Silver-Catalyzed Stereoselective Aminosulfonylation of Alkynes

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Abstract: A silver-catalyzed intermolecular aminosulfonylation of terminal alkynes with sodium sulfinites and TMSN₃ is reported. This three-component reaction proceeds through sequential hydroazidation of the terminal alkyne and addition of a sulfonyl radical to the resultant vinyl azide. The method enables the stereoselective synthesis of a wide range of β-sulfonyl enamines without electron-withdrawing groups on the nitrogen atom. These enamines are found to be suitable for a variety of further transformations.

Alkynes are one of the most common and versatile functional groups in organic synthesis, and catalytic methods that enable their efficient transformation into other useful functionalities are therefore highly appealing in both academic research and industrial applications. Direct difunctionalization reactions of alkynes, capable of affording tri- and tetrasubstituted alkenes, have attracted much attention in recent years. Among these, radical-based 1,2-difunctionalizations of alkynes offer a straightforward means to construct functionalized alkenes by reaction with both carbon and heteroatom-centered radicals with excellent step- and atom-economy. Mechanistically, a common reaction pathway is observed involving initiation of the reaction by radical addition to the alkyne to generate a vinyl radical intermediate, which is then coupled with another component to form the alke ne product (Figure 1a). However, such vinyl radical species are highly reactive and readily undergo hydrogenation by H-atom abstraction, which is a significant challenge in developing radical-based alkyne difunctionalization reactions. Moreover, aliphatic alkynes are generally unreactive in these processes, which is most likely due to the lack of a π-conjugation stabilizing effects of intermediate alkyl-substituted vinyl radicals compared to aryl-substituted analogues. Consequently, conceptually distinct approaches are in high demand. In the last years, the nitrogenation of alkynes with trimethylsilylazide (TMSN₃) has attracted much attention, where carbon–carbon triple bond cleavage leads to a variety of nitrogen-containing molecules. Building from our recent efforts on the activation of alkynes by silver catalysis, we herein report a new strategy to effect radical-based difunctionalization of terminal alkynes through an unprecedented hydroazidation/radical addition cascade (Figure 1b). The key point for this successful transformation is that we discovered a mild and efficient approach to generate sulfonyl radical from sodium sulfinate, thus avoiding the initial competitive radical addition to alkynes. To the best of our knowledge, this is the first example of intermolecular alkyne aminosulfonylation, resulting in stereoselective synthesis of β-sulfonyl N-protected enamines, which are useful synthetic intermediates whose applications are currently limited by a lack of practical synthetic methods for their preparation. Moreover, only one report regarding the synthesis of N-protected enamines by alkyne difunctionalization has been reported.

Initial optimization of the reaction was performed using alkyne 1a, TMSN₃, and sodium p-toluenesulfinate 2a, with variation of reaction parameters including metal catalyst, solvent, and temperature (Table 1). Silver salts proved highly effective in promoting the hydroazidation/sulfonation cascade: Ag₂CO₃, Ag₂PO₄, and AgF all gave the aminosulfonylated product 3a in high yields, with Ag₂PO₄ delivering an optimum yield of 85% (entries 1–3). In contrast, other metal catalysts such as Pd(OAc)₂, CuI, and Mn(OAc)₃ were ineffective, which is presumably due to their inability to catalyze the hydroazidation reaction (entries 4–6). Water was found to be an essential additive, as a poor yield (30%) was obtained in its absence (entry 7); the use of less than two equivalents of TMSN₃ also resulted in a decrease in product yield. The reaction solvent also proved important, with DCE and 1,4-dioxane giving only trace amounts of the desired product using Ag₂PO₄ as catalyst (entries 8 and 9), compared to polar aprotic solvents such as NMP (65%, entry 10) and
DMSO. Finally, increasing or reducing the reaction temperature led to a decrease in product yield (entries 11 and 12).

The scope of the reaction with respect to the alkyne proved broad, with a wide range of aryl- and heteroaryl-functionalized terminal alkynes being suitable for this silver-catalyzed cascade reaction, affording the corresponding β-sulfonyl enamines in good to excellent yields (Scheme 1). For instance, a variety of para-substituted phenylacetylenes 1a–1j underwent smooth reaction with TMSN₃ and 2a to give the products 3a–3j in 69–87% yields. Pleasingly, common functional groups such as alkoxy, alkyl, aryl, halogen, cyano, trifluoromethyl, aldehyde, and ester were all well-tolerated, with X-ray diffraction analysis of 3c confirming the (Z)-configuration of the alkenes. Similarly, ortho-, meta-, and 3,4-disubstituted phenylacetylenes gave the desired enamine products 3k–3p in high yields (79–83%). Heteroaromatic acetylenes including 2- and 3-pyridyl, 2- and 3-thienyl, as well as ferrocenyl acetylene were also evaluated, and the corresponding products 3q–3w were obtained with high efficiency. A more elaborate estrone-derived terminal alkyne could also be successfully transformed into the corresponding β-sulfonyl enamine 3x (79%), underlining the robust nature of the method.

