Steroids

Electrochemically Enabled One-Pot Multistep Synthesis of C19 Androgen Steroids

Florian Sommer,[a, b] C. Oliver Kappe,*[a, b] and David Cantillo*[a, b]

Abstract: The synthesis of many valuable C19 androgens can be accomplished by removal of the C17 side chain from more abundant corticosteroids, followed by further derivatization of the resulting 17-keto derivative. Conventional chemical reagents pose significant drawbacks for this synthetic strategy, as large amounts of waste are generated, and quenching of the reaction mixture and purification of the 17-ketosteroid intermediate are typically required. Herein, we present mild, safe, and sustainable electrochemical strategies for the preparation of C19 steroids. A reagent and catalyst free protocol for the removal of the C17 side chain of corticosteroids via anodic oxidation has been developed, enabling several one-pot, multistep procedures for the synthesis of androgen steroids. In addition, simultaneous anodic C17 side chain cleavage and cathodic catalytic hydrogenation of a steroid has been demonstrated, rendering a convenient and highly atom economic procedure for the synthesis of saturated androgens.

Introduction

Steroids constitute a large and important class of both natural products and pharmaceutical ingredients. Their biosynthesis by plants and animals is fundamental for many physiological processes, as steroids play key roles in signaling, as hormones, and as membrane constituents.[1] Due to their key biological properties, a significant number of medicines have been developed based on steroid derivatives, with a wide range of applications including anti-inflammatory, contraceptive, antibiotic or antihistamine treatments.[2] The vital importance of steroids in modern medicine is underscored by the fact that many of them are among the top selling drugs,[3] and several are also included in the WHO list of essential medicines.[4] It is therefore not surprising that, over the past few decades, significant research efforts have focused on the discovery of novel steroid drugs and the development of more efficient methods for their synthesis.[5]

Within the family of steroidal compounds, C19 steroids, based on the androstane skeleton, are also relevant natural hormones and synthetic or semisynthetic active ingredients, including over 40 marketed drugs.[6] A convenient strategy for the synthesis of C19 steroids entails the generation of a 17-ketosteroid precursor via cleavage of the side chain of more abundant corticosteroids (Figure 1 a).[7] Removal of the C17 side chain of corticosteroids has traditionally involved the use of excess amounts of strong oxidizing agents such as $NaBiO_3$,[8] $NaBH_4/NaIO_4$,[9] CrO_3[10] or MnO_2.[11] Additional methods involving excess I_2/NH_3[12] and strong bases[13] have also been developed, although with either moderate yields or limited applicability. More recently, cleavage of hydroxyacetone side chains with bismuth(III) catalysts has been reported.[14] Due to the shortcomings of these methods and the difficulties associated with the selective side chain removal without degradation of the androstane skeleton, microbial approaches from phytoster-

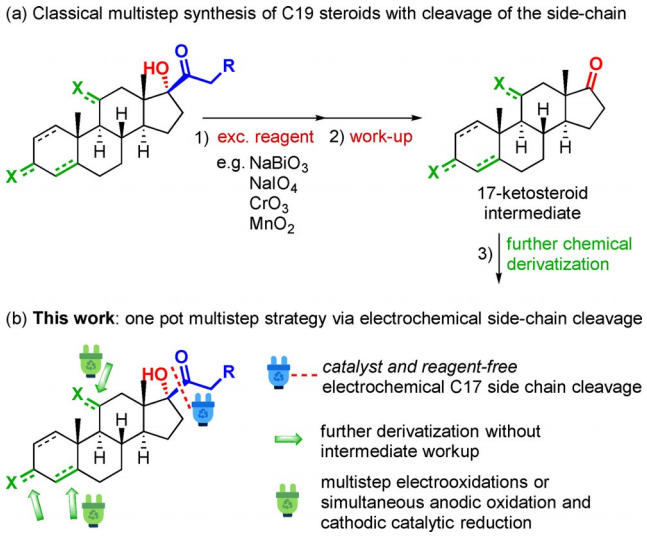

Figure 1. Multistep synthesis of C19 androgens via (a) classical methods and (b) proposed electrochemical strategy.

