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Metal-Free Radical-Triggered Selenosulfonation of 1,7-Enynes for the Rapid Synthesis of 3,4-Dihydroquinolin-2(1*H*)-ones in Batch and Flow

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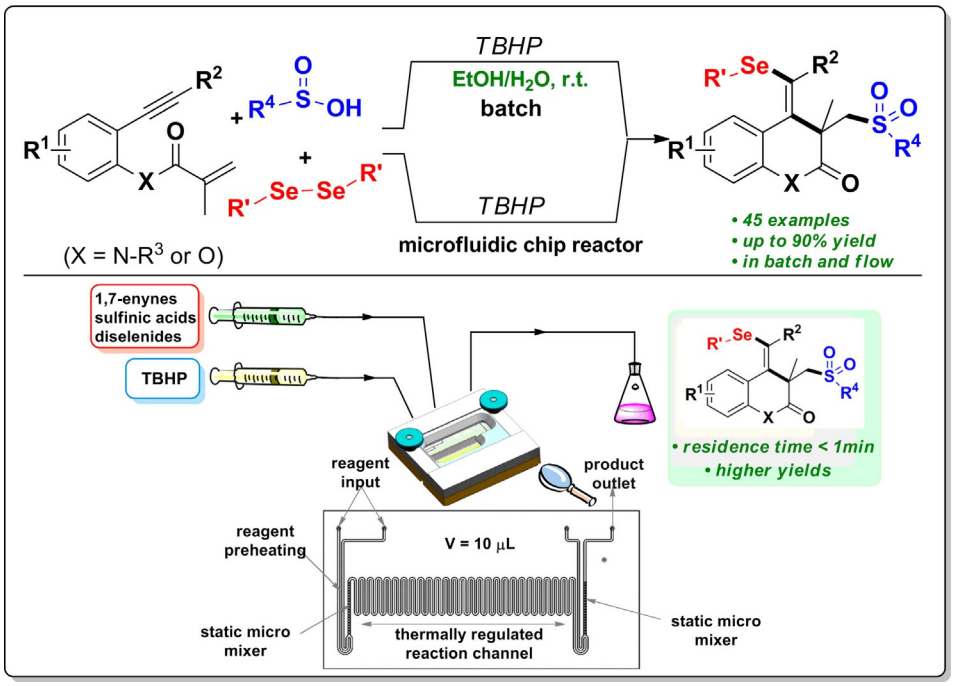
Abstract: A novel three-component selenosulfonation of 1,7-enynes with sulfinic acids and diphenyl diselenides for the formation of multifunctional 3,4-dihydroquinolin-2(1*H*)-ones was developed in batch and flow. This room-temperature protocol provides a highly efficient approach to diverse selenosulfones in moderate to excellent yields and with a broad scope of substrates. It should provide a potential synthesis method for the construction of diverse and meaningful 3,4-dihydroquinolin-2(1*H*)-ones derivatives in the fields of pharmaceutical and biological chemistry. Additionally, an obvious acceleration (20 h to 43 s) was obtained under micro flow conditions.

Keywords: batch and flow procedures; 3,4-dihydroquinolin-2(1*H*)-ones; 1,7-enynes; metal-free process; selenosulfonation

Introduction

Organoselenosulfones represent an extremely important class of compounds that find widespread applications in the fields of pharmaceutical chemistry and organic synthesis.[1] Moreover, they are also widely utilized as the key precursors in the synthesis of natural products as the sulfone and selenium functional groups could be easily introduced and removed from the target molecules through various methods.[2] Accordingly, there is considerable interest in the development of one-pot selenosulfonation reactions toward the construction of the selenosulfone frameworks proceeding from available sulfonyl and selenyl sources.[3] For instance, Zhang and co-workers developed a copper-catalyzed selenosulfonation of alkynes for the synthesis of (*E*)-β-selenovinyl sulfones.[4] Meanwhile, Liu et al. realized the selenosulfonation of acetylenes with arylsulfonylhydrazine and diphenyl diselenide.[5] Despite these significant advances, the utilization of radical-triggered selenosulfonation of 1,7-enynes for forming functionalized 3,4-dihydroquinolin-2(1*H*)-ones,[6] to the best of our knowledge, has not been documented yet. On the other hand, oxidative radical 1,7-enyne cyclizations have been a helpful platform for readily accessing various complex cyclic molecules.[7] In addition to ideal annulation efficiency and functional compatibility, these reactions avoid the prefunctionalization of substrates or the use of transition metals.

