Herein, we report a convenient and environmentally friendly electrochemical technique that enables the regioselective construction of 4-sulfenyl-1H-isochromen-1-ones using readily available precursors such as o-alkynyl benzoates and diaryl disulfides. This electrochemical process has been accomplished through constant current electrolysis in an undivided cell under external acid, catalyst, oxidant, or metal-free conditions. Owing to this protocol’s mild reaction conditions, the products are obtained in good to very good yields, demonstrating a broad substrate scope and functional group tolerance.

Isocoumarins constitute a significant class of heterocyclic compounds and have attracted a lot of interest in the realm of organic chemistry due to their diverse range of applications and structural adaptability. These heterocyclic organic compounds are extensively present in the core structures of various natural products and are distinguished by a fused benzene and α-pyrene ring system. They exhibit a broad range of biological activities such as anti-bacterial, anti-inflammatory, anti-fungal, anti-microbial, cytotoxic, immunomodulatory, anti-angiogenic, and anti-cancer properties, and as weedkillers or protease inhibitors (Fig. 1). Chalcogenyl isocoumarins exhibit significant pharmaceutical potency, boasting superior physicochemical properties. Moreover, medicinal chemistry and drug development efforts find them to be appealing targets due to their potential and synthetic accessibility.

Besides, diaryl disulfides are a valuable class of organic compounds that offer unique chemical properties and applications in pharmaceuticals and materials chemistry due to their diverse reactivity and structural versatility. They have been widely employed as coupling partners in transition-metal-catalyzed cross-coupling reactions and have exhibited promising biological activities, including anti-cancer, anti-microbial, and anti-viral properties. They can serve as building blocks for the synthesis of polymers, liquid crystals, and organic semiconductors. Also, they have been investigated as corrosion inhibitors for metal surfaces, particularly in protecting steel and other alloys against corrosion in harsh environments.

In recent years, electro-organic synthesis has witnessed remarkable progress, revolutionizing traditional approaches to organic chemistry. By harnessing the power of electricity, scientists have unlocked new avenues for the efficient and sustainable synthesis of organic compounds. This burgeoning area of research capitalizes on the principles of electrochemistry to facilitate diverse transformations, offering unprecedented control over reaction conditions and selectivity. In the future, electro-organic synthesis is expected to bring about key breakthroughs and advancements to the forefront of modern organic chem-
Various conventional methods have been reported for constructing 4-organochalcogenyl isochromenones from o-alkynylbenzoates and diaryl organochalcogenides. For instance, Zhou’s research group reported an FeCl3-catalyzed synthesis of 4-sulfenyl isocoumarins in good yields at an elevated temperature. In 2012, Ding et al. demonstrated a Lewis acid (BCl3 and BF3·Et2O) catalyzed electrochemical cyclization of o-alkynylbenzoates with trifluoromethanesulfanylamide. Later, in 2019, Du and co-workers illustrated the use of in situ-generated PhSCI for the synthesis of 4-sulfenylisocoumarins by utilizing a hypervalent iodinating agent (oxidant). Subsequently, the research group of Sahoo reported a Brønsted acid (MsOH) as the solvent using an electrolytic cell equipped with graphite as an anode and platinum as a cathode at ambient temperature (rt). We were delighted to see that, after three hours of reaction at a steady current (I = 12 mA), the anticipated 3-phenyl-4-(phenylthio)-1H-isochromen-1-one 3aa was delivered in 85% yield. When the concentration of LiClO4 was adjusted from 0.15 M to 0.10 M, a slight decrease in the yield was observed, resulting in 82% yield (Table 1, entry 1). Following that, the study was scrutinized by altering various electrode pairs, encompassing “Cgr(+)/Cgr(−)”, “Cgr(+)Ni(−)”, and “Cgr(+)Cglass(−)”; however, none of these electrode pairs demonstrated superior effectiveness compared to “Cgr(+)Pt(−)” (Table 1, entries 2–4).

In addition, the reactions have been explored using several electrolytes, such as Bu4NPF6, Bu4NBF4, Bu4NOAc, Bu4Ni, Bu4NBr, Bu4NCl, Et4NPF6, Et4NBF4, Et4NCIO4, Et4NBr, Et4NCI, KI, and LiOTf, which displayed diminished efficacy to afford the intended 4-sulfenyl-1H-isochromen-1-one 3aa with yields between 0% and 60% (Table 1, entries 5–8).