[a] F. Sommer, Prof. Dr. C. O. Kappe, Dr. D. Cantillo
Institute of Chemistry
University of Graz
Heinrichstrasse 28, 8010 Graz (Austria)
E-mail: oliver.kappe@uni-graz.at
david.cantillo@uni-graz.at

[b] F. Sommer, Prof. Dr. C. O. Kappe, Dr. D. Cantillo
Center for Continuous Flow Synthesis and Processing (CC FLOW)
Research Center Pharmaceutical Engineering GmbH (RCPE)
Inffeldgasse 13, 8010 Graz (Austria)

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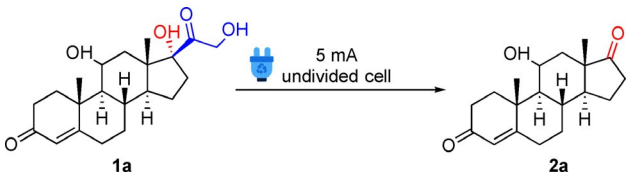
ols have been intensely investigated.[15] However, the low solubility of steroids in aqueous systems severely limits product yield and productivity.[15]

The classical chemical methods for the removal of the C17 side chain outlined above typically require a quench or neutralization of the excess of reagents, in addition to work-up and purification steps to isolate the corresponding 17-ketosteroid before it can be further derivatized to the target compound (Figure 1a).[7,16] We hypothesized that cleavage of the α-hydroxyketone C17-C20 bond might be possible via anodic oxidation in a catalyst- and reagent-free fashion (Figure 1b). Electrochemistry has been shown as a safe and green methodology to induce organic redox transformations.[17,18] Such methodology for the generation of 17-ketosteroids, in the absence of external reagents, would permit direct derivatization of the intermediate without additional work-up or purification steps, resulting in a convenient and sustainable one-pot procedure for the multistep preparation of essential C19 steroids.

Results and Discussion

To test our hypothesis, the electrolysis of hydrocortisone **1a** was initially investigated as model reaction (Table 1). In a typical experiment, the corticosteroid and a supporting electrolyte were placed in an undivided electrochemical cell (5 mL IKA ElectraSyn vial) and, after addition of a solvent, the mixture was electrolyzed under constant current at room temperature. Gratifyingly, a first attempt in acetonitrile/water 40:1 with Et_4NBF_4 as the supporting electrolyte and graphite as the anode, provided a promising 79% conversion of the starting material and an excellent selectivity towards the corresponding 17-ketosteroid **2a** (Table 1, entry 1). Next, a screen of the optimal reaction conditions was carried out. MeCN/H_2O 40:1 indeed proved to be the most suitable solvent mixture. Methanol (entry 2) and THF/H_2O (entry 3) provided lower conversion or selectivity. Other solvent systems (EtOH, acetone/water) and other proportions of MeCN/H_2O resulted in lower conversions as well (see Table S1 in the Supporting Information). When sodium and lithium perchlorate were used as the supporting electrolyte instead of the tetraalkylammonium salt, lower conversions and a significantly lower selectivity was observed (entries 4 and 5). Interestingly, other anode materials such as glassy carbon, reticulated vitreous carbon (RVC) or platinum performed very poorly (entries 6–8), with very low conversions of the substrate (<5% in all cases and rather poor selectivity). Modification of other reaction parameters, including higher current densities and different substrate or supporting electrolyte concentrations (Table S1) did not improve the results. Once the optimal reaction conditions had been established (0.2 M substrate concentration in MeCN/H_2O 40:1, 5 mA constant current with graphite as the anode and stainless steel as the cathode material), the amount of charge was gradually increased (Table 1, entries 9 and 10). To our delight, full conversion of the starting material and excellent selectivity towards the target 17-ketosteroid **2a** was achieved after 4 F mol^{-1} of charge had been passed. The excellent selectivity of the reaction enabled a very simple work-up procedure, which consisted of evaporation of the solvent, dilution of the crude mixture with a saturated aqueous solution of $NaHCO_3$ (or distilled water) and extraction of the product with DCM. Evaporation of the organic solvent provided a quantitative yield of **2a**.