Recently, several groups have focused on developing radical 1,7-enyne cyclizations for the construction of multifunctional carbocyclic and heterocyclic frameworks.[8] Inspired by these results, we envisioned that, under the suitable conditions, sulfonyl radicals generated *in situ* from sulfinic acids would prefer the addition into the terminal alkenyl unit of 1,7-enynes, and be captured by other radicals to create new functional heterocyclic molecules.[9] As expected, the three-component reaction of 1,7-enynes **1** with sulfinic acids **2**



Scheme 1. Selenosulfonation of 1,7-enynes in batch and flow.

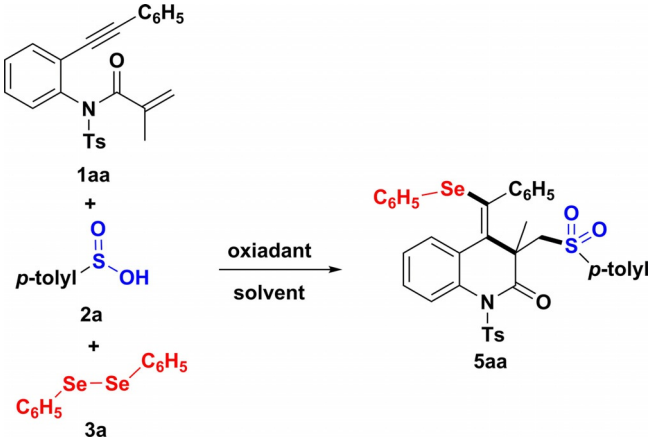
and diselenides **3** proceeded smoothly, affording richly decorated 3,4-dihydroquinolin-2(1*H*)-ones with good to excellent yields through sulfonyl radical-induced 6-*exo*-dig cyclization. Herein, we describe this new three-component selenosulfonation, which tolerated two different radicals in a one-pot manner. This method could be efficiently implemented in batch and flow to afford the desired selenosulfones in moderate to excellent yields (Scheme 1).

Results and Discussion

At the outset, the reaction of *N*-[2-(phenylethynyl)-phenyl]-*N*-tosylmethacrylamide (**1aa**, 0.2 mmol) with 4-methylbenzenesulfinic acid (**2a**, 0.6 mmol) and diphenyl diselenide (**3a**, 0.1 mmol) was chosen as model reaction to optimize the conditions (Table 1). The model reaction was carried out in EtOH under air conditions at room temperature using H_2O_2 (3.0 equiv,) as the oxidant, the expected product **5aa** was obtained, albeit with merely 20% yield(Tables 1, entry 1). Subsequently, we attempted to utilize other oxidants to improve the efficiency of the transformation, such as di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), 1,3-dichloro-2-propanol (DCP), potassium persulfate ($K_2S_2O_8$), *tert*-butyl hydroperoxide (TBHP), 3-chloroperoxybenzoic acid (*m*-CPBA) and sodium hypochlorite (NaClO) (entries 2–8). To our delight, the experiments revealed that TBHP showed the best performance, affording the desired selenosulfonation product **5aa** in 72% yield (entry 6). Furthermore, we conducted a screening of various solvents, including 1,4-dioxane, dichloromethane (DCM), acetone, ethyl acetate (EA), methanol (MeOH), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), H_2O and EtOH/H_2O for this reaction (entries 9–18). As a result, we found that EtOH and H_2O (5:1 v/v) as co-solvent system was the most suitable for the reaction (entry 18). Next, the temperature was raised to 40 °C, but a relatively lower yield 76% of **5aa** was found (Table 1, entry 19). Further increasing the reaction temperature obviously lowered the conversion into **5aa** (entries 20). Our next endeavour was to change other reaction parameters by the use of 0.2 mol% catalyst, such as I_2, tetrabutylammonium iodide (TBAI) and $FeCl_3$, and substrate ratio for this reaction (entries 21–25). After careful optimization, we found that without any catalyst, adjusting the substrate ratio to 1:3:0.75 (**1aa**:**2a**:**3a**) at 25 °C under air conditions gave the best outcome, affording **5aa** in 88% yield (entry 24).