### Results and discussion

The study of screening was initiated to find out the optimal conditions to achieve the synthesis of 4-sulfenyl-1H-isochromen-1-one 3aa through the regioselective electrochemical annihilation of o-alkynyl benzoate 1a with diphenyl disulfide 2a, which serves as the sulfonylating agent. The reactions were carried out in an undivided cell setup, employing a specified electrolyte and solvent, as outlined in Table 1. Initially, the reaction of 1a (1 equiv.) with 2a (1.2 equiv.) was carried out in the presence of LiClO4 (0.15 M) as an electrolyte and CH3CN as the solvent using an electrolytic cell equipped with graphite as an anode and platinum as a cathode at ambient temperature (rt). We were delighted to see that, after three hours of reaction at a steady current (I = 12 mA), the anticipated 3-phenyl-4-(phenylthio)-1H-isochromen-1-one 3aa was delivered in 85% yield. When the concentration of LiClO4 was adjusted from 0.15 M to 0.10 M, a slight decrease in the yield was observed, resulting in 82% yield (Table 1, entry 1). Following that, the study was scrutinized by altering various electrode pairs, encompassing “Cgr(+)/Cgr(−)”, “Cgr(+)Ni(−)”, and “Cgr(+)Cglass(−)”; however, none of these electrode pairs demonstrated superior effectiveness compared to “Cgr(+)Pt(−)” (Table 1, entries 2–4).

In addition, the reactions have been explored using several electrolytes, such as Bu4NPF6, Bu4NBF4, Bu4NOAc, Bu4NI, Bu4NBr, Bu4NCl, Et4NPF6, Et4NBF4, Et4NCIO4, Et4NBr, Et4NCI, KI, and LiOTf, which displayed diminished efficacy to afford the intended 4-sulfenyl-1H-isochromen-1-one 3aa with yields between 0% and 60% (Table 1, entries 5–8).

### Table 1 Screening study to accomplish 3aa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Divergence from standard conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>None</td>
<td>85 (82)</td>
</tr>
<tr>
<td>2</td>
<td>Cgr(+) and Cgr(−)</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>Cgr(+) and Ni(−)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Cgr(+) and Cglass(−)</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Bu4NPF6, Bu4NBF4, Bu4NOAc</td>
<td>60, 55, 0</td>
</tr>
<tr>
<td>6</td>
<td>Bu4NI, Bu4NBr, Bu4NCl</td>
<td>0, 0, 25</td>
</tr>
<tr>
<td>7</td>
<td>Et4NPF6, Et4NBF4, Et4NCIO4</td>
<td>15, 10, 0</td>
</tr>
<tr>
<td>8</td>
<td>Et4NBr, Et4NCI, KI, LiOTf</td>
<td>0, 0, 20</td>
</tr>
<tr>
<td>9</td>
<td>DCM, DMF, DMA</td>
<td>0, 10, 0</td>
</tr>
<tr>
<td>10</td>
<td>CH3CN/H2O (5/1), DMF/H2O (5/1)</td>
<td>20, 0</td>
</tr>
<tr>
<td>11</td>
<td>CH3CN/HFIP (5/1)</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>CH3CN/MeOH (5/1)</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>MeOH, EtOH, DCE</td>
<td>25, 30, 0</td>
</tr>
<tr>
<td>14</td>
<td>I = 5 mA, 8 mA, 10 mA, 15 mA</td>
<td>50, 70, 84, 75</td>
</tr>
<tr>
<td>15</td>
<td>2 h (3.58 F mol−1), 2.5 h (4.48 F mol−1), 4 h (7.16 F mol−1)</td>
<td>68, 75, 70</td>
</tr>
<tr>
<td>16</td>
<td>2a (0.50/0.55/0.60 equivalent)</td>
<td>42, 50, 65</td>
</tr>
<tr>
<td>17</td>
<td>Without electricity</td>
<td>0</td>
</tr>
</tbody>
</table>

*Standard reaction conditions: undivided cell, graphite anode, platinum cathode (I = 12 mA), 1a (0.25 mmol), 2a (0.30 mmol, 1.2 equiv.), LiClO4 (0.15 M), CH3CN (6 mL), RT, and 3 h (5.37 F mol−1). Isolated yields of 3aa. LiClO4 (0.1 M).
Besides, solvents/solvent combination factors have also been investigated; overall, DCM, DMF, DMA, CH$_3$CN/H$_2$O (5/1), DMF/H$_2$O (5/1), CH$_3$CN/MeOH (5/1), MeOH, EtOH, and DCE as media resulted in the formation of 3aa in yields ranging from 0% to 30% (Table 1, entries 9–13).

