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Continuous Electrochemical Synthesis of Iso-coumarin Derivatives from o-(1-Alkynyl) benzoates under Metal- and Oxidant-free

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Abstract: A non-oxidant and metal-free strategy for synthesizing iso-coumarin by using a continuous electrochemical microreactor to initiate an oxidative cyclization reaction of o-(1-Alkynyl) benzoate and radicals. This efficient and clean continuous electrosynthesis method not only avoids the complicated gas protection operation and production of by-products in the batch processes, but also help to overcome the difficulty that batch metal catalysis and electrocatalysis are difficult to scale up, and has the potential for pilotscale experiment.

Introduction

Many natural products and small organic molecules with important biological activities contain iso-coumarin skeleton structures.¹ Furthermore, most of iso-coumarin derivatives have good biological activity, such as antibacterial,² anti-inflammatory, ³ anti-cancer,⁴ inhibiting protease and phytotoxic (Figure 1).⁵ These properties not only have potential medical application value,⁶ but have also attract widespread attention in synthetic research.



Figure 1. Biological activity of iso-coumarin derivatives

Therefore, many methods for synthesizing iso-coumarin derivatives have been reported. ⁷ In 2011, Zeni and co-workers achieved the FeCl₃-mediated cyclization of o - (1-Alkynyl) benzoates to afford iso-coumarins in good yields (Scheme 1, method a). ⁸ In 2019, Du's group reported that PICl₂ forms in-situ formation of RSCI / ArSeCI and was applied to afford iso-coumarins in good to excellent yields with alkynyl aryl esters

(Scheme 1, method b).⁹ Although these two reactions proposed a method for the efficient synthesis of iso-coumarin, it is regrettable that their applicability is limited due to the participation of metals and the generation of halogen pollutants. ¹⁰ Thence, considering the possible environmental pollution problems brought by the reaction and its application prospects, it is still a significant challenge to develop an environmentally friendly and inexpensive synthesis method to synthesize isocoumarin.



 R^2 Scheme 1. Various strategies to synthesize iso-coumarin

OMe

R¹

R³SeSeR³

or PhTeTePh

Iso-coumarin can be formed by o-(1-Alkynyl) benzoate that undergo self-cyclization after radical initiation. Mechanistically, the reaction involves electron transfer and oxidation processes. Electrochemical oxidation provides a metal-free and oxidant-free green cleaning method for the reaction.¹¹ At the same time, with the people's attention on electrochemistry,12 there have been reports about the initiation of selenium radicals under electrochemical conditions. Inspired by those work, we have developed a method for the synthesis of iso-coumarin from o benzoate and diorgano diselenide (1-alkynyl) under electrochemical conditions. However, through previous studies, it was found that the reaction in batch yield can only reach 88% at most, and there are also problems such as complicated operations, easy side reactions and long reaction time. ¹³ The literature investigation found that the electrochemical

e(Te)R³

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microreactor can solve these problems well, and it also has the advantages of small current gradient and effective use of electrical energy. ¹⁴ Herein, we have developed a strategy for the continuous synthesis of iso-coumarin derivatives from o-(1-alkynyl) benzoate at room temperature using the electrochemical microreactor (Scheme 1c).

Results and Discussion

Table 1. Optimization of reaction conditions [a]			
	+ PhSeSePh	Continuous flow C(+) / Pt(-)	O O O Ph SePh
1a	2a		3a
Entry	Deviation from stan	Deviation from standard conditions	
1	none	none	
2	no electr	no electricity	
3	constant current: 5 mA		50
4	constant current: 15 mA		80
5	ⁿ Bu ₄ NBr instead of ⁿ Bu ₄ NBF ₄		37
6	ⁿ Bu ₄ NI instead of ⁿ Bu ₄ NBF ₄		36
7	ⁿ Bu ₄ NPF ₆ instead of ⁿ Bu ₄ NBF ₄		53
8	flow rate =450µL/min, resident time =0.5min		n 45
9	flow rate =225µL/min, resident time =1.0min		n 50
10	flow rate =125µL/min, resident time =2.0min		n 60

^a Optimization of the reaction conditions. C (carbon filled PPS, 5.0 × 4.0 cm) anode, Pt (platinum coated, 5.0 × 4.0 cm) cathode, flow volume (0.225 mL), 1a(0.2mmol), 2a(0.12mmol), ⁿBu₄NBF₄(0.4mmol.), CH₃CN=8mL, I=10mA, resident time =5.0 min (5.5F/mol), room temperature. ^b isolated yield.