Having established the optimal reaction conditions for the selenosulfonation of 1,7-enynes, we set out to evaluate the scope of these transformations by utilizing various of N-tethered 1,7-enynes, sulfinic acids, and diselenides. As shown in Scheme 2, *p*-tolylsulfinic acid **2a** and diphenyl diselenide **3a** were first selected as representative sulfonyl radical donor and selenium source to probe the influence of substituents (R^1–R^3) on the 1,7-enynes. Satisfyingly, with the R^3 group tethered by the Ts group, various substituents with electronically poor and rich natures at different positions of the alkynyl (R^2) moiety were proven to have no

Table 1. Screening for different catalytic conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	–	H_2O_2	EtOH	20
2	–	DTBP	EtOH	51
3	–	TBPB	EtOH	12
4	–	DCP	EtOH	37
5	–	$K_2S_2O_8$	EtOH	49
6	–	TBHP	EtOH	72
7	–	*m*-CPBA	EtOH	trace
8	–	NaClO	EtOH	N.D
9	–	TBHP	1,4-dioxane	73
10	–	TBHP	DCM	60
11	–	TBHP	acetone	76
12	–	TBHP	ethyl acetate	49
13	–	TBHP	MeOH	65
14	–	TBHP	DMF	trace
15	–	TBHP	DMSO	trace
16	–	TBHP	H_2O	23
17	–	TBHP	EtOH/H_2O	64[c]
18	–	TBHP	EtOH/H_2O	80
19	–	TBHP	EtOH/H_2O	76[d]
20	–	TBHP	EtOH/H_2O	71[e]
21	I_2	TBHP	EtOH/H_2O	67
22	TBAI	TBHP	EtOH/H_2O	80
23	$FeCl_3$	TBHP	EtOH/H_2O	76
24	–	TBHP	EtOH/H_2O	88[f]
25	–	TBHP	EtOH/H_2O	87[g]

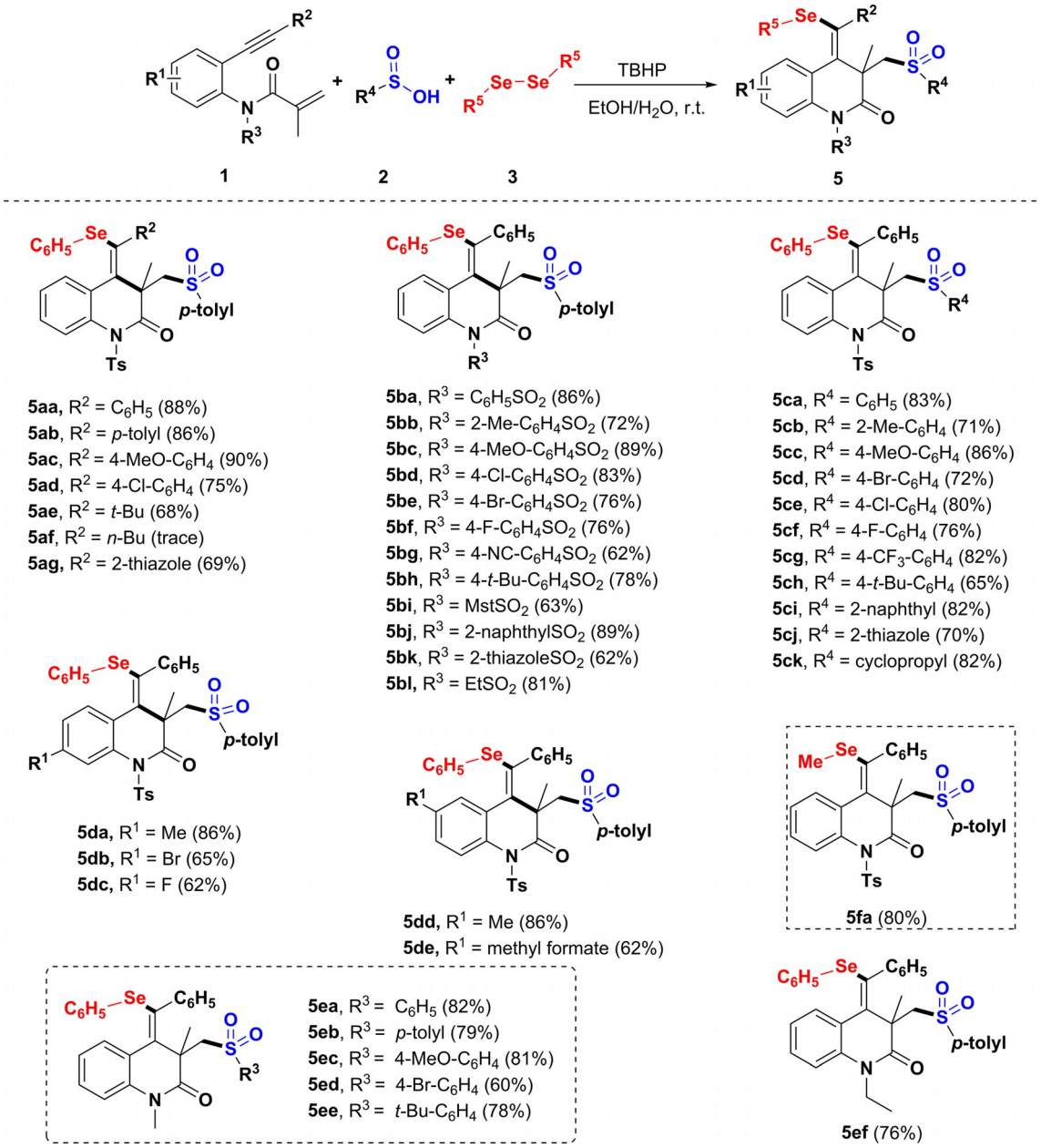
[a] *Reaction conditions:* **1aa** (0.2 mmol), **2a** (0.6 mmol), **3** (0.1 mmol), oxidant (3.0 equiv.), and solvent is EtOH/H_2O = 5:1 (v/v, 2 mL) in the tube at 25 °C under air for 20 h.
[b] Isolated yield is based on **1aa**.
[c] EtOH/H_2O = 1:1
[d] The reaction was carried out at 40 °C.
[e] The reaction was carried out at 60 °C.
[f] **1aa**:**2a**:**3a** = 1:3:0.75.
[g] **1aa**:**2a**:**3a** = 1:3:1.

