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Electrochemical synthesis of aryl-substituted benzothiophenes and phenanthrenes using benzenediazonium salts as the aryl radical precursors

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Keywords: benzothiophenes; phenanthrenes; paired electrosynthesis; aryldiazonium salts; aryl radicals

Abstract: Aryl-substituted benzothiophene and phenanthrene are important structural units in medicinal chemistry and materials science. Although extensive effort has been devoted to prepare these compounds and a variety of approaches have been developed to construct the 2-substituted benzothiophene core structure, environmental-friendly and efficient synthetic means are still desired. Based on our previous electrochemical Minisci-type arylation reaction with aryl diazonium salt as the aryl precursor, as well as the work from König group, herein, we described the use of paired electrolysis to achieve 2-aryl benzothiophenes and 9-aryl phenanthrenes employing benzenediazonium salts as the aryl radical precursors. Initially, 2-methylthiobenzendiazonium salt **1a** and 4-methylbenzene ethyne **2a** were chosen as the model substrates to optimize the reaction conditions by examining solvent, supporting electrolyte, electrode material and current density. After extensive efforts, it was found that an 89% yield of the desired product 3a was afforded in an undivided cell equipped with a graphite felt anode and a Ni plate cathode, using *n*-Bu_4NBF_4 as supporting electrolyte and DMSO as the solvent, while operating at a constant current density of 4 mA/cm^2. Under the optimal conditions, the generality of the electrochemical protocol and substrate scope were then examined. The results showed that both alkyl acetylene and aryl acetylene could be applied to the method, and a series of aryl-substituted benzothiophene derivatives were obtained successfully. Considering the wide range of application of phenanthrene molecules in medicinal chemistry and materials science, we then applied this protocol to the synthesis of phenanthrene derivatives, and succeeded in obtaining the corresponding 9-arylphenanthrene derivatives. Finally, cyclic voltammetry measure was conducted to analyze the possible mechanism. It was found that 2-methylthiobenzene diazonium salt **1a** gave a significant irreversible reduction peak at -0.4 V vs Ag/Ag$^+$ in CH_3CN, whereas no signal was detected for phenylacetylene **2a** in the scanning potential window. In addition, the presence of **2a** did not alter the peak potential of **1a**, albeit the peak current increased slightly. These results indicate that the reduction of **1a** is easier than that of **2a**. Based on our CV analysis and previous photocatalytic results, a sequential paired electrolysis mechanism is proposed, that is the electrochemical reduction of benzodiazonium salt **1a** at the cathode produces aryl radical **5a**, which is then added to phenylacetylene to produce vinyl radical **6a** and sulfonyl radical **7a** following an intramolecular cyclization. Finally, anodic oxidation of **7a**, followed by demethylation with DMSO, generates the target product **3a**. In summary, we have developed a paired electrolysis method for the synthesis of 2-arylbenzothiophene derivatives and 9-arylphenanthrene derivatives. The protocol features wide substrate scope and functional group tolerance, which further demonstrates that the practicability of aryldiazonium salts as versatile aryl radical sources to generate aryl radicals through electrochemical reduction.

Introduction

2-Substituted benzothiophenes are prominent structural features in natural products and organic molecules with diverse biological activities, including anti-tumor, anti-oxidant, anti-tubercular and antimicrobial activities [1-4]. For example, FDA-approved drugs, Raloxifene, Arzoxifene and Zileuton, contain these subunits (Figure 1). It has also been of considerable interest in materials chemistry to introduce this subunit in organic solar cells, organic light-emitting diodes, and semiconductors [5-9]. Phenanthrenes are also important organic compounds with wide range of applications in medicinal chemistry and material sciences.