On the basis of electrochemical conditions in batch screening (Table S2 in SI), the conditions of the reaction in the electrochemical microreactor were screened. The optimal conditions were: using acetonitrile as the solvent, adding 1a, 2a, and two equivalents of "Bu₄NBF₄ and mixing thoroughly. The mixed solution was flowed into the electrochemical microreactor for reaction which with a current set to 10 mA and the flow rate is set to 45 µL/min. And the desired product can be obtained in a yield of 92%. (Table 1, entry 1). When the current is set to 0 mA, no desired product is produced, and then when the current is set to 5 mA or 15 mA, the yield of the target product is reduced. (Table 1, entries 2-4). Next, the electrolyte was simply screened. When "Bu₄NBr, "Bu₄NI, and "Bu₄NPF₆ were used as the electrolyte, the yield was significantly reduced (Table 1, entries 5-7). Finally, the reaction flow rate, that is, the residence time, is investigated. When the residence time is gradually shortened, the yield decreases as it is shortened (Table 1, entries 8-10).

With the optimal reaction conditions established, the substrate adaptability of this reaction was studied in the continuous flow system. First, the reaction of different substituted *o*-(1- Alkynyl) benzoate with diphenyl diselenide was studied to obtain different iso-coumarin. As shown in table 2, a series of *o*-(1- Alkynyl)benzoate derived from ortho-, meta- and para-substituted phenylacetylenes that bear electron-donating groups (Me, Et, OMe) or electron-withdrawing groups (F, Cl, Br, CF₃, NO₂, CN) showed great compatibility to give the corresponding products(Table 2,**3a-3r**). Besides, substrates containing

cycloalkane, thiophene ring, and naphthalene ring substituents attached to alkynes also proved to be well tolerated, providing the corresponding products in relatively higher yields of 83% and 95%, respectively (Table 2, 3s-3v). In addition, substrates containing *n*-butyl, *n*-hexyl, and *t*-butyl groups linked to alkynes were also studied under optimal conditions. To our delight, these substrates are stable under optimized conditions to produce the desired product in good yields (84% to 86%) (Table 2, 3w-3y). Furthermore, the substrate (1z) with a TMS group attached to the alkyne moiety was also converted to the product 3z in 88% yield, respectively (Table 2, 3z). When we explore the effect of different substituents R2, substrates with either an electrondonating methyl group or electron-withdrawing groups including F, CI substituted on the aromatic ring of o-alkynyl benzoate all reacted stably with diphenyl diselenides under the optimized conditions, and the desired product was obtained in good to excellent yields (Table 2,3aa-3ad).Main Text Paragraph.

Table 2. Substrate scope of electrochemical oxidative cyclization of o-(1-
Alkynyl) benzoate with diorganyl diselenides ^[a,b]



^a Optimization of the reaction conditions. C (carbon filled PPS, 5.0×4.0 cm) anode, Pt (platinum coated, 5.0×4.0 cm) cathode, flow volume (0.225 mL), 1a(0.2mmol), 2a(0.12mmol), ⁿBu₄NBF₄(0.4mmol.), CH₃CN=8mL, I=10mA, resident time =5.0 min (5.5F/mol), room temperature. ^b isolated yield.

Next, the electrochemical oxidative cyclization in the continuous flow system was further extended to the substrate adaptability of diphenyl diselenides. In general, diphenyl diselenide reagents or dithienyl diselenide reagents with electron-donating methyl groups or electron-withdrawing chlorine or bromine substituents on the aromatic ring are suitable for this conversion, and the corresponding products can be obtained in moderate to good yield (Table 3,4a-4f). However, it is worth noting that the yield was significantly changed when dithiophene diselenide was used instead of diphenyl diselenide, the corresponding product was only obtained at a yield of 60%. In addition, dialkyl diselenides are also suitable for this conversion, and the corresponding products can be obtained in excellent yields (Table 3,4g-4h). Surprisingly, the desired product can still be obtained in a moderate yield when diphenyl ditelluride is used instead of diphenyl diselenide (Table 3,4i).





