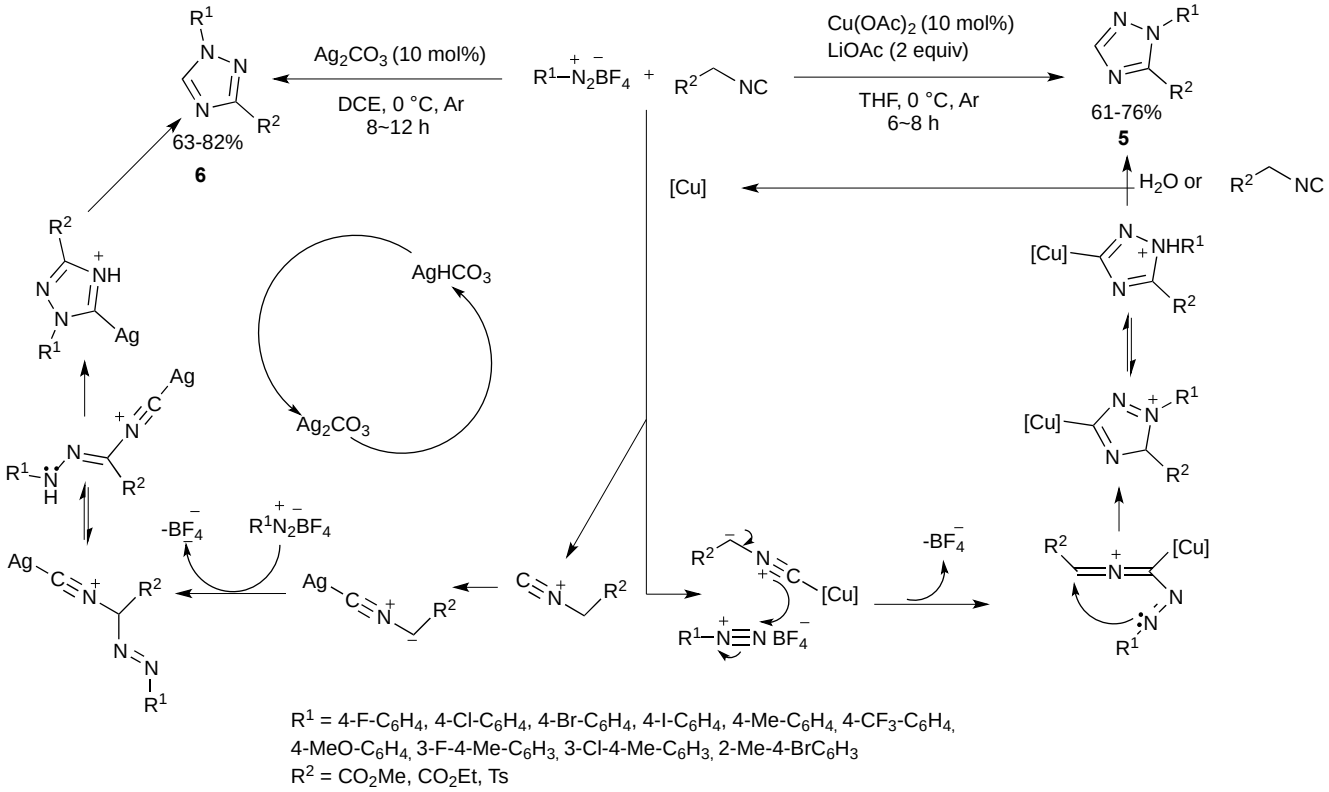


4

R^1 = 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-*i*Pr-C_6H_4, 4-*t*Bu-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3O-C_6H_4, 3-Me-C_6H_4, 3-Cl-C_6H_4,3-Br-C_6H_4, 3-CF_3-C_6H_4, 2-MeO-C_6H_4, PMP
R^2 = Et, *i*Pr, *t*Bu, Cy, Ph, Bn, CH_2CH_2Np
R^3 = *i*Pr, *t*Bu, *n*Bu, Bn, 3-chloropropyl, 2-methoxyethyl, prop-2-en-1-yl, prop-1-en-1-yl, 2-phenylethenyl

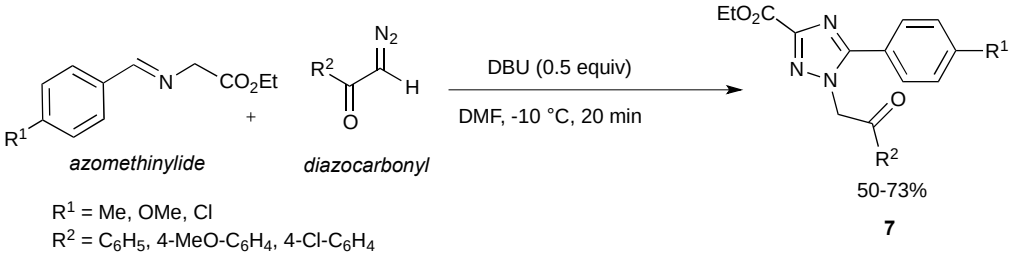
Scheme 4. Formation of 1,2,4-triazoles **4**

An unprecedented catalyst-dependent regioselective [3+2] cycloaddition of isocyanides with aryl-diazonium salts was reported by Liu and co-workers.[25] 1,3-Disubstituted 1,2,4-triazoles **6** were selectively obtained in high yield under Ag(I) catalysis, whereas 1,2-disubstituted 1,2,4-triazoles **5** were formed with Cu(II) catalysis. These catalytic methodologies provide a controlled, modular, and facile access to 1,2,4-triazole scaffolds with high efficiency, broad substrate scope, and excellent functional group compatibility. Under the optimized reaction conditions, authors explored the versatility of the [3+2] cycloaddition to 1,2-disubstituted 1,2,4-triazoles **5** in the presence of catalytic amounts of $Cu(OAc)_2$ (Scheme 5). Both electron-donating and electron-withdrawing substituents on the benzenediazonium tetrafluoroborate reactants were tolerated in the reaction with isocyanide, leading to the desired products **5** in moderate to good yields. The scope and limitations of the silver-catalyzed cycloaddition of isocyanides to diazonium salts with production of 1,3-disubstituted 1,2,4-triazoles **6** were also subsequently investigated in the source.[25] The proposed reaction mechanism is shown in Scheme 5.



