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Electrochemically dehydrogenative C(sp^2)–H/S–H cross-coupling: efficient synthesis of *ortho*-aminophenyl thioglycoside derivatives†

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We have developed an electro-mediated method for synthesizing aryl thioglycosides through intermolecular anodic oxidative cross-dehydrogenative C(sp^2)–S bond coupling reactions involving (un)protected 1-thiosugars and anilines. This protocol is sustainable without the use of external transition-metal catalysts or additional oxidants employed in previous methods. It demonstrates a broader substrate scope concerning both 1-thiosugars and anilines. Furthermore, the reaction is applicable to the late-stage functionalization of drugs. Mechanistic studies using cyclic voltammetry and control experiments reveal that a radical cross coupling process is implicated in this transformation.

Introduction

Glycosides are widely present in the structural framework of many natural products and drugs.[1] *S*-Glycosides, as an important class of glycosides, have received comparatively less attention than *O*-glycosides. These glycomimetics possess significant attributes, including resistance to chemical hydrolysis or enzymatic degradation, while maintaining comparable biological activity to their *O*-glycosides counterparts.[2] Consequently, *S*-glycosides have become the focus of extensive investigation as potential pharmaceutical agents in the field of medicinal research, serving as mimetics of natural *O*-glycosides (Fig. 1).[3] Furthermore, *S*-glycosides are frequently employed as glycosylation donors to establish a diverse range of glycosidic linkages due to their ease of handling and rapid activation under various conditions (Fig. 1).[4] The broad biological and synthetic applicability has triggered tremendous interest in the development of efficient methods for constructing *S*-glycosides. Traditional methods for synthesizing aryl thioglycosides primarily depend on nucleophilic substitution reactions between glycosyl donors and aryl thiophenols. However, these procedures involve harsh reaction conditions, and the resulting products often exhibit poor stereoselectivity.[5] In addressing this issue, Zhu's group and Walczak's group independently reported methods involving the reversal of polarity at the anomeric carbon. However, the use of alkyl tin/lithium regents restricts the scope to saccharides, although this elegant strategy enables stereoselective control.[6] In recent years, a synthetic strategy of aryl thioglycosides *via* transition metal catalysis has been developed, in which 1-thiosugars or their precursors reacts with an aryl halide or arylboronic acid under the catalysis of Cu, Pd, or Ni, resulting in the formation of the desired thioglycoside derivative (Scheme 1a).[7] Although the synthesis of aryl thioglycosides has made remarkable progress, certain limitations persist, such as high catalyst loadings, extended reaction times, and the requirement for specialized phosphine ligands. In 2019, Messaoudi and co-workers reported a method for synthesizing aryl thioglycosides through a single-electron Ni/photoredox dual-catalyzed cross coupling reaction.[8] This method is suitable for protected thiosugars and aryl iodides, although some aryl bromides are not compatible with this protocol. Additionally, the Messaoudi group developed the first electrochemical method for coupling 1-thiosu-

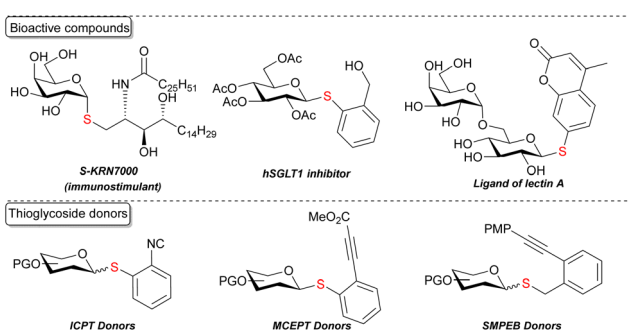

Fig. 1 Selected bioactive compounds and thioglycoside donors.

