Electrooxidative dearomatization of biaryls: synthesis of tri- and difluoromethylated spiro[5.5] trienones†

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Radical spirocyclization via dearomatization has emerged as an attractive strategy for the rapid synthesis of structurally diverse spiro molecules. We report the use of electrochemistry to perform an oxidative dearomatization of biaryls leading to tri- and difluoromethylated spiro[5.5]trienones in a user friendly undivided cell set-up and a constant current mode. The catalyst- and chemical oxidant-free dearomatization procedure features ample scope, and employs electricity as the green and sole oxidant.

Introduction

The development of new approaches for the construction of CF3- or CF2H-containing target molecules is becoming increasingly important owing to the growing applications of organo-fluorinated compounds in inter alia pharmaceutical and agrochemical industries.1-3 Thus, the incorporation of fluoroalkyl groups into organic molecules can significantly improve their physical, chemical, and biological properties, such as permeability, bioavailability, and metabolic stability.4-6 Although a multitude of methods have been developed for the preparation of trifluoromethylated or difluoromethylated compounds by radical addition to unsaturated bonds,7 a protocol for directly introducing CF3 or CF2H onto spiro[5.5] trienone has thus far proven elusive, despite these motifs being prevalent in a number of natural products and bioactive molecules (Fig. 1).

Electrochemistry has surfaced as an attractive technique for the discovery of new modes of reactivity and transformations that are not readily accessible with chemical reagents.9 As radical spirocyclization by dearomatization of biaryls is an attractive strategy for the rapid construction of spiro[5.5] molecules,9,11,12 we questioned whether the efficiency and mildness noted in the CF3-radical formation could be translated into an electrooxidative biaryl dearomatization strategy. However, significant challenges would need to be overcome (Fig. 1).

Regioselectivity between 5-exo-trig, 6-exo-trig and 7-endo-trig cyclization needs to be controlled. (2) The low reactivity of alkynes towards fluoroalkyl radicals needs to be addressed. Compared to the radical addition onto alkenes,9,10 alkyny functionalization by radical addition is more challenging.11 Herein, we report an unprecedented dearamatization of biaryllyones under green and operationally-simple electrochemical conditions. The salient features of our strategy comprise the following: (a) the first efficient dearamatization of biaryls to CF3-containing spiro[5.5]trienones, (b) a most user-friendly undivided cell set-up, (c) simple reaction conditions devoid of a redox mediator, (d) the absence of catalysts and chemical oxidants, and (e) high regioselectivity.

Fig. 1 Electrooxidative biaryl dearamatization: (a) reaction design and (b) selected examples of bioactive spiro compounds.
Results and discussion

Optimization of reaction conditions

We initiated our studies by probing various reaction conditions for the envisioned electrochemical dearomatization reaction of biarylynone 1a in a most user-friendly undivided cell set-up (Tables 1 and S2 in the ESI†), using the bench-stable and inexpensive Langlois’ reagent (CF₃SO₂Na, 2a) as the CF₃ source. A considerable preliminary experimentation, we observed that the desired trifluoromethylation/dearomatization was accomplished with a mixed solvent system consisting of DCE/MeCN (1 : 1) and Et₄NClO₄ as the electrolyte (entry 1). Different solvents and a series of supporting electrolytes were tested but found not to be beneficial (entries 2–7). Neither decreasing nor increasing the reaction temperature improved the yield of product 3a (entry 8). In contrast to previous literature reports,¹²⁻¹⁴ a catalytic redox mediator was not required for this transformation (entries 9 and 10). When the dearomative reaction was performed on a 1 mmol scale, the product 3a was isolated in 50% yield (entry 11). Control experiments confirmed the essential role of electricity for the electrooxidative dearomatization (entry 12). The structure of 3a was unambiguously confirmed by single-crystal X-ray analysis (Scheme 1).¹⁵a

Robustness

With the optimized reaction conditions in hand, we explored the viable scope of the electrochemical transformation. Various biarylnones 1 were investigated and the results are shown in Scheme 1. Generally, the electronic effect of substituents on the arene Ar’ did not influence the reaction efficiency and synthetically useful yields of spirot[5,5]trienones were obtained (3a–3h). We were pleased to find that ortho- and meta-substituted arene Ar’ underwent this transformation efficiently despite a possible steric repulsion (3i–3l), even for

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Table 1 Optimization of the electrooxidative dearomatization

| Entry | Variation from standard conditions | Yieldb/% |
|-------|-----------------------------------|---------|
| 1     | No change                         | 60      |
| 2     | MeCN                              | 40      |
| 3     | MeCN/H₂O (2 : 1)                  | 15      |
| 4     | In the absence of Et₄NClO₄        | 46      |
| 5     | n-BuNBF₄ instead of Et₄NClO₄      | 20      |
| 6     | Et₄NF₆ instead of Et₄NClO₄        | 18      |
| 7     | Na₂CO₃ and H₂O instead of Et₄NClO₄| 55      |
| 8     | At room temperature (25 °C)       | 40      |
| 9     | Addition of [Mes-Acr]ClO₄ (10 mol%) | 50      |
| 10    | Addition of Cp₂Fe (10 mol%)       | 45      |
| 11    | 1 mmol scale (4 mL solvent)       | 50      |
| 12    | No electricity                    | 0       |

a Standard conditions: undivided cell, GF anode, Pt cathode, constant current (CCE) = 4 mA, 1a (0.3 mmol), 2a (0.6 mmol), Et₄NClO₄ (0.1 M, 0.4 mmol), DCE/MeCN (4 mL), under air, 8 h. b Yield of isolated products. c H₂O (1 mL) was added. d 30 W, blue LED. GF = graphite felt.
polysubstituted substrates. A naphthyl substituent was also compatible (3m). Substitutions on the phenome scaffold were next examined. Substrates bearing either electron-withdrawing or electron-donating groups did not significantly alter the reaction outcome and the spiro compounds 3 were efficiently obtained (3o–3x). As depicted, the dearomatization approach was compatible with several functional groups, such as chloro, bromo, ether, nitro and ester. A heterocyclic substrate was also applicable in this electrooxidative transformation to afford the corresponding product 3y in a moderate yield. It is noteworthy that a substrate with a substituent at the ortho-position of OMe (1z) also formed the desired compound 3z.16

As the difluoromethyl group (CF2H) can serve as a hydrogen bond donor, it has been employed as a lipophilic isostere in drug design for functionalities such as amides, alcohols, thioles and hydroxamic acids.17 Thus, we turned our attention to electrochemical difluoromethylation/dearomatization with differently substituted biarylynones 1 and CF2HSO2Na (2b). Similarly, the electronic properties of arenes Ar and Ar’ in substrate 1 did not have distinct influence on the efficiency of the dearomatization, and moderate to good yields of the spiro[5.5]trienones 4 were obtained (Scheme 2). The structure of product 4o was unambiguously verified by X-ray crystallographic analysis.15

We further demonstrated the synthetic utility and showed that the trifluoromethylated spiro[5.5]trienones are a versatile framework that can be readily transformed into more value-added scaffolds in single step reactions (Scheme 3). The biologically relevant epoxyquinone 5 could be obtained in excellent yield via oxidation, while reduction of the ketone selectively furnished alcohol 6. Alcohol 7 was synthesized by selective addition of Grignard reagent, while alkene 8 could be prepared by a Wittig reaction.

To gain mechanistic insight into this electrochemical dearomatization reaction, the radical clock reaction using (1-cyclopropylvinyl)benzene (10) as the radical-trapping reagent provided the known product 9 in 25% yield (Fig. 2a). Based on these results, a radical mechanism is proposed in Fig. 2c for this electrooxidative dearomatization reaction. First, radical CF3 is generated from 2a through anodic oxidation. Radical addition of CF3 to C–C triple bonds of 1a affords a vinyl radical A, which undergoes 6-exo-trig cyclization to the radical species B. Intermediate B is reoxidized to oxocarbenium ion C at the anode. Finally, the corresponding product 3a is formed after demethylation. The incorporation of the difluoro moiety proceeds via the same mechanism, but the oxidation peak of CF2HSO2Na was found much lower than that of CF3SO2Na by a cyclic voltammetry (CV) experiment.18 In addition, inspired by the pioneering work of Jiao for 1,2-dichloroethane (DCE) dehydrochlorination,19 we also found that when the model

Scheme 2  Scope of difluoromethylated spiro[5.5]trienones 4.

Scheme 3  Reaction conditions: (1) H2O2 (1.5 equiv.), Na2CO3 (1.5 equiv.), EtOH, 45 °C, 2 h. (2) DIBAL (1.0 equiv.), THF, –78 °C, 3 h. (3) CH3MgCl (2.0 equiv.), THF, room temperature, 3 h. (4) Methyltriphenylphosphonium bromide (2.0 equiv.), t-BuOK (2.0 equiv.), THF, room temperature, 6 h.
reaction between 1a and 2a was performed under the standard conditions, the reaction mixture clearly became acidic as shown by pH measurement (in ESI†). Hence, we propose that HCl was generated from the dehydrochlorination of DCE. Notably, the analogue of ion generated from the dehydrochlorination of DCE could be trapped by water while changing the reaction solvent system with 1-(4′-tert-butyl)-3-phenylprop-2-yn-1-one 1f. The trapping product 10 was here isolated in 30% yield (Fig. 2b).

Conclusions

In summary, we have developed an efficient approach for the electrochemical dearomatization of biaryls under metal catalyst- and chemical oxidant-free conditions. This green and environmentally friendly strategy showed a broad scope and great compatibility with sensitive functional groups, affording a series of CF3- and CF2H-substituted spiro[5,5]trienones in moderate to good yields. It represents the first electrooxidative 6-exo-trig radical dearomatative spirocyclization process, and a plausible mechanism was proposed.

Data availability

All experimental data, procedures for data analysis and pertinent data sets are provided in the ESI.

Author contributions

Y. Z. and L. A. conceived the project. Y. Z. and C. M. performed the experiments, Y. Z., J. F. and J. S. analyzed and interpreted the experimental data. Y. Z. and J. S. drafted the paper. G. Z., Y. Z. and L. A. supervised the project. All of the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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