Scheme 5. Formation of 1,2-disubstituted 1,2,4-triazoles **5** and 1,3-disubstituted 1,2,4-triazoles **6**

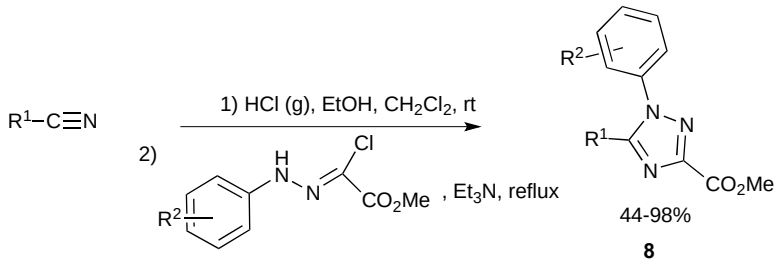
The DBU-catalyzed [3+3] and [3+2] cyclization reactions of azomethine ylides with α-diazocarbonyls as *N*-terminal electrophiles have been developed.[26] This reaction involves a sequential intermolecular nucleophilic addition / intramolecular cyclization / oxidation procedures. By the assembly of readily available starting materials, this transformation offers novel, highly efficient one-pot syntheses of various functionalized 1,2,4-triazole derivatives in an atom-economical manner under ambient and metal-free conditions with high regio and diastereoselecty. The reaction mixture was stirred at room temperature for 15 min with the obtaining of **7** as a yellow solid in 50-73% yields (Scheme 6).



Scheme 6. Formation of compounds **7**

In 2014, Wang and co-workers reported the one-flask strategy for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles **8** starting from nitriles with *N*-arylhydrazonoyl hydrochlorides under basic conditions.[27] The reaction provided the desired 1,2,4-triazoles **8** in moderate to excellent yields (56–98%), and was

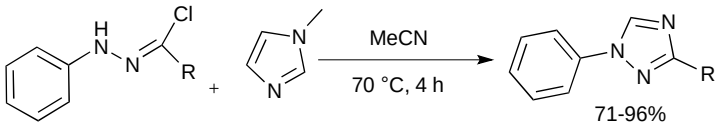
applicable to aliphatic and aromatic nitriles as well as *N*-phenylhydrazonoyl hydrochlorides bearing ester and acetyl functionalities. During the optimization of reaction conditions stage it was noted that the 1,3-dipolar cycloaddition does not take place without a base, neither does the usage of diethylamine, *N*,*N*-diisopropylethylamine or pyridine. It was found that only the addition of triethylamine displayed a satisfactory result. Triethylamine was thus used as the base for all the following studies. On the other hand, the above reaction readily gave the corresponding 1,2,4-triazoles **8** in 56–91% yields in a case of hydrazonoyl chlorides bearing *o*-CF_3, *m*-Br, *p*-Me, *p*-CF_3, *p*-OMe, *p*-F, and *p*-Cl on the phenyl group. Also the one-flask 1,3-dipolar cycloaddition strategy was applicable to various aliphatic nitriles. The reaction of ethyl, *i*-propyl, *n*-butyl, and cyclopentyl nitriles with *p*-chloro-*N*-phenylhydrazonoyl chloride in the presence of triethylamine provided the corresponding 1,3,5-trisubstituted 1,2,4-triazoles **8** in 57–98% yields (Scheme 7).



R^1 = Me, Et, *i*Pr, *n*Bu, cyclopentyl, phenyl, 2-furyl, 2-thienyl, 2-pyrrolyl
R^2 = H, *o*-CF_3, *m*-Br, *p*-Me, *p*-CF_3, *p*-OMe, *p*-F, *p*-Cl, *m*-CF_3

Scheme 7. Formation of 1,3,5-trisubstituted 1,2,4-triazoles **8**

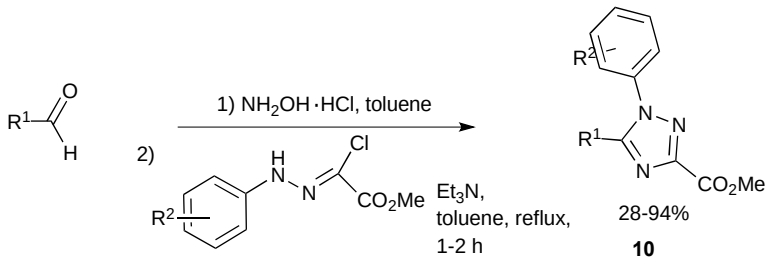
N-Methylimidazole (NMI) can act as a masked HCN in the synthesis of 1,3-disubstitued-1*H*-1,2,4-triazoles *via* a formal cycloaddition reaction of hydrazonoyl chloride with NMI.[28] The product was proved to be formed *via* an initial nuclophilic substitution of hydrazonoyl chloride with NMI following cyclization and two sequential C-N bond cleavages. In order to examine the synthetic scope and the functional group tolerance of this formal cycloaddition reaction, Yavari and Khaledian studied the reaction with a variety of hydrazonoyl chlorides. Results showed excellent yields for almost all of the hydrazonoyl chloride substrates bearing aromatic, heteroaromatic, or aliphatic moieties. In particular, a number of *N*′-arylbenzohydrazonoyl chlorides with various substituents in the aryl fragments were tested, and afforded excellent yields of **9** (Scheme 8). With the aryl moiety bearing an electron-withdrawing functional group (4-chloro-, 4-fluoro-, and 2,4-dichloro-) a higher efficiency could be attained compared to that having an electron-donating groups (4-methyl-, 4-methoxy-).



R = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 2,4-Cl_2-C_6H_3, 4-NO_2-C_6H_4

Scheme 8. Formation of 1-phenyl-3-substituted-1,2,4-triazoles **9**

A new one-pot synthesis of 3,5-disubstituted 1,2,4-triazoles **10** has been successfully developed to synthesize a series of compound **10**.[29] The transformation involves the 1,3-dipolar cycloaddition reaction of hydrazonoyl hydrochlorides with oxime intermediates prepared from aldehydes with hydroxylamine hydrochloride in the presence of excess amount of triethylamine. In this 1,3-dipolar reaction, hydrazonoyl hydrochlorides were concerned as the masked 1,3-dipole nitrilimines under basic condition. The newly developed method includes the treating of toluene solution of aldehydes with hydroxylamine hydrochloride with excess amount of triethylamine at room temperature for 0.5 h. When the aldehydes were completely consumed and converted to the oxime intermediates, the hydrazonoyl chloride was added into the reaction mixture in the presence of excess amount of triethylamine and the solution was heated to reflux for 1-2 h. The desired 3,5-disubstituted 1,2,4-triazole products **10** were isolated in solid form (Scheme 9).

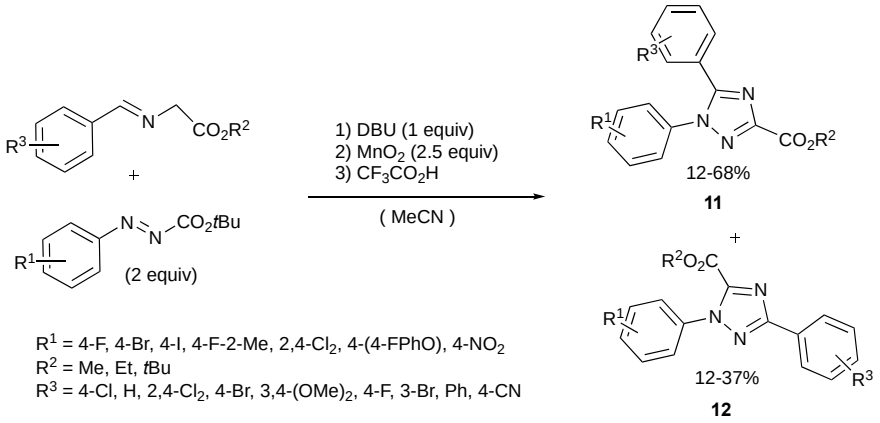


R^1 = Me, Et, *i*Pr, *n*Bu, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, 3-furyl, 3-thienyl, 2-pyrrolyl, 2-naphthyl
R^2 = H, *o*-CF_3, *m*-Br, *p*-Me, *p*-CF_3, *p*-OMe, *p*-F, *p*-Cl, *m*-CF_3

Scheme 9. Formation of 3,5-disubstituted 1,2,4-triazoles **10**

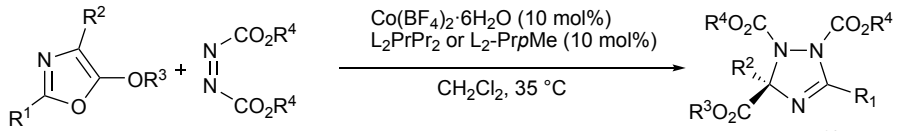
As phenylazocarboxylic acid *tert*-butyl esters have been shown to be highly versatile building blocks due to their ability to undergo nucleophilic aromatic substitutions under mild conditions, and to act as precursors for aryl radicals, Lasch and Heirich[30] have reported the first example for cycloaddition reactions to phenylazocarboxylates. So, a variety of highly substituted 1,2,4-triazoles **11**,**12** could be obtained with an unexpected preference for one regioisomer in a one-pot reaction with readily accessible glycine imines. The major isomers obtained in experiment were resulted from an attack of the nucleophilic glycine imine onto the α-nitrogen atom. Whereas electronic modifications on the glycine

imine or the azocarboxylate had no or small impacts on the regioselectivity, only the increased steric demand was able to reverse it, but at the cost of lower yields. Studies on the reaction course revealed that the initial addition of the deprotonated glycine imine to the azocarboxylate is irreversible for both regioisomers **11** and **12**. Differences between both pathways were observed in the subsequently occurring cyclization step, which turned out to be in one case sensitive to the presence of additional azo compounds. The mixture of the imine, *tert*-butyl phenylazocarboxylate and molecular sieve in dry acetonitrile under nitrogen was cooled to -15 °C and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene and stirred for 45 min. Then, the manganese dioxide was added, the cooling is removed and the reaction is stirred for 4 h at ambient air. Trifluoroacetic acid was added and the reaction is stirred for 1 h (Scheme 10).



Scheme 10. Formation of 1,3,5-trisubstituted 1,2,4-triazoles **11** and **12**

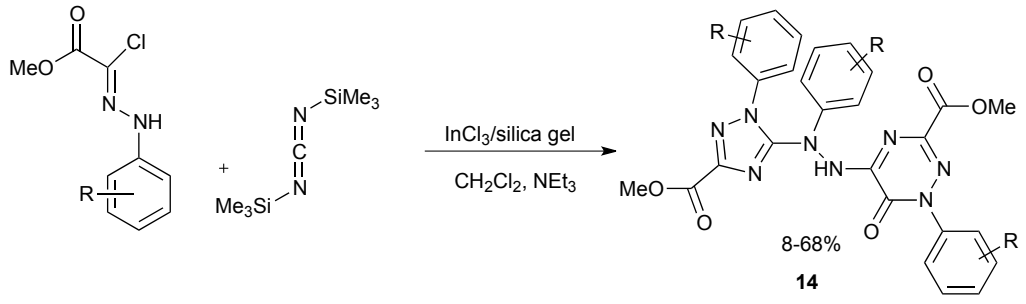
A highly efficient catalytic asymmetric formal [3+2] cycloaddition reaction of 5-alkoxyoxazoles with azodicarboxylate compounds has been realized due to a chiral *N*,*N'*-dioxide/$Co(BF_4)_2 \cdot 6H_2O$ complex.[31] A series of poly-substituted 1,2,4-triazoline compounds **13** were obtained in moderate to excellent yields (70-99%) with high enantioselectivities (82-98%) (Scheme 11). Under the optimized reaction conditions the substrate scope of the reaction by varying substituents in the 5-alkoxyoxazole derivatives was evaluated. A wide range of 5-alkoxyoxazoles with varied aryl or alkyl substituents at C2 and C4 carbons were found to be excellent substrates. The reactions of 5-methoxyoxazoles bearing either electron-donating or electron-withdrawing phenyl groups could proceed smoothly affording the corresponding 5-aryl-substituted 1,2,4-triazolines **13** in excellent yields (94-99%) and high enantioselectivities (92-98%). Aromatic type group R^1 at C2 carbon of 5-methoxyoxazoles afforded a good result in 89-94% yields and enantioselectivities (ES) 75-95%. When the type of substituent R^1 at C2 carbon of 5-methoxyoxazoles was transformed into aliphatic group, such as methyl or *n*-pentyl, 90% yield, 92% (ES) and 81% yield, 89% (ES) were obtained, respectively.



