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Electrosynthesis of Dihydropyrano[4,3-b]indoles based on Double Oxidative [3+3] Cycloaddition

Subin Choi, Jinhwi Park, Eunsoo Yu, Jeongwoo Sim and Cheol-Min Park*

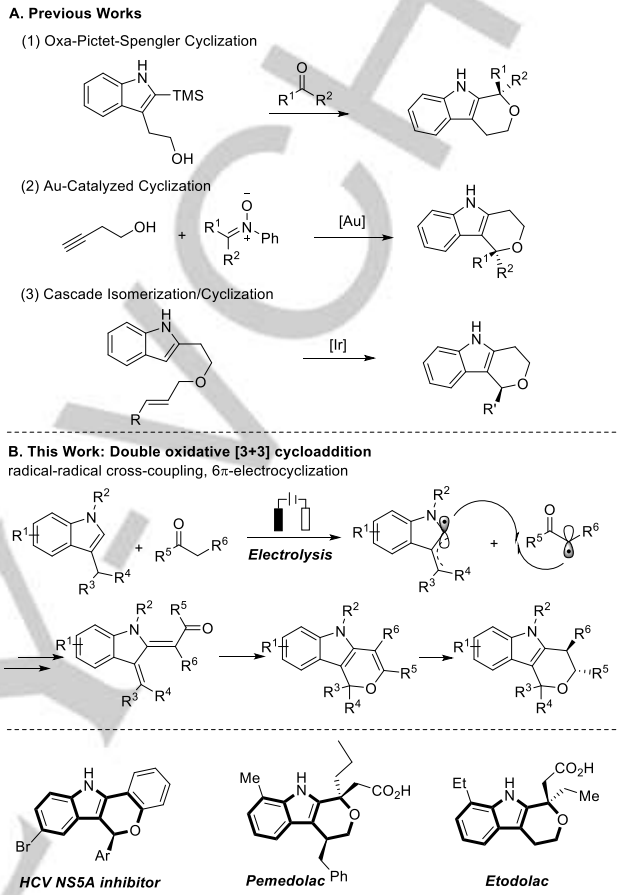
Abstract: *Oxidative [3+3] cycloaddition offers an efficient route for 6-membered ring formation. This approach has been realized based on electrochemical oxidative coupling of indoles/enamines with active methylene compounds followed by tandem* 6π-electrocyclization *leading to the synthesis of dihydropyrano[4,3-b]indoles and 2,3-dihydrofurans. The radical-radical cross-coupling of the corresponding radical species by anodic oxidation combined with cathodic generation of the base from O_2 allows mild reaction conditions for the synthesis of the structurally complex heterocycles.*

Indoles are a privileged structural motif that display diverse biological activities.[1] Structural elaboration of indoles with additional ring fusion would serve as a useful approach to exploit the indole scaffold for new biological activities.[2] Indeed, various indole-fused ring systems including carbazoles and carbolines show interesting bioactivities.[3] Dihydropyrano[4,3-b]indoles are a structural motif of interest, which may extend the utility of indoles for various biological activities as found in HCV NS5A inhibitor,[4] Pemedolac,[5] and Etodolac (Scheme 1).[6]

The broad bioactivities led to the development of several synthetic methods for dihydropyrano[4,3-b]indoles. For example, the synthesis based on Oxa-Pictet-Spengler cyclization has been described, in which indole dimerization occurs as a side reaction (Scheme 1, Eq. 1).[7] Gold-catalyzed dual annulation of nitrones with alkynols (Scheme 1, Eq. 2)[8] and tandem alkene-isomerization followed by cyclization (Scheme 1, Eq. 3)[9] have been developed. These previous syntheses typically rely on transition metal catalysis, pre-functionalization, or harsh stoichiometric conditions.

