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Supporting-electrolyte-free electrochemical [2 + 2 + 1] annulation of benzo[*d*]isothiazole 1,1-dioxides, *N*-arylglycines and paraformaldehyde

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ABSTRACT

The H-bond promoted electrochemical [2 + 2 + 1] annulation of benzo[*d*]isothiazole 1,1-dioxides, *N*-arylglycines and paraformaldehyde for the synthesis of various benzo[*d*]imidazo[1,5-*b*]isothiazole 5,5-dioxide derivatives under redox mediator, catalyst and electrolyte-free conditions was developed.

Imidazo-fused *N*-heterocycles are high-value structural units in tremendous naturally occurring compounds, biologically active molecules and functional materials [1]. During the past decades, much effort has been paid to their synthesis and functionalization [2–4]. Benzo[*d*]isothiazole 1,1-dioxides are an extensively valuable class of sultam molecules, possesses a range of biological activities [5,6]. Recently, the imidazo-fused benzo[*d*]isothiazole 1,1-dioxides have engrossed a growing interest from both synthetic and medicinal scientists for drug discovery, as these compounds can exhibit interesting pharmacological and therapeutic effects. Despite their significance, the synthetic strategies for such *N*-bridged heterocycles are limited. In 2022, Sun and Yu reported the heterogeneous synthesis of benzo[*d*]imidazo[1,5-*b*]isothiazole 5,5-dioxide (BIIO) derivatives through the visible light induced-annulation of benzo[*d*]isothiazole 1,1-dioxide and *N*-phenylglycine with $CsPbBr_3$ [7] or oxygen-doped g-C_3N_4 [8] as the photocatalyst. Later, Yu, Li and Chen disclosed the homogeneous photosynthesis of BIIO in the presence of Eosin Y as the photocatalyst (Scheme 1a) [9]. Despite these advances, the employment of un-commercial *N*-phenylglycine as the methylene source led to the inevitable formation of large amounts of aniline side product. Nevertheless, the requirement of harmful and/or un-commercial photocatalyst involves a common limitation to their large-scale and industrial application. Clearly there is an urgent demand for novel synthetic strategies, able to construct BIIO in a more cost-effective and eco-friendly manner.

Organic electro-synthesis has gained more and more attention in sustainable organic synthesis because it can produce reactive radical intermediates through a direct single-electron-transfer manner [10–16]. Most electrochemical reactions require electrolyte additives [17–27] to ensure adequate ionic conductivity, which not only result in tedious operation procedures and the formation of chemical waste but also added production cost. Similar problems arise from the employment of redox mediators [28–35], which are frequently use to eliminate kinetic inhibitions associated with the heterogeneous electron transfer, avoid electrode passivation and achieve better selectivity [36]. Hence, the development of redox mediator- and electrolyte additive-free [37–44] electrochemical reactions is highly desirable.

Paraformaldehyde is regarded as one of the most abundant and cost-effective methylene sources and has been extensively applied to construct a variety of value-added chemicals [45–50]. In view of the key iminium ion intermediates generated from *N*-phenylglycines and sultams in the photocatalytic protocols, we speculated that the iminium ion intermediates can be generated with paraformaldehyde as the methylene source *via* Mannich reaction. Such processes are highly desirable in green chemistry, because potentially tedious workup procedures and the generation of aniline side products can be avoided. Herein, we report the successful development of an electrochemical [2 + 2 + 1] annulation for the construction of BIIO. Advantageously, this process proceeds in a catalyst-, redox mediator-, electrolyte- and chemi-

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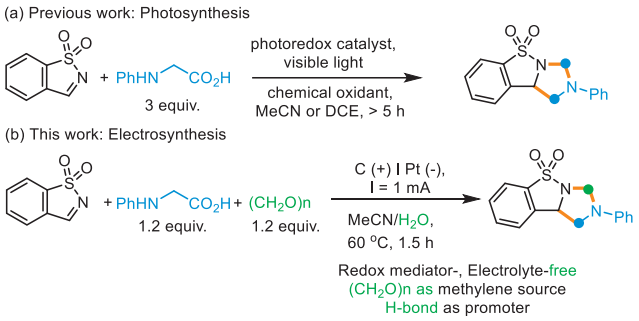
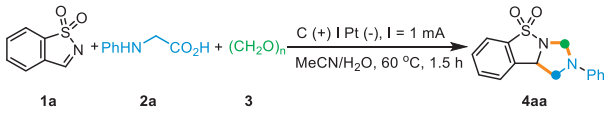


Scheme 1. Annulation of benzo[*d*]isothiazole 1,1-dioxides.