R^1 = 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-*t*BuOC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3,5-$Me_2C_6H_3$, Ph, 2-naphthyl, 2-furyl, 2-thienyl, Me, *n*-pentyl
R^2 = Ph, H, Me, Et, *i*Pr, 4-BrC_6H_4,4-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4
R^3 = Me, Et
R^4 = Et, *t*Bu

Scheme 11. Formation of poly-substituted 1,2,4-triazolines **13**

An indium(III) chloride/silica gel promoted one-pot multicomponent reaction for the synthesis of 5-[2-(1,2,4-triazol-3-yl)hydrazinyl]-1,2,4-triazin-6-ones **14** was developed by treating hydrazonoyl hydrochlorides with *N,N'*-bis(trimethylsilyl)carbodiimine.[32] On the basis of the proposed reaction mechanism, the $InCl_3$/silica gel promoted 1,3-dipolar cycloaddition and the sequential multicomponent cyclization/substitution reactions were conceived as two key steps of this synthetic method. The silylamide anion was assumed to be liberated from the 1-aryl-5-(trimethylsilylamino)-1*H*-1,2,4-triazole intermediate and regarded as the leaving group to initiate the complex cyclization/substitution process. The mixture of *N,N'*-bis(trimethylsilyl)carbodiimine and $InCl_3$/silica gel was disolved in anhydrous CH_2Cl_2 and stirred at room temperature for 0.5 h. Then, triethylamine and the hydrazonoyl hydrochloride in anhydrous CH_2Cl_2 were added, and the resulting mixture was heated at reflux over 5 h. Then, the received crude product was purified by column chromatography on silica gel to give the corresponding 1,2,4-triazole carrying 1,2,4-triazin-6-one moiety **14** in yields of 8–68%.

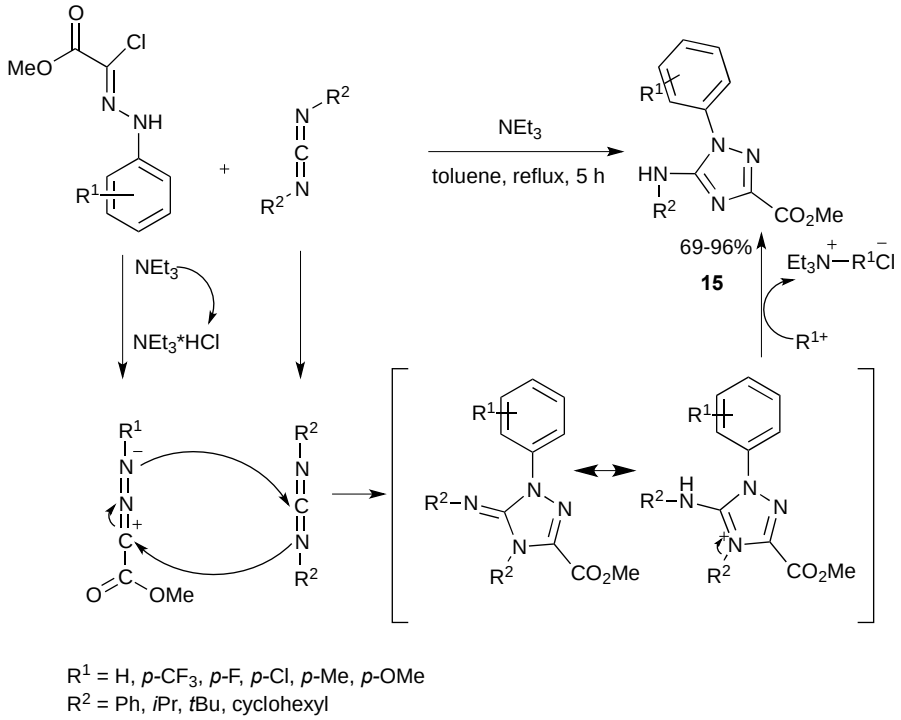


R = H, *o*-CF_3, *m*-CF_3, *p*-CF_3, *o*-F, *m*-F, *p*-F, *p*-Cl, *p*-Br, *p*-Me, *p*-CN, *p*-NO_2, *p*-OMe

Scheme 12. Formation of 5-[2-(1,2,4-triazol-3-yl)hydrazinyl]-1,2,4-triazin-6-ones **14**

An effective 1,3-dipolar cycloaddition was developed for the synthesis of 5-amino-1,2,4-triazoles **15** by interaction of hydrazonoyl hydrochlorides with carbodiimides in the presence of triethylamine as a base

(Scheme 13).[33] Both symmetric and asymmetric carbodiimides are compatible with this reaction; diphenylcarbodiimide is the one exception. Further mechanistic investigation suggests that the alkyl moieties of the carbodiimides function as suitable leaving groups is able to readily depart from the 4,5-dihydro-5-imino-1,2,4-triazole intermediate thus forming the corresponding carbocations. Such carbocations can then be trapped by triethylamine to generate the quaternary triethylalkylammonium chloride salt. This proposed mechanism is supported by the isolation and characterization of the intermediate ammonium salt. Further, the relative reactivity of asymmetric and symmetric carbodiimides was found to be consistent with the stability of subsequently formed carbocations: *tert*-butyl >cyclopentyl> isopropyl>cyclohexyl> ethyl >> phenyl.