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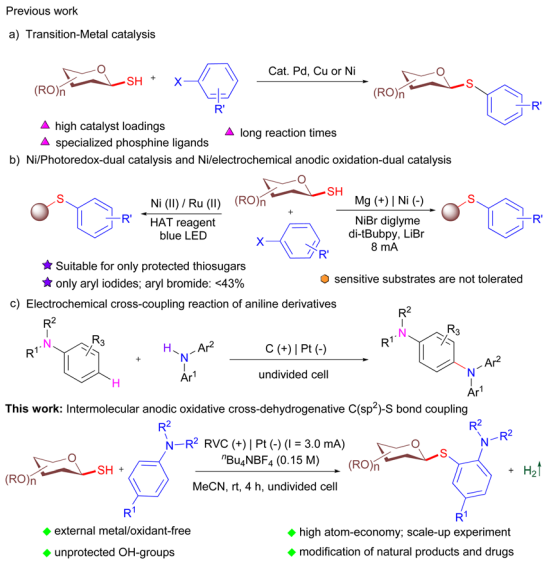
†Electronic supplementary information (ESI) available. CCDC 2324843. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4qo00171k



Scheme 1 Previous methods for the synthesis of aryl thioglycosides and this work.

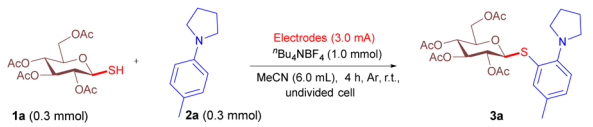
gars with aryl, alkenyl, and alkynyl bromides under nickel-catalyzed conditions.[9] This method requires the addition of expensive catalysts and ligands, although the substrate scope has been broadened to a certain extent (Scheme 1b).

In recent years, electrochemical dehydrogenative cross-coupling reactions have shown new possibilities for green organic synthesis due to their ability to avoid substrate prefunctionalization, ensuring highly atom-economic construction of C–C and C–heteroatom bonds.[10] As early as 2019, Lei and co-workers discovered an electrooxidative *para*-selective C–H/N–H cross-coupling between arenes and diarylamine derivatives.[11] This transformation required no external oxidants with hydrogen gas as the sole byproduct (Scheme 1c). To the best of our knowledge, the strategy of employing direct C–H/S–H dehydrogenative cross-coupling for constructing C–S bonds has been rarely reported.[10c–e,12] We sought to investigate whether the synthesis of aryl thioglycosides could be achieved through anodic oxidative C(sp^2)–H/S–H dehydrogenative cross-coupling under redox-catalyst-free conditions. The present study is outlined herein (Scheme 1). The reaction conditions are mild enough to tolerate free hydroxyl groups and complex molecules.

Results and discussion

To assess the feasibility of this study, we selected the coupling of tetra-*O*-acetylated 1-thio-β-D-glucopyranose **1a** (1.0 equiv.) with 1-(4-methylphenyl)pyrrolidine **2a** (1.0 equiv.) as a model study under various reaction conditions (Table 1 and Tables S1–S3†). 30% of **3a** could be obtained as a single β-anomer by using $^{n}Bu_4NBF_4$ as the electrolyte, and dry CH_3CN as the solvent under a constant electric current of 9.0 mA at room temperature in an undivided cell equipped with a graphite plate as the anode and a platinum plate as the cathode

Table 1 Reaction optimization[a]



1a (0.3 mmol) **2a** (0.3 mmol) **3a**

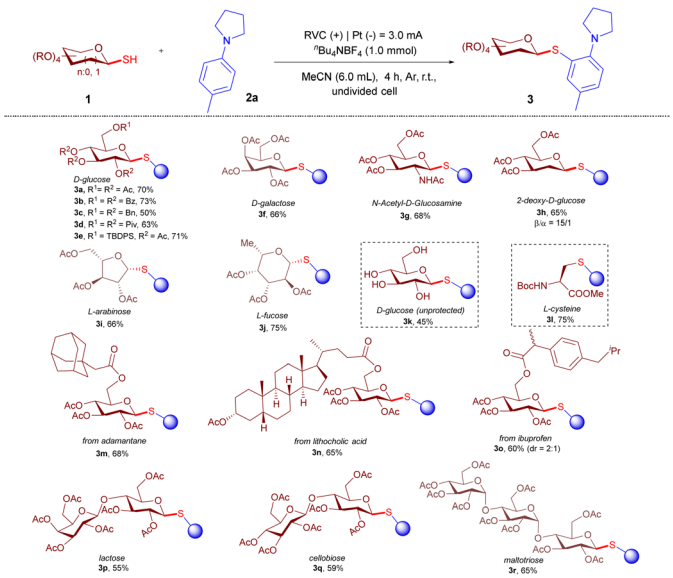
Entry	Deviation from above	Yields[b] (%)
1	C(+)|Pt(−), 9.0 mA, 2 h	30
2	C(+)|C(−), 9.0 mA, 2 h	7
3	GC(+)|CF(−), 9.0 mA, 2 h	Trace
4	Pt(+)|Pt(−), 9.0 mA, 2 h	15
5	RVC(+)|Pt(−), 9.0 mA, 2 h	28
6	C(+)|Pt(−), 60 °C	60
7	Pt(+)|C(−),60 °C	15
8	**RVC(+)|Pt(−)**	**70**
9	RVC(+)|Pt(−), 2 equiv. of **2a**	68
10	RVC(+)|Pt(−), DMF as solvent	Trace
11	RVC(+)|Pt(−), MeOH as solvent	20
12	RVC(+)|Pt(−), DMSO as solvent	18
13	RVC(+)|Pt(−), open-air	15
14	No electric current	N.R.

