A Metal-Free, Aqueous and General Route to 1,5-Disubstituted-1,2,3-triazoles: ‘Reversed Regioisomeric’ 1,3-Dipolar Cycloaddition of Azides and Vinyl Sulfones

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Abstract: A metal-free, vinyl sulfone-based synthesis of 1,5-disubstituted-1,2,3-triazoles is reported for the first time. 1,5-Disubstituted-1,2,3-triazoles are easily formed in a regioselective fashion by heating under reflux a mixture of a substituted vinyl sulfone and an organic azide ‘on water’. This powerful and practical route has the potential to be exploited for the synthesis of complex 1,5-disubstituted-1,2,3-triazoles.

Key words: triazoles, on water, vinyl sulfone, organic azide, click chemistry

In addition to the wide-ranging applications of 1,4-disubstituted-1,2,3-triazoles, the recently noted importance of 1,5-disubstituted-1,2,3-triazoles as cis-peptide bond surrogates has triggered the search for a reliable and operationally simple avenue for accessing the latter class of heterocycles. However, synthetic strategies for accessing 1,5-disubstituted-1,2,3-triazoles are limited in number. Synthetic approaches towards 1,5-regioisomers using halomagnesium acetylenes or trimethylsilyl acetylenes have achieved only limited success. The ruthenium-mediated strategy of ligation of alkynes and organic azides requires optimization to identify an effective catalyst capable of efficiently combining both alkyl and aryl azides with any alkyne. Alternatively, the demand for easier access to disubstituted 1,2,3-triazoles also encouraged research groups to devise metal-free routes. For example, the ligation of aromatic azides and aromatic alkynes in the presence of a catalytic amount of tetraalkylammonium hydroxide did produce 1,5-disubstituted-1,2,3-triazoles, but the method is limited because alkyl acetylenes failed to react under these conditions.

Most of the metal-catalyzed and metal-free approaches for the synthesis of 1,5-disubstituted-1,2,3-triazoles involve the use of alkynes. Although different types of activated olefins have been used in the past for the synthesis of triazoles, there are only a few reports on the use of olefinic compounds since 1,2,3-triazoles were revisited during the last decade. The under-utilization of olefins in recent times despite their better regioselectivity profile over alkynes may be attributed to various factors, but, one of the major problems associated with the use of olefin-based synthesis of triazoles is that an overwhelming number of olefins generate triazoles, which require an additional step of acid/base treatment or oxidation to afford 1,2,3-triazoles in moderate to poor overall yields. For example, most enamines, which are one of the most commonly used electron-rich olefins for the synthesis of 1,2,3-triazoles, afforded triazolines. It should be noted that the general application of activated olefins in 1,2,3-triazole synthesis would also crucially depend on the availability of straightforward preparative methods for these olefins from easily accessible starting materials. Thus, a large number of olefin-based methods for triazole synthesis cannot be used simply because modification of polyfunctionalized molecules with those functional groups is synthetically challenging.

Although electron-poor olefins such as vinyl sulfones are known to produce 1,2,3-triazoles on reaction with sodium azide, perfluoroalkyl-substituted phenyl vinyl sulfones reacted with sugar azides to afford a single regioisomeric 4-perfluoroalkyl-1,2,3-triazole derivative. Since a wide range of functionalized vinyl sulfones, including vinyl sulfone-modified biomolecules are easily available, we set out to study the versatility of using vinyl sulfones in the synthesis of disubstituted 1,2,3-triazoles. Thus, 1,5 equivalents of azidobenzene was reacted with the p-tolyl vinyl sulfone in either toluene or water at reflux temperature until was consumed. The absence of a sharp singlet at δ = 8.2 ppm in the 'H NMR spectrum indicated that the expected 1,4-disubstituted triazole was not the product (Scheme 1). Surprisingly, the reaction produced the 1,5-regioisomer, a compound synthesized from phenyl acetylene in the presence of catalytic tetraalkylammonium hydroxide, with the triazolyl proton appearing as a sharp singlet at δ = 7.87 ppm. We presume that, due to the polarization of the double bond of vinyl sulfone, attack from the partially positively charged β-position to afford a cyclic intermediate, which eliminated sulfinic acid to afford 1,5-disubstituted-1,2,3-triazole, regioselectively. This mechanistic explanation raised our expectations that the reaction should be general in nature and be capable of generating a wide range of 1,5-disubstituted triazoles.