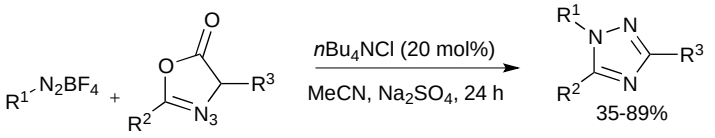


R^1 = H, *p*-CF_3, *p*-F, *p*-Cl, *p*-Me, *p*-OMe
R^2 = Ph, *i*Pr, *t*Bu, cyclohexyl

Scheme 13. Formation of 5-amino-1,2,4-triazoles **15**

A metal-free cycloaddition/decarboxylation reaction between azlactones and aryldiazonium salts was developed by Yu and co-workers.[34] This reaction provided an efficient and facile access to 1,3,5-trisubstituted 1,2,4-triazoles **16**. The aryldiazonium salts in this protocol serve as two-nitrogen units rather than sources of aryl radicals. The reaction tolerated different substituted functional groups on the aryl moiety such as Me or F, furnishing the desired products **16** with good yield. Authors examined the generality of the reaction by using various azlactones. The reaction was performed in a Schlenk tube under argon where corresponding azalactones, aryldiazonium salts, *n*-butylammonium chloride and Na_2SO_4 were dissolved in MeCN. The resulting mixture was stirred continuously until the reaction was

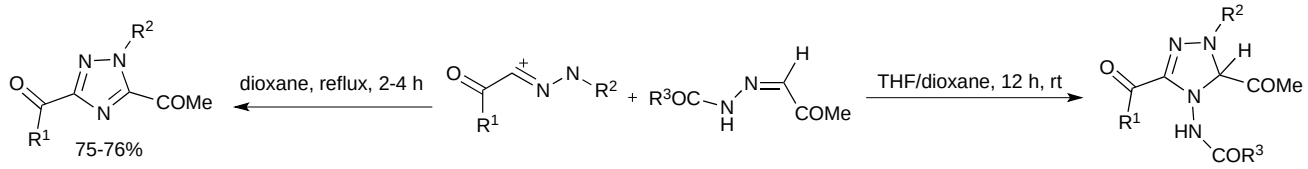
completed as monitored by TLC analysis. The crude reaction mixture was purified by flash column chromatrography, eluting with petroleum ether and diethyl ether to afford the corresponding products **16** in 35-89% (Scheme 14).



R^1 = 4-$NO_2C_6H_4$, 4-BrC_6H_4, Ph, 3-$NO_2C_6H_4$, 2-FC_6H_4, 4-CNC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CO_2EtC_6H_4$
R^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, Me
R^3 = Me, *i*Pr, Ph, H

Scheme 14. Formation of 1,3,5-trisubstituted1,2,4-triazoles **16**

1,3-Dipolar cycloaddition of nitrilimines was carried out via generation *in situ* from hydrazonoyl halides in tetrahydrofuran or 1,4-dioxane in the presence of triethylamine, to 2-oxo-propanal hydrazones (R^3 =COPh, CO_2Me, and CO_2Et). Reaction led to the formation of 4,5-dihydro-1,2,4-triazole derivatives **17** as cycloaddition products at room temperature for 12 h (Scheme 15).[35] This can be explained on a basis of the weak nucleophilicity of the nitrogen atom of the hydrazones carrying the electron withdrawing groups in comparison to that of the nitrogen atom carrying methyl group in methylhydrazones. Noteworthy, the same dihydrotriazoles **17** and aromatic triazoles **18** were obtained when above reaction was carried out under refluxing conditions (Scheme 15). Some of them proved to have potent antibacterial and antifungal activity.

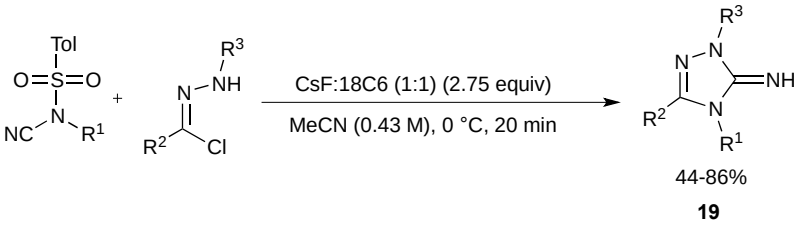


R^1 = Me, Ph, PhNH, 2-C_4H_3O, 2-C_4H_3S, 2-$C_{10}H_7$
R^2 = Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4
R^3 = Ph, OEt, OMe

Scheme 15. Formation of dihydrotriazoles **17** and aromatic triazoles **18**

A convenient method for the synthesis of 1,2,4-triazol-3-imines **19** was reported through a selective 1,3-dipolar cycloaddition of organo-cyanamide ions with nitrile imine dipoles.[36] A stepwise mechanism, supported by DFT calculations, is invoked to explain the reaction selectivity. The scope of the reaction was explored with a range of substituted hydrazonoyl chlorides (both at R^2 and R^3). Both hydrazonoyl chlorides bearing electron-donating (EDG) and/or electron-withdrawing (EWG) aryl groups on R^2 were well tolerated. Introducing an EDG on R^3 had a profound effect on the reaction outcome; for example, *p*-methoxy substituents on the aryl group led to excellent yields (83%). On the other hand, the sterically

hindered nitrile imines gave the target imines in moderate yields (44%). The reaction of 4-fluoro substituted cyanamide with the model substrate afforded in only 44% yield, whereas the corresponding *p*-methoxy substituted cyanamides yielded cyclized product **19** in moderate yields (61%). The reaction of 4-fluoro substituted cyanamides with an electron-rich nitrile imine (R^3 = EDG) yielded the imine product with much improved yields (78%). The same was true when a combination of electron-rich cyanamide was reacted with electron-poor nitrile imine (R^3 = EWG) (71%). Heterocyclic hydrazonoyl chlorides, such as thiophene and pyridine, were also well tolerated, giving **19** in 85% and 70% yields, respectively. Other hydrazonoyl chlorides such as cyclopropyl, alkyl esters gave good product yields (58−82%). The reaction underwent in solution of CsF and corresponding cyanamide in anhydrous MeCN under an ice-bath conditions, followed by addition of 18C6. Then, corresponding hydrazonoyl chloride was added and the volatile components were removed under vacuum (Shcheme 16). After the purification the product **19** was isolated.