Moreover, altering the constant current and reaction time could not improve the yield of 3aa (Table 1, entries 14 and 15).

In the reactions using 0.50, 0.55 and 0.60 equiv. of 2a instead of 1.2 equiv., the yields of the product 3aa decreased (Table 1, entry 16). The reaction showed no progress without

**Scheme 2** Substrate scope of 2-alkynylbenzoates 1 and diaryl disulfides 2.

*Standard reaction conditions: undivided cell, graphite anode, platinum cathode (I = 12 mA), 1 (0.25 mmol), 2 (0.30 mmol, 1.2 equiv.), LiClO$_4$ (0.15 M), CH$_3$CN (6 mL), RT, and 3 h (5.37 F mol$^{-1}$). $^b$ Isolated yields of the products 3aa–3yc. $^c$ Scale up synthesis. $^d$ 4-Methoxybenzenethiol 4 was used instead of 2c. $^e$ Ethyl 2-[(oct-1-yn-1-yl)benzoate 1k.

---

This journal is © The Royal Society of Chemistry 2024

Org. Biomol. Chem. Published on 09 August 2024. Downloaded on 8/19/2024 5:19:31 AM.
electricity, emphasizing that electricity is an indispensable function in propelling the reaction (Table 1, entry 17).

With the optimized conditions in hand (Table 1, entry 1), we scrutinized the substrate scope of o-alkynylbenzoates 1 and diaryl disulfides 2, as depicted in Scheme 2. As mentioned in the above optimization study, the reaction between 2-(phenylethynyl)benzoate 1a and diphenyl disulfide 2a afforded 3-phenyl-4-(phenylthio)-1H-isochromen-1-one 3aa in 85% yield; to illustrate the feasibility of this procedure, a scale-up reaction was also performed with 1a (0.508 g, 2.15 mmol) and 2a (2.58 mmol, 1.2 equiv.) under the optimized electrochemical conditions for 12 h, resulting in the construction of 3aa in 80% isolated yield, as shown in Scheme 2. Besides, the reactions were compatible with 1a and diaryl disulfides (2b and 2c) and delivered the corresponding cyclized products, i.e., lactones 3ab (80%) and 3ac (87%). Remarkably, the reaction was carried out using 4-methoxybenzenethiol as a sulfenylating agent rather than 2c under the standard conditions for 5 h (comparatively longer period); the intended product 3ac was furnished in 75% yield. Next, the reaction was carried out with a para-substituted aromatic compound (R2) derived from the acetylene moiety. Specifically, p-Me (1b), p-OMe (1c), p-NO2 (1d), and p-Bu (1e) provided the expected products 3bc-3ec in 74% to 86% yields. In addition, the structure of 3cc (CCDC 2344681) was determined by single crystal X-ray diffraction analysis.

Moreover, the substrate scope was demonstrated with meta-Me and ortho-Me substituents on the R^3 group, which were well tolerated and successfully gave 3fc (80%) and 3gc (81%) in good yields. Significantly, the method was compatible with halo substituents (1f and 1i), electron-withdrawing groups (1j), and aliphatic alkynes (1k) with 2c and afforded the respective products 3hc, 3ic, 3jc, and 3kc in 76%, 84%, 78%, and 86% yields, respectively. Next, the reaction was performed with methyl 5-chloro-2-(phenylethynyl)benzoate 1l and various diaryl disulfides (2a-2e), which furnished 3la-3le in good yields. Here, we were delighted to note that substrate 1l reacted smoothly with an aliphatic disulfide, i.e., 1,2-diisopropyl disulfane 2d, giving the corresponding product 3ld in 84% yield. Regrettably, the reaction was unable to produce the desired product 3le; instead, it furnished methyl 5-chloro-2-[2-oxo-2-phenylacetyl]benzoate 9, with a very low yield of 35% (for details, see the ESI†). This could be attributed to either the higher oxidation potential of 2e compared to 1l or the electron-withdrawing effect of 1,2-di(pyridin-2-yl)disulfane 2e, which prevents the formation of a sulfenyl radical. Furthermore, the substrate scope of 1 was checked with the R^3 group bearing mild electron-releasing to electron-withdrawing groups such as –Me, –pMe, –pBu, –pCl, and –F, which afforded 3mc-3sc in good to very good yields ranging from 72% to 85%. Despite the aromatic ring substituent position pattern, the procedure yielded 3tc-3yc [3tc (74%), 3uc (72%), 3vc (84%), 3we (80%), 3xc (82%), and 3yc (78%)], which showed the generality of this protocol.