[a] Conditions A: reticulated vitreous carbon RVC anode, platinum plate cathode, constant current = 3.0 mA, **1a** (0.3 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.0 equiv.), $^{n}Bu_4NBF_4$ (1.0 mmol), CH_3CN (6.0 mL), Ar, room temperature, 4 h. [b] Isolated yield.

(Table 1, entry 1). $^{n}Bu_4NBF_4$ was identified as the optimal electrolyte, with other electrolytes like $^{n}Bu_4NPF_6$ and TBAB proving less effective (Table S1†). When the graphite plate anode was replaced with reticulated vitreous carbon (RVC), **2a** can be consumed completely, despite **3a** was afforded with similar yield (Table 1, entry 5). This suggests that the efficiency of the RVC electrode in this reaction is higher than that of the graphite electrode, to the extent that an unwanted side reaction of aniline occurred. To our delight, by reducing the electric current to 3.0 mA and employing RVC as the anode, a 70% isolated yield of the desired product **3a** was observed (Table 1, entry 8). These experimental results indicated that the product **3a** is unstable under a high current. For instance, it may undergo further oxidation at the anode. Moreover, a comparable reaction efficiency was achieved by increasing the amount of the **2a** from 1.0 equiv. to 2.0 equiv. (Table 1, entry 9). The optimization of the reaction conditions was extended to include different solvents (Table 1, entries 10–12). However, no significant improvement in the yield of **3a** was observed with DMF, MeOH, and DMSO. Further research showed that the reaction in an air atmosphere was less efficient and gave product **3a** in only 15% yield (Table 1, entry 13). This may due to the fact that 1-thiosugars are easily oxidized by oxygen. The presence of electricity was critical for the transformation (Table 1, entry 14).

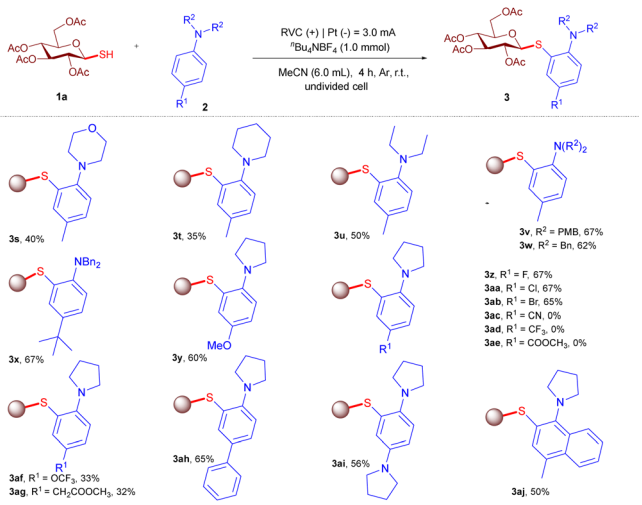
With the optimal conditions in hand (standard conditions A), the substrate scope with respect to the sugar component was investigated. As shown in Table 2, a variety of mono-, di- and trisaccharides-derived 1-thiosugars were initially subjected to the optimal conditions. D-Galactose, *N*-acetyl-D-glucosamine, 2-deoxy-D-glucose, L-arabinose, and L-fucose-derived 1-thiosugars underwent this reaction smoothly to give aryl thioglyco-

Table 2 Substrate scope of thiosugars[a]



[a] Conditions A: reticulated vitreous carbon RVC anode, platinum plate cathode, constant current = 3.0 mA, **1** (0.3 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.0 equiv.), ^{n}Bu$_4$NBF$_4$ (1.0 mmol), CH$_3$CN (6.0 mL), Ar, room temperature, 4 h.

