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Transition-metal-free Regioselective Construction of 1,5-Diaryl-1,2,3-triazoles through Dehydrative Cycloaddition of Alcohols with Arylazides Mediated by SO_2F_2

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Abstract : A novel, simple and practical method for mild, efficient, cost-effective and regioselective synthesis of the highly valuable 1,5-diaryl-1,2,3-triazoles was achieved through dehydrative annulation of the readily available alcohols with arylazides. The reaction proceeded at room temperature, without requiring any metal catalysts feathering an excellent compatibility to a large variety of functional groups (>50 examples) in up to quantitative yields.

Substituted 1,2,3-triazoles are ubiquitously present in functional materials, dyes, agrochemicals, ligands, catalysts, natural products and biologically active molecules.[1] The construction of substituted 1,2,3-triazole motifs was an irreplaceable powerful tool for material science, chemical biology, medicinal chemistry and drug discovery.[2] Therefore, the development of general, efficient, mild and reliable methods for assembly of substituted 1,2,3-triazoles has been extensively investigated and continues to be of great significance.[3] The original Huisgen's 1,3-dipolar cycloaddition of an organic azide and an alkyne produces two regioisomers of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles which requires elevated temperatures to break the thermal barriers together with poor regioselectivity (Figure 1 a).[4] Fortunately, by using Cu-catalyst,[5] the regioselective construction of 1,4-disubstituted 1,2,3-triazoles was achieved; and the regiospecific synthesis of 1,5-disubstituted 1,2,3-triazoles was also accomplished through employing Ru-catalyst,[6] Ni-catalyst,[7] metal acetylide (Figure 1 b),[8] Ir-catalyst[9a,b] or without transition-metals.[9c] Besides terminal alkynes, the use of enamines,[10] phosphonium ylides (Figure 1 c),[11] electron-deficient olefins[12] and carbonyl derivatives (enones, keto esters, nitriles, aldehydes, et al.)[13] to react with organoazides (or substituents) provides additional options for regioselective construction of 1,2,3-triazoles.

Nonetheless, many of the well-established methods for 1,2,3-triazoles synthesis suffer from narrow substrate scope, requiring elevated temperature, metal-catalysts, or harsh conditions which have significantly limited their applications. On the other hand, comparing to alkynes and their substituents which generally require tedious procedure to make, alcohols are readily available, inexpensive and abundant industrial chemicals, some of which can be obtained from renewable resources (biomass). [14] In these respects, the development of novel protocols for mild, efficient, cost-effective, and regioselective synthesis of 1,2,3-triazoles from alcohols are highly desirable and of great importance. Herein, we report a powerful, sustainable (water as by-product), and robust method for construction of 1,5-disubstituted-1,2,3-triazoles with exclusive regioselectivity through dehydrative cycloaddition of alcohols with aryl azides (Figure 1 d).

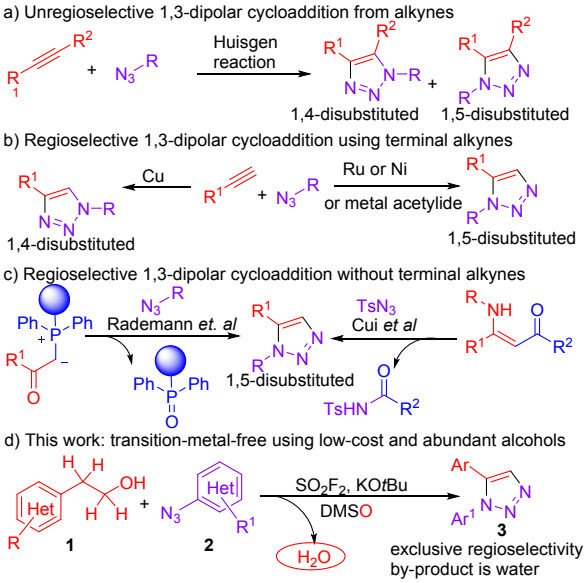

Fig 1. Strategies for the construction of 1,2,3-triazoles.