Dehydrogenative cross-coupling has been recognized as an eco-friendly atom-economic approach that allows direct C-C bond formation obviating pre-functionalization of reactants.[10] Inspired by the strategy, we envisioned the development of [3+3] cycloaddition based on oxidative cross-coupling. The recent surge in the efforts to develop electrosynthesis reflects its potential toward more efficient and environmentally friendly reactions.[11] Moreover, the ability to precisely control redox potentials applied to substrates offers an advantage over conventional reagents with intrinsic redox potentials. Recently, Lei and co-workers described an elegant synthesis of benzofuro[3,2-*b*]indolines based on [3+2] cycloaddition of indoles with phenols based on direct electrolysis, in which the indoles were limited to N-acetyl indoles presumably to enhance their oxidative stability.[12]

The broad application of electrosynthesis to complex polycyclic heterocycles is hampered owing to the redox liability of competing functionalities. Whereas the direct control of



Scheme 1. Previous synthetic methods and bioactive [2,3]-fused indoles.

chemoselectivity by electrode potential alone may be difficult, the use of redox mediators may allow fine-tuning of reactivity to include more complex substrates.[13]

In this context, we developed the synthesis of highly substituted dihydropyrano[4,3-b]indoles based on indirect electrochemical double oxidative [3+3] cycloaddition, which, to the best of our knowledge, represents the first example of oxidative [3+3] cycloaddition. The tandem radical-radical cross-coupling/6π-electrocyclization is realized by employing the readily available NaI as a redox mediator with O_2 as an abundant pre-base.[14]

We initiated our study by screening the optimal electrolysis conditions employing indole **1a** and acetylacetone **2a** (See SI, S5). The electrolysis of **1a** and **2a** in the presence of NaI at constant voltage of 3.0 V, a graphite anode and reticulated vitreous carbon (RVC) cathode in acetonitrile in an undivided cell, and $NaBF_4$ as the electrolyte at room temperature provided the desired product **3aa** in 77% yield.

With the optimized conditions in hand, the scope was examined with **1** bearing various substituents (Table 1).[15] The halides including Br and Cl remained intact, which are useful functional handles (**3ia** and **3ja**). Examination of N-substitution on

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the indole showed that the unsubstituted and N-aryl indoles were also tolerated (**3ka** and **3la**). The method readily allows the introduction of various electron-withdrawing groups on the dihydropyrano[4,3-b]indoles including ketoester, diketone and ketophosphonate in addition to the malonate group (**3ma**-**3oa**). It is notable that heteroindole such as 7-azaindole is compatible with this method (**3pa**, 53%).