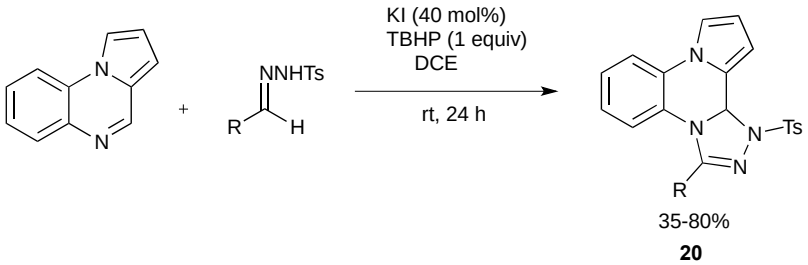
R^1 = Ph, 4-F-C_6H_4, 4-MeO-C_6H_4
R^2 = Ph, 2-F-C_6H_4, 4-MeO-C_6H_4, Ph, 4-F-C_6H_4, 4-NO_2-C_6H_4, 4-F-C_6H_4, 4-CF_3-C_6H_4, 2-thiophenyl, 2-pyridyl, cyclopropyl, 4-EtO-C_6H_4, 4-CO_2Et-C_6H_4
R^3 = Ph, 2-Me-C_6H_4, 4-MeO-C_6H_4, H, 4-Br-C_6H_4, 2-Cl-C_6H_4

Scheme 16. Formation of 1,2,4-triazol-3-imines **19**

3. CYCLOADDITION REACTIONS LEADING TO FORMATION OF FUSED DERIVATIVES OF 1,2,4-TRIAZOLE

An efficient KI/TBHP-promoted [3+2] cycloaddition of pyrrolo[1,2-*a*]quinoxaline and *N*-tosylhydrazones was described in the source.[37] A series of diversified fused [1,2,4]triazolo[3,4-*c*]quinoxalines **20** were obtained in moderate to good yields with wide functional group tolerance. This reaction can be performed on a gram-scale synthesis, even by one-pot fashion. The electronic effects of the substituents in the phenyl ring had no significant influence on the reactivity. It should be noted that the Cl, Br, and I substituents in the phenyl ring were well tolerated, which can facilitate further modifications at the halogenated positions. However, the 2-methyl substituted *N*-tosylhydrazones exhibited lower reactivity due to steric hindrance, and the product **20** was obtained in low yield. Heterocyclic *N*-tosylhydrazones including 2-pyridyl, 3-thienyl, and 2-furyl groups worked well in this reaction, affording products **20** in 51-63% yields. The reaction was performed in a Schlenk tube which was filled with pyrrolo[1,2-*a*]quinoxaline, *N*-tosylhydrazone, KI, TBHP and DCM; the reaction mixture was stirred at

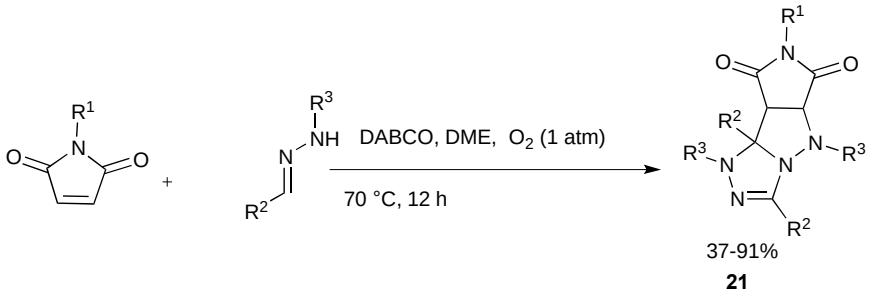
room temperature for 24 h (Scheme 17). The target compounds **20** were obtained in 35-80% yields after purifying.



R = 4-$NO_2C_6H_4$, 4-BrC_6H_4, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-NCC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-$CF_3C_6H_4$, 2-MeC_6H_4, cyclohexyl, 2-pyridyl, 2-furyl, 3-thiophenyl

Scheme 17. Formation of [1,2,4]triazolo[3,4-*c*]quinoxalines **20**

A DABCO-catalyzed double cascade cycloaddition reaction of diverse maleimides with bisarylhydrazones has been developed for the synthesis of a variety of synthetically challenging pyrazolo[5,1-*c*][1,2,4]triazole derivatives **21**.[38] Dioxygen gas is employed as the sole oxidant in this transformation. The last proceeds with high step- and atom-efficiency and shows a broad substrate scope and functional group tolerance. The experiment began with adding of maleimides, bisarylhydrazones and DABCO to an oven-dried Schlenk tube with a magnetic stir bar. Then DME as the solvent was added to the reaction system via syringe. The tube was sealed with a Teflon-coated cap and the resulting mixture was stirred at 70 °C for 12 h (Scheme 18). The combined organic phases were concentrated and the residue was purified by column chromatography on silica gel to give product **21**.

