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## Recent advances in the chemistry of 1,2,4-triazoles: Synthesis, reactivity and biological activities

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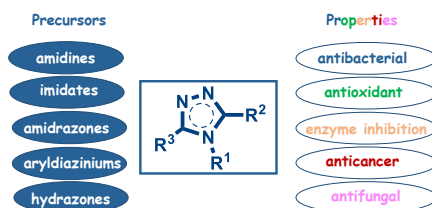
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## Graphical Abstract

### Recent Advances in the Chemistry of 1,2,4-Triazoles: Synthesis, Reactivity and Biological Activities

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# Recent Advances in the Chemistry of 1,2,4-Triazoles: Synthesis, Reactivity and Biological Activities

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## ABSTRACT

1,2,4-Triazoles are important heterocyclic motifs that are widely found in molecular architectures with medicinal and pharmaceutical properties. Considering the importance of these scaffolds, many works have been published over the last few decades. This review provides a focus on the synthetic approaches towards 1,2,4-triazole derivatives from common precursors such as amidines, imidates, amidrazones, aryldiazoniums and hydrazones over the last decade. This review also aims to provide an overview of triazole derivatives biological properties within the last two years.

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4. Conclusion
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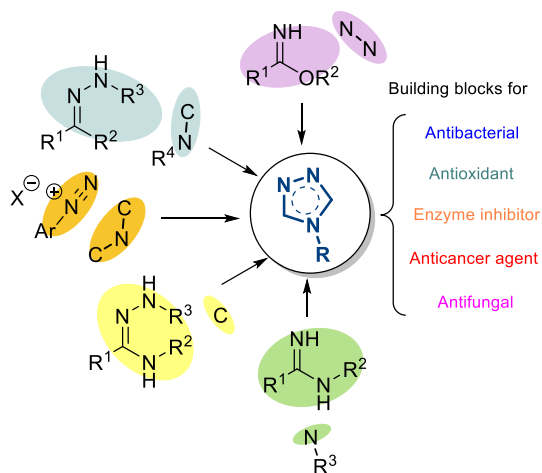
## 1. Introduction

Triazoles are part of a family of five membered heterocycles that has attracted a sustainable and increasing interest from the scientific community, notably due to their wide applications in pharmaceutical,<sup>1</sup> agricultural<sup>2</sup> and material sciences fields.<sup>3</sup> Among them, the 1,2,4-triazoles result from a precise arrangement of the three nitrogen atoms and the two carbon atoms which confer unique properties combining different weak interactions, a characteristic basicity and several coordination modes.<sup>1, 2</sup> 1,2,4-Triazoles are key scaffold in a large number of molecular architectures that display antibacterial, antifungal, antitubercular, antioxidant, antitumor, analgesic, anti-inflammatory or pesticidal activities.<sup>3-12</sup> The ability to install various substituents on all the nitrogen and carbon atoms of the skeleton is therefore of crucial importance to modulate these properties and contributes to the use of triazoles for a broad panel of applications. In this context, the scientific community has

competed creatively to develop strategies for the construction of triazoles bearing valuable substituents. The purpose of this review is first to provide an overview of triazole platform construction methods from the last decade. This first part is organized in several sections according to the nature and combination of 1, 2, 3, or 4 atom-based fragments, used to elaborate the triazole (figure 1). Second, we will focus on the most recent uses of triazole building blocks towards biological activities such as antibacterials, antioxidants, anticancer agents, antifungals and enzyme inhibitors.

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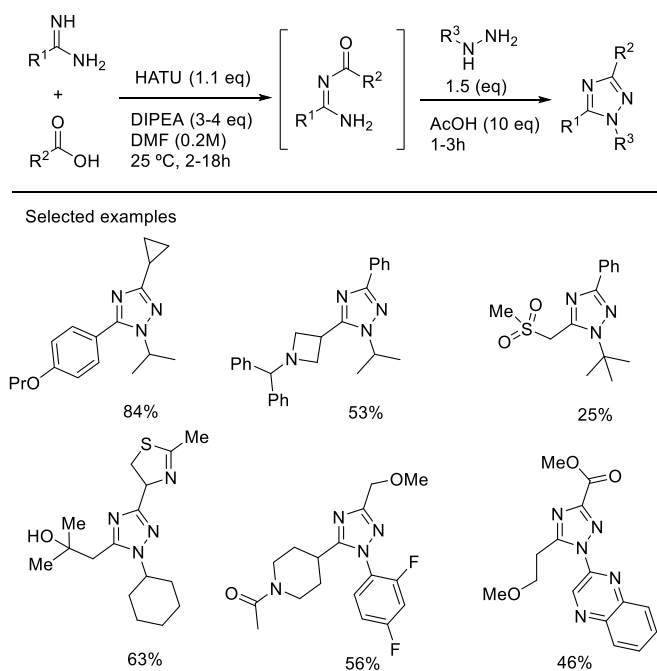
**Fig 1.** Strategies towards the construction of 1,2,4-triazoles.

## 2. Synthesis of 1,2,4-triazoles

### a. From Amidines

Taking advantage of the reactivity of their nucleophilic nitrogen atoms, amidines were widely used as, organo-catalysts, ligands and as key precursor to form nitrogen-carbon bond.<sup>13</sup> In this section we report the use of amidines as starting material in the synthesis of 1,2,4-triazoles.

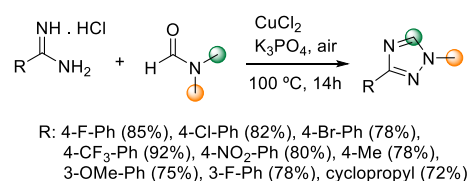
**Castanedo, Staben** *et al.*<sup>14</sup> developed a general one-pot two steps method for the preparation of 1,3,5-trisubstituted 1,2,4-triazoles. The sequence involves first the *in-situ* formation of an acylamidine from carboxylic acids and amidines. The acylamidine reacts further with monosubstituted hydrazines and **undergoes** cyclization towards trisubstituted triazoles (Scheme 1). As stated by the authors the process is highly regioselective, displays a good function group tolerance and allows a rapid access to a wide chemical diversity at the 1,2,4-triazole ring.



**Scheme 1.** One-pot synthesis of 1,3,5-trisubstituted 1,2,4-triazoles.

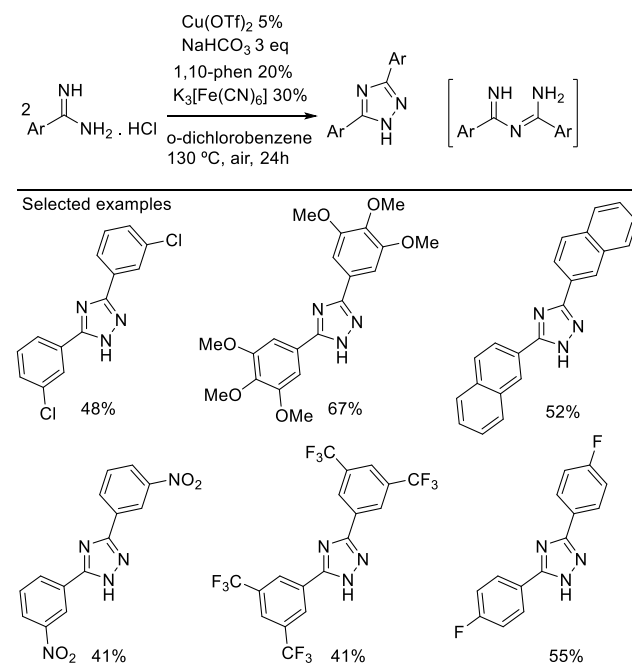
Copper-catalyzed construction of 1,2,4-triazole skeletons from amidines as starting materials has attracted considerable interest. Jiang *et al.*<sup>15</sup> described an efficient  $\text{CuCl}_2$  promoted construction of 1,3-disubstituted 1,2,4-triazoles using  $\text{K}_3\text{PO}_4$  as the base and air as the oxidant from amidines and DMF (Scheme 2). The presence of a stoichiometric amount of  $\text{CuCl}_2$  and DMF are

mandatory to the preparation of triazoles in high yield. Indeed, both the nitrogen atom and methyl groups of DMF were integrated into the final triazoles. The reaction sequence appears to be very efficient for amidines substituted by variously functionalized aromatic fragments (fluoro, bromo, methyl, methoxy and trifluoromethyl).



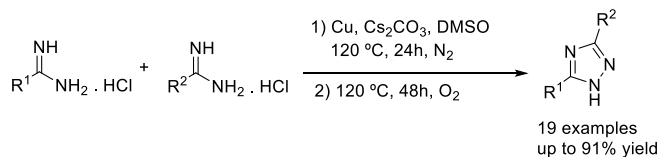
**Scheme 2.** Synthesis of 1,2,4-triazoles from amidines and DMF.

$\text{Cu}(\text{OTf})_2$ -catalyzed reaction between two amidines to prepare 3,5-diaryl-1,2,4-triazoles was reported by Beifuss *et al.*<sup>16</sup> The method is performed in the presence  $\text{NaHCO}_3$  as the base, 1,10-phenanthroline (1,10-phen) as an additive and the combination  $\text{K}_3[\text{Fe}(\text{CN})_6]/\text{O}_2$  as a suitable oxidant (Scheme 3). The same catalytic system has been used successfully to access the 3,5-diaryl-1,2,4-triazoles by reaction between two imidates and an ammonium source.

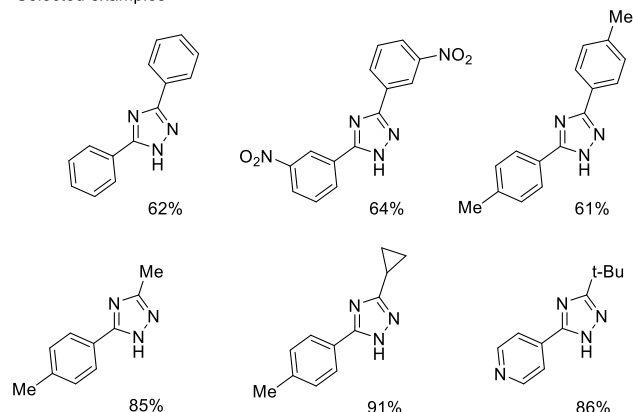


**Scheme 3.** Synthesis of 3,5-diaryl-1,2,4-triazoles from amidine hydrochlorides.

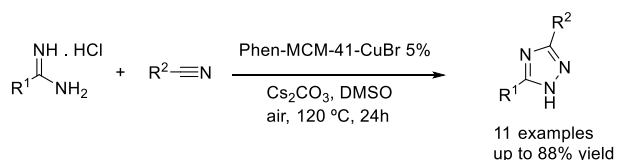
If the former methodology was dedicated to the formation of “symmetrical” triazoles bearing identical substituents at both C atoms from the same amidine, Fu *et al.*<sup>17</sup> described a similar process that give an access to “unsymmetrical” triazoles (Scheme 4). This method is based on a coupling between two different amidines followed by an intramolecular aerobic oxidative dehydrogenation. If the reaction looks very similar, homo coupling of one amidine is prevented by sequential addition over the reaction course. In this practical process, Cu powder exhibited the highest activity.