effect on this radical-induced process, giving the **5aa**–**5ag** in moderate to excellent yields. Among them, a slight increase in the yield was obtained (**5ac**, 90%) when the *p*-methoxyphenyl (PMP) counterpart (**1ac**) served as a reaction partner whereas the presence of a *t*-Bu group resulted in a significantly lower yield (**5ae**). However, the *n*-butyl counterpart **1af** was not a suitable substrate for this reaction (**5af**), which may be caused by the relative instability of the *in-situ* generated vinyl radical intermediate during the process.

Moreover, high yields could be obtained independent of the electronic characteristics of the substituents at the *para*-position of the benzenesulfonyl protected group on the amine anchor (**5ba**–**5bl**). Next, sulfinic acids with different substitution patterns and electronic properties were tested. The results indicate that sulfinic acids **2** bearing both electronically rich (MeO, **5cc**), neutral (H, **5ca**; methyl, **5cb**; *t*-Bu, **5ch**) and poor (Cl, Br, F, CF_3, **5cd**–**5cg**) groups at different positions of the phenyl ring enabled the sulfonyl radical-triggered *6-exo-dig* cyclization to open the way to a collection of *N*-sulfonylated quinolin-2(1*H*)-ones **5ca**–**5ck** in 65–86% yields. Generally, electron-donating substituents on the phenyl ring of **2** favor this transformation more than their electron-deficient ones (**5cb**, **5cc**, **5ch** *vs.* **5cd**-**5cg**). Fortunately, substrates **2** carrying other sulfonyl groups such as 2-naphthyl, 2-thiazole and cyclopropyl were also suitable for this process (**5ci**–**5ck**). Additionally, we tested different functional groups (R^1) like methyl, methoxy, bromo and fluoro located at the 4-position or 5-position of the internal arene ring of 1,7-enynes **1** to explore its synthetic utility. All these substituents **1da**–**1de** were tolerated well, giving access to the desired products **5da**–**5de** with yields ranging from 62% to 86%. *N*-Methyl- and *N*-ethyl-protected 1,7-enynes **1ea**–**1ef** still showed high reactivity in the current selenosulfonation, delivering the corresponding products **5ea**–**5ef** in 60–82% yields. Besides, dimethyl diselenide was also suitable for this transformation, affording the selenosulfonation product **5fa** in 80% yield. Finally, the configuration of **5aa** was confirmed by X-ray analysis (see Figure 1 in the Supporting Information).[10]

Interestingly, the selenosulfonations of phenol-linked 1,7-enynes **4a**–**4d** were successfully realized to construct chroman-2-one derivatives **6a**–**6d** with 46–70% yields under the standard conditions (Scheme 3). The results indicated that the reaction could tolerate various O-tethered 1,7-enynes **4a**–**4d**, but gave relatively lower yields as compared with the N-linked counterparts.[11] This is due to the fact that the electronegativity of oxygen atom is larger than that of nitrogen, thereby decreasing the reactivity of the substrates.