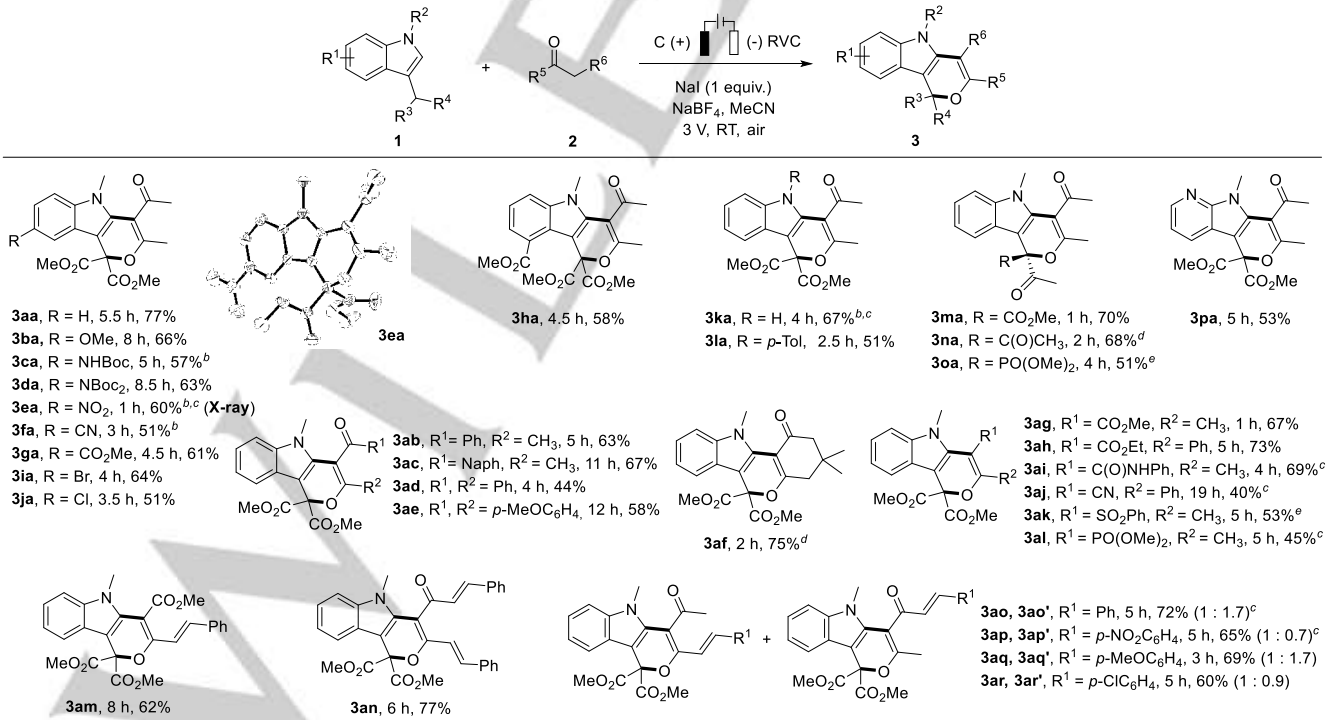
At this juncture, we turned our attention to the scope of the active methylene compounds (AMCs) **2**. Notably, unsymmetrical diketones proceeded with complete regioselectivity (**3ab** and **3ac**). The reaction with dimedone furnished a tetracyclic compound in good yield (**3af**, 75%). In addition to diketones, various eletron-withdrawing groups were tolerated to give the corresponding products in good to moderate yields (**3ag**-**3al**). The reaction allowed the synthesis of alkenyl-substituted dihydropyrano[4,3-b]indoles **3am**-**3ar'** in good yields for further elaboration. For several substrates, we found that the addition of di-*tert*-butyl peroxide was beneficial, which may be attributed to the higher basicity of *tert*-butoxide formed by cathodic reduction of di-*tert*-butyl peroxide.

With the scope established on the indoles, we became interested in whether the method could be extended to enamines. To our surprise, the reaction afforded 2,3-dihydrofuran **5aa** as single diastereomer. Since the optimized conditions for dihydropyrano[4,3-b]indoles turned out to be unsatisfactory, minor adjustment was required (See SI, S6). The reaction was sluggish with the constant voltage mode resulting in the decomposition of the enamine, however, changing to the constant current mode gave an improved yield (67%). Examination of the electronic effect of the aryl groups revealed that while the reaction with substrates bearing electron-deficient aryl groups proceeded smoothly to give good yields of 2,3-dihydrofurans (**5fa** and **5ga**), moderate to low yields were observed for those with electron-rich aryl groups (**5ba**-**5da**). Similar to the scope of the dihydropyrano[4,3-b]indoles, various AMCs were well tolerated to furnish the corresponding 2,3-dihyrofurans **5ag** and **5ak**. However, the reaction with ketophosphonate **2l** gave the corresponding product in low yield (**5al**, 29%).

To probe the mechanism for the activation of **1a**, we performed several control experiments. First, the participation of I_2 formed by *in situ* oxidation of NaI was ruled out based on the experiment Scheme 2-a, in which the use of I_2 failed to give **3aa**. Second, we considered the direct anodic oxidation of **1a**. It turned out that no product was observed when direct electrolysis at 3.0 V was performed in the absence of NaI (See SI, S8). Next, the possibility of hydrogen atom transfer (HAT) on **1a** by iodine radical was examined by performing voltage-controlled experiments. Based on the half-wave potentials of NaI and **1a** measured by CV (0.68 V and 1.17 V, respectively; Scheme 2), the electrolysis was conducted at 1.0 V in the absence of acetylacetone. When performed at 1.0 V, which is unable to oxidize **1a** but sufficient for iodide oxidation, indole dimer **6** was obtained in 46% yield (Scheme 2-b). This observation combined with the previous results supports the formation of the indole radical via iodine radical-mediated HAT.