Furthermore, some control experiments were carried out to gain insight into the reaction pathway, as depicted in Scheme 3. At the outset, the reaction was carried out with 1a and 2c in the presence of radical inhibitors TEMPO and BHT, but the formation of the desired cyclized product 3ac was prevented and BHT trapped adduct 5 was observed in HRMS analysis (Schemes 3a and b). When the reaction was performed with DPE as a radical scavenger, 3ac was produced in 20% yield, and a DPE-trapped product 6 was detected in the HRMS study, which signifies that the reaction likely proceeded via a radical pathway (Scheme 3c). To explore the synthetic applicability of 3-phenyl-4-(phenylthio)-1H-isochromen-1-one (3aa), it was directly amidated with NH4OAc, yielding 3-phenyl-4-(phenylthio)isoquinolin-1(2H)-one (7) in 75% yield (Scheme 3d).

In addition, we carried out cyclic voltammetry to get insight into the reaction pathway, as portrayed in Fig. 2. The cyclic voltammograms of methyl 2-(phenylethynyl)benzoate 1a and diphenyl disulfide 2a in CH3CN displayed oxidation peaks at

![Scheme 3 Control experiments and synthetic transformation.](image)

![Fig. 2 Cyclic voltammetry.](image)
1.77 V (curve 2, red line) and 1.65 V (curve 3, blue line), respectively. When testing the mixture of methyl 2-(phenylethynyl)benzoate 1a and diphenyl disulfide 2a, two oxidation signals were observed at 1.81 V and 1.52 V, as shown in curve 4 (pink line), respectively. This indicates that 2a may be more susceptible to undergoing anodic oxidation, which could initiate the oxidation procedure to produce 4-sulfenyl-1H-iso- chromen-1-one 3aa. Based on the outcomes of the cyclic voltammetry, control experiments, mechanistic analysis, and earlier literature findings,\textsuperscript{16,37,49} a plausible reaction mechanism has been postulated and illustrated in Scheme 4. Initially, diphenyl disulfide 2a undergoes anodic oxidation and gives the radical cation I, which on fragmentation furnishes phenylsulfenyl radical II and cation III. Then, intermolecular addition of phenylsulfenyl radical intermediate II to the alkyne moiety of 1a generates the alkenyl radical intermediate IV. Subsequently, the radical intermediate IV undergoes intramolecular $6$-endo-trig cyclization to yield the anticipated product 4-sulfenyliso- coumarin 3aa via demethylation of intermediate IV. The released methyl cation captures the hydroxide anion from the solvent to form MeOH.

**Conclusions**

In summary, we have established a green and effective electrochemical approach to synthesize 4-sulfenyl-1H-isochromen-1-ones through the oxidative regioselective radical cyclization of o-alkynylbenzoates with diaryl disulfides. This reaction takes place at room temperature, exhibits a wide range of substrates regardless of electronic effects, and accomplishes the desired products with good to exceptional yields. Additionally, cyclic voltammetry and scale-up synthesis were performed. A mechanistic study reveals the radical pathway.

**Data availability**

The data supporting this article have been included as part of the ESL.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

We greatly acknowledge the financial support from the Science and Engineering Research Board (SERB), Government of India, New Delhi [File Number CRG/2023/000775]. The authors thank the Indian Institute of Technology, Hyderabad (IITH) for the facilities and infrastructure. A. B. D. gratefully acknowledges PMRF and MoE for the research fellowship.

**References**

Communication

Organic & Biomolecular Chemistry