Table 1. Optimization of the reaction conditions for the anodic C17 side chain cleavage of hydrocortisone **1a**.



1a **2a**

Entry	Conditions[a]				Conv[b]/Select (%)[c]
1	MeCN:H_2O (40:1)	Et_4NBF_4	(+)G/Fe(−)	2 F/mol	79/99
2	MeOH	Et_4NBF_4	(+)G/Fe(−)	2 F/mol	65/92
3	THF:H_2O (10:1)	Et_4NBF_4	(+)G/Fe(−)	2 F/mol	78/91
4	MeCN:H_2O (40:1)	$NaClO_4$	(+)G/Fe(−)	2 F/mol	47/73
5	MeCN:H_2O (40:1)	$LiClO_4$	(+)G/Fe(−)	2 F/mol	35/73
6	MeCN:H_2O (40:1)	Et_4NBF_4	(+)GC/Fe(−)	2 F/mol	<1/–
7	MeCN:H_2O (40:1)	Et_4NBF_4	(+)RVC/Fe(−)	2 F/mol	9/67
8	MeCN:H_2O (40:1)	Et_4NBF_4	(+)Pt/Fe(−)	2 F/mol	11/75
9	MeCN:H_2O (40:1)	Et_4NBF_4	(+)G/Fe(−)	3 F/mol	84/99
10	**MeCN:H_2O (40:1)**	**Et_4NBF_4**	**(+)G/Fe(−)**	**4 F/mol**	**99/98**

[a] Undivided cell (Electrasyn 2.0, 5 mL vial), 0.6 mmol **1a**, 3 mL solvent, 1000 rpm stirring speed, constant current electrolysis at rt. [b] Determined by HPLC peak area percent (254 nm). [c] Determined by HPLC peak area percent (254 nm) as the percentage of product with respect to all other peaks except the substrate. G: graphite. GC: glassy carbon. RVC: reticulated vitreous carbon. Fe: stainless steel.

The scope and applicability of this electrochemical C17 side chain cleavage protocol was subsequently investigated. Thus, several key 17-ketosteroids **2** were prepared from their corresponding corticosteroid precursors (Figure 2). As mentioned above, 11β-hydroxyandrostenedione **2a** was obtained in quantitative yield (Figure 2a). When cortisone and cortexolone were used as starting materials, Reichstein's substance G (adrenosterone) **2b** and androstenedione **2c** were obtained in quantitative and excellent yield, respectively. Anodic side chain cleavage of the more sensitive prednisone and prednisolone also provided satisfactory results, and 17-ketosteroids **2d** and **2e** were obtained in excellent yields. Importantly, it could also be shown that this reagent-free electrochemical procedure does not require the presence of a hydroxyketone side chain, a rather common limitation of some conventional chemical cleavage methods. Thus, 17α-hydroxyprogesterone **3**, which contains a methylketone side chain, could be cleanly electrolyzed to the corresponding 17-ketosteroid **2c** in quantitative yield (Figure 2b). In contrast, the presence of the 17-hydroxyl group proved to be essential for the side chain cleavage. Thus, when the standard electrolysis conditions were applied to corticosterone, 17-ketosteroid formation was not observed.