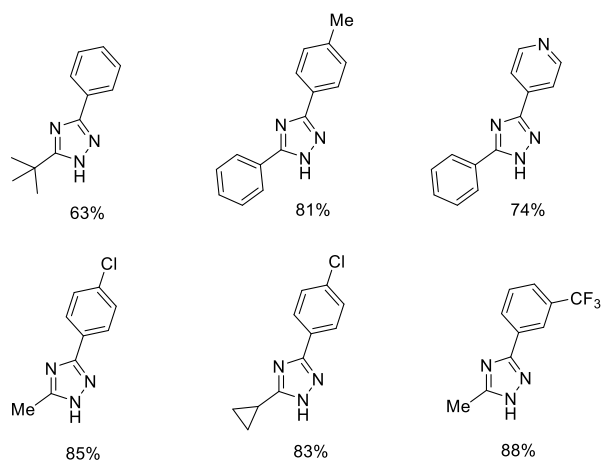
Selected examples

**Scheme 4.** Synthesis of 1,2,4-triazoles using amidines.

As recently shown by Cai *et al.*<sup>18</sup> access to 1H-1,2,4-triazoles can also be obtained from amidines and nitriles through a cascade addition-oxidative cyclization. The reaction is catalyzed by 1,10-phenanthroline-functionalized MCM-41-supported copper(I) complex [Phen-MCM-41-CuBr] and requires the presence of O<sub>2</sub> as the oxidant to afford the heterocycles in good yields (Scheme 5). The transformation appears quite general, as primary, secondary, tertiary alkyl- and aryl-amidines could be successfully employed. It was also demonstrated that the catalyst remained stable during the process and it could be easily recovered and recycled up to eight times. Interestingly, the same catalytic system could be used to prepare 1,2,4-triazolo[1,5-a]pyridine derivatives from 2-aminopyridines and nitriles.

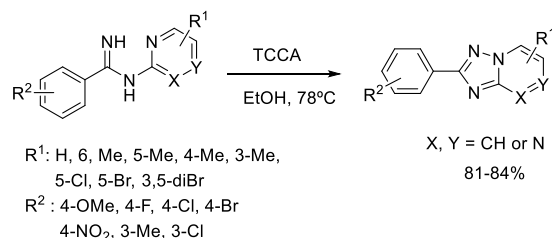


Selected examples

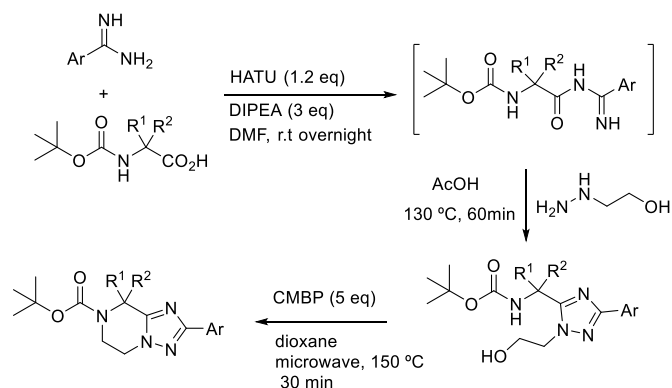
**Scheme 5.** Copper catalyzed cascade addition-oxidative cyclization of amidines with nitriles.

1,2,4-Triazole-fused heterocycles have become popular mainly due to the biological activities displayed by such compounds. Selected examples and results will be detailed in section 3 of this review. Within this series of fused heterocycles, 1,2,4-triazolopyridines recently attracted attention. A characteristic feature of these skeleton lies in the fact one of the

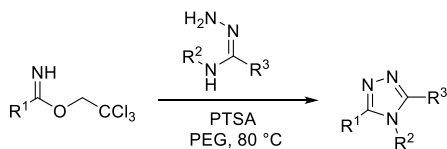
three nitrogen atoms is **common** to both the triazole and the pyridine rings. Such targets can be readily obtained from 2-hydrazinopyridines and various carboxaldehydes under mild electrolytic conditions.<sup>19</sup> An elegant alternative was recently developed by Bhatt *et al.*<sup>20</sup> involving *N*-heteroaryl benzamidines as starting material and direct metal-free oxidative N–N bond formation promoted by trichloroisocyanuric acid (TCCA) (Scheme 6). This high yielding method takes advantage on a high functional group tolerance and a possible extension to pyrimidine substrates.

**Scheme 6.** Synthesis of various 1,5-fused 1,2,4-triazoles.

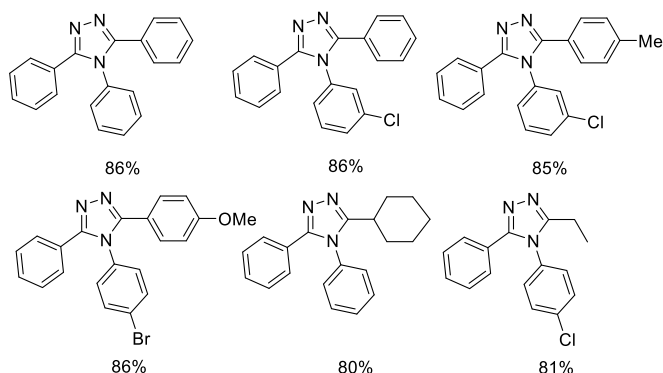
The preparation of 1,5-fused 1,2,4-triazoles from amidines was also reported by Lorthioir *et al.*<sup>21</sup> In fact, they firstly prepared 1,3,5-substituted 1,2,4-triazoles from amidines, amino acids and (2-hydroxyethyl)hydrazine. In a second step, the use of Tsunoda reagent led successfully to the desired triazolopiperazine scaffolds (Scheme 7). Starting from  $\alpha,\alpha'$ -disubstituted amino acids, this protocol provides a convenient access to chiral and spirocyclic systems. Two triazolopiperazines with methyl group as substituent at position 5 and 6 were also isolated using  $\alpha$ - and  $\beta$ -methyl hydrazino alcohols.

**Scheme 7.** Synthesis of triazolopiperazines.**b. From imidates**

Imidates represent useful precursors of triazoles, which have been widely used in this context over the last years. In 2014, Vidavalur *et al.*<sup>22</sup> showed that the reaction between 2,2,2-trichloroethyl imidates and amidrazones efficiently afford 3,4,5-trisubstituted 1,2,4-triazoles. The reaction proceeds in polyethylene glycol (PEG) and uses *p*-Toluenesulfonic acid (PTSA) as catalyst leading to the corresponding 1,2,4-triazoles in excellent yields (Scheme 8). This methodology was mainly developed for aromatic imidates, but revealed a high functional group tolerance.

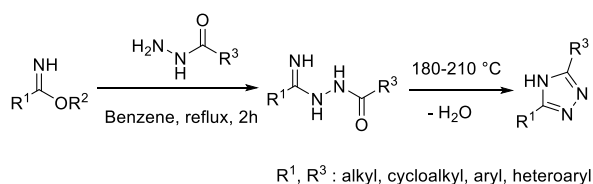


Selected examples



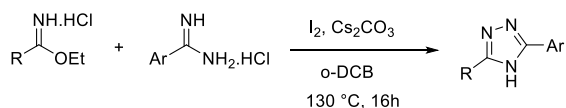
**Scheme 8.** Synthesis of various 3,4,5-trisubstituted 1,2,4-triazoles from 2,2,2-trichloroethyl imidates and amidrazones.

Kutkin *et al.*<sup>23</sup> described the synthesis of 1,2,4-triazole derivatives from imidates in 2 steps. The reaction sequence begins by the condensation of imidates with carboxylic acid hydrazides to form *N'*-(1-iminoalkyl)hydrazides. The latter was then heated under reduced pressure (10–20 mm) to afford the corresponding 3,5-disubstituted 1,2,4-triazoles (Scheme 9).

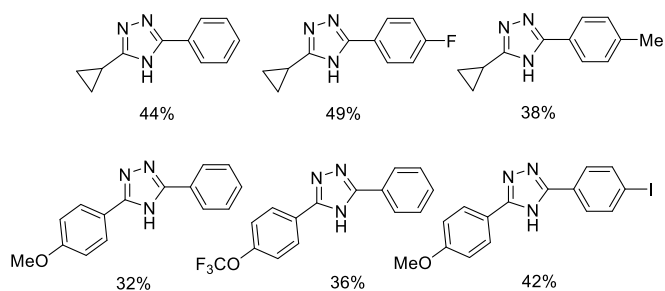


**Scheme 9.** Reaction sequence for the preparation of 3,5-disubstituted 1,2,4-triazoles.

Kalita, Ahamed *et al.*<sup>24</sup> reported the synthesis of 3,5-disubstituted-1*H*-1,2,4-triazole derivatives from a combination of imidates and amidines. This one-pot reaction is mediated by  $I_2/Cs_2CO_3$  in ortho dichlorobenzene (*o*-DCB) and involves readily available imidates and amidines as starting materials (Scheme 10). In limited cases, the formation of the expected triazoles is accompanied by a minor amount (up to 10%) of the symmetrical triazole arising from the homocondensation of two molecules of amidine.

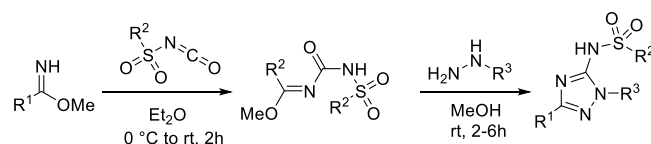


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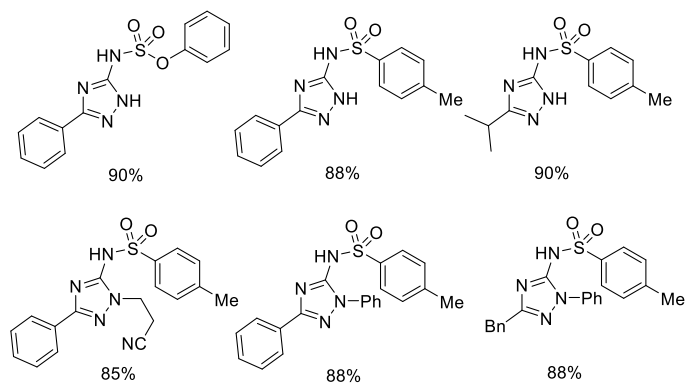


**Scheme 10.** Synthesis of unsymmetrical 3,5-disubstituted 1,2,4-triazoles from imidates and amidines.

For several years, Balti *et al.*<sup>25</sup> developed complementary methods for the synthesis of polysubstituted 1,2,4-triazoles from *N*-functionalized imidates and hydrazine derivatives. For example, the preparation of 1,3,5-trisubstituted 1,2,4-triazole derivatives was set in two steps involving the formation of sulfonamide imidate as the key intermediate (Scheme 11). Indeed, imidates were first converted into *N*-sulfonamide imidates by reaction with sulfonyl isocyanates. As the second step, the treatment of the latter imidates with hydrazine derivatives in methanol afforded the desired 1,2,4-triazoles in good yields.