Consequently, extensive effort has been devoted to prepare these compounds and a variety of approaches have been developed to construct the 2-substituted benzothiophene core structure. Intermolecular cross-couplings of benzothiophenes with halogenated hydrocarbon or aryl diazonium salts are frequently employed, although this method often generates C2- and C3- regioisomers (Figure 2A) [13-14]. The cyclization approaches illustrated in Figure 2B are more attractive since only the desired regioisomers are delivered. Among the cyclization approaches, the electrophilic cyclization of o-alkynyl thioanisoles has proven to be particularly effective (Figure 2B, method 1). For example, in 2016, Ingleson [15] and Blum [16] independently reported the electrophilic cyclization of *o*-alkynyl thioanisoles to give 2-aryl-3-Bpin substituted benzothiophenes using BCl_3 or ClBcat as electrophilic reagents in the presence of pinacol. The use of iodine, NBS, or NCS as electrophilic reagents also afforded 2-amino benzothiophenes [17]. In addition, metal-catalyzed electrophilic cyclization of 2-alkylthio- or 2-trialkylsilylthio alkynyl benzene has also been used as starting materials to generate 2-aryl benzothiophenes [18-21].

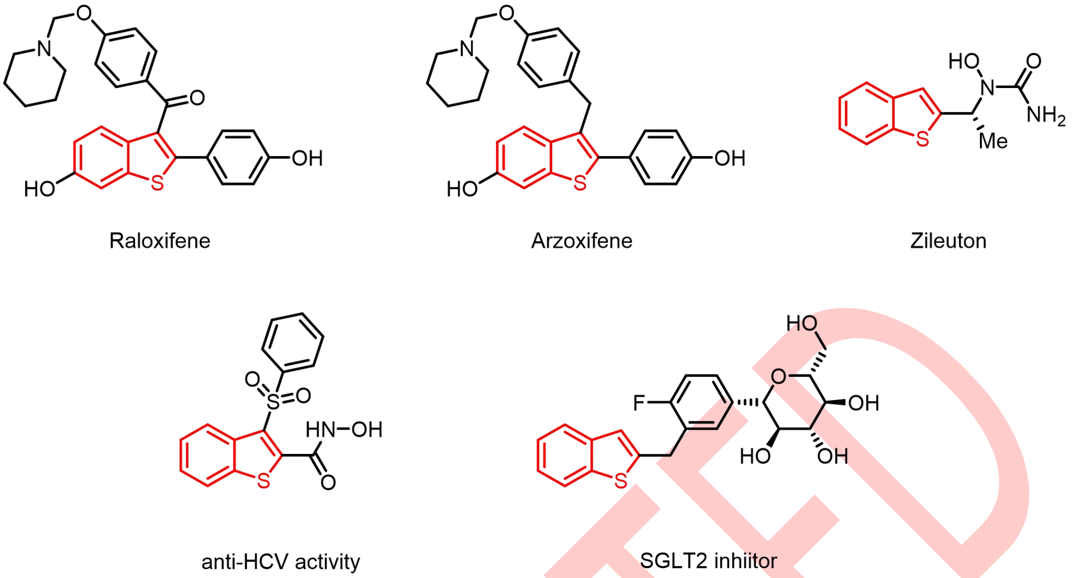
Raloxifene
Arzoxifene
Zileuton
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Figure 1. Representative structures containing the benzothiophene framework

Metal-mediated annulation of 2-halogenated alkylbenzenes in the presence of sulfur sources constitutes another approach to 2-benzothiophenes (Figure 2B, method 2). Paradies et al. [22] achieved the synthesis of benzothiophenes through a Pd-catalyzed reaction of 2-bromo arylethynyl benzenes with thiourea Using Na_2S as a source of sulfur and CuI as catalyst, Zhang synthesized 2-aryl benzothiophenes in high yields [23].

In addition to these pathways, radical annulation of omethylthio-diazonium salts with alkynes also affords 2-substituted benzothiophenes (Figure 2B, method 3). In 2012, König [24] utilized Eosin Y as a photoredox catalyst to generate 2-substituted benzothiophenes via a sequence of intermolecular aryl radical addition to the alkyne, followed by intramolecular cyclization of an sp^2 C-centered radical to a pendant methylthio group and oxidative demethylation.

In order to demonstrate that a paired electrolysis provides an alternative to the visible light photoredox-based oxidation approach, we have previously developed an efficient electrochemical approach to the Minisci-type arylation reaction using aryldiazonium salts as the aryl radical precursors [25]; an example of our approach is illustrated in Figure 2C. With these results in mind and inspired by the work of König [24], we envisioned that 2-methylthio aryldiazonium salts may also undergo radical annulation under electrochemical conditions to construct 2-substituted benzothiophenes via a paired electrolysis.