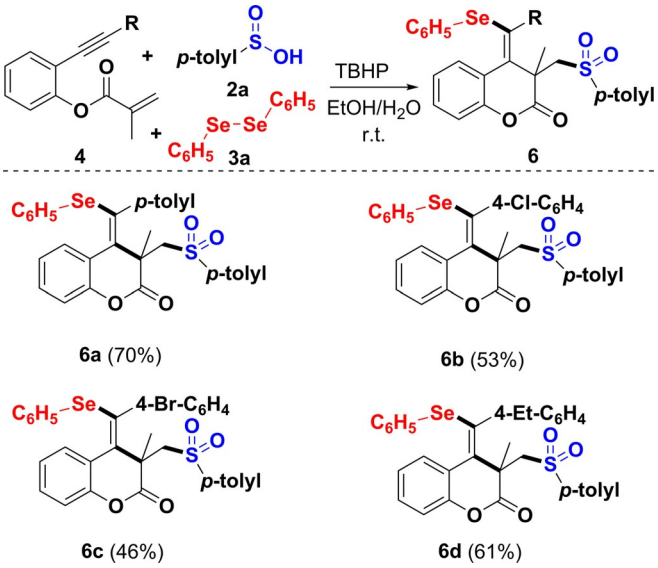
To further investigate the mechanism, we carried out several control experiments (Scheme 4). 1,7-Enyne **1aa** was reacted with **2a** and **3a** under the standard conditions in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) without observation of product **5aa**, indicating that an SET-type mechanism is at hand (Scheme 4a). Subsequently,



Scheme 2. Substrate scope for the synthesis of **5**. *Reaction conditions:* **1aa** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.15 mmol), oxidant (3.0 equiv.), solvent (2 mL) in the sealed reaction tube under air for 20 h. Isolated yield based on **1aa**.

without an oxidant, the reaction did not occur and the substrate was recovered completely (Scheme 4b). Without sulfinic acids, on treatment of **1aa** and 2.0 equiv. of diphenyl diselenide **3** under the standard conditions, no expected product **7** was observed (Scheme 4c). Finally, 4-methylbenzenesulfonyl hydrazide (**1d**) was utilized as the the sulfonyl source, and an 82% yield of **5aa** was obtained under the standard condition (Scheme 4d). These results confirmed that the arylsulfonyl radical, generated *in-situ* from arylsulfinic acid, favorably triggered the addition-cyclization to form the vinyl radical intermediate, followed by the interception of the phenylselenyl radical. Therefore, we can speculate that the sulfonylation occurred prior to the selenylation step.

Based on our observations and the reported investigations,[12] a reasonable radical mechanism is proposed in Scheme 5. Initially, sulfonyl radical **A** was formed through oxidation of the arylsulfinic acid in the presence of TBHP *via* a single electron transfer process. Similar to this procedure, diphenyl diselenide generates a phenylselenyl radical.[13] Subsequently the sulfonyl radical **A** attacks thze terminal olefin of 1,7-enynes **1aa** to give radical **B**, followed by a 6-*exo-dig*