^a Optimization of the reaction conditions. C (carbon filled PPS, 5.0 × 4.0 cm) anode, Pt (platinum coated, 5.0 × 4.0 cm) cathode, flow volume (0.225 mL), 1a(0.2mmol), 2a(0.12mmol), ⁿBu₄NBF₄(0.4mmol.), CH₃CN=8mL, I=10mA, resident time =5.0 min (5.5F/mol), room temperature. ^b isolated yield.



Scheme 2. Gram scale synthesis in continuous flow

A scale-up reaction using 1 mmol and 5 mmol of **1a** (1.18g) in batch and continuous system was performed simultaneously in order to verify the practical application of electrochemical oxidation and the advantages of continuous flow (Scheme 2, for more details about gram scale synthesis, see the ESI†). Compared with the reaction in batch, the yield is greatly reduced with the expansion of the scale, the reaction in a continuous system can stably obtain the desired product in 91% yield even if it is scaled up to 5 mol scale. It can be imagined the reaction in flow can not only make the reaction simpler, greener, and more efficient, but also has great potential in future industrial applications.



For further investigation of the mechanism, some control experiments were performed. When 2equiv of radical inhibitor 2,2,6,6-tertramethypiperidine oxide (TEMPO) or butylated hydroxytoluene (BHT) was loaded, the reaction ceased and no desired product 3a was obtained (Scheme 3a-b, for more control experiment, see the ESI†), which indicated that the reaction is a radical reaction. Furthermore, cyclic voltammetry (CV) experiments were carried out to investigate the redox potential of substrates (for more details about the cyclic voltammetry experiments, see the ESI†). The oxidation peak of 1a was

observed at 2.12 V, while the oxidation peak of diphenyl diselenide 2a was observed at 1.74 V. And this result illustrated that diphenyl diselenide 2a is more easily oxidized at the anode.



Scheme 4. Plausible reaction mechanism.

On the basis of above results and previous literature reports, ¹² a plausible reaction mechanism for electrochemical oxidative cyclization is suggested in Scheme 4. Firstly, diphenyl selenide is oxidized at the anode to a cationic radical intermediate A, divided into phenyl-selenium radical B and phenyl-selenium cation C, respectively. Phenyl-selenium cation C was reduced to diphenyl-selenide at the cathode for the next cycle., while phenyl-selenium radicals attack the C-C triple bond of o-(1-Alkynyl) benzoates 1a to provide vinyl radical D in high regioselectivity. This in situ generated vinyl group then undergoes intramolecular cyclization by reaction with OMe moiety, resulting in the formation of the final product 3a and the release of methyl positive ion, and then the methyl cation captures the hydroxide anion in the solvent to generate CH₃OH.

Conclusion

In conclusion, we have successfully developed a green and highly efficient continuous electrocatalytic strategy to synthesis iso-coumarin derivatives via o - (1-Alkynyl) benzoates under oxidant-free and metal-free. This environmentally-friendly strategy can efficiently use electrical energy, reduce postprocessing steps and emissions. And it shows broad substrate adaptability and functional group tolerance, affording a series of

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phenyl-selenium-substituted iso-coumarin good to excellent yield. Although there are no more green improvements in the postprocessing process, the greening process of this synthesis method will have a lot of room for improvement due to the improvement of the reaction effect. In the meantime, the continuous electrochemical synthesis can achieve gram scaleup reaction and obtain the desired product in excellent yield, which also shows that it has great potential value in future industrial production. The research on the mechanism and application of electrochemical continuous synthesis system is continuing in the next in our laboratory.

Experimental Section

General methods: o-(1-Alkynyl)benzoates (0.2 mmol, 1equiv.), diphenyl diselenide (0.12 mmol, 0.6 equiv.) and ${}^nBu_4NBF_4(0.4mmol, 2.0 equiv.)$ were dissolved in CH₃CN (8 mL). At ambient temperature, the reaction mixtures were introduced into the electrochemical microreactor at 0.045 mL/min at a constant current of 10 mA. The reaction solution was concentrated under reduced pressure. The reaction solution was extracted with water (2 × 20 mL), and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography using a gradient of EtOAc/hexane (0-5%) as eluent to afford the product.Experimental Details.

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Keywords: cyclization • electrochemistry • iso-coumarin • microreactor

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A novel method for the continuous synthesis of iso-coumarin derivatives by selenization and self-cyclization of alkynes through electrochemical oxidation under metal-free and oxidant-free conditions has been developed.