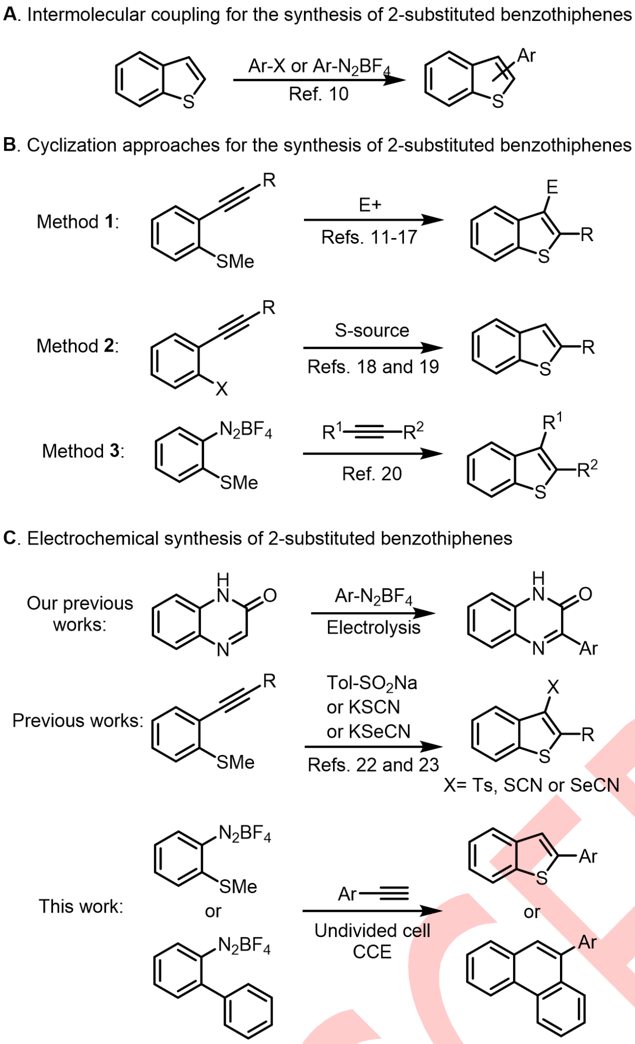


Figure 2. The synthesis of 2-substituted benzothiaphenes

Similar radical annulation reactions may also give 9-aryl phenanthrene when biphenyldiazonium salts are used as the radical precursor (Figure 2C). For the research described herein, a paired electrolysis was carried out under galvanostatic conditions in a simple undivided cell without the need for an external supporting electrolyte. The chemistry was applicable to a wide range of substrates and was easy to scale-up. The results further demonstrate that photoredox catalyzed reactions may also be achievable under electrochemical conditions. Notably, while preparing the manuscript, the Ts-, NCS- or NCSe-substituted benzothiophenes have recently been synthesized from the electrochemical oxidation of o-alkynyl thioanisoles with $TsSO_2Na$ [26], KSCN or KseCN [27], respectively (Figure 2C).

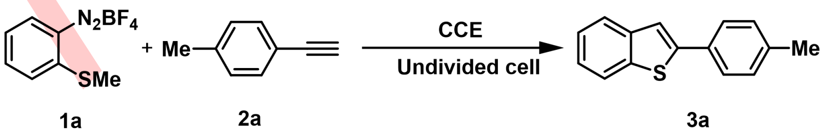


Table 1. Optimization of reaction conditions[a]

entry	Solvent	Ratio of **1a** to **2a**	Supporting electrolyte	*J* (mA/cm^2)	Anode materials	Yield [b]
1	DMSO	1:2	*n*-Bu_4NBF_4	4	C felt	37
2	MeOH	1:2	*n*-Bu_4NBF_4	4	C felt	Trace
3	CH_3CN	1:2	*n*-Bu_4NBF_4	4	C felt	8
4	DCE	1:2	*n*-Bu_4NBF_4	4	C felt	0
5	DMF	1:2	*n*-Bu_4NBF_4	4	C felt	15