Table 1
Optimization of reaction conditions.[a]

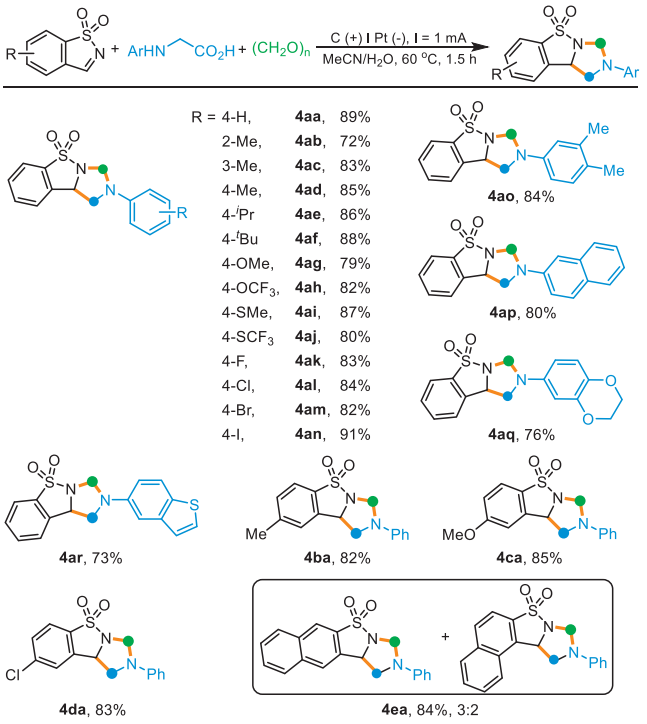


Entry	Variation from the standard reaction conditions	Yield (%)[b]
1	None	93
2	C(+)|C(-) instead of C(+)|Pt(-)	48
3	C(+)|RVC(-) instead of C(+)|Pt(-)	50
4	C(+)|Ni(-) instead of C(+)|Pt(-)	56
5	C(+)|Cu(-) instead of C(+)|Pt(-)	33
6	Pt(+)|Pt(-) instead of C(+)|Pt(-)	62
7	Pt(+)|RVC(-) instead of C(+)|Pt(-)	66
8	MeCN instead of MeCN/H_2O (3/1)	42
9	H_2O instead of MeCN/H_2O (3/1)	N.R.
10	MeOH/H_2O (3/1) instead of MeCN/H_2O (3/1)	40
11	DMSO/H_2O (3/1) instead of MeCN/H_2O (3/1)	25
12	DMF/H_2O (3/1) instead of MeCN/H_2O (3/1)	trace
13	25 °C instead of 60 °C	22
14	75 °C instead of 60 °C	81
15	Without $(CH_2O)_n$	46
16	Without electricity	N.R.
17	Under nitrogen	N.R.

[a] Conditions: C plate (15 mm × 10 mm × 2 mm), Pt plate (15 mm × 10 mm × 0.1 mm) cathode, **1a** (0.2 mmol), **2a** (0.24 mmol), **3** (0.24 mmol), MeCN (2.25 mL), H_2O (0.75 mL), I = 1 mA, r.t., 1.5 h, undivided cell.
[b] Yield estimated by GC with dodecane as the internal reference.

cal oxidant-free fashion to yield a diversity of functionalized BIIO (Scheme 1b).