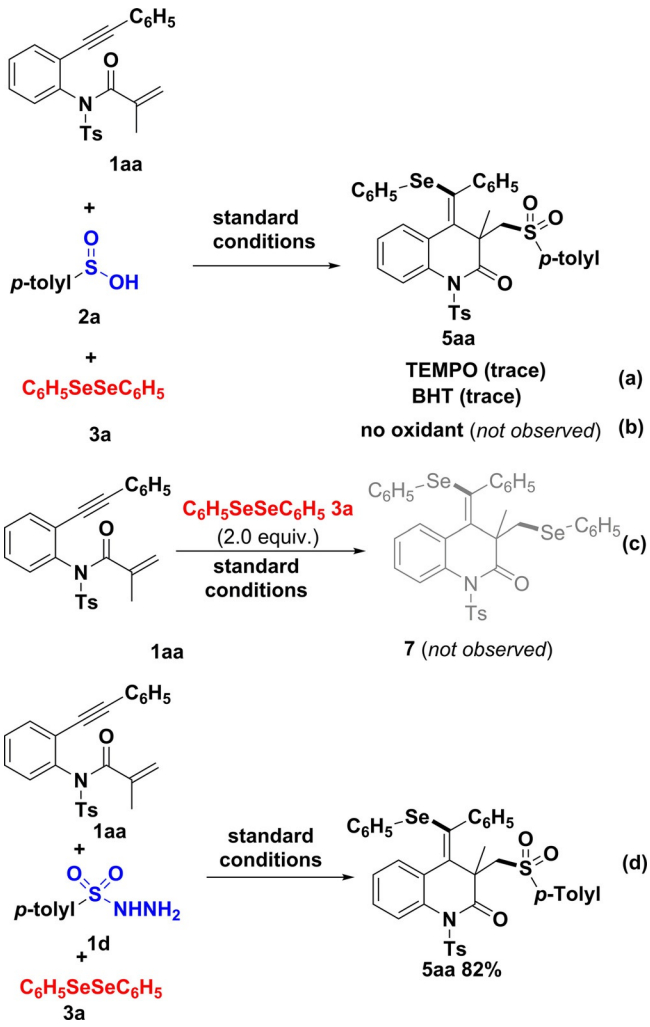


Scheme 3. Substrate scope for the synthesis of **6**. *Reaction conditions:* **4a** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.15 mmol), oxidant (3.0 equiv.), solvent (2 mL) in the sealed reaction tube under air for 20 h.Isolated yield based on **4a.**

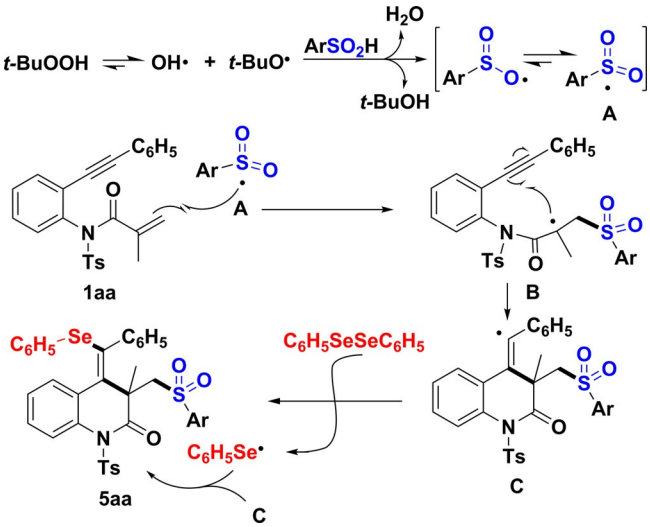
cyclization to form vinyl radical intermediate **C**. In the presence of phenylselenyl radicals, intermediate **C** is transformed to the final 3,4-dihydroquinolin-2(1*H*)-ones **5** *via* radical coupling (Scheme 5). Further investigations unravel the more detailed mechanism are under way in our laboratory.

As we know, reactions in continuous flow system can have numerous advantages over the standard batch reactions, especially in the field of radical chemistry.[14] In order to improve the reaction efficiency and shorten the reaction time, we tried to transfer the three-component reaction of 1,7-enynes **1**, arylsulfinic acids **2** and diselenides **3** from batch to a chip flow microreactor (Figure 1). Next, we designed a micro-reactor flow system which was assembled from a microfluidic chip reactor and two syringe pumps. The volumes of the microfluidic chip reactor and syringes are 10 μL and 1000 μL, respectively. The mole ratio of reactants and reaction time can be modified by switching the flow rates of the syringes. To our delight, after the relative flow rates and solvents has been optimized (Table 2), a 90% yield of **5aa** was obtained. When the flow rate was 7.0 μL min^{-1}, the residence time was only 43 s.

It is notable that the improved product yield (90% in flow *vs.* 88% in batch) and decreased reaction time (43 s in flow *vs.* 20 h in batch) can be explained by considering the short length scale, which led to a high reaction efficiency in the microfluidic chip reactor. The reaction conditions were also compatible with other selenosulfones, and **5ba** and **5ca** were produced under similar reactions in up to 85% and 86% yields, respectively. Morever, we calculated the space-time



Scheme 4. Trapping experiments.