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It has been documented that five-membered N-containing heterocycles bearing vicinal chemically stable aromatic rings have a broad of biological activities, and many approved drugs possess this type of moieties, such as Valdecoxib, Parecoxib, Celecoxib and Tepoxalin (Figure 2a).[15] On the other hand, compared with their 1,4-disubstituted counterparts, the *cis*-locked geometry of 1,5-disubstituted-1,2,3-triazoles have been well established to be an advantage to increase the biological activity and binding affinity towards many biological targets,[11b,16] among which, 1,5-diaryl-1,2,3-triazoles have gained significant attention for the discovery and development new therapeutics (Figure 2b).[17] The importance of 1,5-diaryl-1,2,3-triazoles has also inspired our interest on developing novel and regioselective method to synthesize this class of motifs.

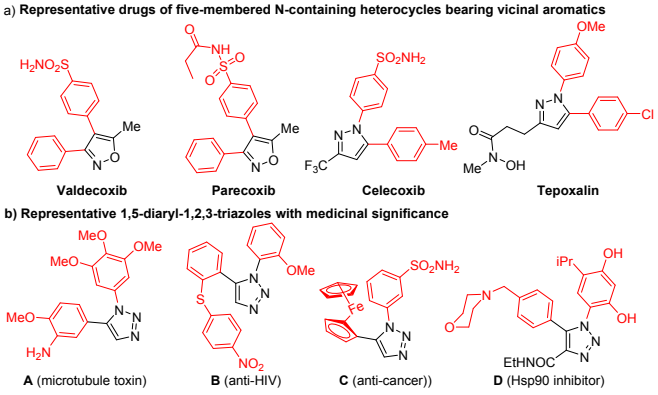
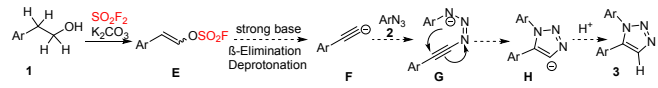


Fig 2. Representative five-membered N-containing heterocycles bearing vicinal aromatic rings with medicinal significance.

Besides the advantages of alcohols, sulfuryl fluoride (SO_2F_2) is also an inexpensive (about 1$/kg),[18a] abundant (millions-kilograms annual production) reagent,[18a] which as a relatively inert electrophile (stable up to 400 ℃ when dry) has gained significant attention in recent years for SuFEx click chemistry and a variety of other chemical transformations.[18] Our previous study has revealed that with the promotion of SO_2F_2/K_2CO_3 in DMSO, alcohols **1** can be smoothly transformed to enolates **E** in nearly quantitative yields at room temperature.[18h] Therefore, we envisioned that (Scheme 1) after simultaneous (or subsequent) elimination and deprotonation by using a suitable base, without any purification, the *in situ* generated intermediate **E** would be converted to the corresponding reactive acetylide **F**,[9c] which would undergo a nucleophilic attack to the terminal nitrogen of aryl azide **2** to form the triazenide intermediate **G** to subsequently proceed a cyclization and a protonation to form the desired product **3**.

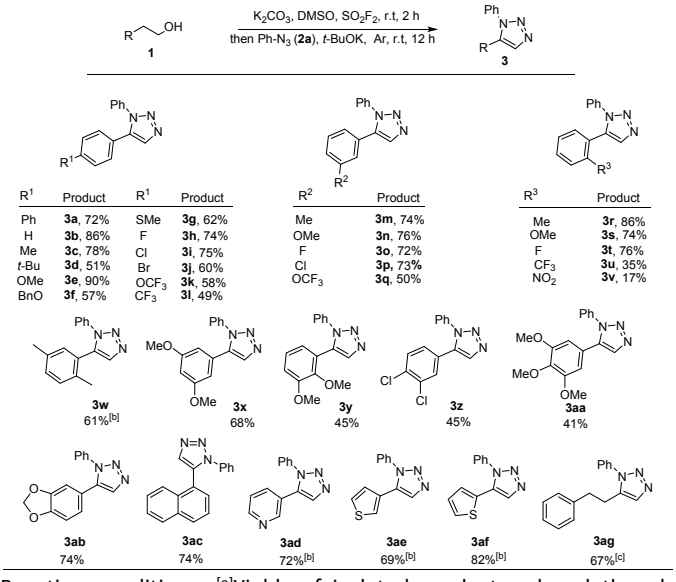


Scheme 1. Proposed dehydrative annulation process.

Fortunately, after screening a large variety of conditions (see supporting information), we were delighted to find that the use of 1.0 equivalent alcohol **1**, 1.5 equivalent of azide **2** and 3.0 equivalent of *t*-BuOK furnished the desired 1,2,3-triazoles product **3** in excellent yields at room temperature.