Table 3 Substrate scope of tertiary arylamines[a]



[a] Conditions A: reticulated vitreous carbon RVC anode, platinum plate cathode, constant current = 3.0 mA, **1a** (0.3 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.0 equiv.), ^{n}Bu$_4$NBF$_4$ (1.0 mmol), CH$_3$CN (6.0 mL), Ar, room temperature, 4 h.

sides **3f–j** in 65–75% yields, which all maintain the configuration of glycosyl thiols. In cases involving D-glucose containing common protecting groups, such as benzoyl, benzyl, pivaloyl and silyl, the reaction proceeded smoothly, affording **3b–e** in good yields. To further demonstrate the synthetic utility of our protocol, we evaluated whether the *S*-arylation of unprotected thiosugars or cysteine amino acid could be realized using this electrochemical method. To our delight, the reaction of unprotected 1-thio-β-D-glucopyranose and L-cysteine yielded the respective products **3k** and **3l** in moderate yields. In addition, adamantane (**3m**, 68% yield), lithocholic acid (**3n**, 65% yield), and ibuprofen (**3o**, 60%) could also be introduced into aryl thioglycosides. Moreover, this coupling reaction exhibited good compatibility with disaccharides, such as lactose and cellobiose, leading to the formation of disaccharide products **3p** (55% yield) and **3q** (59% yield). The trisaccharide maltotriose was also examined, and the desired product **3r** was obtained with 65% yield.

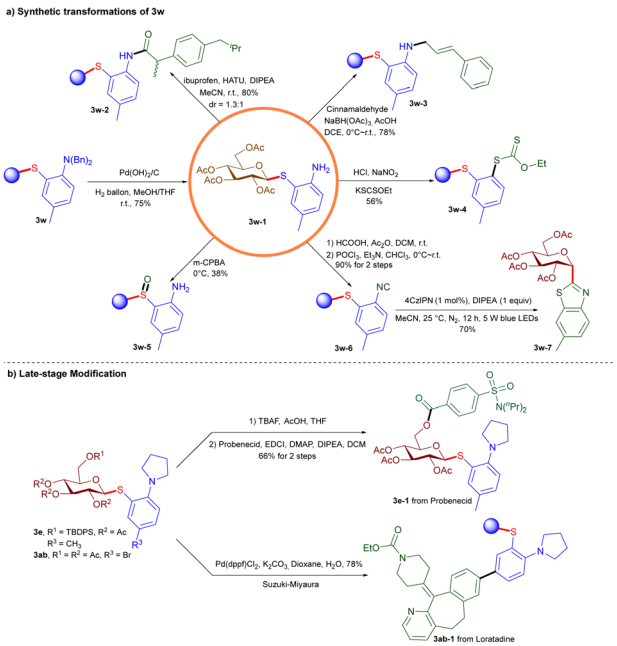
The electro-oxidative dehydrogenative reaction was further investigated with various substituted tertiary arylamines, affording the corresponding aryl thioglycosides **3s–aj** in reasonable yields (Table 3). We were pleased to find that anilines **2s–u**, bearing morpholine, piperidine, and acyclic amine on the aryl rings, were applicable under the optimal reaction conditions. The desired products **3s–u** could be obtained with moderate yields from 35 to 50%. Gratifyingly, it is found that anilines with *N*-protecting groups could react with thiosugar **1a** to generate the corresponding products **3v–w** in good yields (62–67%). A variety of tertiary arylamines bearing electron-donating groups, such as tertiary butyl and methoxyl, were examined, yielding moderate yields (Table 3, **3x–y**, 60–67%). The interaction between **1a** and anilines substituted with weakly electron-withdrawing groups (F, Cl, and Br) resulted in the desired products in yields ranging from 65% to 67% under the optimal conditions (Table 3, **3z–ab**). However, when aniline substrates with strongly electron-withdrawing groups (CN, CF$_3$, and COOCH$_3$) were used, the target compounds were not detected, primarily due to their poor electronic effect on oxidation potential (**2ad** E_p = 1.23 V; **2ae** E_p = 1.18 V).[13,14] In contrast, **3af–ag** could be obtained when the strongly electron-withdrawing groups were not directly linked to the phenyl group (**2af** E_p = 1.09 V; **2ag** E_p = 0.91 V). Additionally, phenyl-substituted tertiary arylamine was tolerated in this reaction, and the desired product **3ah** could be obtained in 65% yield. Similarly, tertiary arylamine bearing another pyrrolidine was also suitable for the reaction, giving product **3ai** in 56% yield. Notably, α-naphthylamine was also compatible with the electrolysis protocol (Table 3, **3aj**, 50%). It should be noted that unsubstituted tertiary arylamines or tertiary arylamines with *ortho*-substitution (**2ak**, E_p = 0.84 V, see the Supporting Information for details) do not participate in the reaction under this system. This may be attributed to the lower oxidation potential of tertiary arylamines with *para*-substitution (**2a**, E_p = 0.79 V).

It is worth mentioning that when *N*, *N*, 4-trimethylaniline **2b** was subjected to the reaction conditions, both the product **3ak** (*via* C(sp^2)–S coupling, 18% yield) and **3bk** (*via* C(sp^3)–S coupling, 18% yield) were obtained. After a series of optimizations of conditions (Tables S4 and S5†), the target product **3ak** (CCDC 2324843†) was obtained in 65% isolated yield utilizing ^{n}Bu$_4$NBF$_4$ as the electrolyte and dry CH$_3$CN as the solvent under a constant electric current of 3.0 mA at 60 °C. The reaction took place in an undivided cell equipped with a

platinum plate as the anode and a graphite plate as the cathode. Notably, **3bk** was not produced under these conditions (Table S5,† entry 1).

With these encouraging results, we next investigated the scope and limitations of this electro-oxidative dehydrogenative reaction using a series of *N*, *N*-dimethylanilines **2** bearing different functional groups. As showed in Table 4, cross-couplings of 1-thio-β-D-glucopyranose with *N*, *N*-dimethylanilines bearing various functions (–Me, –Et, –iPr, –Br, –F, –OMe) at *para* positions have been successfully achieved, affording the corresponding thioglycosides (**3al–av**) in yields up to 72%. Besides, this coupling reaction tolerates different glycosyl thiols such as *O*-acetylated 1-thio-β-D-glucopyranose **1ar**, *O*-acetylated 1-thio-β-D-galactopyranose **1as**, *O*-acetylated 1-thio-β-D-mannopyranose **1at**, *O*-acetylated 1-thio-β-D-fucopyranose **1au**, and *O*-acetylated 1-thio-β-D-xylopyranose **1av**. These substrates react smoothly with (4-methoxyphenyl)-dimethylamine, leading to thioglycosides **3ar–av** in yields up to 70%.

To demonstrate the practical applicability of our strategy, several synthetic transformations of aryl thioglycoside **3w** were conducted (Scheme 2a). Deprotection of **3w** could easily proceed with H_2 under $Pd(OH)_2/C$ catalysis, yielding *ortho*-aminophenyl thioglycoside **3w-1** in 75% yield. **3w-1** could undergo a condensation reaction with ibuprofen to give **3w-2** in 80% yield. **3w-3** could be synthesized from **3w-1** and cinnamaldehyde using reductive amination. **3w-1** can also be converted into an aryl diazonium salt and then reacts with KSCSOEt to form **3w-4**. The sulfoxide compound **3w-5** could be obtained through the oxidation of **3w-1** with *m*CPBA in 38% yield. The *ortho*-isocyanophenyl thioglycoside **3w-6** (ICPT donor) could be prepared from **3w-1** in a 90% overall yield in two steps (formyl protection and dehydration). Subsequently, the *C*-glycosylation

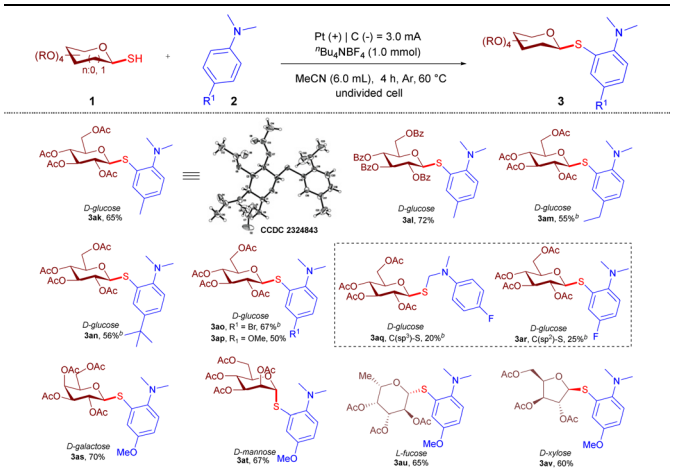


Scheme 2 Synthetic application.

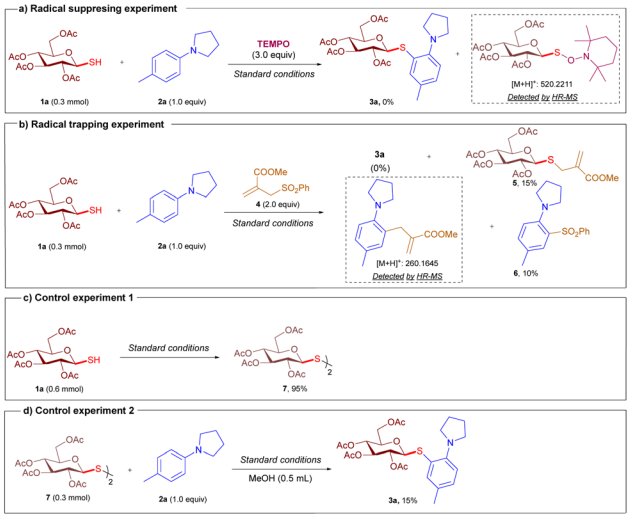
of **3w-6** with our previously developed "Boomerang" strategy proceeded smoothly to provide *C*-nucleoside analogue **3w-7** in 70% yield with an α configuration (Scheme 2a).[4a] The deprotection and ester condensation reaction of **3e** proceed sequentially, yielding the probenecid derivative **3e-1** in useful overall yields. Furthermore, mixing **3ab** and loratadine boronic ester with $Pd(dppf)Cl_2$ and K_2CO_3, the Pd-catalyzed Suzuki–Miyaura coupling occurred smoothly, resulting in the loratadine derivative **3ab-1** in 78% yield (Scheme 2b).

To gain more insight into the reaction mechanism, we conducted the following experiments. The addition of TEMPO completely shut down the reaction, and the possible reactive intermediate generated from **1a** was trapped by TEMPO, as monitored by HR-MS in the meantime (Scheme 3a). Next, under the standard conditions, electrolysis was carried out in the presence of 2.0 equiv. of **4**, which is used as a radical acceptor. This led to the formation of **5** and **6** in 15% and 10% yield, respectively, and impeded the generation of **3a** (Scheme 3b). These results indicated that this *S*-glycosylation reaction probably undergoes a radical pathway. Glycosyl thiol radical and aniline radical cation intermediate might be involved in the transformation. In a control experiment in the absence of aniline substrates, 1-thiosugar **1a** underwent dimerization to afford disulfide **7** in 95% yield (Scheme 3c). Then the reaction between disulfide **7** and **2a** was conducted. When a small amount of methanol was added as a proton source, **3a** was obtained in 15% yield under the standard conditions (Scheme 3d). Cyclic voltammetry (CV) experiments of 1-thiosugar **1a**, aniline **2a**, coupling product **3a** and the mixture of 1-thiosugar **1a** and aniline **2a** were performed. As shown in Fig. 2a, the oxidation peak of **2a** was observed at 0.79 V, while the oxidation peak of **1a** was observed at 0.58 V, indicating that

Table 4 Substrate scope of tertiary arylamines and thiosugars[a]



[a] Conditions B: platinum plate anode, graphite plate cathode, constant current = 3.0 mA, **1** (0.3 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.0 equiv.), $^nBu_4NBF_4$ (1.0 mmol), CH_3CN (6.0 mL), Ar, 60 °C, 4 h. [b] Graphite plate anode, platinum plate cathode, constant current = 9.0 mA, **1** (0.3 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.0 equiv.), $^nBu_4NBF_4$ (1.0 mmol), CH_3CN (6.0 mL), Ar, room temperature, 2 h.



Scheme 3 Mechanistic experiments.

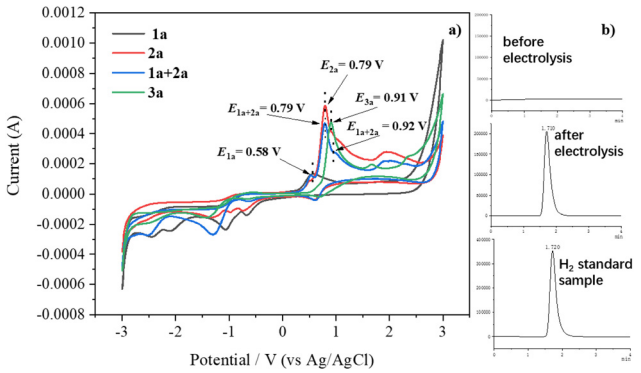
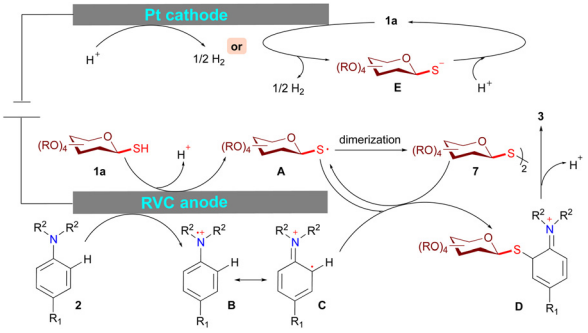


Fig. 2 (a) Cyclic voltammograms of **1a**, **2a**, the mixture of **1a** and **2a**, and **3a** in 0.1 M $^{n}Bu_4NBF_4$ in MeCN, using glassy carbon as working electrode, Pt wire as counter electrode, and Ag/AgCl as reference electrode at 0.1 V s^{-1} scan rate; (b) GC detection for H_2.

1a easily undergoes an oxidation reaction at the anode. Moreover, the oxidation peak of **3a** was observed at 0.91 V, and the mixture of **1a** and **2a** featured two main oxidation potentials, one for aniline **2a** (E_{1a+2a} = 0.79 V) and the other for **3a** (E_{1a+2a} = 0.92 V). This result indicated that the oxidation of both substrates is possible under the standard conditions, and **1a** seems to be more easily oxidized at the anode. As for the cathode, concurrent release of molecular hydrogen was disclosed by GC analysis (Fig. 2b).

Based on the above mechanistic studies and literature reports,[10d,15] we proposed a plausible mechanism as depicted in Scheme 4. Firstly, 1-thiosugar **1a** loses an electron under the oxidation of the anode to form glycosyl thiol radical **A**, which can undergo dimerization to generate a disulfide **7**. Simultaneously, aniline **2** is oxidized to produce radical cation **B**, which then produces radical-cation **C** through tautomerization. The generated aniline radical-cation intermediate **C** can undergo either direct coupling with the thiyl radical **A**



Scheme 4 Proposed reaction mechanism.

(primary path) or radical substitution (low efficiency) with the generated disulfide **7** to afford a cation intermediate **D**. Final successive deprotonation and aromatization of the cation intermediate afford the desired aryl thioglycoside **3**. At the cathode, 1-thiosugar **1a** is reduced to give hydrogen gas during the reaction.

Conclusions

We have developed an external metal-/oxidant-free, electrocatalytic method to synthesize aryl thioglycosides through the C(sp^2)–H/S–H dehydrogenative cross-coupling between 1-thiosugars and anilines. The only by-product of the reaction is hydrogen released at the cathode, making the method clean and providing enormous atom-economic advantages. A variety of monosaccharides (D-galactose, *N*-acetyl-D-glucosamine, D-ribose, L-arabinose, D-glucose, 2-deoxy-D-glucose, D-mannose, D-glucuronide, and L-fucose), disaccharides (lactose, and cellobiose), polysaccharide (maltotriose), and L-cysteine can couple with a series of non-prefunctionalized aniline derivatives using our developed method. Interestingly, thiosugars with four hydroxy groups were compatible. Moreover, the method is amenable to late-stage modification of complex molecules, and the thioglycoside products can be used as potential glycosyl donors to construct *O*-glycosides or *C*-glycosides. We believe that this simple and effective synthetic protocol will become a useful tool for the synthesis of aryl thioglycosides.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgements

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