Scheme 5. Proposed mechanism.

yield and the productivity for a better comparison between batch and flow. The results showed that the

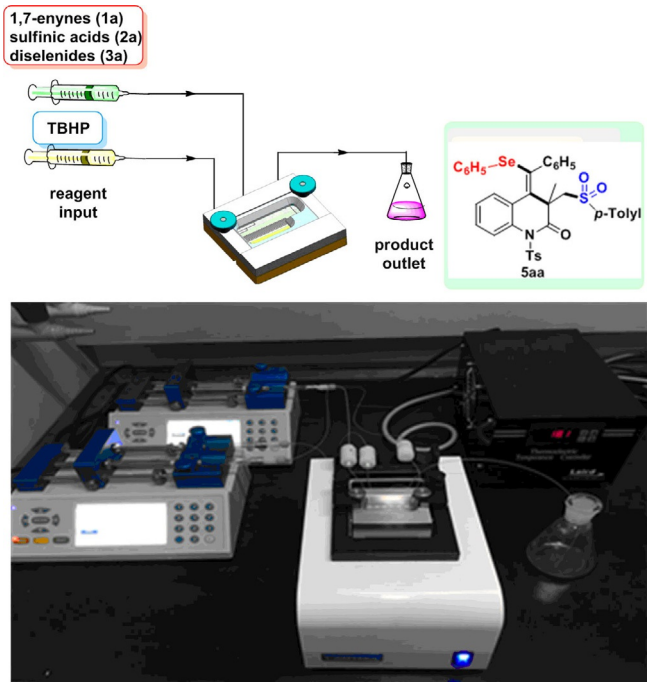


Figure 1. Microfluidic chip reactor for the preparation of 3,4-dihydroquinolin-2(1*H*)-ones.

Table 2. Optimization of the conditions in a microfluidic chip reactor.[a]

Entry	Flow rate [μL/min]	Solvent	Yield [%][b]
1	5	THF	34
2	5	DCM	77
3	5	EtOH/H_2O	80
4	5	dioxane	66
5	5	MeCN	33
6	5	DMF	12
7	10	EtOH/H_2O	72
8	9	EtOH/H_2O	83
9	8	EtOH/H_2O	87
10	7	EtOH/H_2O	90
11	6	EtOH/H_2O	86
12	4	EtOH/H_2O	76
13	3	EtOH/H_2O	57
14	2	EtOH/H_2O	45
15	1	EtOH/H_2O	42

[a] *Reaction conditions:* **1aa** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.15 mmol), EtOH/H_2O = 5:1 (v/v, 1 mL) in one syringe, oxidant (3.0 equiv.) and EtOH/H_2O = 5:1 (v/v, 1 mL) in the other syringe, the reaction was carried out in the microfluidic chip reactor (10 μL) under air.

[b] Isolated yield based on **1aa**.

space-time yields which were conducted in the microfluidic chip reactor were much higher than in the batch (see Table 3 in the Supporting Information).

Conclusions

In conclusion, we have developed a novel three-component selenosulfonation strategy *via* 6-*exo*-*dig* cyclization of 1,7-enynes. This method was conducted both in batch and flow under metal-free conditions, obtaining various poly-functionalized 3,4-dihydroquinolin-2(1*H*)-ones. A wide range of functional groups can be tolerated well with the standard conditions, and the corresponding selenosulfones were obtained in good to excellent yields. A significant feature of the developed process is the cascade-type formation of successive C–S, C–C, and C–Se bonds initiated by the addition of a sulfonyl radical. Moreover, continuous-flow chemistry proved its effectiveness by decreasing the reaction time from 20 h to 43 s. It also indicates the major advantage of continuous flow systems to allow reaction parameters to be independently adjusted. Further studies towards understanding the mechanistic details and synthetic applications of this kind of transformation in the synthesis of other selenosulfone compounds are currently underway.

Experimental Section

General Methods

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 500 or 300 MHz spectrometer in $CDCl_3$ with chemical shifts (δ) given in ppm relative to TMS as internal standard [(s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz)]. HR-MS (ESI) were determined by using a microTOF-QIIHR-MS/MS instrument (Bruker). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

Procedure for the Synthesis of Product 5aa in Batch

N-[2-(Phenylethynyl)phenyl]-*N*-tosylmethacrylamide (**1aa**, 0.2 mmol, 0.055 g), 4-methylbenzenesulfinic acid (**2a**, 0.6 mmol, 0.0936 g), diphenyl diselenide (**3a**, 0.15 mmol, 0.04682 g) and EtOH/H_2O (v:v = 5:1, 2 mL) were added to a 10-mL Schlenk tube, followed by addition of TBHP (70% aqueous, 3.0 equiv.). The mixture was stirred at 25 °C as monitored by TLC, after the starting material **1aa** had completely gone, the mixture was poured into water (15 mL). The solution was then extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether = 1:15) to afford the desired product **5aa**.