After several trial reactions, we decided to replace the p-tolysulfonyl group with much less expensive 2-mercaptopentothiazole. Thus, we synthesized two simple but structurally varied vinyl sulfones starting from...
easily accessible styrene epoxide 3 and mono-tosylated glycerol 7, respectively (Scheme 2). In both cases, C–S bond formation at elevated temperature followed by oxidation of the sulfides 4/8 and elimination of mesylates from sulfones 5/9 were used as a general strategy to access the desired vinyl sulfones 6 and 10 in relatively large quantities (Scheme 2). Vinyl sulfone 6 was selected for further study because it was expected to produce the known 1,5-disubstituted-1,2,3-triazoles reported earlier and prepared through alternative routes.2a Thus, a mixture known 1,5-disubstituted-1,2,3-triazoles reported earlier further study because it was expected to produce the quantities (Scheme 2). Vinyl sulfone from sulfones the desired vinyl sulfones bond formation at elevated temperature followed by oxidation of the sulfides 4/8 and elimination of mesylates from sulfones 5/9 were used as a general strategy to access the desired vinyl sulfones 6 and 10 in relatively large quantities (Scheme 2). Vinyl sulfone 6 was selected for further study because it was expected to produce the known 1,5-disubstituted-1,2,3-triazoles reported earlier and prepared through alternative routes.2a

As a control, a selection of azides used in Scheme 4 were reacted with the benzyl protected propargyl alcohol (HCCCH2OBN)16 under Cu(I) mediated click conditions; all products were found to be the 1,4-regioisomers of the corresponding triazoles described herein and were different to the products listed in Scheme 4.17 Although yields of the mono-triazolyl derivatives were in the range 74–85%, no other products could be isolated. The ditriazolyl compounds 11a–n, with yields around 65%, were also the sole products of their respective reactions. Reactions of vinyl sulfones with higher amounts (>1.5 equiv) of azides did not improve the yield nor could the yields be improved significantly by using vinyl sulfone and organic azide in a ratio of 1.5:1.Compound 10 was recovered almost quantitatively even after heating to reflux temperature in water for more than 12 hours, which indicated that vinyl sulfone did not decompose at high temperature.

It should be noted that the regioselectivity of formation of 2b–d and 11a–n is not clear because 1-nitroalk-1-enes (RCH=CHNO2), which are the closest relatives of vinyl sulfones 1, 6, or 10 reportedly react with organic azides to afford mixtures of the regioisomeric triazoles; the relative proportions of these compounds being dependent on the experimental conditions.2b Therefore, the route affording compounds 2b–d and 11a–n is regioselective in nature.

This report also highlights a reversal of the reaction pattern of vinyl sulfones leading to regioisomeric triazole formation that depends on the functional groups attached to the substituted vinyl sulfones.9
may be categorized as organic synthesis ‘on water’. It used in this report are insoluble in water, the reactions often proceed optimally. Since all organic reactants reported observation that water-insoluble organic reactants and environmental concerns, as well as because of the re-

Water was used as a solvent for reasons of cost, safety, and environmental concerns, as well as because of the reported observation that water-insoluble organic reactants often proceed optimally. Since all organic reactants used in this report are insoluble in water, the reactions may be categorized as organic synthesis ‘on water’. It should be noted that we could not isolate, nor identify by TLC, any intermediate corresponding to C (Scheme 1) in the transformations listed in Scheme 3 or Scheme 4. It is probable that the formation of cyclic intermediates such as C and the generation of the final products 2b–d and 11a–n is a concomitant process in the reactions reported here-in.

Since vinyl sulfones can be easily synthesized from 1,2-diols, olefins, epoxides, and aldehydes, in the context of the previous lack of a metal-free, efficient, flexible, and general methods for the synthesis of 1,5-regiosomeric triazoles, our expedient and general strategy offers a practical route to simple as well as more complex 1,5-disubstituted-1,2,3-triazoles using combinations of aryl/alkyl vinyl sulfones and aryl/alkyl azides. This operationally less complicated method is applicable to both phenyl- and alkyl vinyl sulfones, avoids the use of high-boiling solvents such as DMSO, and does not require a CO2-free environment or inert atmosphere. Research is currently in progress to study the reactions in depth by varying the functional groups attached to the vinyl group as well as by using different sulfones and sulfoxides. We are also ligating a wide range of polyfunctionalized molecules such as carbohydrates and nucleosides, with different organic molecules for the synthesis of a wide range of new chemical entities with potential applications in biology and medicine.

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References and Notes

Scheme 4 Synthesis of 1,5-disubstituted-1,2,3-triazoles from the vinyl sulfone 10

Water was used as a solvent for reasons of cost, safety, and environmental concerns, as well as because of the reported observation that water-insoluble organic reactants often proceed optimally. Since all organic reactants used in this report are insoluble in water, the reactions may be categorized as organic synthesis ‘on water’.
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(2) For the synthesis of 11k from 5-azido-5-deoxy-2,3-O-isopropylidene-[β-D-ribofuranosidase, 2 equiv of NaHCO₃ was used in the reaction mixture to neutralize the acid generated after elimination. NaHCO₃ is not required for the synthesis of 2b–d, 11a–j or 11l–n.


(20) General procedure for the synthesis of 1,5-disubstituted-1,2,3-triazoles (2b–d and 11a–n): A mixture of vinyl sulfone 6 or 10 (1 mmol), and azide (1.5 mmol for monoazide and 0.5 mmol for diazide) in water (10 mL/mmol of 6 or 10) was heated at reflux temperature for 3–19 h. After completion of the reaction (monitored by TLC) the reaction mixture was treated with sat. NaHCO₃ and the product was isolated by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was purified by silica column chromatography to afford the following 1,5-disubstituted-1,2,3-triazoles 2b–d and 11a–n.