The interaction of **1a** with iodine radical was further investigated by the CV analysis. When compared with the cyclic voltammogram of **1a** alone, the presence of NaI significantly shifted the oxidation peak of **1a** to 0.35 V (Scheme 2), for which the formation of the corresponding radical species from **1a** by iodine radical appears to be responsible (See SI for the detailed

Table 1: Electrosynthesis of dihydropyrano[4,3-b]indoles[a]



[a] Reaction conditions: Reactions were performed with **1** (0.10 mmol) and **2** (0.11 mmol) in MeCN (3.0 mL). Isolated yield. [b] 1.5 equiv. of NaI was used. [c] Di-*tert*-butyl peroxide was used as an additive (1.0 or 2.0 equiv. See SI). [d] 3.5 V. [e] 2-3 equiv. of AMC was used.

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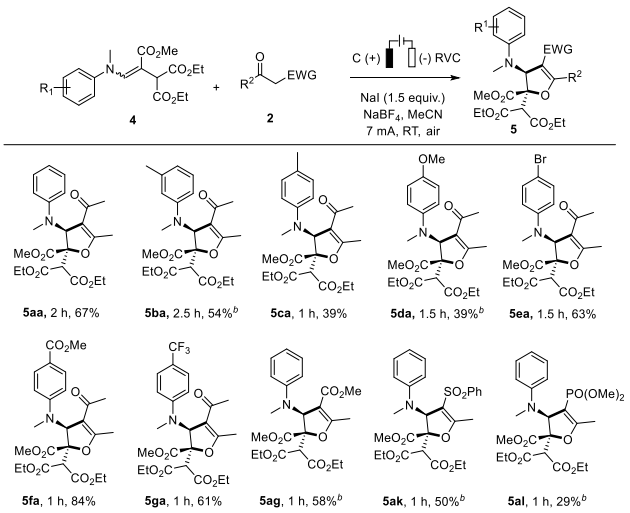
Table 2: Electrosynthesis of 2,3-dihydrofurans scope of the dihydropyrano[4,3-b]indoles, various AMCs.[a]



[a] Reaction conditions: Reactions were performed with **1** (0.10 mmol) and **2** (0.15 mmol) in MeCN (3.0 mL). Isolated yield. [b] 2-3 equiv. of AMC was used.