6	DMSO/MeOH	1:2	n-Bu_4NBF_4	4	C felt	18
7	DMSO/HFIP	1:2	n-Bu_4NBF_4	4	C felt	3
8	DMSO	1:3	n-Bu_4NBF_4	4	C felt	89 (87)[c]
9	DMSO	1:5	n-Bu_4NBF_4	4	C felt	69
10	DMSO	1:3	Et_4NBF_4	4	C felt	39
11	DMSO	1:3	Me_4NBF_4	4	C felt	49
12	DMSO	1:3	n-Bu_4NPF_6	4	C felt	44
13	DMSO	1:3	Et_4NHSO_4	4	C felt	49
14	DMSO	1:3	Et_4NClO_4	4	C felt	43
15	DMSO	1:3	$LiClO_4$	4	C felt	9
16	DMSO	1:3	none	4	C felt	39
17	DMSO	1:3	n-Bu_4NBF_4	6	C felt	54
18	DMSO	1:3	n-Bu_4NBF_4	2	C felt	91 (6h)
19	DMSO	1:3	n-Bu_4NBF_4	4	Graphite plate	25
20	DMSO	1:3	n-Bu_4NBF_4	4	Pt wire	30

[a] Conditions: **1a** (0.3 mmol) and **2a** in 3 mL solvent in a beaker type undivided cell equipped with Ni plate cathode. [b] Yield determined by HPLC used 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield

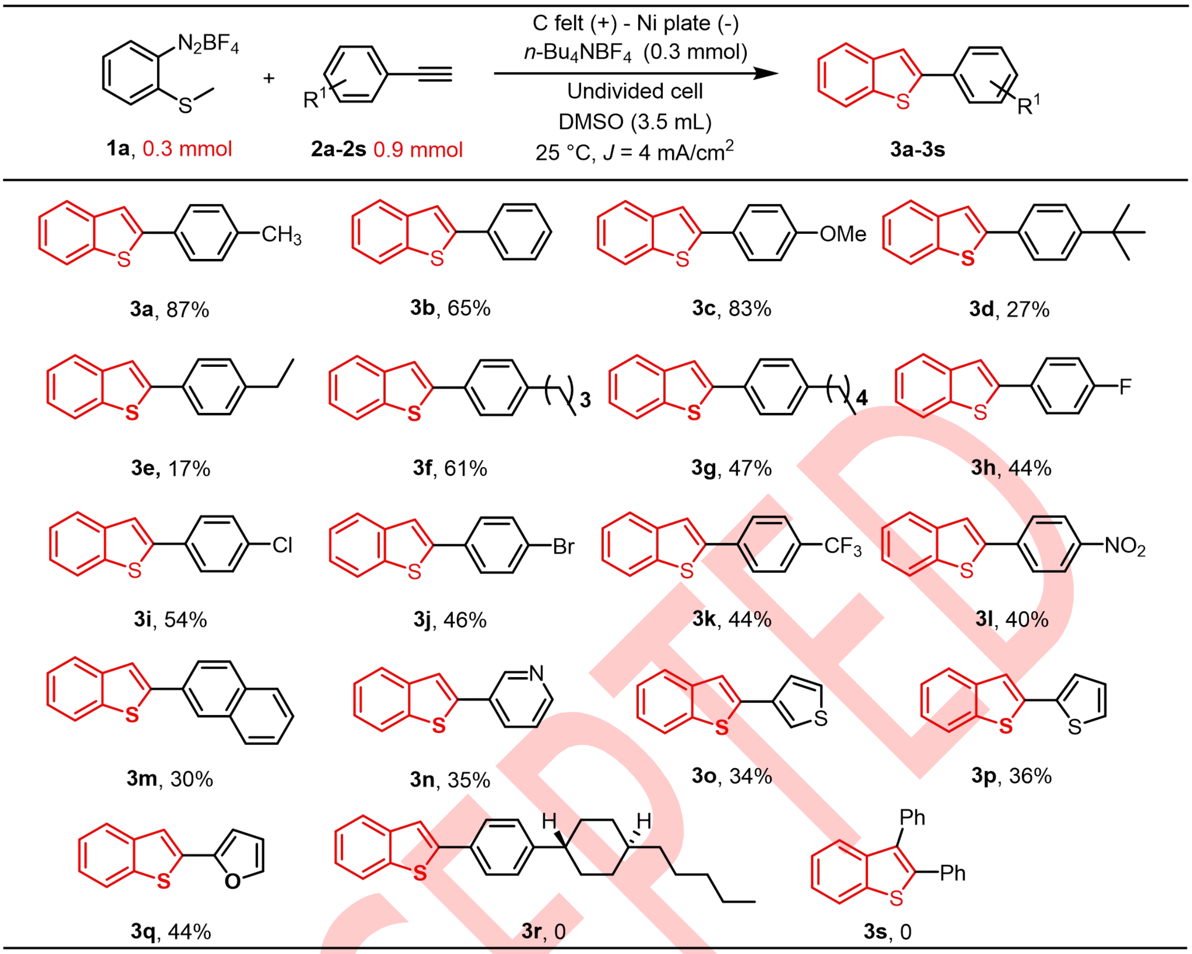
Results and Discussion

We began our search for optimal conditions by investigating the model reaction of 2-methylthiobenzendiazonium salt **1a** with 4-methylbenzene ethyne **2a**. As shown in Table 1, when a mixture of **1a** and 2 equiv of **2a** in DMSO with n-Bu_4NBF_4 as supporting electrolyte was electrolyzed in a beaker-type undivided cell equipped with a carbon felt anode and a Ni plate cathode, the corresponding benzothiophene **3a** was produced in 37% yield (entry 1). Replacing the solvent with MeOH, CH_3CN, DCE, DMF or a mixed solution of DMSO with MeOH or HFIP gave inferior yields (entries 2-7). Given the fact that **2a** rapidly disappeared during the electrolysis, the amount of **2a** was increased, this led to an 89% (87% isolated yield) or 69% yield of **3a** in the presence of 3 or 5 equiv of **2a**, respectively (entries 8 and 9). Compared with the photocatalytic synthesis [24] of benzothiophene **2a**, this electrochemical variation gave a higher yield (89% vs 75%) and required fewer equivalents of **2a** (3 equiv vs 10 equiv).

The screening of supporting electrolyte indicated that *n*-Bu_4NBF_4 was superior, since other conducting salts, such as Et_4NBF_4, Me_4NBF_4, *n*-Bu_4NPF_6, Et_4NHSO_4, Et_4NClO_4 and $LiClO_4$ (entries 10-15) gave less than 50% of yields. Notably, without external supporting electrolyte, **3a** was still produced although in a slightly lower yield. This is likely due to the conductivity of the starting material **1a** (entry 16). The reaction was less effective when the electrolysis was performed at 6 mA/cm^2 (entry 17). In the case of 2 mA/cm^2, a nearly identical yield (91%) of **3a** was observed, but twice as much time (6 h) was required (entry 18). Finally, we investigated the choice of anodic material on the reaction. When a graphite plate or a Pt plate was used as the anode, 25% or 35% yields of **3a** were obtained, respectively (entries 19-20). Based on the results described above, we concluded that the reaction was most efficient when conducted in an undivided cell equipped with a praphite felt anode and a Ni cathode at a constant current density of 4 mA/cm^2 using *n*-Bu_4NBF_4 in DMSO as electrolyte system (89% yield of **3a**).