In the beginning, the reaction conditions for the electrochemical annulation of benzo[*d*]isothiazole 1,1-dioxide (**1a**), *N*-phenylglycine (**2a**) and $(CH_2O)_n$ (**3**) were preferentially screened (Table 1). After a meticulous investigation of the reaction parameters, the optimized conditions were identified as graphite plate (C+) as anode and platinum plate (Pt-) as cathode in a solvent mixture of MeCN and H_2O at a 3:1 vol ratio at 60 °C, wherein the target product BIIO (**4aa**) was obtained in 93% GC yield after 1.5 h (entry 1). As shown in entries 2 to 7, unsatisfying experimental results were obtained when using other electrode pairs in the electrochemical transformation. With pure MeCN as the reaction medium, only 42% GC yield of **4aa** was observed (entry 8). No reaction occurred when water was used as the solvent, perhaps due to the insolubility of the reagents (entry 9). Varying the aqueous solutions did not provide an improved yield of **4aa** (entries 10–12). A strong temperature effect was noticed. Performing the annulation at 25 °C only gave 22% GC yield of **4aa** (entry 13). Increasing the temperature from 60 °C to 75 °C led to an inferior result (entry 14). Product **4aa** was generated in 46% GC yield in the absence of $(CH_2O)_n$ (entry 15), indicating that $(CH_2O)_n$ played an important role in this reaction. No product was observed in the absence of



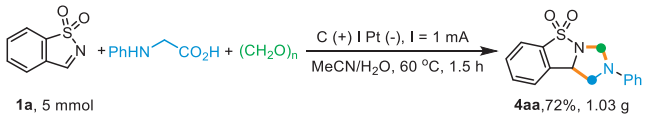
Scheme 2. Substrate scope. C plate (15 mm × 10 mm × 2 mm), Pt plate (15 mm × 10 mm × 0.1 mm), cathode, **1** (0.2 mmol), **2** (0.24 mmol), **3** (0.24 mmol), MeCN (2.25 mL), H_2O (0.75 mL), I = 1 mA, r.t. 1.5 h, undivided cell. Isolated yields.

electricity (entry 16). Performing the reaction under nitrogen atmosphere failed to give the target product (entry 17).

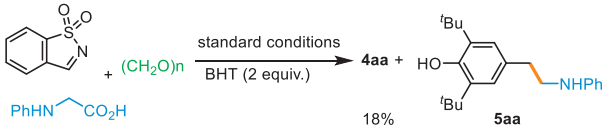
With the optimized reaction conditions in hand (Table 1, entry 1), the scope of the electrochemical [2 + 2 + 1] annulation was investigated. As shown in Scheme 2, the present electrochemical reaction was appropriate for a multitude of *N*-arylglycines. No matter whether the phenyl ring of *N*-phenylglycines was modified with either sterically hindered, electron-rich or electron-poor group, all of them gave the corresponding products (**4aa**-**4an**) in good to excellent yields. Many valuable functional-groups, such as alkyl (-Me, -*i*Pr and -*t*Bu), alkoxy (-OMe and -OCF_3), methylthio (-SMe), trifluomethylthio (-SCF_3) and halogen (F, Cl, Br and I) were introduced into the terminal products, proving the excellent functional group tolerance of this reaction. (3,4-Dimethylphenyl)glycine can also be used as the substrate, furnishing the annulation product **4ao** in 84% yield. Importantly, *N*-functionalized glycine substrates with naphthalene (**4ap**) or heterocyclic ring (**4aq** and **4ar**) were also compatible in the annulation system. No reaction occurred when pyridin-4-ylglycine or furan-3-ylglycine was used as the aminomethyl source. Electron-rich (**4ba** and **4ca**) group-substituted as well as the electron-poor group-substituted benzo[*d*]isothiazole 1,1-dioxides (**4da**) delivered the annulation products in 82%–85% yields. Furthermore, when a regioisomeric mixture of **1e** and **1e'** was used, the corresponding products **4ea** and **4ea'** were formed as a mixture of regioisomeric with the same ratio.

Next, the amplified reaction was carried out in order to further verify the practicality of electrolyte-free electrochemical annulation reaction (Scheme 3). Performing the reaction with 5 mmol **1a** under the modified conditions gave the annulation product **4aa** in 72% yield, demonstrating that the present reaction could be readily scalable.