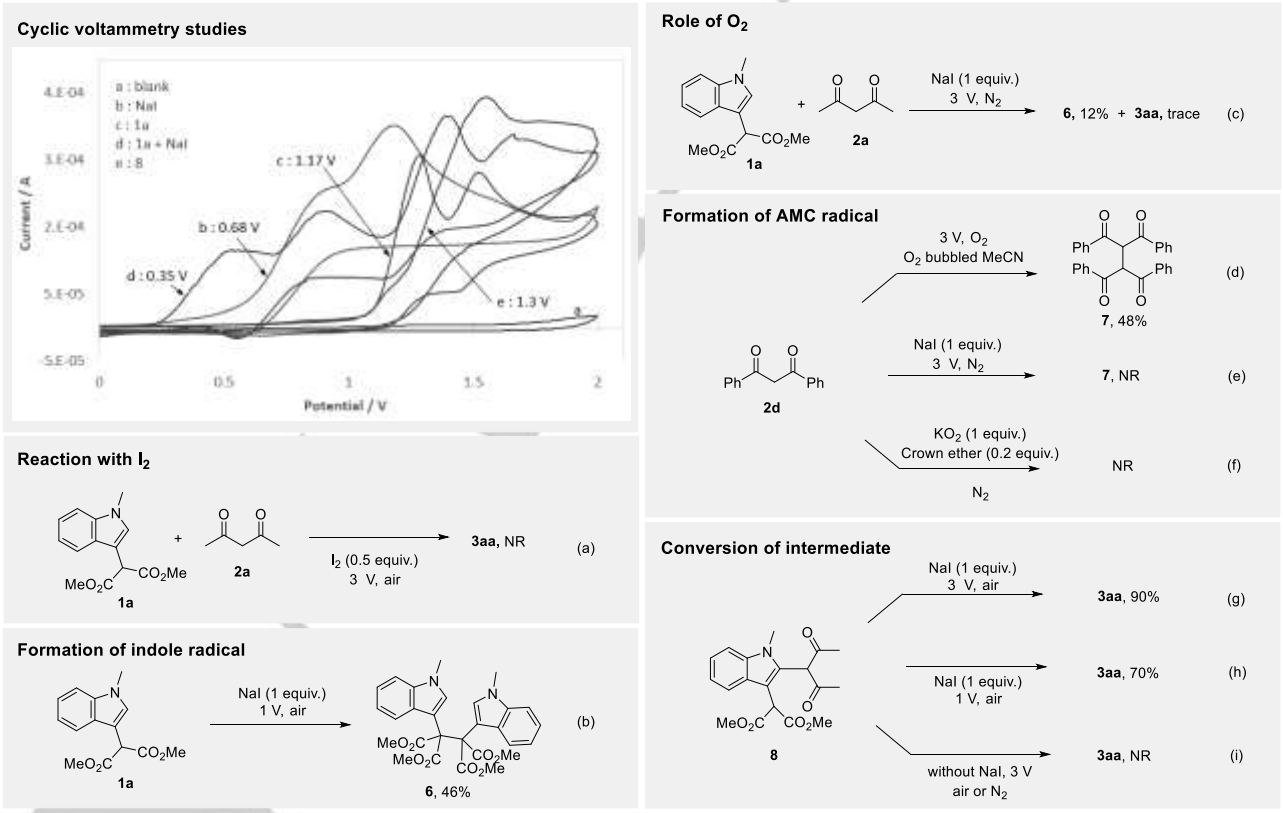
analysis, S6).

Next, studies were conducted to shed light on the role of O_2. The observation that the reaction afforded only indole dimer **6** in the absence of O_2 suggested that superoxide formed by cathodic reduction of O_2 plays a crucial role in activating the coupling partner **2a** (Scheme 2-c). One plausible pathway is that superoxide serves as a base to generate the corresponding enolate from acetylacetone **2a**, which undergoes anodic oxidation to form a radical species. To confirm the formation of diketone radical, an electrolysis of **2d** in a solvent saturated with O_2 was performed, which resulted in the formation of the corresponding dimer **7** in 48% yield (Scheme 2-d).

The possibility of HAT on **2d** by iodine radical was ruled out by the absence of dimer **7** when performed in the presence of NaI but with exclusion of O_2 (Scheme 2-e). To further examine an alternative HAT pathway mediated by superoxide, we performed a reaction with **2d** and KO_2 under non-electrolytic conditions (Scheme 2-f). The fact that no reaction was observed indicates that HAT between **2d** and superoxide is not a viable pathway.

To elucidate the mechanism responsible for the conversion of the intermediate **8** to dihydropyrano[4,3-b]indole, we performed several experiments. First, the intermediacy of **8** in the pathway was confirmed by the conversion to **3aa** in 90% (Scheme 2-g). As observed in Scheme 2-b, the electrolysis at 1.0 V provided **3aa** in 70% yield (Scheme 2-h). Also, the reaction did not proceed in the absence of NaI (Scheme 2-i), which, in combination with the result from the voltage control experiment, suggests that the reaction proceeds through iodine radical-mediated HAT excluding the possibility of direct oxidation of **8** on the anode.

Density functional theory (DFT) calculations were performed to obtain an in-depth understanding on the reaction mechanism



Scheme 2. Cyclic voltammetry studies in 2 mL MeCN (0.1 M $NaBF_4$), 100 mV/s. a) 0.02 mmol NaI; b) 0.02 mmol **1a**; c) 0.02 mmol NaI, 0.02 mmol **1a**; d) 0.02 mmol **8.** Control experiments. (See SI, S6-9).