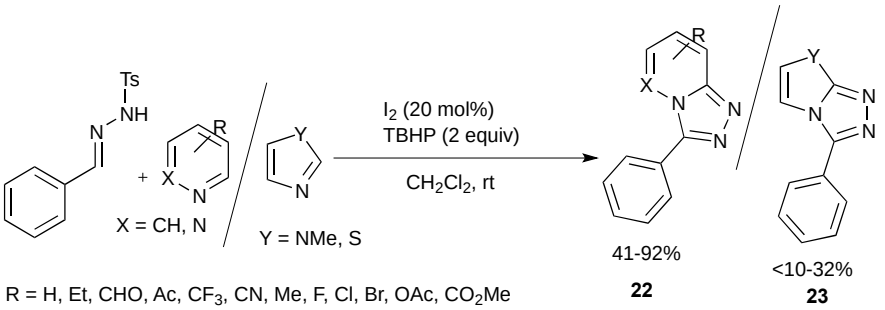


R^1 = Me, Ph, Bn, H, Cy
R^2 = Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-$(CO_2Me)C_6H_4$, 4-$CF_3C_6H_4$, 3-NCC_6H_4, 2-ClC_6H_4, 4-FC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 4-$TsOC_6H_4$, 4-$BinPC_6H_4$
R^3 = Ph, 3-ClC_6H_4, 4-MeC_6H_4, 4-$CF_3C_6H_4$

Scheme 18. Formation of pyrazolo[5,1-*c*][1,2,4]triazole derivatives **21**

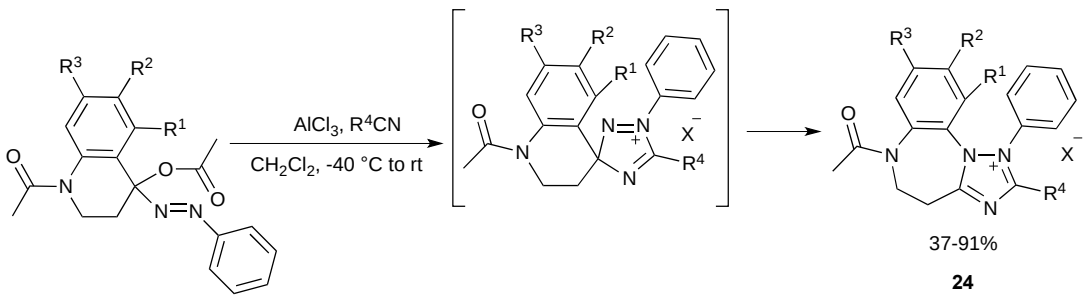
I_2-TBHP-catalyzed azomethine imine generation and subsequent regioselective 1,3-dipolar cycloaddition with aromatic *N*-heterocycles were developed to afford various 4,3-fused 1,2,4-triazoles **22** and **23** in moderate to excellent yields.[39] The reaction proceeded under mild and metal-free conditions using readily available starting materials and gave high yields with wonderful regioselectivity and wide functional

group tolerance, which clearly demonstrates the unique reactivity of the I_2-TBHP system. After a thorough optimization of the reaction conditions, the optimized catalytic system was established as: azomethine imine (1 equiv), corresponding *N*-heterocycle (2 equiv), I_2 (20 mol%), *tert*-butyl hydroperoxide (2 equiv) in CH_2Cl_2 at room temperature. The desired products **22**,**23** were obtained with complete regioselectivity, as shown in Scheme 19.



Scheme 19. Formation of 4,3-fused 1,2,4-triazoles **22** and **23**

Two new series of tricyclic heterocycles, namely 5,6-dihydro-4*H*-benzo[*b*][1,2,4]triazolo[1,5-*d*][1,4]diazepinium salts **24** were synthesized from 4-acetoxy-1-acetyl-4-phenylazo-1,2,3,4-tetrahydroquinolines and nitriles in the presence of aluminium chloride by the [3+2]-cycloaddition reaction of the *in situ* generated azocarbenium intermediates followed by a ring-expansion rearrangement.[40] The phenyl substituent in the initially formed *spiro*-triazolium adducts, which has a strong proclivity for ring expansion to occur, underwent a [1,2]-migration from C(3) to the electron-deficient N(2) in the rearrangement reaction. This led to the ring expansion from 6-membered piperidine to 7-membered diazepine furnishing the tricyclic 1,2,4-triazole-fused 1,4-benzodiazepines. It is noteworthy that the intermediate products bear a diazenium function where the electron-deficient N(2) displayed the feature of a latent nitrenium ion. The subsequent [1,2]-shift after cationic Huisgen-type cycloaddition occurs with complete regioselectivity to N(2) not to N(4).

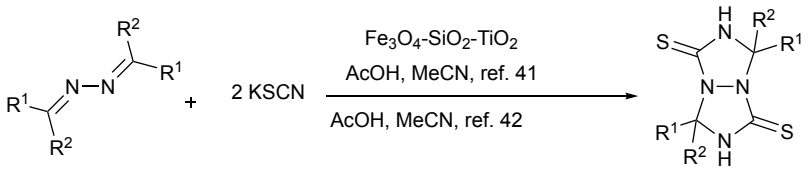


R^1 = H, Me
R^2 = H, Me, OMe, F, Cl, CF_3
R^3 = H, Me
R^4 = Me, cyclopropyl, CH_2Cl, Bn, Ph, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 3-pyridyl
X = Cl, picrate

Scheme 20. Formation of 5,6-dihydro-4*H*-benzo[*b*][1,2,4]triazolo[1,5-*d*][1,4]diazepinium salts **24**

In 2015, Safari and Javadian[41] described the synthesis of tetrahydro[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1,5-dithiones **25** via condensation of different aldazine derivatives with potassium isothiocyanate using Fe_3O_4-SiO_2-TiO_2 composite nanoparticles as a magnetic nanocatalyst (Scheme 21). The reaction indicated a lot of significant advantages in the presence of recent magnetic catalyst – such as: eco-friendly and recyclable catalyst, excellent product yields, low reaction times and simplicity of work-up. Noteworthy that the nanocatalyst was recycled for up to 6 cycles with minimal loss in catalytic activity.