Following this success with aryl-substituted alkynes, we turned our attention to the reactivity of aliphatic alkynes, where it is notable that alkyl-substituted β-sulfonyl enamines have not been prepared by other methods. In the event, we were delighted to find that reactions of alkyl-substituted terminal alkynes generally proceeded with equal efficiency to aryl alkynes, affording a number of functionalized β-sulfonyl enamines 4 in high yields. Apart from simple alkyl acetylenes (4a–4d, 69–81%), cyclopropyl, hydroxyl, and phthalimide substituents were all tolerated, giving the functionalized sulfonyl enamines 4e–4h (59–82%). Further, enyne systems such as 1-cyclohexenyl and styril acetylenes also participated efficiently in this three-component reaction, giving the 1,3-butadienes 4i and 4j in reasonable yields. The presence of an internal alkyne did not affect the formation of β-sulfonyl enamines 4k (79%), illustrating the exquisite chemoselectivity between internal and terminal alkynes. All of these heteroaryl- and alkyl-substituted β-sulfonyl enamines in Scheme 1 are novel compounds that could prove useful as intermediates in organic and medicinal chemistry research.

We next set out to evaluate the reaction scope with respect to the sulfinate component in reactions with 4-phenyl phenylacetylene 1y (Table 2). Whether electron-rich or electron-deficient, aryl sulfonates afforded the corresponding β-sulfonyl enamines in high yields (5a–5c, 75–82%). Alkyl sulfinate salts also proved suitable reaction partners, giving products 5d–5f with similar efficiency.

To gain insight into the reaction mechanism, the reaction of 4-ethynyltoluene 1b was monitored by ¹H NMR spectroscopy under standard reaction conditions in [D₆]DMSO (Figure 2a). By comparison with authentic samples, signal A at 4.1 ppm was assigned as the acetylenic proton of 1b. After 40 min, this signal had almost completely disappeared, and new doublets at 4.97 and 5.61 ppm were assigned as the olefinic hydrogens of vinyl azide VA, which reached a maximum intensity after 20 min. The singlet at 5.07 ppm was assigned as the olefinic hydrogen of product 3b, which
The latter is captured by water to produce \( \text{N}_2 \) with release of \( \text{H}_2 \). This in turn is readily attacked by the sulfonyl free radical C, leading to carbon-centered radical D, which rapidly converts to iminyl radical E with release of \( \text{N}_2 \).

Stereochemistry of the product should be ascribed to the intramolecular hydrogen-bonding effect. Note that the screening of a variety of potential radical precursors, such as Togni’s reagent, diphenylphosphine oxide, and potassium 2-oxo-2-phenylacetate, were not successful in the desired aminofunctionalization of terminal alkyne, and therefore demonstrated the generation of sulfonyl radical under above mild conditions appears to play a crucial role in controlling the reaction sequence.

Finally, a gram scale reaction of phenylacetylene 1c, TMSN\(_3\), and sodium \( p \)-tolenesulfinate 2a was tested; delightfully, this reaction could be performed on 20 mmol scale and proceeded smoothly to give product 3e with only a modest decrease in yield (3.11 g, 57%; Scheme 3). Next, further synthetic manipulations were conducted to explore its reactivity. As reported by Jiang, \( \beta \)-ketosulfone 6 could be prepared by treatment of 3e with silica gel (95%), while 2H-azirine 7 was obtained in 65% yield through hypervalent iodine-induced oxidative cyclization.

Unexpectedly, dihydropyrrole 8 was obtained under Bao and Guan’s K\(_2\)S\(_2\)O\(_5\)-mediated oxidative cyclization conditions, instead of a pyrrole as observed with analogous \( \beta \)-keto or \( \beta \)-ester enamines.

Similarly, a new reaction pattern was discovered on treatment of 3e with NBS, which afforded polybrominated imine 9 in 72% yield. N-brominated imines have rarely been reported.

In summary, a convenient and functional-group-tolerant silver-catalyzed three-component reaction of terminal alkyne, TMSN\(_3\), and sodium sulfinites has been developed, which shows broad substrate scope with respect to both the products and functional groups.
alkyne and sulfinate. The reaction proceeds through an unprecedented sequence of alkyne hydrazidization, and radical addition of a sulfonyl radical to the in situ generated vinyl azide. This strategy represents an appealing means to achieve alkyne aminofunctionalization under mild reaction conditions; extension to other radical species is under way, and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkyne · aminosulfonylation · radical reactions · silver catalysis · stereoselectivity

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