10.1002/anie.202003364

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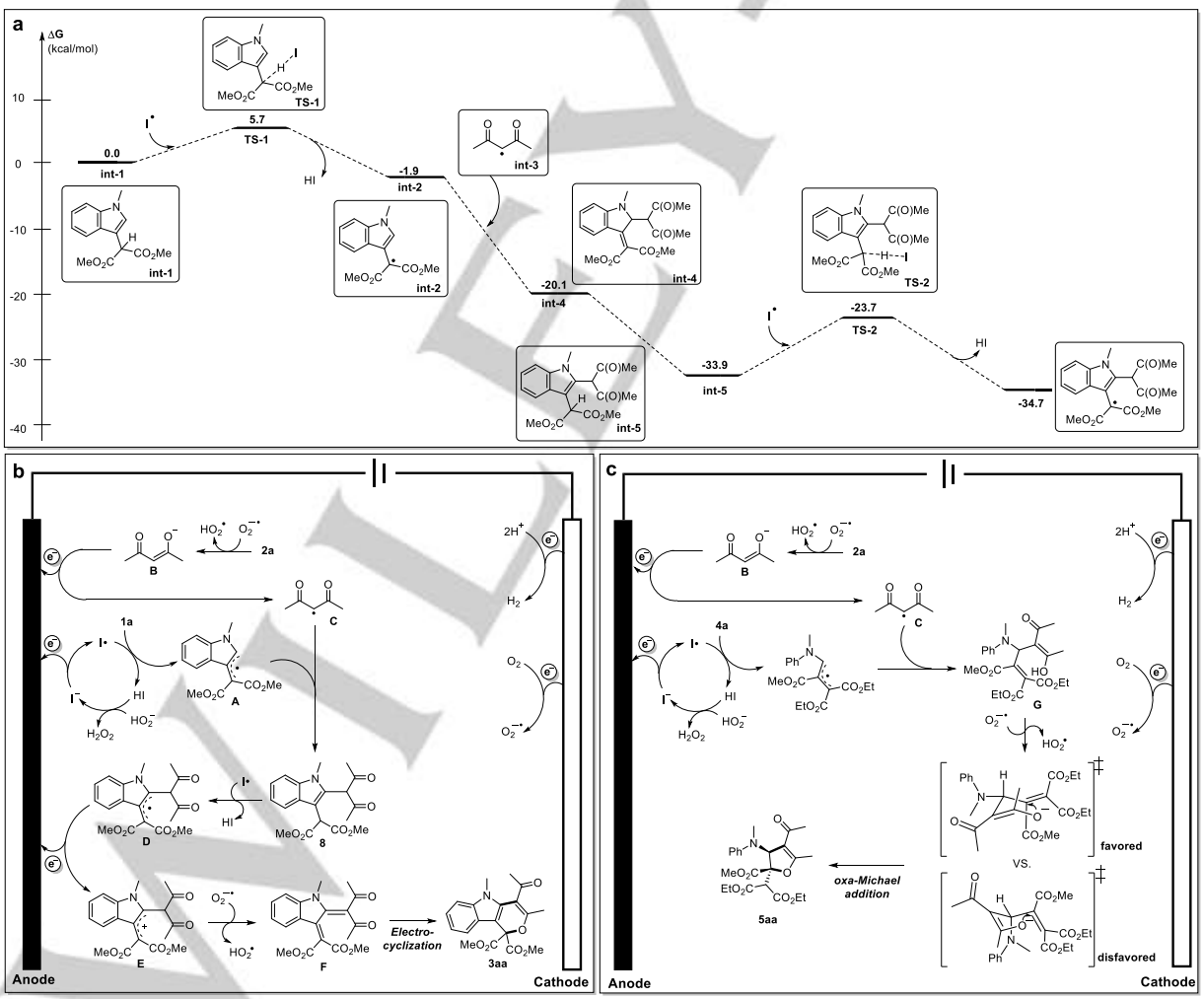
(Scheme 3-a, see SI, S10). Based on the control experiments above and DFT calculations, a reaction mechanism is proposed in Scheme 3-b. Overall, cathodic reduction of O_2 affords superoxide, which serves as a base to generate enolate **B**. Subsequent anodic oxidation of **B** affords diketone radical **C**. Concurrently, anodic oxidation of iodide results in the formation of iodine radical, which mediates HAT on **1a** to afford **A**. Radical-radical cross-coupling of **A** with **C** provides **8**, which undergoes a second HAT by iodine radical followed by anodic oxidation of **D** to furnish oxatriene **F**. Finally, spontaneous 6π-electrocyclization provides **3aa**.