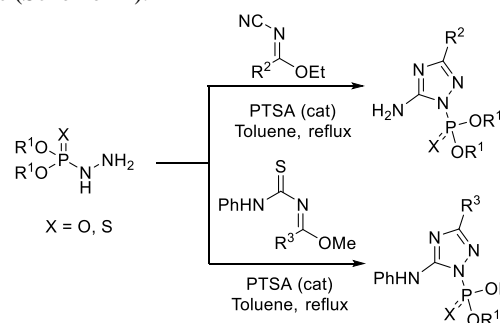


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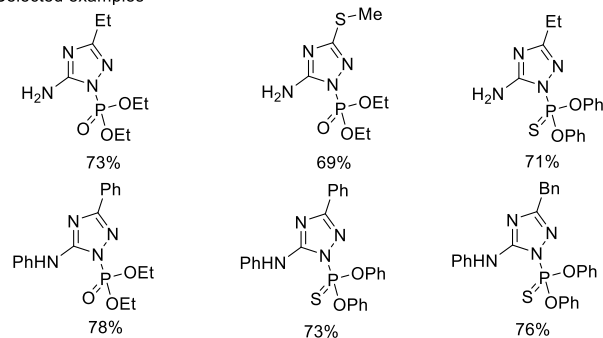


**Scheme 11.** Synthesis of 1,2,4-triazole-sulfonamides.

One year later, the same group contributed to this area in developing an efficient approach towards 1-(thio)phosphonated 5-amino-1,2,4-triazoles from *N*-functionalized imidates.<sup>26</sup> Indeed, heating phosphorylated hydrazines with *N*-cyanoimidates and *N*-carbothioamidoimidates in toluene in the presence of a catalytic amount of PTSA led to 5-amino-1-(thio)phosphonyl-1,2,4-triazole and 5-(*N*-phenyl)amino-1-(thio)phos-phenyl-1,2,4-triazole derivatives respectively in good yields (Scheme 12).

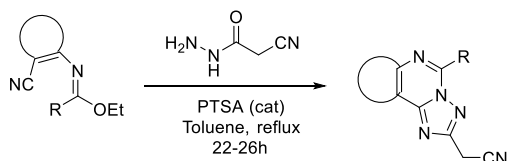


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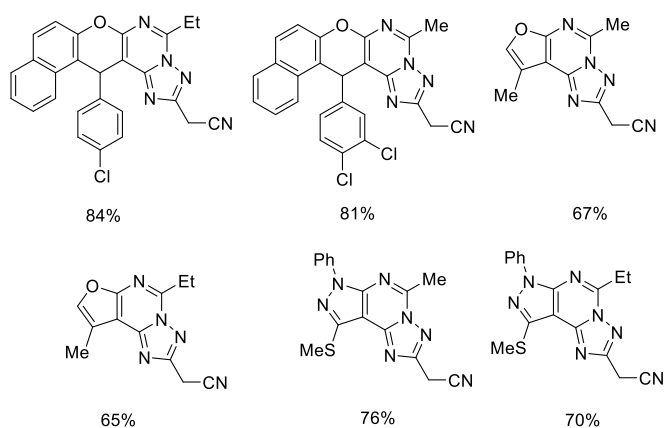


**Scheme 12.** Synthesis of 1-(thio)phosphonated 5-amino-1,2,4-triazole derivatives.

Using the same reaction conditions, [Jabli et al.](#)<sup>27</sup> extended this methodology and reported the synthesis of 1,2,4-triazolopyrimidine derivatives from cyano-imidates and cyanoacetic acid hydrazide (Scheme 13). Antibacterial evaluation showed that all synthesized compounds exhibit a moderate to good activity against four types of bacteria using disc diffusion method.

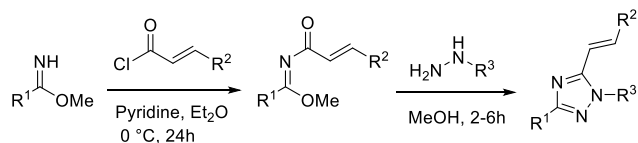


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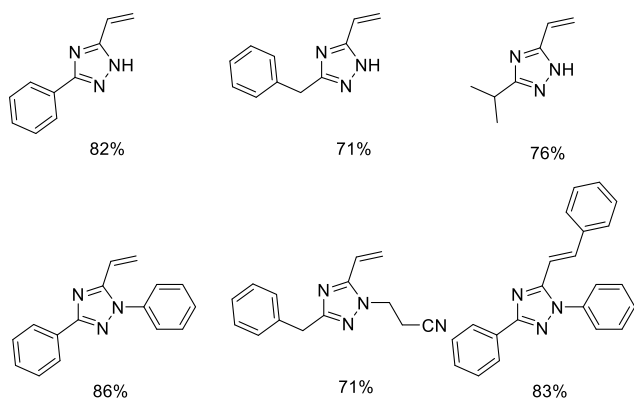


**Scheme 13.** Preparation of 1,2,4-triazolopyrimidine compounds from cyano-imidates and cyanoacetic acid hydrazide.

In 2018, [Prim et al](#) turned their attention to the synthesis and reactivity of vinylimidates as precursors of functionalized triazoles. They demonstrated that key vinylimidates represent helpful advanced starting material for the preparation of 5-vinyl-1,2,4-triazole derivatives.<sup>28</sup> This method allowed the installation of a wide array of substituents at the N(1), C(3) and C(5) positions of the 1,2,4-triazole in good yields (Scheme 14). Theoretical calculations and NMR experiments reveal the selectivity of this reaction towards 5-vinyl-1,2,4-triazoles precluding the formation of potential five- and seven-membered side-products.



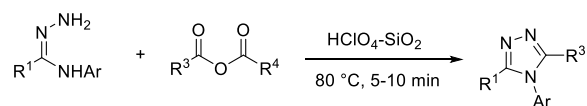
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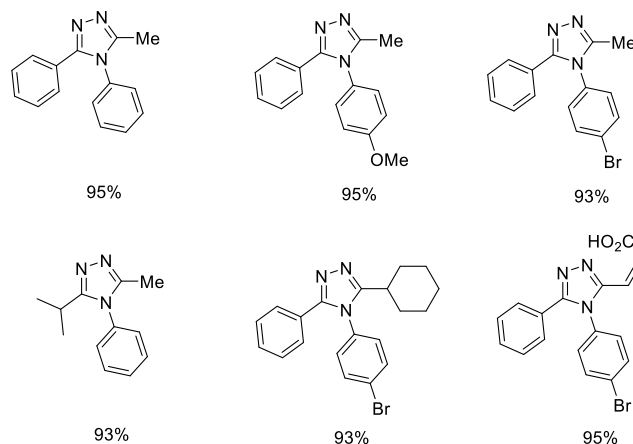
**Scheme 14.** Synthesis of variously substituted vinyl 1,2,4-triazoles.

### c. From amidrazones

Amidrazones differ from amidines by the presence of an additional nitrogen atom. In this section all nitrogen atoms of the triazole arise from the same substrate. A convenient protocol for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from amidrazones involves anhydrides as reactants. As reported by [Vidavalur et al.](#)<sup>29</sup> the 1,2,4-triazole derivatives can be prepared in moderate to good yields using  $\text{HClO}_4\text{-SiO}_2$  as the catalyst at  $80^\circ\text{C}$  under solvent free conditions (Scheme 15). As advantages, a wide range of substituents on both amidrazones and anhydrides is well tolerated under the optimized conditions and the  $\text{HClO}_4\text{-SiO}_2$  catalyst can be recycled as least three consecutive times.

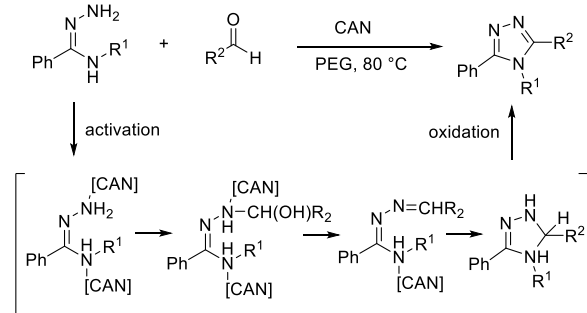


Selected examples



**Scheme 15.** Synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from amidrazones and anhydrides.

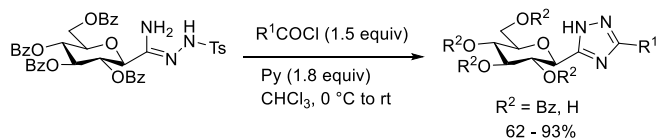
A similar methodology was developed by [Vidavalur et al.](#)<sup>30</sup> involving amidrazones and aldehydes. The synthesis of 3,4,5-trisubstituted 1,2,4-triazoles was promoted by ceric ammonium nitrate (CAN) in polyethylene glycol (Scheme 16). A plausible mechanism described by authors reveals that ceric ammonium nitrate acts as both an oxidant and a Lewis acid and the 1,2,4-triazole skeleton is formed via activation of nitrogen atoms of the amidrazone followed by addition of the benzaldehyde, formation of a bishydrazone intermediate and finally an oxidative cyclization.



**Scheme 16.** Preparation of 3,4,5-trisubstituted 1,2,4-triazoles from amidrazones and aldehydes.

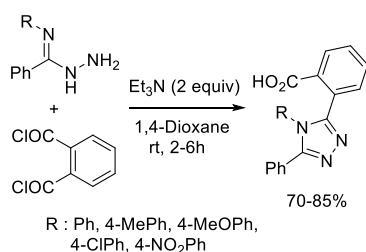


In 2013, Somsák *et al.*<sup>31</sup> reported the synthesis of C-Glucopyranosyl-1,2,4-triazoles from C-Glucosyl tosylamidrazones (Scheme 17). Acylations of the C-Glucosyl tosylamidrazones with aromatic acid chlorides were accompanied by complete *N*-detosylation affording the 3-( $\beta$ -D-Glucopyranosyl)-5-substituted-1,2,4-triazoles in good yields. This series of compounds were evaluated as potent inhibitors of glycogen phosphorylase.



**Scheme 17.** Preparation of C-Glucopyranosyl-1,2,4-triazoles.

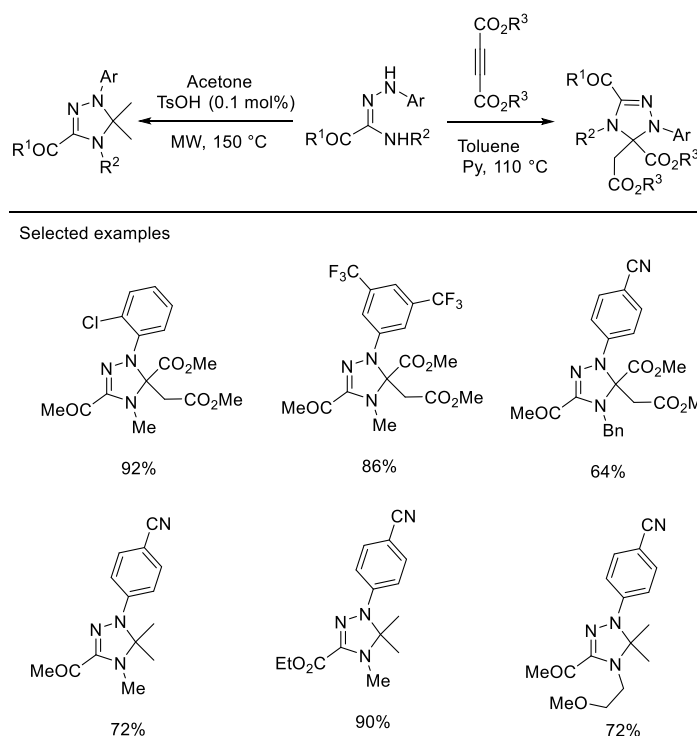
1,2,4-triazole–benzoic acid derivatives can also be obtained from benzamidrazones and phthaloyl chloride in the presence of two equivalents of triethylamine as reported by Aly *et al.*<sup>32</sup> in 2017. Although only described for amidrazones bearing aromatic substituents, the method revealed efficient, can be run at room temperature and yield 1,2,4-triazoles in good yields (Scheme 18). Interestingly, the reaction can be realized in the absence of  $\text{Et}_3\text{N}$ , leading in this case to the corresponding triazolium dihydrochloride salts.



**Scheme 18.** One-pot synthesis of 1,2,4-triazole–benzoic acid derivatives from benzamidrazones.

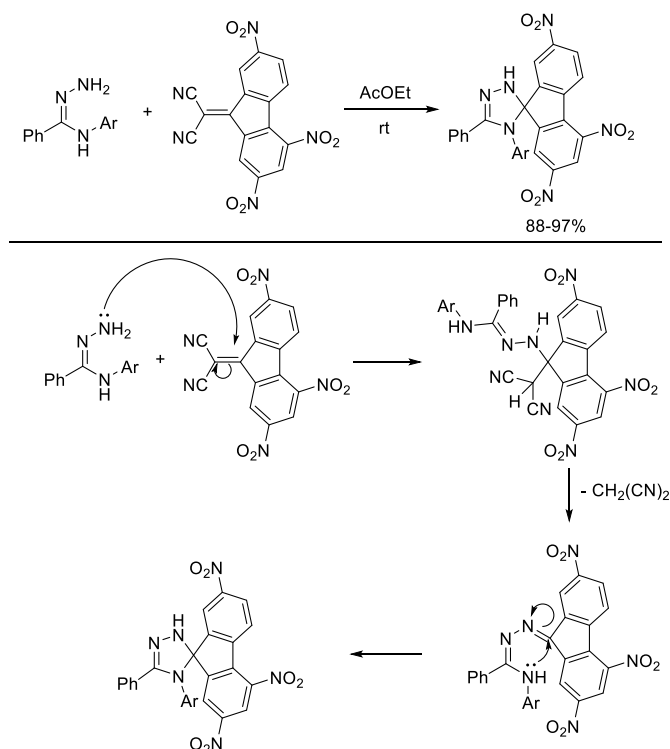
The installation of various substituents on the three accessible sites of triazoles (N1, C3 and C5) is an area of major interest that still remains a challenge. Dihydro triazoles are partially aromatic heterocycles generally discussed with their aromatic counterparts. Thus we have chosen to include in this literature review the most relevant triazole syntheses with a quaternary center in position 5.

In this context, Benassi, Belskaya *et al.*<sup>33</sup> described the synthesis of a series of 4,5-dihydro-1H-1,2,4-triazoles from a variety of amidrazones (Scheme 19). The first family of 1,2,4-triazoles were prepared from amidrazones and dimethyl or diethyl esters in the presence of pyridine in toluene to give the corresponding 2-aryl-4,5-dihydro-1H-1,2,4-triazoles. Amidrazones were then reacted with large excess of acetone in the presence of TSA as a catalyst under microwave irradiation to obtain a family of 5,5-dimethyl-4,5-dihydro-1H-1,2,4-triazoles. Photophysical studies showed that most of synthesized 1,2,4-triazoles displayed emission of blue or yellow-green light and exhibited a medium fluorescence-emitting ability.



**Scheme 19.** Synthesis of 4,5-dihydro-1H-1,2,4-triazole derivatives from amidrazones.

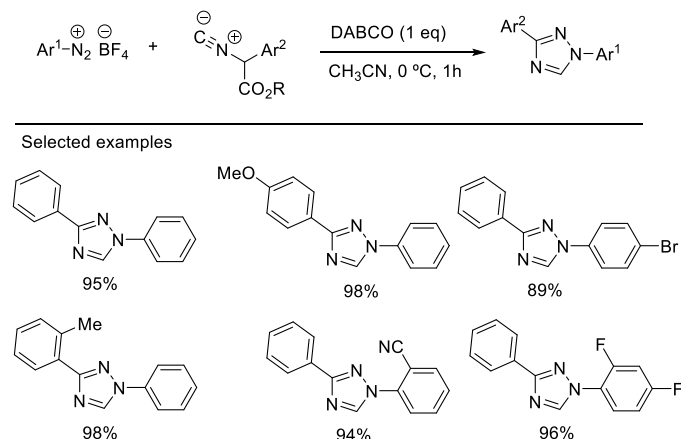
A further example of quaternary center within the triazole scaffold consist in the formation of a spirocyclic derivative. As described by Goma *et al.*<sup>34</sup> the synthesis of novel spiro[fluorene-9,3'-[1,2,4]triazole derivatives can be realized by reaction of benzamidrazones and (2,4,7-trinitro-9H-fluorene-9-ylidene) malononitrile in ethyl acetate at room temperature (Scheme 20). The first step consists in a Michael-type nucleophilic addition of the terminal amino group of the benzamidrazonane to the malononitrile acceptor. Secondly, cyclisation towards the corresponding spirocyclic 1,2,4-triazoles goes through an intramolecular nucleophilic addition of the amino group to the imidic carbon atom.



**Scheme 20.** Preparation of spiro[fluorene-9,3'-[1,2,4]triazoles.

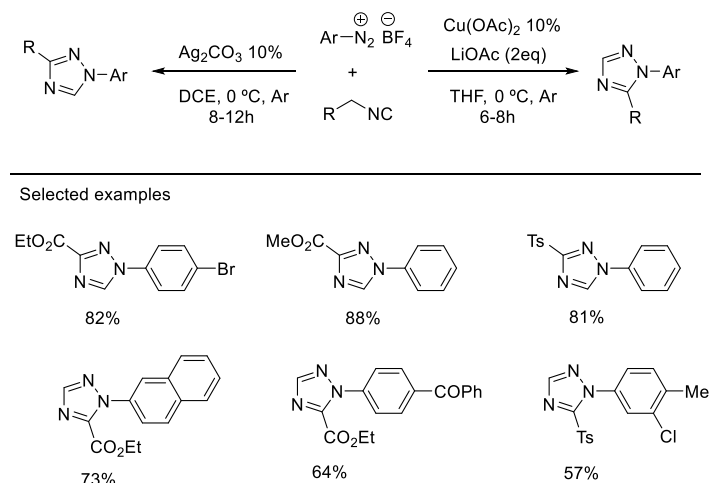
#### d. From aryldiazonium salts

Aryldiazonium salts are readily available, highly reactive intermediates, which were widely used as nitrogen sources for the preparation of large number of heterocycles.<sup>35</sup> **Cheung, Ma *et al.***<sup>36</sup> reported the synthesis of 1,2,4-triazoles by decarboxylative annulation reaction of 2-aryl-2-isocyanoacetates with aryldiazonium salts (Scheme 21). Interestingly, the use of 1,4-diazabicyclo-[2.2.2]octane (DABCO) as a weaker base was particularly indispensable for this metal-free reaction. The regioselectivity of the reaction was ascertained by the X-ray crystallographic analysis of 1,3-diphenyl-1H-1,2,4-triazole.



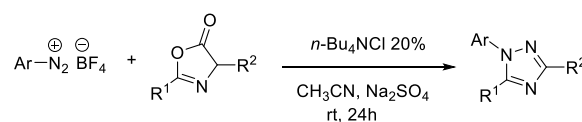
**Scheme 21.** Access to 1,2,4-triazoles via decarboxylative annulation of 2-aryl-2-isocyanoacetates with aryldiazonium salts.

An efficient method for the preparation of 1,3- and 1,5-disubstituted 1,2,4-triazoles was developed by **Fu, Bi *et al.***<sup>37</sup> (Scheme 22). Depending on the nature of catalytic system, the synthesis of triazoles was carried out by [3+2] cycloaddition of isocyanides with aryldiazonium salts. Indeed, the use of Ag(I) catalyst gave selectively 1,3-disubstituted 1,2,4-triazoles, whereas Cu(II) led to 1,5-disubstituted 1,2,4-triazoles. Interestingly both catalytic systems are complementary and afford triazoles substituted with a wide range of functional groups.

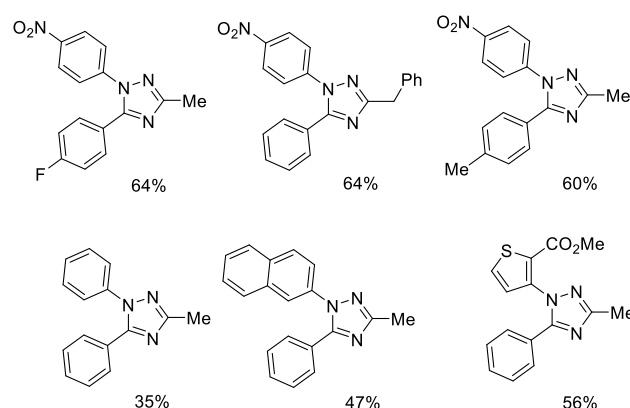


**Scheme 22.** Preparation of 1,3- and 1,5-disubstituted 1,2,4-triazoles from aryldiazonium salts and isocyanides.

Chen *et al.*<sup>38</sup> developed for the first time a metal-free [3+2] cycloaddition/decarboxylation reaction between aryldiazonium salts and azalactones to access 1,3,5-trisubstituted 1,2,4-triazoles (Scheme 23). The optimized reaction conditions involved 20 mol% *n*-Bu<sub>4</sub>NCl, Na<sub>2</sub>SO<sub>4</sub> as drying reagent in acetonitrile at room temperature. *n*-Bu<sub>4</sub>NCl might serve as chlorine source which is assumed to stabilize the intermediate formed in the [3+2] cycloaddition between aryldiazonium and the enol form of azalactone. Then, the intermediate undergoes a ring-opening decarboxylation to give the 1,2,4-triazole targets.

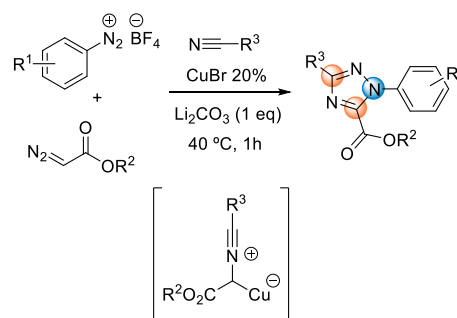


Selected examples



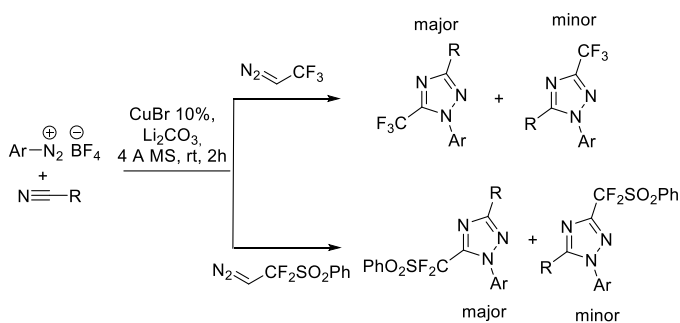
**Scheme 23.** Preparation of 1,2,4-triazoles from aryldiazonium salts and azalactones.

The preparation of polysubstituted triazoles remains a challenge. Indeed, only a few research groups have described the synthesis of fully substituted 1,2,4-triazoles in which the heterocycle is bearing substituents at both carbon atoms and one nitrogen atom. As an example, **Bao, Wan *et al.***<sup>39</sup> have developed a three-component reaction involving diazonium salts, nitriles and diazoacetates accounts for the preparation of a new series of 1,2,4-triazoles (Scheme 24). The reaction is carried out at 40 °C in the presence of CuBr as the catalyst and Li<sub>2</sub>CO<sub>3</sub> as the base. 1,2,4-Triazole were isolated in moderate to good yields using aryldiazonium salts bearing electron-donating groups. In contrast, yields were relatively low when aryldiazonium bearing electron-withdrawing groups were used in this reaction. Based on computational studies and DFT calculations, a plausible mechanism illustrates that CuBr catalysed the formation of a nitrile ylide from diazoacetate and nitrile. The latter undergoes [3+2] cycloaddition with aryldiazonium in the presence of Li<sub>2</sub>CO<sub>3</sub> to afford the 1,2,4-triazole target.



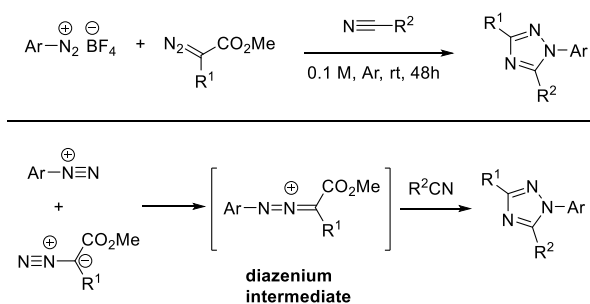
**Scheme 24.** One-pot synthesis of 1,2,4-triazoles.

Using the same catalytic system, **Zhang, Ma *et al.***<sup>40</sup> described the preparation of a series of original difluoro- and trifluoromethylated *N*-Aryl-1,2,4-triazoles from aryldiazonium salts, nitriles and fluorinated diazo reagents (Scheme 25). The reaction is regioselective and fluorinated triazoles were isolated in moderate to good yields. The mechanism is expected to follow similar elementary steps and thus proceed through the formation of a similar nitrile ylide intermediate.



**Scheme 25.** Copper-catalyzed synthesis of fluorinated 1,2,4-triazoles.

As recently shown by **Whang**, Shi *et al.*<sup>41</sup>, reacting aryl diazonium salts, nitriles and diazo reagents in the absence of catalytic system also leads to the formation of 1,2,4-triazoles (Scheme 26). In this case, the key intermediate markedly differs from the aforementioned methods, a diazenium intermediate being formed in the key step. In the presence of the nitrile reagent, the diazenium intermediate undergoes cyclization to afford 1,2,4-triazoles in good yields. Interestingly in the absence of the nitriles derivative the same protocol affords indazole derivatives.



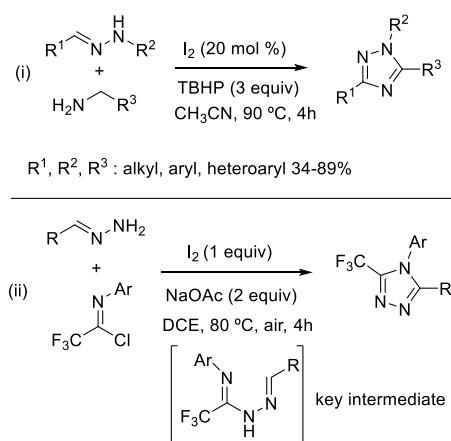
**Scheme 26.** Catalyst-free one-pot synthesis of 1,2,4-triazoles.

### e. From hydrazones

Hydrazones are known precursors of aza-heterocycles. Such compounds are characterized by the presence of highly reactive pair of nitrogen atoms and  $sp^2$  carbon atom. The reaction of hydrazones with various nitrogen atom sources lead to triazoles.

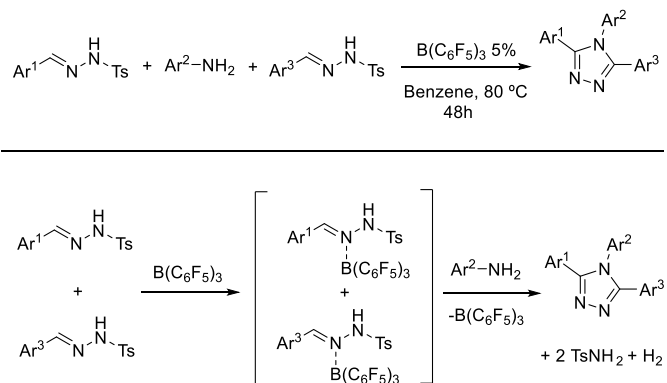
The use of aliphatic amines led to the formation of 1,2,4-triazoles. The approach developed by Chen involves the combination of  $I_2$ /TBHP.<sup>42</sup> Under aerobic oxidative conditions, and iterative TBHP induced radical process followed by dehydrogenative aromatization, hydrazones are readily transformed into trisubstituted triazoles (Scheme 27i). A wide range of functional groups at both the hydrazine and the amine fragments are well tolerated leading to an enhanced molecular diversity.

More recently, the same group reported the synthesis of 5-Trifluoromethyl-1,2,4-triazoles from hydrazones and trifluoroacetimidoyl chlorides under aerobic oxidative conditions (Scheme 27ii).<sup>43</sup> The presence of NaOAc accounts for the formation of key intermediate which is not isolated. Finally, an  $I_2$ -mediated annulation allows a clean formation of C-N bond and cyclisation towards the targets.



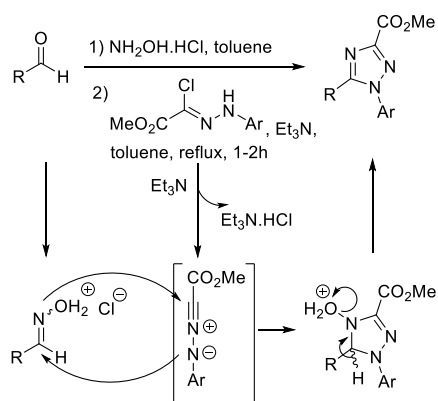
**Scheme 27.**  $I_2$ -catalyzed synthesis of 1,2,4-triazoles from hydrazones.

*N*-Tosylhydrazones also react with aromatic amines to afford triaryl triazoles (Scheme 28). In 2019, **Koley**, Maji *et al.*<sup>44</sup> developed a metal-free catalytic protocol based on a dehydrogenative-cyclization catalyzed by  $B(C_6F_5)_3$ . Mechanistic experiments and DFT calculations suggest that  $B(C_6F_5)_3$  activates the hydrazine moiety for the nucleophilic attack followed by a sequential amination, intramolecular cyclization, and a dehydrogenation step to finally isolate substituted 1,2,4-triazoles.



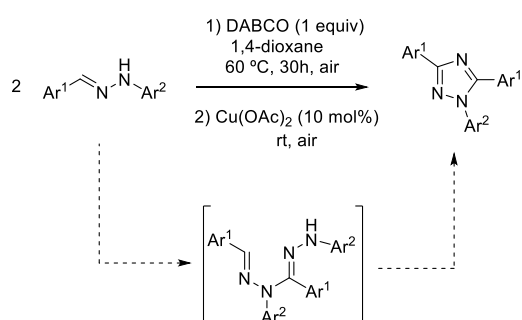
**Scheme 28.** Access to 1,2,4-triazoles from *N*-tosylhydrazones and aromatic amines.

The synthesis of 3,5-disubstituted 1,2,4-triazoles from hydrazonoyl hydrochlorides and aldehydes was reported by Wong *et al.*<sup>45</sup> Hydrazonoyl hydrochlorides was used as 1,3-dipole nitrilimine source in the presence of triethylamine and various substituents on the aromatic ring were suitable for this methodology. In this 'one-pot' protocol, aldehydes are first converted into oxime intermediates by reaction with hydroxylamine. The resulting oxime and hydrazonoyl hydrochlorides undergo then 1,3-dipolar cycloaddition to give 3,5-disubstituted 1,2,4-triazoles in moderate to good yields (Scheme 29).

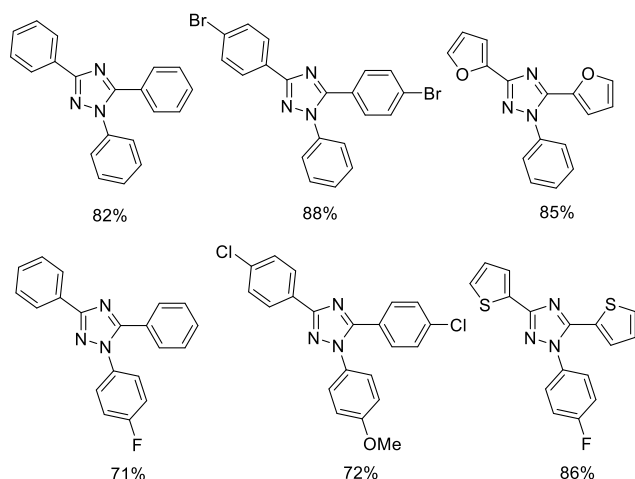


**Scheme 29.** Synthesis of 1,2,4-triazole from hydrazonoyl hydrochlorides and aldehydes.

Bisarylhydrazones have been used as unique precursors of 1,3,5-triaryl-1,2,4-triazoles. The homocondensation of the bisaryldiazene fragments obtained under  $\text{Cu}(\text{OAc})_2$ -catalyzed aerobic oxidative conditions as reported by Punniyamurthy *et al.*<sup>46</sup> (Scheme 30). As stated, the sequence starts with a base mediate the dimerization of bisaryldiazene followed by Lewis acid assisted heterocyclization. It should be mentioned that under a similar Cu-catalyzed process but in the absence of base, 2,4,5-triaryl-1,2,3-triazoles could be obtained from bisarylhydrazones.



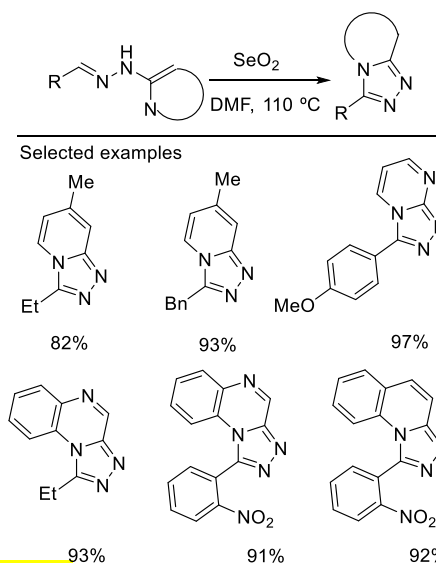
Selected examples



**Scheme 30.** Cu(II)-Catalyzed synthesis of 1,2,4-triazoles from bisarylhydrazones.

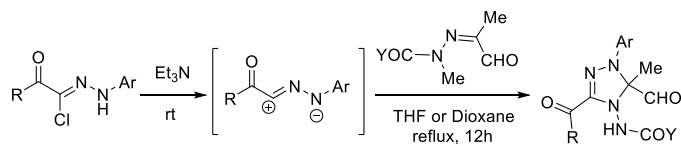
In 2015, Zheng *et al.*<sup>47</sup> developed a synthetic method for the preparation of fused 1,2,4-triazole derivatives via oxidative intramolecular cyclization of heterocyclic hydrazones using selenium dioxide (Scheme 31). The reaction was found to be general, tolerating various aliphatic and aromatic substituents in the substrate. All triazole compounds were tested for their cytotoxic activity against HCT-116, A549 and Colo-205 cell

lines. Two triazole derivatives exhibited significant antiproliferative activity against the three cell lines.

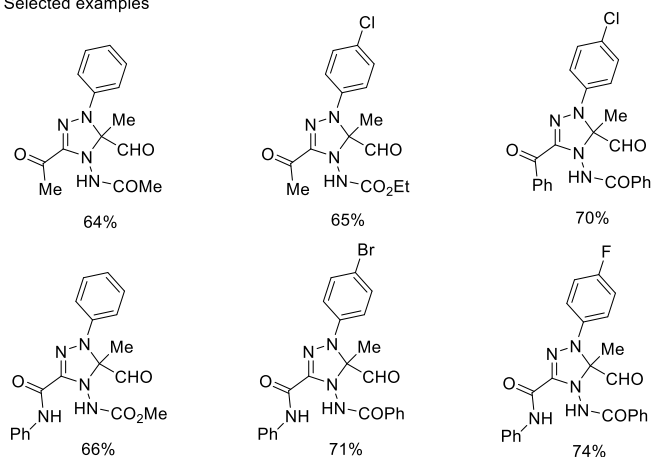


**Scheme 31.**  $\text{SeO}_2$ -mediated transformation of heterocyclic hydrazones into fused 1,2,4-triazoles.

In this section again, access to dihydrotriazoles has been described. A series of 1,3,4,5,5-pentasubstituted-1,2,4-triazoles has been prepared through the 1,3-dipolar cycloaddition of nitrilimines to 2-oxopropanal hydrazones (Scheme 32).<sup>48</sup> The sequence begins with the generation of nitrilimines *in-situ* from hydrazonoyl halides in the presence of trimethylamine. Then hydrazones undergo the 1,3-dipolar cycloaddition leading to the formation of 1,2,4-triazole derivatives. Antimicrobial evaluation of the synthesized compounds shows that they exhibited weak to moderate activity against a variety of bacterial strains.



Selected examples



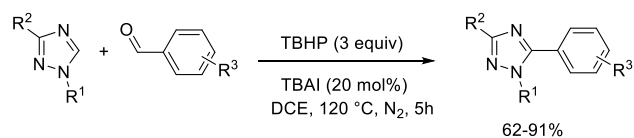
**Scheme 32.** Synthesis of 1,2,4-triazoles from hydrazones and nitrilimines.

### 3. Reactivity and biological activities of 1,2,4-triazoles

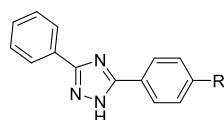
This section summarizes the recent new synthetic approaches, with particular focus on the last two years on 1,2,4-triazoles as building blocks towards the preparation of biologically active compounds. This section illustrates the biological properties of triazoles obtained either by functionalization of the C and N atoms of a preformed heterocycle or by modification on the pendant arms of a heterocycle.

### a. Functionalization of preformed 1,2,4-triazole rings

In 2020, Agisho *et al.*<sup>49</sup> reported the C5-arylation of 1,2,4-triazoles via oxidative decarbonylation of aromatic aldehydes (Scheme 33). Indeed, they developed an efficient method for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles and 3,5-disubstituted-1,2,4-triazoles from 1,3-disubstituted-1,2,4-triazoles and 3-monosubstituted-1,2,4-triazoles respectively using tetrabutylammonium iodide (TBAI) as the catalyst and tert-Butyl hydroperoxide (TBHP) as the oxidant. A range of substituted benzaldehydes with different substitutions were used in this method and 1,2,4-triazole targets were obtained in moderate to excellent yields. Antibacterial evaluation using a disc diffusion method showed that four 3,5-disubstituted 1H-1,2,4-triazoles exhibited potent activity against *Escherichia coli* and *Staphylococcus aureus* strains.



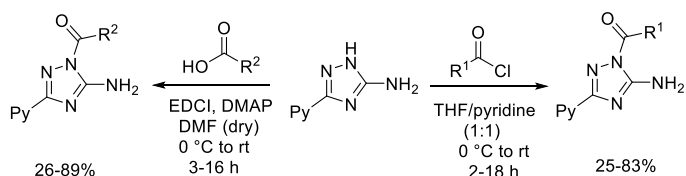
Selected examples



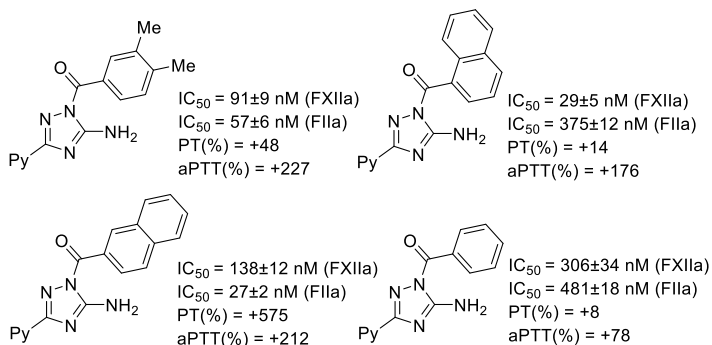
R	Zone of inhibition (mm)	
	<i>E. Coli</i>	<i>S. aureus</i>
CF <sub>3</sub>	12	8
OMe	10	8
H	12	8
Cl	8	10

**Scheme 33.** TBHP/TBAI-mediated C5-arylation of 1,2,4-triazoles / Antibacterial activity evaluation.

Kalinin *et al.*<sup>50</sup> described a conventional and microscale parallel synthesis of acylated 1,2,4-triazol-5-amines which exhibit anticoagulant properties. The products were obtained through a direct regioselective acylation of the nitrogen atom (N-1) of the 3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine with acid chlorides or carboxylic acids (Scheme 34). All acylated 1,2,4-triazoles were evaluated *in vitro* for their capacity to inhibit FXIIa, FIIa, FXa and trypsin enzymes. Results showed that all compounds inhibited FXIIa and FIIa without affecting FXa and trypsin. 14 acylated 1,2,4-triazoles have also been tested for their anticoagulant properties in aPTT and PT tests.

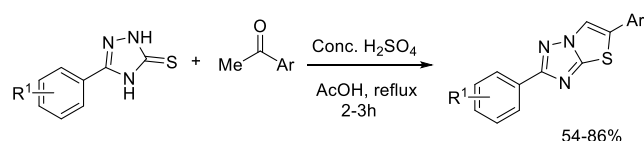


Selected examples

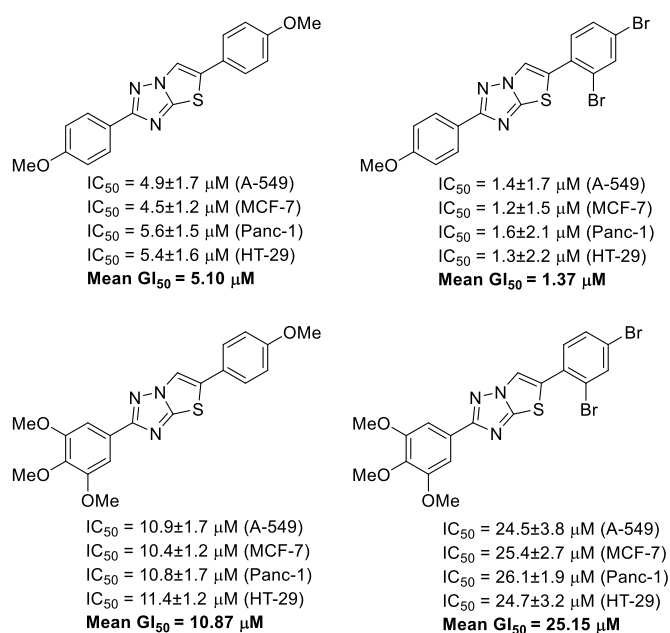


### Scheme 34. N(1)-Acylation of 3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine / Anticoagulant properties.

The development of original synthetic approaches for the preparation of fused 1,2,4-triazoles has received a great deal of interest because of their wide range of biological activities.<sup>51</sup> For examples, Hayallah, Youssif *et al.*<sup>52</sup> have prepared a series of novel thiazolo[3,2-b][1,2,4]-triazoles and they evaluated *in vitro* their antiproliferative activity (Scheme 35). The synthesis of such fused triazoles was performed in one step by reactions between 5-aryl-2,4-dihydro-1,2,4-triazole-3-thione derivatives and aromatic ketones in acidic conditions. The antiproliferative activity of the thiazolo[3,2-b][1,2,4]-triazoles was tested against four lines of human cancer cells: lung cancer cell line (A-549), breast cancer cell line (MCF-7), pancreatic cancer cell line (Panc-1) and colon cancer line (HT-29). The results show that all compounds have shown antiproliferative activity against all examined cell lines and the most effective triazole exhibited GI<sub>50</sub> value of 1.37  $\mu$ M compared to doxorubicin (GI<sub>50</sub> 1.13  $\mu$ M).

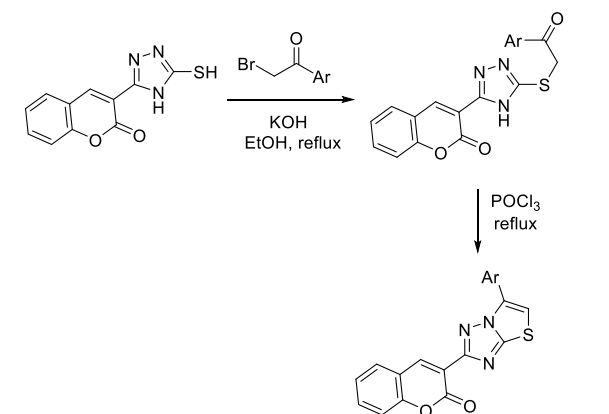


Selected examples

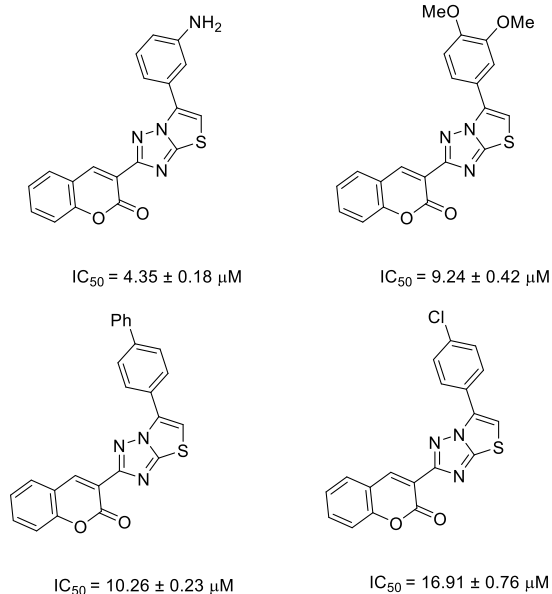


**Scheme 35.** Reaction of 5-aryl-2,4-dihydro-1,2,4-triazole-3-thione derivatives with aromatic ketones / Antiproliferative activity.

Further, Ibrar *et al.*<sup>53</sup> reported an efficient synthetic method to the synthesis of thiazolo[3,2-b][1,2,4]triazole derivatives and evaluated their urease inhibition potential. The sequence proceeds through coupling coumarinyl 3-mercapto-1,2,4-triazole with substituted acetophenones to form the corresponding substituted ethanones which after treatment with phosphorus oxychloride were transformed to coumarinyl thiazolotriazoles (Scheme 36). *In vitro* examination of urease inhibition showed that several synthesized compounds can inhibit the enzyme with IC<sub>50</sub> values in the range of 4.35  $\pm$  0.18 – 193.7  $\pm$  3.4  $\mu$ M. Seven thiazolotriazoles exhibited urease inhibition activity more efficient than thiourea used as the standard (IC<sub>50</sub> = 20.8  $\pm$  0.59  $\mu$ M).

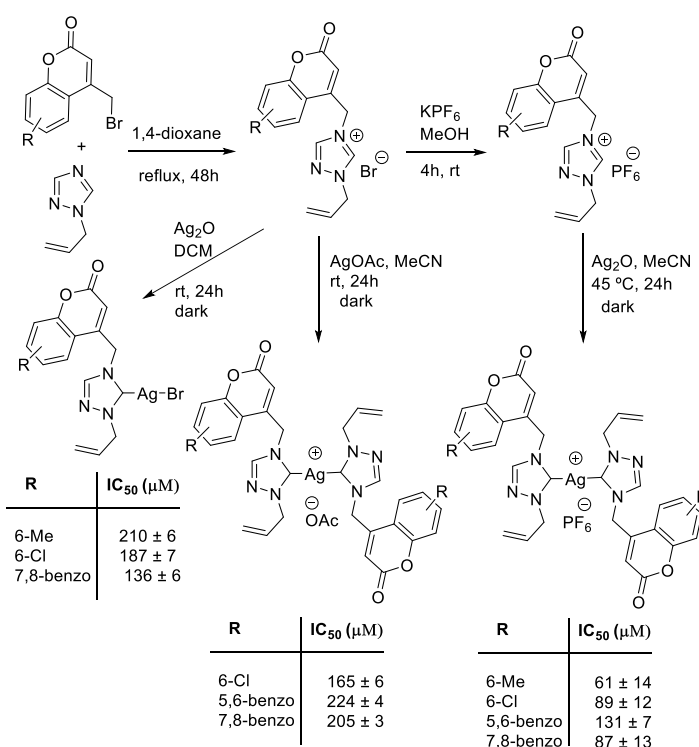


Selected examples



**Scheme 36.** Preparation of coumarinyl thiazolotriazole derivatives / Evaluation of urease inhibition.

Three series of silver complexes of functionalized *N*-heterocyclic carbene (NHC) ligands derived from the 1,2,4-triazole scaffold have been synthesized and evaluated as efficient antioxidant and antihemolytic agents by **Betageri**, Budagumpi *et al.*<sup>54</sup> (Scheme 37). The protocol consists first in preparing ionic 1,2,4-triazolium salts by *N*-alkylation of 1-allyl-1,2,4-triazole with 4-bromomethylcoumarin derivatives, followed by a sequence of deprotonation and addition of silver sources to obtain bis- and mono-NHC coordinated silver complexes. DPPH free radical scavenging assays showed that silver NHC complexes displayed potent antioxidant activities with  $IC_{50}$  value in the range  $61 \pm 14$  to  $224 \pm 4 \mu M$ . Antihemolytic activity has been also achieved at  $100 \mu M$  concentration, the complexes exhibited percentage lysis of red blood cells in the range  $2.32 \pm 0.05$  to  $9.47 \pm 0.38\%$ .

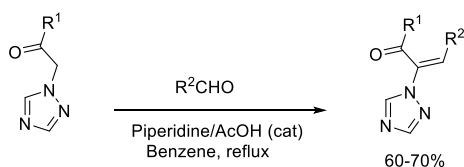


**Scheme 37.** Synthesis of silver complexes from 1-allyl-1,2,4-triazole / Antioxidant and antihaemolytic activities.

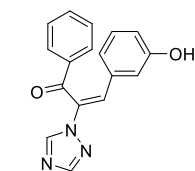
#### b. After modification on the pendant arms of 1,2,4-triazoles

Macaev *et al.*<sup>55</sup> reported the reaction of *N*-acylmethyl-1,2,4-triazole derivatives with aldehydes in the presence of piperidine and acetic acid as the catalysts to give new vinyl-1,2,4-triazole scaffolds with a high level of selectivity for the *Z*-isomer (Scheme 38). Antimicrobial activity of the obtained triazoles was performed against *Bacillus subtilis*, *Pseudomonas fluorescens*, *Erwinia* species (*Erwinia amylovora* and *Erwinia carotovora*) and *Xanthomonas campestris* strains. Within these series, all compounds displayed potent antibacterial activity with MIC and minimum bactericidal concentration (MBC) values ranging from 0.0002 to 0.0069 mM. The antifungal activity was also examined against eight different fungal species. All compounds showed good antifungal activity with MIC and minimum fungicidal concentration (MFC) values better than those obtained using ketoconazole and bifonazole reference drugs.

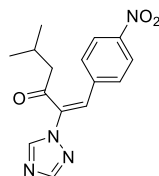
**Scheme 39.** Synthesis of 1,2,4-triazole derivatives carrying thiazole and benzothiazole scaffolds / Evaluation of aldose reductase inhibition.



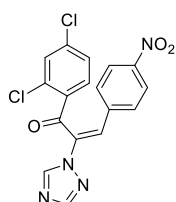
Selected examples



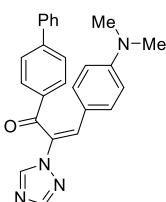
MIC = 0.0069 mM (*B. subtilis*)  
MIC = 0.0017 mM (*P. fluorescens*)  
MIC = 0.0017 mM (*E. amylovora*)  
MIC = 0.0017 mM (*E. carotovora*)  
MIC = 0.0017 mM (*X. campestris*)



MIC = 0.0008 mM (*B. subtilis*)  
MIC = 0.0033 mM (*P. fluorescens*)  
MIC = 0.0004 mM (*E. amylovora*)  
MIC = 0.0004 mM (*E. carotovora*)  
MIC = 0.0008 mM (*X. campestris*)



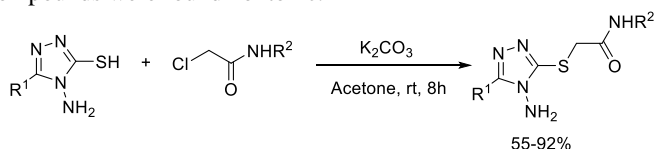
MIC = 0.0013 mM (*B. subtilis*)  
MIC = 0.0006 mM (*P. fluorescens*)  
MIC = 0.0013 mM (*E. amylovora*)  
MIC = 0.0013 mM (*E. carotovora*)  
MIC = 0.0013 mM (*X. campestris*)



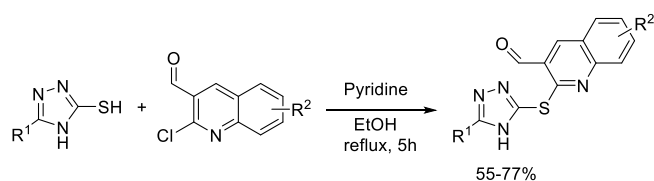
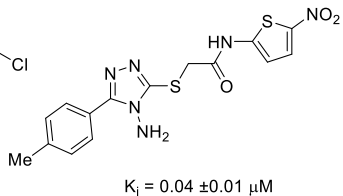
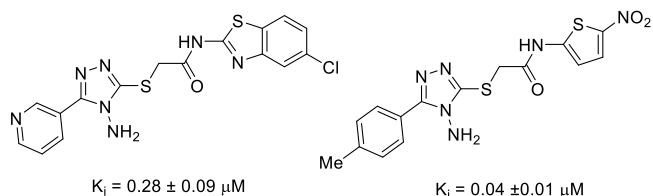
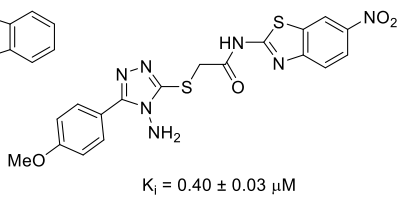
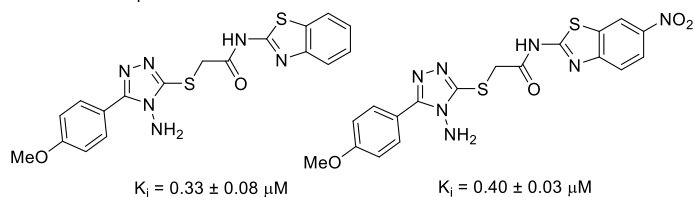
MIC = 0.0025 mM (*B. subtilis*)  
MIC = 0.0025 mM (*P. fluorescens*)  
MIC = 0.0025 mM (*E. amylovora*)  
MIC = 0.0025 mM (*E. carotovora*)  
MIC = 0.0051 mM (*X. campestris*)

**Scheme 38.** Synthesis of vinyl-1,2,4-triazole / Evaluation of antibacterial and antifungal activities.

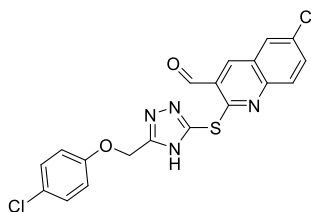
This year, **Sever** *et al.*<sup>56</sup> described the *S*-functionalization of 1,2,4-triazole-3-thiol derivatives to prepare new aldose reductase inhibitors. The alkylation is performed between 4-amino-5-aryl-4H-1,2,4-triazole-3-thiol and 2-chloro-*N*-(thiazol/benzothiazol-2-yl)acetamide in the presence of potassium carbonate (Scheme 39). *S*-functionalized 1,2,4-triazoles were evaluated for their inhibitory capacities on aldose reductase. Among the tested 18 products, the most effective aldose reductase inhibitor was identified with inhibition constant  $K_i$  value of  $0.04 \pm 0.01 \mu\text{M}$  as compared to quercetin ( $K_i = 5.66 \pm 0.66 \mu\text{M}$ ) which used as a reference standard. Cytotoxic effects were determined using MTT assay (a tetrazolium-based cell viability assay). Tests performed on L929 mouse fibroblast cell line indicated that 15 compounds were found nontoxic.



