



A pseudo multi-component electrochemical synthesis of spiro dihydrofuran derivatives



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ABSTRACT

An electrochemical strategy to the assembly of tricyclic spiro dihydrofuran scaffold via the reaction of aryl aldehyde and dimedone has been developed successfully. This protocol has the advantages of high yields, wide application scope and an environmental benign procedure compared with the reported methods.

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1. Introduction

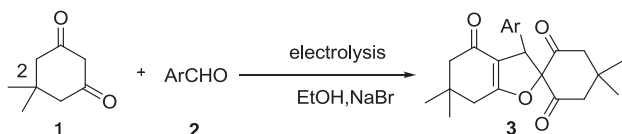
The spiro dihydrofurans are frequently presented as core units in diverse classes of natural products showing importantly biological significance and pharmaceutical value.¹ For example, coumestans, isolated from plants of the family of fabaceae, are used in folk medicine against snake poison.² The spiro dihydrofuran diterpenoid nepetaefolin exhibits biological activities, such as anti-hypertensiveness, sedativeness, bactericidal, insecticidal and antiviral.³ In view of their biological importance, several procedures for the synthesis of spiro dihydrofurans have been developed for years. The majority of approaches for the assembly of spiro dihydrofuran include the oxidative 1,3-dipolar cycloaddition of 1,3-dicarbonyl compounds with exocyclic alkenes,⁴ the three-step protocol of addition, halogenation, cyclo-dehydrohalogenation of cyclic 1,3-diones with aldehydes,⁵ and the *N*-heterocyclic carbene-mediated cycloaddition.⁶ Very recently, one-pot synthesis of substituted dihydrofurans through Lewis base-catalyzed three-component condensation was reported by Shi's group.⁷ The NaOH-catalyzed splitting of dimedone fragment of spiran could also give rise to the spiro dihydrofuran derivatives in aqueous dioxane.⁸ Sahu's group put forward a route towards spiro dihydrofurans by the reaction of dimedone and aldehydes

mediated by iodine and ammonium acetate through the sequence of Knoevenagel condensation, Michael addition, iodination and cyclodehydroiodination.⁹ In addition, several reports described the synthesis of spiro dihydrofurans promoted by 1,4-diazabicyclo [2.2.2]octane (DABCO),¹⁰ Dess–Martin periodinane (DMP) and tetraethylammonium bromide (TEAB).¹¹ The ball-milled reaction of aldehydes with 5,5-dimethylcyclohexane-1,3-dione in the presence of molecular iodine and dimethylaminopyridine could afford spiro dihydrofuran framework readily as well.¹² The above-mentioned methods could establish the spiro dihydrofuran skeleton effectively. However, some external volatile oxidants, e.g., molecular iodine should be used to complete the assembly. Hence, it is necessary to develop an efficient alternative strategy to construct the framework considering the atom economy and environmental concern.

The electrosynthesis has provided organic chemists with novel and versatile synthetic protocols of great promise due to its prominent advantages including high material utilization, mild reaction condition, decreased energy requirement, ease of control of the reaction, less hazardous process, and the ability to perform wide range of precisely tunable oxidation and reduction reactions.^{13,14} Pronounced growth of investigations in organic electrochemistry during last three decades has made electrosynthesis one of the most competitive methods of modern organic chemistry.¹⁵ The multi-component reactions (MCRs) have been employed for preparing compound libraries by virtue of straightforward reaction condition, atomic economy, high bond forming efficiency

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and great diversity generating potential.¹⁶ Methods of organic transformations based on electrochemically induced MCRs involving carbonyl compounds have been extensively developed.¹⁷ To continue our work on the multi-component synthesis of heterocyclic compound library,¹⁸ herein we shall report an electrochemical pseudo multi-component procedure for the fabrication of tricyclic spiro dihydrofuran scaffold through the reaction of dimedone and aldehydes in an undivided cell (Scheme 1).



Scheme 1.

2. Results and discussion

In an initial study, to optimize the electrolytic conditions, the electrochemical multi-component transformation of dimedone **1** and 4-bromobenzaldehyde **2a** into 3-(4-bromophenyl)-4',4',6,6-tetramethyl-6,7-dihydro-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4,6'(5*H*)-trione **3a** was studied using sodium bromide as supporting electrolyte in ethanol (Table 1).

Table 1
The optimization of electrolysis conditions for the synthesis of **3a**^a

Entry	<i>I</i> (mA)	Time (min)	Solvent	Charge passed (F/mol) ^b	Current yield (%)	Yield of 3a (%) ^c
1	50	130	EtOH	2.02	99	72
2	100	65	EtOH	2.02	99	83
3	150	45	EtOH	2.10	95	94
4	250	30	EtOH	2.33	86	87
5	150	45	MeOH	2.10	95	84
6	150	50	<i>i</i> -PrOH	2.33	86	89
7	150	45	<i>n</i> -BuOH	2.10	95	75

^a General procedure: **1** (4 mmol), **2a** (2 mmol), NaBr (1 mmol), alcohol (20 mL), iron cathode (5 cm²), graphite anode (5 cm²), at room temperature.

^b Calculated for 4-bromobenzaldehyde **2a**.

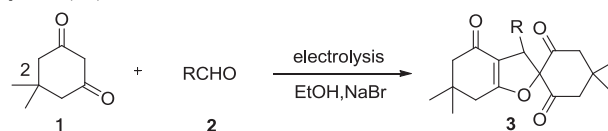
^c Yield of isolated product.

As can be seen in Table 1, the reaction proceeded to provide the desired product **3a** smoothly when the reaction was carried out under a constant current of 150 mA after 2.10 F/mol of electricity passed. We were pleased to find that the current of 150 mA was optimal for the electrochemical synthetic process for the desired product was obtained in excellent yield. However, raising the current up to 250 mA resulted in a slight decrease in the reaction yield and it should be attributed to the oligomerization of the starting material.¹⁹ Lately, we examined the effect of alcoholic solvents on the reactions. This electrochemical synthesis could be carried out in *n*-BuOH with relatively low conversion of starting materials. The similar results were found in the case of MeOH and *i*-PrOH. Thus EtOH was the optimal solvent for this electrochemical reaction.

Under the optimal conditions, the scope and generality of the reaction was explored. A variety of aryl aldehydes were investigated to react with dimedone, and the results are summarized in Table 2. This protocol can be applied not only to electron-rich (entry 10 and entry 13) and electron-deficient (entry 7 and entry 9) aryl aldehydes, but also to heteroaromatic aldehydes (entry 14) with excellent yields under the mild conditions, which highlighted the wide scope of this pseudo multi-component electrosynthesis. However, when the aliphatic aldehydes were employed in this reaction, no expected product was obtained.

Table 2

Electrochemical transformation of cyclic 1,3-diketones **1**, aldehyde **2**, into 3-substituted-4',4',6,6-tetramethyl-6,7-dihydro-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4,6'(5*H*)-trione **3**^a



Entry	Product	R	Charge passed (F/mol) ^b	Current yield (%)	Yield of 3 (%) ^c
1	3a	4-BrC ₆ H ₄	2.10	95	94
2	3b	C ₆ H ₅	2.10	95	95
3	3c	4-ClC ₆ H ₄	2.10	95	96
4	3d	4-FC ₆ H ₄	2.10	95	95
5	3e	3-ClC ₆ H ₄	2.33	86	93
6	3f	3,4-Cl ₂ C ₆ H ₃	2.56	78	92
7	3g	3-NO ₂ C ₆ H ₄	2.56	78	96
8	3h	3,4-Me ₂ C ₆ H ₃	2.33	86	90
9	3i	4-NO ₂ C ₆ H ₄	2.56	78	96
10	3j	4-Me ₂ NC ₆ H ₄	2.33	86	88
11	3k	3-CH ₃ OC ₆ H ₄	2.56	78	93
12	3l	4-CH ₃ C ₆ H ₄	2.10	95	90
13	3m	4-CH ₃ OC ₆ H ₄	2.33	86	90
14	3n	Thien-2-yl	2.80	71	89
15	3o	<i>n</i> -C ₃ H ₇	2.00	—	—

^a General procedure: **1** (4 mmol), **2** (2 mmol), NaBr (1 mmol), alcohol (20 mL), iron cathode (5 cm²), graphite anode (5 cm²), current density 30 mA/cm², at room temperature.

^b Calculated for aryl aldehyde **2**.

^c Yield of isolated product.

With the above results and related reference taken into consideration,²⁰ the plausible mechanism for the electrochemical transformation of dimedone **1**, aldehydes **2** into substituted spiro dihydrofurans **3** was proposed. The initial formation of bromine on the anode is a well-known process and the corresponding halogen color was observed at the anode when the electrolysis was conducted without stirring the reaction mixture. The solvent, EtOH was reduced to EtO⁻, an electrochemically generated base (EGB) on the cathode at the same time. The condensation of aldehyde **2** and dimedone **1** initiated by the deprotonation of **1** by EGB would give rise to 2-(arylmethylene)-5,5-dimethylcyclohexane-1,3-dione **4**. The Michael addition of dimedone **1** to **4** yielded anion **5** in the presence of EtO⁻. Then, bromination of anion **5** led to the formation of substituted bromoadduct **6**, which was further cyclized into 3-substituted-4',4',6,6-tetramethyl-6,7-dihydro-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4,6'(5*H*)-trione **3** (Scheme 2).

3. Conclusions

In conclusion, we have presented a novel, efficient, convenient and electrochemical way to the construction of spiro dihydrofuran skeleton. The ready availability of the simple equipment, the environmental benignness and the useful skeleton of the products would make this strategy quite attractive. More importantly, these

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