Procedure for the Synthesis of Product 6a in Batch

2-(Phenylethynyl) phenylmethacrylate (**4a**, 0.2 mmol, 0.055 g), 4-methylbenzenesulfinic acid (**2a**, 0.6 mmol, 0.0936 g), diphenyl diselenide (**3a**, 0.15 mmol, 0.04682 g) and

EtOH/H_2O (v:v = 5:1, 2 mL) were added to a 10-mL Schlenk tube, followed by addition of TBHP (70% aqueous, 3.0 equiv.). The mixture was stirred at 25 °C as monitored by TLC, after the starting material **1a** had completely gone, the mixture was poured into water (15 mL). The solution was then extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether = 1:15) to afford the desired product **6a**.

Microfluidic Chip Reactor Set-Ups

Reactions were performed in a Labtrix® Start R2.2 system (Chemtrix BV, NL). This commercially available microreactor system can be fitted with different glass chip reactors, of which in this project a 10.0 μL microreactor chip (Chemtrix 3227 reactor, 3 inlets) was employed. This reactor chip employs staggered oriented ridge (SOR-2) static micromixers to assure fast mixing. Reaction temperatures were controlled *via* a MTTC1410 temperature controller (Melcor Thermal Solutions, temperature range −20 to 195 °C), while the reactor pressure was maintained at 20 bar backpressure *via* a preset back-pressure regulator (Upchurch Scientific). Reactant solutions were injected into the reactor *via* 1 mL gastight syringes (SGE). Flow rates were varied between 0.1 and 40 μL min^{-1}, and were controlled *via* syringe pumps (Chemyx).

Flow Procedure for the Preparation of 5aa

N-[2-(Phenylethynyl)phenyl)-*N*-tosylmethacrylamide (**1aa**, 0.2 mmol, 0.055 g), 4-methylbenzenesulfinic acid (**2a**, 0.6 mmol, 0.0936 g) and diphenyl diselenide (**3**, 0.15 mmol, 0.04682 g) were dissolved in 1 mL of EtOH/H_2O (v:v = 5:1). The solution was charged in a 1-mL BD Discardit II syringe. Subsequently, the TBHP (a 70% solution in water, 3.0 equiv., approximately 0.39 g) was diluted in 1 mL of EtOH/H_2O (v:v = 5:1). The solution was charged in the other 1-mL BD Discardit II syringe. Next, the two syringes were fitted to the syringe pump (Fusion 200 Classic) and connected to the inlet of the 10-μL microfluidic chip reactor, respectively. The outlet of the microfluidic chip reactor was fitted to a collection flask. The syringe pumps were operated at a flow rate of 7 μL min^{-1} (43 s residence time). The resultant reaction mixture was monitored using TLC and/or LC-MS. The organic mixture was diluted in ethyl acetate and was introduced into a separation funnel. The organic phase was washed 3× with saturated aqueous $NaHCO_3$ and 1× with brine solution sequentially. The aqueous phase was backwashed once with ethyl acetate. The collected organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica afforded the product. If necessary, recrystallization was conducted: solids were dissolved in a minimum of acetone (or dichloromethane) and petroleum ether was added. Next, the resultant mixture was kept in the freezer (−26 °C) overnight. The formed crystals were filtered off and washed with a minimum of petroleum ether. The final product was weighed and characterized by ^1H NMR, ^{13}C NMR and melting point analysis.

Batch Procedure for the Preparation of 6a

The substrate 2-(phenylethynyl) phenylmethacrylate (**4a**, 0.2 mmol, 0.055 g), 4-methylbenzenesulfinic acid (**2a**, 0.6 mmol, 0.0936 g), diphenyl diselenide (**3a**, 0.15 mmol, 0.04682 g) and EtOH/H_2O (v:v = 5:1, 2 mL) were added to a 10-mL Schlenk tube, followed by addition of TBHP (70% aqueous, 3.0 equiv.). The mixture was stirred at 25 °C as monitored by TLC, after the starting material **1a** had completely gone, the mixture was poured into water (15 mL). The solution was then extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether = 1:15) to afford the desired product **6a**.

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