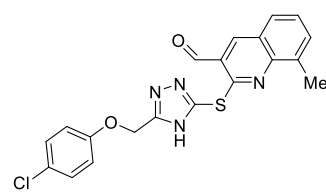
Selected examples



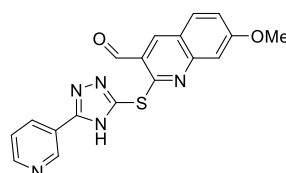
Selected examples



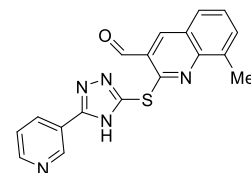
MIC = 6.25  $\mu\text{g/mL}$  (*P. marneffei*)  
MIC = 6.25  $\mu\text{g/mL}$  (*T. mentagrophytes*)  
MIC = 6.25  $\mu\text{g/mL}$  (*A. flavus*)  
MIC = 6.25  $\mu\text{g/mL}$  (*A. fumigatus*)



MIC = 12.5  $\mu\text{g/mL}$  (*P. marneffei*)  
MIC = 12.5  $\mu\text{g/mL}$  (*T. mentagrophytes*)  
MIC = 12.5  $\mu\text{g/mL}$  (*A. flavus*)  
MIC = 12.5  $\mu\text{g/mL}$  (*A. fumigatus*)



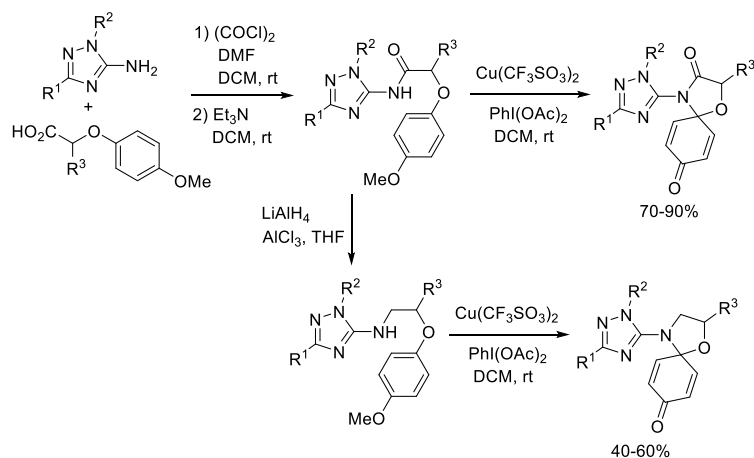
MIC = 12.5  $\mu\text{g/mL}$  (*P. marneffei*)  
MIC = 6.25  $\mu\text{g/mL}$  (*T. mentagrophytes*)  
MIC = 12.5  $\mu\text{g/mL}$  (*A. flavus*)  
MIC = 6.25  $\mu\text{g/mL}$  (*A. fumigatus*)



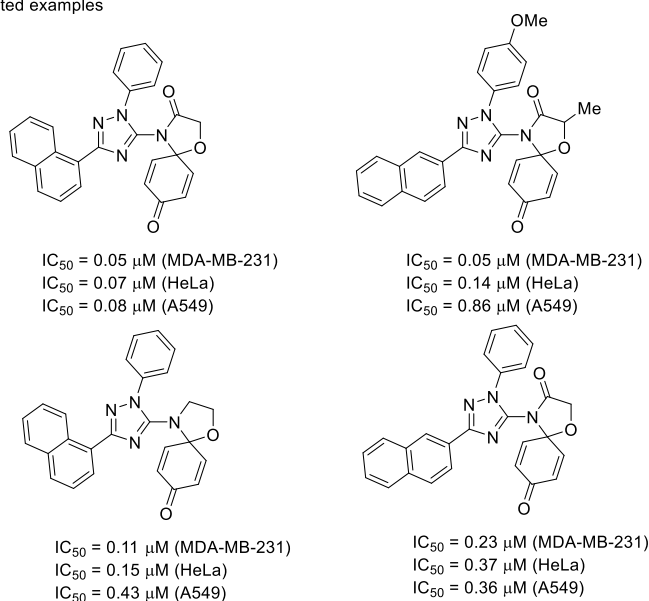
MIC = 6.25  $\mu\text{g/mL}$  (*P. marneffei*)  
MIC = 6.25  $\mu\text{g/mL}$  (*T. mentagrophytes*)  
MIC = 6.25  $\mu\text{g/mL}$  (*A. flavus*)  
MIC = 12.5  $\mu\text{g/mL}$  (*A. fumigatus*)

**Scheme 40.** Preparation of 1,2,4-triazole incorporated quinoline derivatives / Antibacterial and antifungal proprieties.

The synthesis of new family of 1,2,4-triazole-spirodienone derivatives from 1,3-disubstituted 1,2,4-triazol-5-amines was reported by He *et al.*<sup>58</sup> (Scheme 41). In this case, authors benefit from the presence of an  $\text{NH}_2$  group at position 3 of the triazole to build up the spirodienone fragment. The reaction sequence begins by the acylation of the amino group with phenoxyacetic acid derivatives. Direct oxidative amination reaction (or reduction-amination) of the obtained phenoxyacetamides, leads to the corresponding 1,2,4-triazole-spirodienones. The antiproliferative activity of the synthesized compounds were tested against the triple-negative human breast carcinoma (MDA-MB-231), the human cervical epithelioid carcinoma (HeLa) and the non-small cell lung carcinoma (A549). All the 1,2,4-triazole-spirodienone derivatives displayed high activity against the three cancer cell lines and  $\text{IC}_{50}$  values showed that all compounds are more potent than Vorinostat and Bendamustine used as reference standards.

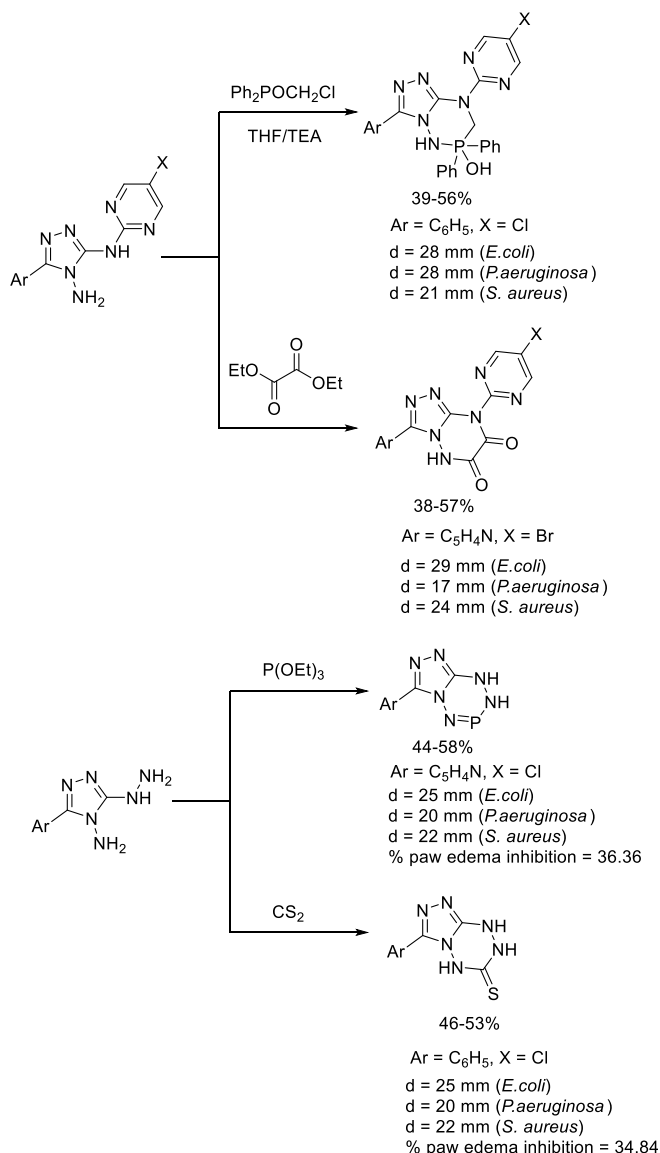


## Selected examples



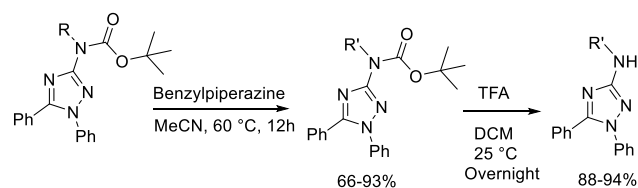
**Scheme 41.** Synthesis of 1,2,4-triazole-spirodienone derivatives / Evaluation of the anticancer activity.

The presence of two amino group located at positions 3 and 4 of the triazole platform allowed Soliman *et al.*<sup>59</sup> to construct various fused heterocycles incorporating several nitrogen and phosphorus atoms (Scheme 42). The antibacterial activity of the synthesized heterocycles was evaluated using disc diffusion method at concentrations of 25, 50 and 100  $\mu\text{g/mL}$  respectively. All tested compounds showed the highest activity at 100  $\mu\text{g/mL}$  concentrations and diameter of the growth inhibition zone (d) was measured. The antifungal activity for some synthesized heterocycles was also examined against *Candida albicans*. Results showed potent activity with the inhibition zone in the range of 11 to 40 mm. Fused 1,2,4-triazoles obtained from 4-amino-5-hydrazino-1,2,4-triazoles were examined as well for their anti-inflammatory activity using Carrageenan-induced paw edema method and the inhibition percentage of inflammation was calculated at test dose of 25 mg/Kg.



**Scheme 42.** Synthesis of 1,2,4-triazolo-tetrazines and -triazines derivatives / Study of biological proprieties.

Very recently, Kümmerle *et al.*<sup>60</sup> developed a two-step reaction sequence for the transformation of 3-carbamate-1,2,4-triazoles into *N*-substituted 1,2,4-triazol-3-amine derivatives (Scheme 43). The cholinesterase (AChE and BuChE) inhibition activities of the obtained aminotriazoles were evaluated. Results showed that all tested compounds inhibit cholinesterases with good  $IC_{50}$  values of up to 1  $\mu\text{M}$ . Kinetic study showed that aminotriazoles exhibit good mixed-type inhibition activities but without revealing selectivity between AChE and BuChE enzymes.



## Selected examples

n	AChE $IC_{50}$ ( $\mu\text{M}$ )	BuChE $IC_{50}$ ( $\mu\text{M}$ )
3	1.14 $\pm$ 0.031	1.79 $\pm$ 0.060
4	3.79 $\pm$ 0.061	1.63 $\pm$ 0.111
5	11.00 $\pm$ 0.251	1.65 $\pm$ 0.059
6	5.22 $\pm$ 0.188	2.21 $\pm$ 0.068



**Scheme 43.** Synthesis of *N*-alkyl-1,5-diphenyl-3-amine-1,2,4-triazoles / Evaluation of cholinesterase inhibition activities.

#### 4. Conclusion

The broad spectrum of the biological and therapeutic properties of 1,2,4-triazoles have intrigued the scientific community for decades to develop synthetic methods for these scaffolds. In this review, we have summarized the synthetic protocols over the past decade as well as the use of 1,2,4-triazoles as building blocks for the preparation of biologically active compounds over the last two years. The synthetic methods were classified according to the key starting material used for the preparation of the 1,2,4-triazole skeleton. Amidines, imidates, amidrazones, aryldiazoniums and hydrazones are among the most relevant triazole precursors. The wide range of precursors but also the numerous textbook methods of access to these precursors ensures possibilities of "on-demand" triazole ring construction. The ease of construction and robustness of this heterocycle, but also the possibilities of highly selective late-stage installation of valuable substituents on this heterocyclic platform are undoubtedly advantages for an increased molecular diversity and scalable biological properties with applications in life sciences. A second section of this review illustrates several biological activities of compounds obtained by functionalization or modification on the preformed 1,2,4-triazole ring which can give a vision of the latest advances to researchers working in this field.

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