Regarding 2,3-dihydrofuran (Scheme 3-c), while the formation of **5aa** shares in part the same mechanism with that for **3aa**, the inability for aromatization available in the dihydropyrano[4,3-b]indole formation steers **G** toward oxa-Michael addition. The high diastereoselectivity observed in the scope could be rationalized by the highly ordered chair-like transition state.

The synthetic potential of our electrolysis was demonstrated by the gram scale electrolysis (70%, Scheme 4-a). We have further demonstrated that the dihydropyrano[4,3-b]indoles are a versatile framework, which can be readily transformed into more elaborate scaffolds in single steps. Thus, the synthesis of tetrahydropyrano[4,3-b]indoles **9** and **10** were shown by hydrogenation-epimerization of **3aa** and **3ba**, respectively (Scheme 4-b). In addition, dihydro-γ-carbolines (**11**-**13**) were prepared in excellent yields by treating **3aa** with the corresponding amines (Scheme 4-c). Tetracyclic compound **14** could be prepared via the 6π-electrocyclization of the corresponding silyl enol ethers derived from ketones **3ao** and **3ao′** (Scheme 4-d).

In summary, we developed the synthesis of highly substituted dihydropyrano[4,3-b]indoles and 2,3-dihydrofurans based on electrochemical double oxidative [3+3] cycloaddition. The shared mechanistic manifold allows the versatile synthesis of the two important heterocyclic scaffolds with high substitution. The mechanistic study suggests that the reaction proceeds via radical-radical cross-coupling of the indole/enamine radicals with the radical species derived from AMCs followed by tandem 6π-electrocyclization. Anodic oxidation promotes the formation of the radical species from the corresponding coupling partners, while cathodic reduction of O_2 leads to the formation of superoxide as the base.



Scheme 3. Plausible reaction pathways. DFT was calculated at the B3LYP-D3/6-31+G(d,p)/LANL2DZdp level in MeCN (SMD).

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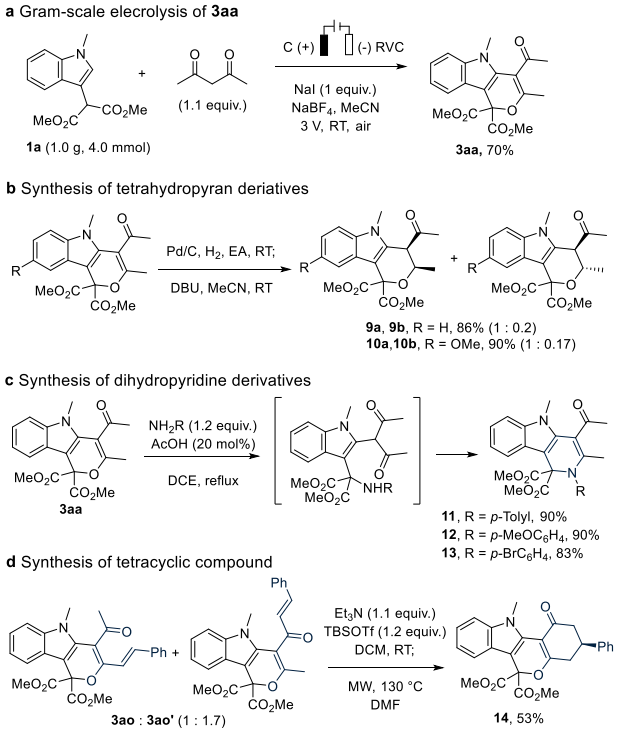

Scheme 4. Gram-scale synthesis and transformation of electrolysis products.

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Keywords: electrochemistry • radical-radical cross-coupling • [3+3] cycloaddition • hydrogen atom transfer • indole

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[15] CCDC 1881731 (**3ea**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre.