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A new cascade halosulfonylation of 1,7-enynes toward 3,4-dihydroquinolin-2(1*H*)-ones *via* sulfonyl radical-triggered addition/6-*exo-dig* cyclization

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Abstract

A new cascade three-component halosulfonylation of 1,7-enynes for efficient synthesis of densely functionalized 3,4-dihydroquinolin-2(1*H*)-ones has been established from readily accessible arylsulfonyl hydrazides and NIS (or NBS). The reaction pathway involves *in situ*-generated sulfonyl radical-triggered α,β -conjugated addition/6-*exo-dig* cyclization/radical coupling sequence, resulting in continuous multiple bond-forming events including C–S, C–C and C–I (or C–Br) bonds to rapidly build up molecular complexity.

Organosulfones represent a highly valuable class of compounds and serve as “privileged motifs” in the field of agrochemistry and pharmaceutical chemistry owing to their significant biological activities such as anticancer, *anti*-HIV, and antibacterial.¹ They are also extensively utilized as the key precursors in numerous total syntheses² as the sulfone

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functionality can be removed readily by various desulfonylation methods.³ Therefore, considerable efforts have been made toward the formation of sulfones.⁴ Traditional methods for sulfone preparation involved *S*-nucleophilic substitution between carbon electrophiles and sodium sulfonates or thiophenols followed by oxidation (Scheme 1a).⁵ These methods suffer from multistep sequences to preinstall a leaving group and incompatibility with many functional groups. Most recently, the addition of sulfonyl radicals to unsaturated systems such as alkenes and alkynes which offers a straightforward approach for the synthesis of sulfone compounds has been extensively explored.⁶ Various in-situ generated sulfonyl radicals, from sulfonyl halides,⁷ sodium sulfinate,⁸ arylsulfinic acids,⁹ cyanide¹⁰ and azide¹¹ by treatment of radical initiators or photolysis, have been successfully applied in these radical additions (Scheme 1b). Alternatively, easily available arylsulfonyl hydrazides also behave as a sulfonyl radical source in the presence of a stoichiometric amount of oxidants,¹² which have been specially developed in addition-cyclization toward sulfonylated indolin-2-ones (Scheme 1c).¹³ Recently, we reported the addition of a variety of C-center radicals to the double bond of *N*-tethered 1,7-enynes **1**. In these transformations, regioselective radical addition cascades were postulated involving the participation of a vinyl intermediate, followed by hydrogen abstraction and radical coupling to give spiro-substituted cyclopenta[*c*]quinolones (Scheme 1d).¹⁴ We reasoned that under suitable oxidative conditions, the sulfonyl radicals could be engaged in additional bond-forming events with *N*-tethered 1,7-enynes **1** to form the vinyl intermediates, which would be trapped by adequate radicals partners through radical coupling, thus expanding the synthetic utility of these processes. Herein we report the successful realization of this concepts *via* a novel cascade 1,7-enyne-cyclization trapped by two different radicals, which enabled the one-pot synthesis of densely functionalized 3,4-dihydroquinolin-2(1*H*)-ones with unprecedented substitution patterns through halosulfonylation of 1,7-enynes (Scheme 1e).

We first investigated the reaction between 1,7-enynes **1a** and tosylhydrazide (**2a**) in the presence of different iodine sources and oxidants to identify the optimal reaction conditions and the results are summarized in Table 1. Using tetrabutylammonium iodide (TBAI, 1.0 equiv.) as an iodine source and *t*-butyl hydroperoxide (TBHP, 2.0 equiv.) as an oxidant in CH₃CN (acetonitrile) at 60 °C, the expected 3,4-dihydroquinolin-2(1*H*)-ones **3a** was obtained in 60% yield (Table 1, entry 1). A slightly lower yield (58%) was afforded in the presence of 1.0 equivalent of I₂ (entry 2). In another case of NIS, the reaction work more efficiently and delivered a higher 69% yield (entry 3). However, use of KI completely compressed the reaction process (entry 4). Screening followed by other oxidants revealed that *tert*-butyl peroxybenzoate (TBPB), benzoyl peroxide (BPO) and di-*tert*-butyl peroxide (DTBP) all met little success in this radical addition-cyclization (entries 5–7). Subsequently, taking the combination of TBHP with NIS, we utilized 1,4-dioxane, DMF, DMSO, DCE or toluene as the solvent in this reaction to examine the solvent effects and found that DCE was the best choice, which provided **3a** in 76% yield (entries 8–12). To our delight, the yield of **3a** could be improved to 84% when the dosage of NIS was increased to 1.2 equivalents in DCE at 60 °C (entry 13). Further increasing load of NIS or TBHP did not facilitate reaction process (entries 14–16). It was also found that the reaction temperature impacted an important influence on the reaction efficiency. The lower conversion was observed with reaction temperature being at either 40 °C or 80 °C (entry 13 vs entries 17 and 18). Some

control reactions showed that the transformation did not take place in the absence of either NIS or TBHP (entries 19 and 20).

Having the optimized conditions in hand, we turned to evaluate the generality of the halosulfonylation using a variety of *N*-tethered 1,7-enynes **1** and arylsulfonyl hydrazides. Satisfyingly, a wide range of highly substituted 3,4-dihydroquinolin-2(1*H*)-ones **3b–3y** were obtained in a highly selective and functional-group-compatible manner using NIS as the stoichiometric halogen source (Scheme 2). Substrates **1** with different substitution patterns on the aromatic rings of both the alkynyl (R^2) and sulfonyl (Ar) moieties can be efficiently transformed into the corresponding poly-functionalized 3,4-dihydroquinolin-2(1*H*)-ones **3** in good to excellent yields. Similarly, arylsulfonyl hydrazides possessing various electron-deficient or electron-rich substituents at different positions of aromatic ring were well-tolerated. Additionally, 2-naphthalenyl (2-Np) counterpart was an adaptable substrate in this transformation, allowing the radical-initiated addition-cyclization to the corresponding 3,4-dihydroquinolin-2(1*H*)-ones **3w** in 71% yield. The reaction can be extended to different functional group such as methyl, fluoro, and chloro on *N*-phenyl moiety, with the realization of domino iodosulfonylation of 1,7-enynes. Unluckily, replacing aryl group with *n*-butyl group on the alkynyl unit, 1,7-enynes **1s** was not an adaptable substrate for this reaction (Scheme 2, **3aa**), which may be ascribed to the relative instability of the vinyl radical intermediate **B**, generated in situ from sulfonyl radical-triggered addition/6-*exo-dig* cyclization. On the basis of our success with domino iodosulfonylation of 1,7-enynes, we turned our attention to probing the feasibility of domino bromosulfonylation of 1,7-enynes by exchanging NIS for *N*-bromosuccinimide (NBS). As expected, this protocol tolerates various 1,7-enynes, leading to a highly stereoselective synthesis of structurally diverse 3,4-dihydroquinolin-2(1*H*)-ones **4a–4d** in generally good yields (Scheme 2). The halogen atom was introduced into the exocyclic vinyl unit in this process (products **3** and **4**), offering an opportunity for further elaboration. Unfortunately, *N*-chlorosuccinimide (NCS) did not work in this halosulfonylation of 1,7-enynes.

The resultant densely functionalized 3,4-dihydroquinolin-2(1*H*)-ones **3** and **4** were fully characterized by their NMR spectroscopy and HRMS. Furthermore, in the case of compound **3y** (Figure 1), its structure was unambiguously determined by X-ray diffraction (see the Supporting Information).

To gain the mechanistic insights of this reaction, several control experiments were conducted. 1,7-Enynes **1a** was subjected to reaction with 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylhydroxytoluene (BHT) (Scheme 3a), but without observation of desired product **3a**, which indicates the possible radical process. Next, without arylsulfonyl hydrazides, the reaction between **1a** and 2.2 equiv. of NIS under standard conditions failed to yield diiodinated 3,4-dihydroquinolin-2(1*H*)-ones **5** (Scheme 3b), confirming that arylsulfonyl radical, generated in situ from aryl sulfonylhydrazide, triggered α,β -conjugated addition/6-*exo-dig* cyclization to form vinyl radical intermediate, which was captured by iodine radical. Therefore, sulfonylation occurred prior to iodination step. Unfortunately, exchanging methyl group for hydrogen on the terminal olefin unit, 1,7-conjugated enynes **5** failed to give product **6** under the standard conditions (scheme 3c),

showing that the methyl group located in terminal olefin unit plays a key role in the success of this reaction.

A plausible mechanism is depicted in Scheme 4 on the basis of control experiments mentioned above and the previously reported literature. The first step is to form the sulfonyl radical from sulfonyl hydrazides under the oxidative conditions (Schemes 4a and 4b) with the release of N₂ (Scheme 4c).¹⁵ The intermolecular α,β -conjugated addition of the resulting sulfonyl radical onto 1,7-conjugated enynes **1**, followed by 6-*exo-dig* cyclization gives vinyl radical intermediate **B**.¹⁴ In the presence of iodine radical, **B** is converted into highly substituted 3,4-dihydroquinolin-2(1*H*)-ones **3** (Scheme 4d). The formation of products **4** is similar to this mechanism. Although sulfonyl radicals triggered addition-cyclization reaction has been achieved well,¹² the halosulfonylation of 1,7-enynes toward densely functionalized 3,4-dihydroquinolin-2(1*H*)-ones *via* a three-component radical addition/6-*exo-dig* cyclization is very rare in organic chemistry as mentioned earlier.

In summary, we have developed a new metal-free arylsulfonyl radical-triggered 1,7-enyne-cyclization that offers efficient construction of densely functionalized 3,4-dihydroquinolin-2(1*H*)-ones *via* three-component domino halosulfonylation. This reaction enables sequential arylsulfonyl radical addition/6-*exo-dig* cyclization/radical coupling process, allowing the formation of successive C–S, C–C, and C–I (or C–Br) bonds. The method provides a direct and practical access to important functional *N*-sulfonylated quinolin-2(1*H*)-one derivatives for potential applications in organic and medicinal chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
X-Ray structure of **3y**

a) Traditional nucleophilic substitution

b) Arylsulfonyl radical addition

c) Arylsulfonyl radical addition-cyclization

d) Radical-triggered 1,7-enyne-cyclization

Scheme 1.

Various methods for the synthesis of sulfones

Scheme 2.

Domino synthesis of quinolin-2(1H)-ones **3** and **4**. Yields of isolated products based on substrates **1** by recrystallization for methanol. **1** (0.5 mmol), **2** (1.0 mmol) and NIS (or NBS, 0.6 mmol), TBHP (1.0 mmol, 70% in water), DCE (2.0 mL), at 60 °C for 8.0 hours.

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Scheme 4.
Proposed mechanisms for forming products **3**

Optimization of the reaction conditions^a

^a 1,7-Enynes (**1a**, 1.0 equiv., 0.5 mmol), aryl/sulfonyl hydrazides (**2a**, 2.0 equiv., 1.0 mmol), **I**-source, and oxidant (2.0 equiv.) in solvent (2.0 mL) for 8 hours.

^b Isolated yield.