With the optimal reaction conditions in hand, we then examined the reaction generality and substrate scope using 2-methylthio-benzenediazonium **1a** and a variety of phenyl acetylene derivatives. As shown in Table 2, phenyl acetylene and methoxy substituted phenyl acetylene worked well to give 65% and 83% yields of corresponding products **3b** and **3c**, respectively. Alkyl-substituted phenyl acetylene derivatives were also useful, albeit in low yields (**3d** and **3e**) due to the messy reaction mixture, to moderate yields (**3f**-**3g**). Benzothiophene derivatives **3h**-**3l** were also formed in moderate yields. The presence of halogen

Table 2. Synthesis of 2-Arylbenzothiophenea[a]



3a, 87% **3b**, 65% **3c**, 83% **3d**, 27%

3e, 17% **3f**, 61% **3g**, 47% **3h**, 44%

3i, 54% **3j**, 46% **3k**, 44% **3l**, 40%

3m, 30% **3n**, 35% **3o**, 34% **3p**, 36%

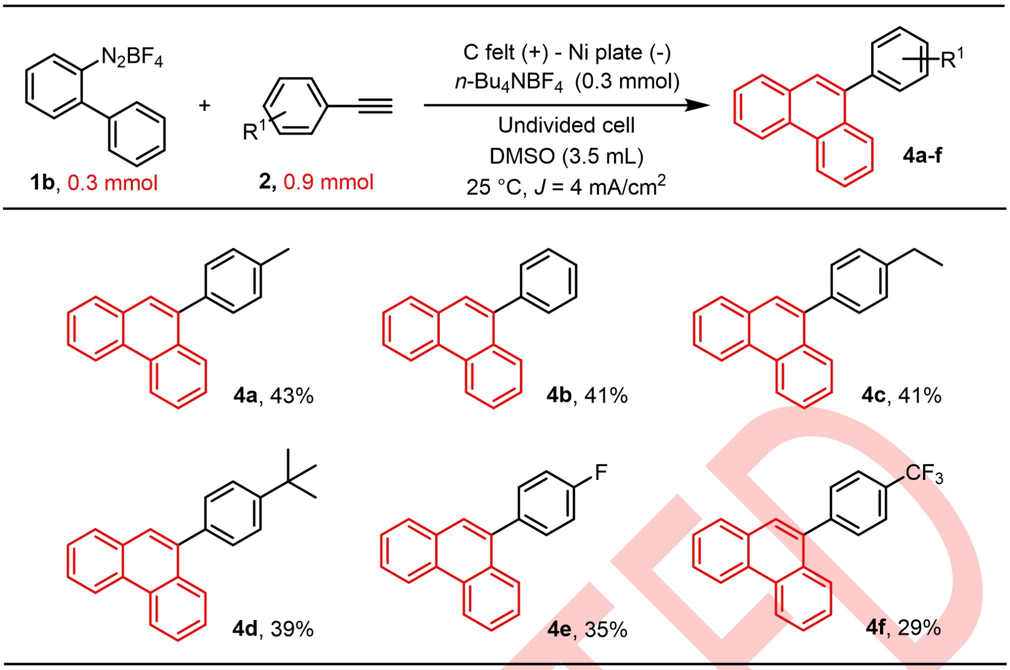
3q, 44% **3r**, 0 **3s**, 0

[a] Reaction conditions: 1a (0.3 mmol), 2 (0.9 mmol) in 3.5 mL of DMSO, undivided cell, 25 °C, *n*-Bu$_4$NBF$_4$ (0.3 mmol), current density of J = 4 mA/cm^2, C felt anode and Ni plate cathode. [b] Isolated yield.

or nitro groups provides a handle for late-stage functionalization. The compatibility of other aryl acetylenes with **1a** under the standard conditions was also examined. In the case of naphthyl-, pyridinyl-, thiophenyl- and furanyl acetylene, the corresponding products **3m**-**3q** were delivered in 30%-44% yields, whereas **3**r and **3s** were not produced and the starting acetylenes **2r** and **2s** were consumed completely.

Considering the wide range of applications of phenanthrene containing molecules in medicinal chemistry and materials science, we next explored the paired electrolysis approach to the synthesis of phenanthrene derivatives. As listed in Table 3, when a mixture of biphenyldiazonium salt **1b** and aryl acetylene **2** was electrolyzed under the standard conditions, the corresponding 9-arylphenanthrene derivatives **4** were formed in moderate yields. For example, in the reactions with alkylsubstituted phenyl acetyl-enes, isolated yields of **4a**-**4d** ranged from 39 to 43 %. Electron-withdrawing groups, such as F or CF$_3$ were also tolerated, leading to **4e** and **4f**, although in a lower yield.