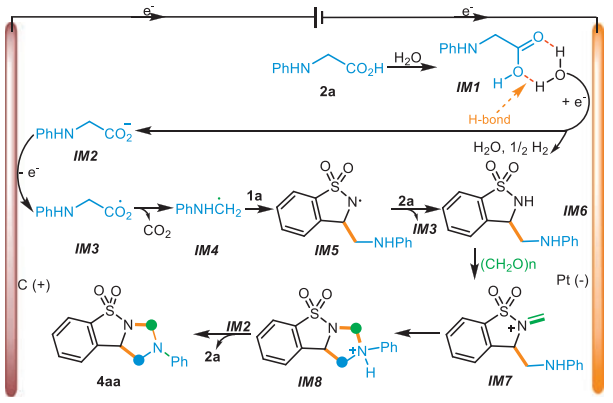
Subsequently, a series of control experiments were carried out to gain insight into the reaction mechanism. Firstly, the radical-trapping experiment was conducted. The electro-oxidative annulation could be strongly suppressed by the radical scavenger buty-



Scheme 3. Large-scale synthesis of **4aa**.



Scheme 4. Radical-capturing experiments.



Scheme 5. Proposed reaction mechanism.

lated hydroxytoluene (BHT), and the BHT-CH_2NHPh adduct **5aa** was detected by mass spectroscopy (Scheme 4). This result revealed that the $PhNHCH_2$ radical was the critical intermediate in the current reaction. Secondly, the intermittent electrolysis experiments were performed. This annulation proceeded or stop depending on electricity on/off, ruling out a radical chain mechanism (Fig. S2 in Supporting information). Finally, the cyclic voltammetry experiment was conducted to measure the redox potential of **1a** and **2a**. No oxidation peak of **1a** was observed in the region of 0–1.75 V (*vs.* Ag/AgCl), suggesting the anodic oxidation of **1a** was not easy to occur (Fig. S3 in Supporting information). With anhydrous MeCN as the solvent, **2a** presented an oxidation peak at 1.35 V. The addition of water into MeCN solution led to an obviously reduced in the oxidation potential of **2a**, and an oxidation potential of **2a** was found at 0.93 V in MeCN/H_2O (3:1). These results agreed with the yield of **4aa** in MeCN aqueous solution and anhydrous MeCN (Table 1, entry 1 *vs.* 8). The reduction potential of **2a** in anhydrous MeCN and MeCN/H_2O (3:1) was recorded at −1.24 V and −0.82 V, respectively (Fig. S4 in Supporting information). And a similar decreased in reduction potential of **2a** in the different volume of water of the reaction medium was also observed. The results suggested that the H-bond complex generated from **2a** and water was more likely to be cathodically reduced [51].

Based on previous reports [7,35,51,52] and the results of mechanism investigations, a plausible mechanism for the electrolyte-free electrochemical [2 + 2 + 1] annulation was proposed in Scheme 5 with taking **1a** and **2a** as an example. First, an H-bond association between **2a** and water resulted in the generation of complex **IM1**, which was reduced into the carboxylate anion (**IM2**), water and hydrogen gas at the surface of platinum cathode. At the surface of graphite anode, the intermediate **IM2** was oxidized into the oxygen-centred carboxyl radical **IM3**, which underwent decarboxylation to generate a carbon-centred aminomethyl radical **IM4**. Subsequently, the radical **IM4** regio-selectively attacked benzo[*d*]isothiazole 1,1-dioxide **1a** to produce a nitrogen-centred radical **IM5**, which abstracted a hydrogen atom from **2a** to yield intermediate **IM6** (detected by ESI-MS), followed by Mannich reaction with $(CH_2O)_n$ to deliver a iminium ion intermediate **IM7**. Finally, this intermediate **IM7** *via* the intramolecular cyclization and dehydrogenation sequences furnished the annulation product **4aa** with the assistance of **IM2**.

In summary, an H-bond promoted electrochemical [2 + 2 + 1] annulation of benzo[*d*]isothiazole 1,1-dioxides, *N*-arylglycines and $(CH_2O)_n$ was successfully developed. This reaction allowed accessing various benzo[*d*]imidazo[1,5-*b*]isothiazole 5,5-dioxide derivatives in good to excellent yields. A paramount advantage of this method is that it does not require any catalyst, chemical oxidant, redox mediator and electrolyte. With $(CH_2O)_n$ as the methylene source, this reaction offers a superior atom economy and practicability over the previous dual-component reactions. Mechanistic studies indicated that the hydrogen bond plays a vital role for generating the active $PhNHCH_2$ radical at lower voltage. The present electrocatalytic reaction provides an economical and sustainable manner to make use of low-cost abundant paraformaldehyde, and would lead to tremendous applications in pharmaceutical chemistry and synthetic chemistry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109246.

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