The same group of researchers[42] one year later have reported a novel and highly efficient procedure for the synthesis of perhydrotriazolotriazoledithions **25** from two successive 1,3-dipolar cycloadditions under ultrasound irradiation. Aromatic 2,3-diazabuta-1,3-diene ligands with thiocyanates in glacial AcOH produced the corresponding perhydro[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1,5-dithiones **25** via criss-cross cycloaddition reactions under ultrasound irradiation. The major advantages of the reported synthesis are its selectivity, operational simplicity, extremely mild reaction conditions, short reaction times, and excellent yields. The experimental procedure for this process is remarkably simple and requires no toxic organic solvents. The reactions were carried out at room temperature for 10–35 min by taking a 1:2 mol ratio mixture of benzaldazine derivatives and potassium isothiocyanate, using glacial AcOH as solvent at 24 kHz under sonication (Scheme 21). It was found that benzaldazine bearing *ortho*-substituent slightly affords lower yield than benzaldazines bearing *meta*- or *para*-substituents. This is possibly due to the steric effect. There is more steric hindrance for the 2-substituted benzaldazine on the product formation than the 3- or 4-substituted benzaldazines. In the case of aldazine derivatives with a hydroxy group at the second position, the desired products **25** were not synthesized. This can be reasoned by the tautomeric phenomena of these compounds.

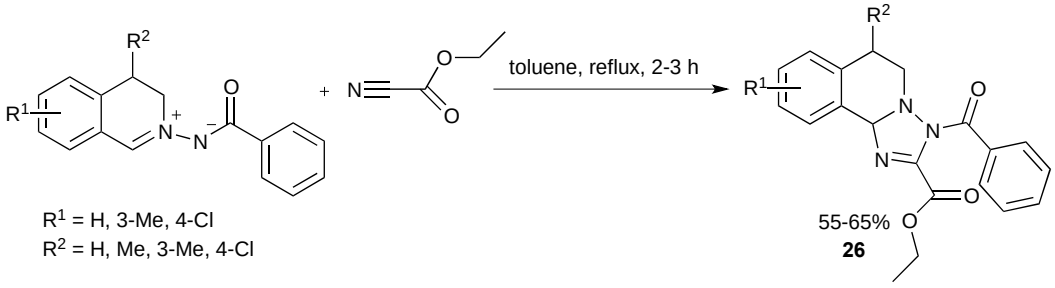


R^1 = Ph, 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-HO-C_6H_4, 2-HO-C_6H_4, 3-HO-4-MeO-C_6H_3, 2-HO-4-MeC_6H_3
R^2 = H, Me

Scheme 21. Formation of perhydro[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1,5-dithiones **25**

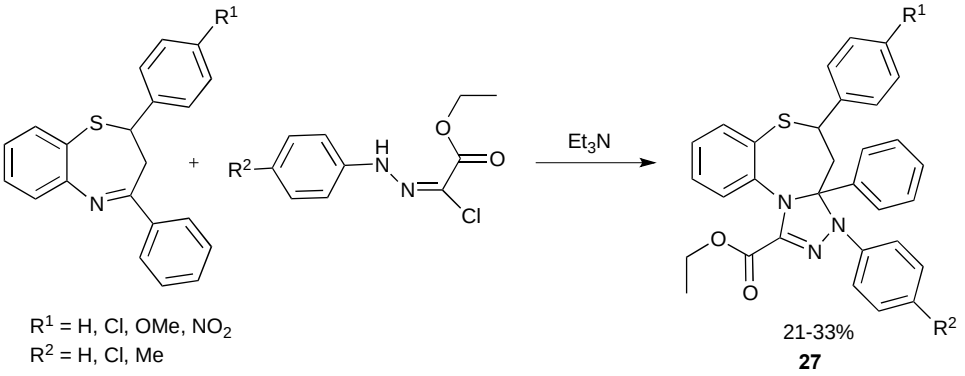
A series of novel 1,2,4-triazoloisoquinoline derivatives **26** were synthesized starting from 2-phenylethan-1-ol derivative in a 7 step synthetic sequence.[43] The key step in the scheme involves 1,3-dipolar [3+2] cycloaddition of azomethine imine and ethyl cyanoformate as unknown reaction protocol. Swapnaja and co-workers demonstrated the hydrolysis of both ester and benzoyl group in a

single step and the corresponding carboxylic acid derivatives were coupled with various amines to generate unknown 1,2,4-triazoloisoquinoline derivatives **26**. The reaction was executed via refluxing for 2-3 h with the obtaining of target compounds **26** in 55-65% yields (Scheme 22).



Scheme 22. Formation of 1, 2, 4-triazoloisoquinoline derivatives **26**

Reaction of 1,5-benzothiazepines with the (phenylhydrazino)chloromethylenecarboxylates in the presence of Et_3N led to a series of new [1,2,4]triazolo[5,4-*d*][1,5]benzothiazepine derivatives **27**.[44] This 1,3-dipolar cycloaddition reaction was provided via following procedure: to a solution of 1,5-benzothiazepine derivatives and the (phenylhydrazino)chloromethylenecarboxylates in CH_2Cl_2, a solution of triethylamine in the same solvent was added. The reaction mixture was kept under stirring at room temperature for 3 days (Scheme 23).



Scheme 23. Formation of [1,2,4]triazolo[5,4-d][1,5]benzothiazepine derivatives **27**

CONCLUSION

This review article covers the sources published in the past decade concerning on cycloaddition reactions which lead to formation of 1,2,4-triazole ring and its fused derivatives. In should be noted that in the synthesis of polisubstituted 1,2,4-triazoles the most convenient starting materials are hydrazonoyl halides or diazonium salts, while the reactions' conditions are very diverse in the used catalysts and synthetic perticularities. The synthetic approaches for the obtaining of fused 1,2,4-triazole derivatives are much more various in term of used starting materials as well as reaction conditions. It can be summarized that

cycloaddition process, mostly [3+2], is an useful method for construction various polisubstituted both functionalized 1,2,4-triazoles and fused derivatives.

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