Table 3. Synthesis of 9-arylphenanthrene derivatives [a,b]



[a] Reaction conditions: 1a (0.3 mmol), 2 (0.9 mmol) in 3.5 mL of DMSO, undivided cell, 25 °C, n-Bu$_4$NBF$_4$ (0.3 mmol), current density of J = 4 mA/cm^2, C felt anode and Ni plate cathode. [b] Isolated yield.

To gain mechanistic insights, cyclic voltammetry was employed. As shown in Figure 3, phenylacetylene **2a** was not reducible in the scan range from 0.0 V to -1.0 V vs Ag/Ag+ in CH_3CN, whereas 2-methylthio benzenediazonium salts **1a** gave an obvious irreversible reductive peak at -0.4 V vs Ag/Ag$^+$ in CH_3CN. When **2a** was present, the reduction peak potential **1a** did not change, although there was a slight increase of peak current. These results indicate that electrochemical reduction of a mixture of **1a** and **2a** begins with the reduction of **1a**.

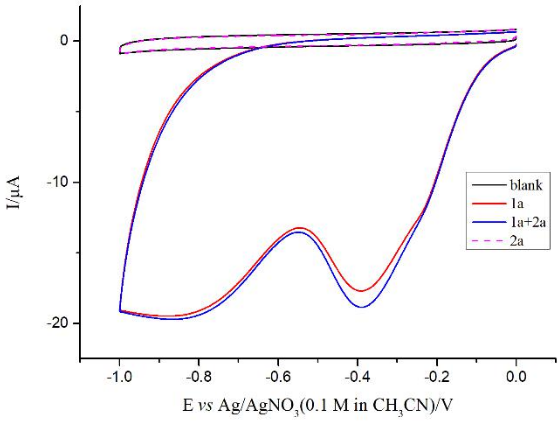


Figure 3. Cyclic voltammograms of related compound (5 mM) in 0.1 M Bu_4NBF_4/DMSO

Based on our CV analysis and previous photocatalytic results [24], a sequential paired electrolysis pathway is proposed. Taking the electrosyn-thesis of **3a** as an example, the electrochemical reduction of benzenediazonium salt **1a** at the cathode affords the aryl radical **5a**, along with the release of nitrogen gas. The radical **5a** then adds to phenyl acetylene to generate vinyl radical **6a** and sulphuraryl radical **7a** following an intramolecular cyclizat Anodic oxidation of **7a**, followed by demethylation using DMSO leads to the target structure **3a**.

Conclusion

In summary, we have developed a paired electrolysis approach for the synthesis of 2-aryl benzothiophenes and 9-aryl phenan-threnes. The chemistry is initiated from the cathodic reduction of benzenediazonium salts, and is conducted in an undivided cell equipped with graphite felt anode and Ni plate cathode using *n*-Bu_4NBF_4 supporting electrolyte and DMSO solvent at constant current density of 4 mA/cm^2. The methodology features wide substrate scope and functional group tolerance. It further demonstrates the utility of the electrochemical reduction of aryldiazonium salts as a source of aryl radicals.

Acknowledgements

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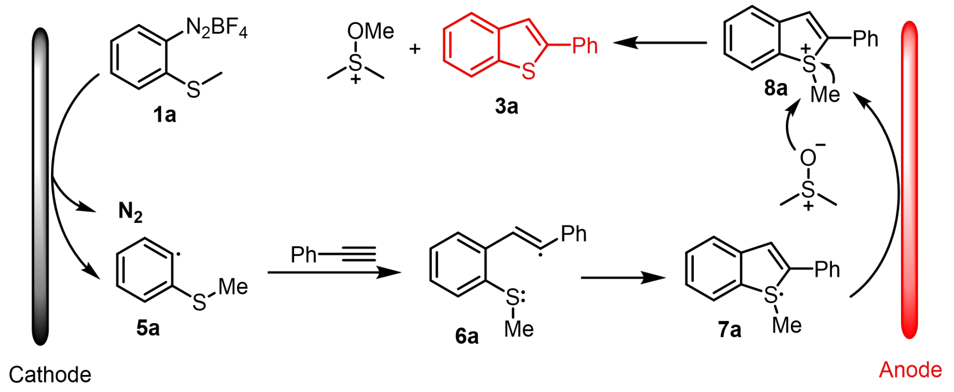