The substrates scope and functional-group compatibility of arylethanols **1** were examined as illustrated in Table 1. Arylethanols **1** bearing both electron-donating and electron-withdrawing groups at different positions of the aromatic rings successfully afforded their corresponding triazole products **3** in good to excellent isolated yields (**3a**-**3v**). It has to be mentioned that for arylethanols bearing strong electron-withdrawing groups such as NO_2 and CF_3 on the aromatic rings, the yields of their corresponding triazoles were significantly lower (**3l**, **3u** and **3v**) owing to the electron-deficient effect on the substrates. Furthermore, multi-substituted arylethanols (**1w**-**1aa**) were also smoothly transformed to their 1,5-diaryl-1,2,3-triazoles in moderate isolated yields regio-selectively. The starting material functionalized with acetal moiety tolerated this reaction system well (**3ab**). In addition, fused aromatic ethanol **1ac** also provided the corresponding 1,2,3-triazole (**3ac**) in good yield. Significantly, this method was applied to the alcohols bearing heteroarenes **1ad**-**1af** to generate products **3ad**, **3ae** and **3af** in 72%, 69% and 82% isolated yield, respectively, when 4-fold excess of base was added in the annulation step. In addition, the long-chain aliphatic alcohol (**1ag**) was also testified for the construction of 1,5-diaryl-1,2,3-triazole (**3ag**). Excitingly, by modification of the new method using a two-step process (enolate formation and annulation), the **3ag** was successfully obtained in 67% overall isolated yield from the corresponding alcohol.

Table 1 Substrates scope of arylethanols. [a]

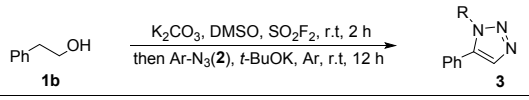


Reaction conditions: [a]Yields of isolated products, phenylethanol (**1b**, 1 mmol), K_2CO_3 (2 mmol, 2.0 eq.), DMSO (7.5 mL, 0.13 M) under SO_2F_2 atmosphere (balloon) for 2 h, aryl azide (**2**, 1.5 mmol, 1.5 eq.), *t*-BuOK (3 mmol, 3.0 eq.) were added and stirred for 12 h. [b]4 eq. *t*-BuOK was used. [c]4-phenylbutan-1-ol (**1ag**, 1.0 mmol), K_2CO_3 (1.2 mmol, 1.2 eq.), DMSO (0.13 M), SO_2F_2 (balloon) for 12 h; then DBU (6 eq.) was added and stirred for another 12 h before

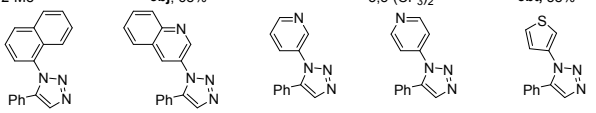
isolation. Then *t*-BuOK (2 eq.), PhN_3 (**2a**, 1.5 eq.), DMSO : THF= 5:2 (V : V), 0 °C-r.t, Argon atmosphere, 12 h.

After investigating the scope of alcohols for the dehydrative cycloaddition reaction, we next turned our attention to examine the scope and functional groups compatibility of different arylazides (**2**) with phenyl ethanol (**1b**) subsequently. As illustrated in Table 2, various arylazides **2** containing different functional groups, such as halogen, nitro, cyano, alkyl, ether and heteroaryl were evaluated in the developed reaction system, and their corresponding 1,5-diaryl-1,2,3-triazoles **3ba**-**3by** products were furnished in moderate to quantitative yields (27%-99%) regio-exclusively. Importantly, some azides carrying strong electron-withdrawing groups of NO_2 also provided their triazoles (**3bc**) (**3bi**) smoothly while their counterparts bearing electron donating functional groups typically generated their triazoles in higher yields, for example (**3bf** 98% vs **3bi** 61%). However, when the arylazide possessing strong electron-withdrawing group NO_2 at the *ortho* position, the reactivity of this transformation was sharply frustrated and only 27% yield of the desired product was obtained (**3bl**). It is worth highlighting that the efficiency of transforming heteroarylazides (**2bv-2by**) were also satisfactory to generate **3bv-3by** in 67% to 81% yields indicating that this methodology has high potential for assembly medicinally significant 1,2,3-triazole-containg heterocycles for discovery of new therapeutics.