Scheme 1. Proposed mechanism for the paired electrochemical synthesis of benzothiophenes

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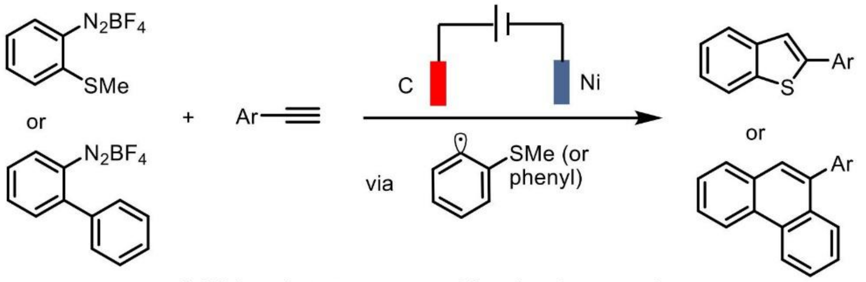

- Wide substrate scope and functional group tolerance
- Aryldiazonium salts are versatile aryl radical sources

以芳基重氮盐为芳基前体电化学合成芳基取代的苯并噻吩和菲

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摘要：芳基取代的苯并噻吩和菲是药物化学和材料科学中的重要结构单元。尽管已经投入了很多来制备这类化合物，并且已经开发了多种方法来构建 2-取代的苯并噻吩核心结构，但是仍然需要环境友好且有效的合成方法。基于我们以前的以芳基重氮盐为芳基前体的电化学 Minisci 型芳基化反应，以及来自 König 小组的工作，我们在本文中描述了使用成对电解以苯重氮盐为芳基前体来获得 2-芳基苯并噻吩和 9-芳基菲。首先，选择 2-甲硫基苯重氮盐 **1a** 和 4-甲基苯乙炔 **2a** 作为模型底物，通过考察溶剂、支持电解质、电极材料和电流密度来优化反应条件。经过大量的努力，发现在装备有石墨毡阳极、镍片阴极的单室电解池中，使用 *n*-Bu_4NBF_4 作为支持电解质，DMSO 作为溶剂，控制在 4 mA/cm^2 条件下恒流电解，获得 89%产率的所需产物 **3a**。在最佳条件下，然后考察该电化学方案和底物范围的普适性。结果表明，烷基乙炔和芳基乙炔都适用于该方法，并成功地得到了一系列芳基取代的苯并噻吩衍生物。考虑到菲类化合物在药物化学和材料科学中的广泛应用，我们将此方案应用到菲衍生物的合成中，成功地获得了相应的 9-芳基菲衍生物。最后，通过循环伏安法分析了可能的机理。发现 2-甲硫基苯重氮盐 **1a** 在 CH_3CN 中相对于 Ag/Ag^+ 在-0.4 V 处产生一个显著的不可逆还原峰，而在扫描电位窗口中没有检测到苯乙炔 **2a** 的信号。此外，**2a** 的存在没有改变 **1a** 的还原峰电位，尽管峰电流略有增加。这些结果表明 **1a** 的还原比 **2a** 的还原容易。基于我们的循环伏安分析和以前的光催化结果，我们提出了一个成对电解的机制，即芳基重氮盐 **1a** 在阴极的电化学还原产生芳基 **5a**，然后芳基 **5a** 加成到苯乙炔上，在分子内环化后产生乙烯基 **6a** 和磺酰基 **7a**。最后，**7a** 的阳极氧化，接着用 DMSO 脱甲基化，生成目标产物 **3a**。总之，我们发展了一种成对电解法来合成 2-芳基苯并噻吩衍生物和 9-芳基菲衍生物。该方案具有广泛的底物范围和官能团耐受性，进一步证明了芳基重氮盐作为多用途芳基自由基来源通过电化学还原产生芳基自由基的实用性。

关键词：苯并噻吩；菲；成对电合成；芳基重氮盐；芳基自由基