Table 2 Substrates scope of aryl azides.[a]



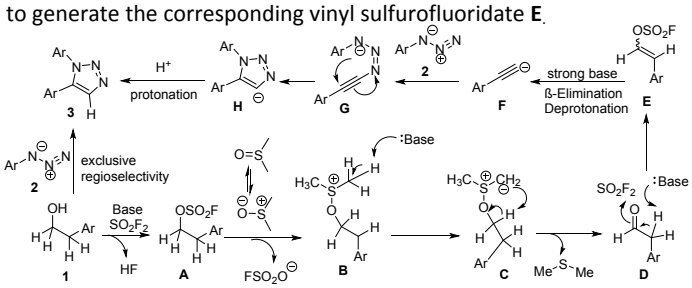
R^1	Product	R^1	Product
4-F	**3ba**, 80%	2-iPr	**3bk**, 84%
4-Br	**3bb**, 91%	2-NO_2	**3bl**, 27%
4-NO_2	**3bc**, 70%	2,6-$(Me)_2$	**3bm**, 53%
4-CN	**3bd**, 70%	2,6-$(Et)_2$	**3bn**, 53%
4-OCF_3	**3be**, 81%	2,3-$(Me)_2$	**3bo**, 51%
3-Me	**3bf**, 98%	3,5-$(Me)_2$	**3bp**, 75%
3-Cl	**3bg,** 99%	2-OMe-5-Me	**3bq**, 82%
3-OCF_3	**3bh**, 63%	2,6-$(F)_2$	**3br**, 91%
3-NO_2	**3bi**, 61%[b]	3,4-$(Cl)_2$	**3bs**, 44%[b]
2-Me	**3bj**, 68%	3,5-$(CF_3)_2$	**3bt,** 58%[b]



3bu	**3bv**	**3bw**	**3bx**	**3by**
83% [b]	67%	79%	81%	80%

Reaction conditions: [a] Isolated yield, phenylethanol (**1b**, 1 mmol), K_2CO_3 (2 mmol, 2.0 eq.), DMSO (7.5 mL, 0.13 M) under SO_2F_2 atmosphere (balloon) for 2 h, aryl azide (**2**, 1.5 mmol, 1.5 eq.), *t*-BuOK (3 mmol, 3.0 eq.) were added and stirred for 12 h.[b] 4.0 equivalent of *t*-BuOK was used.

A plausible mechanism was illustrated in Scheme 2. Initially with the promotion of base, the formation of a fluorosulfate ester **A** occurred from the reaction of corresponding alcohol **1** and SO_2F_2.[18c,g,h] The fluorosulfate ester was subsequent displaced by DMSO acting as the nucleophile to generate cationic intermediate **B**.[19] The intermediate **B**, followed a Swern-type oxidations pathway providing the sulfur ylide **C** after deprotonation.[20] proceeded an intramolecular deprotonation-elimination to produce Me_2S and the aldehyde **D**. Under basic condition, the aldehyde **D** was tautomerized to an enol to react with another equivalent SO_2F_2 to generate the corresponding vinyl sulfurofluoridate **E**.



Scheme 2 A plausible mechanism for the dehydrative annulation.

Subsequently, a base-assisted *β*-elimination and deprotonation furnished the reactive acetylide **F**,[9c] which underwent a nucleophilic attack to the terminal nitrogen of aryl azide **2** to form the triazenide intermediate **G**. The intermediate **G** proceeded an intramolecular cyclization to generate the 1,5-aryl-1,2,3-triazolyl anion **H** which reacted with a proton cation to furnish the final 1,5-diaryl-1,2,3-triazole **3** with exclusive regioselectivity.

In summary, we have developed a novel, simple and practical method for mild, efficient, cost-effective, and regioselective synthesis of 1,5-diaryl-1,2,3-triazoles through dehydrative annulation of the readily available alcohols with aryl azides. The reaction proceeded at room temperature, without requiring any metal catalysts feathering an excellent compatibility to a large variety of functional groups (over 50 examples) in good to quantitative yields. This pot, atom and step-economical (PASE) fashioned protocol will be an irreplaceable asset for various modern research fields.

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There are no conflicts to declare.

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