As mentioned above, the preparation of many C19 androgen steroids require several reaction steps. Side chain cleavage utilizing conventional reagents complicate these multistep synthetic routes, as quench and workup procedures for the purification of the 17-ketosteroid intermediates are required. The

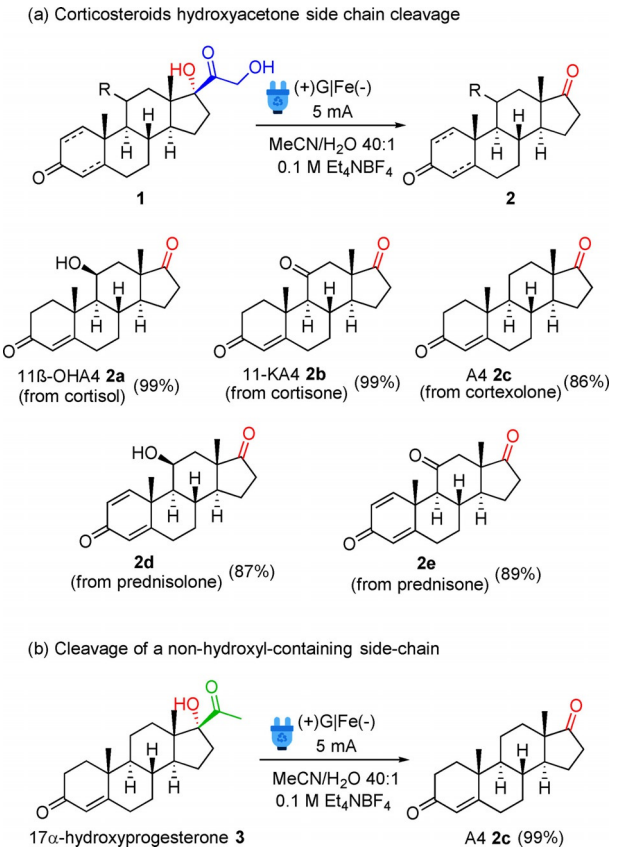


Figure 2. Scope of the anodic generation of 17-ketosteroids **2** via (a) hydroxyacetone side chain cleavage and (b) alkylketone side chain cleavage.

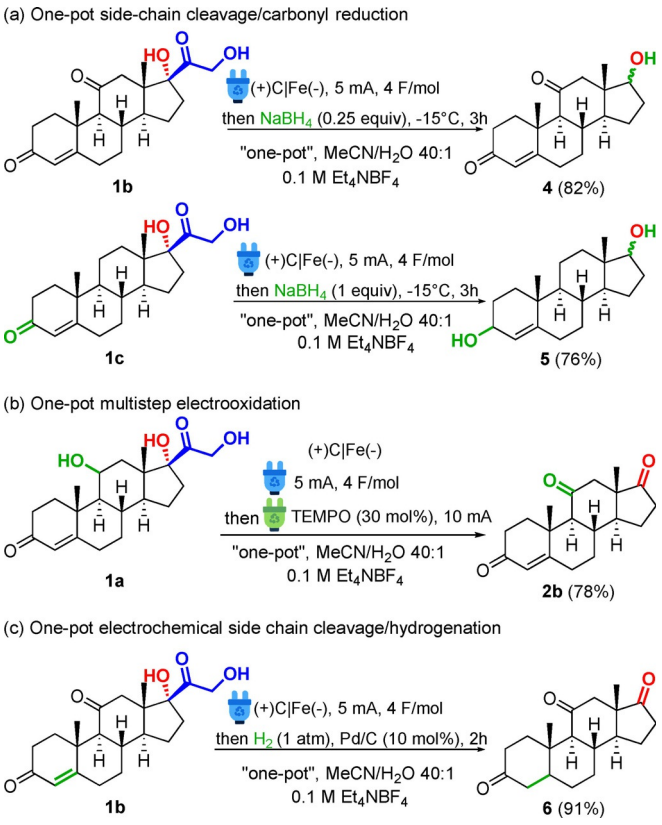


Figure 3. One-pot multistep synthesis of several 17-keto and 17-hydroxy steroids based on anodic side chain cleavage of C21 precursors.

catalyst and reagent free electrochemical procedure presented herein permitted the execution of several multistep C19 steroid syntheses in one pot, by simply adding additional reagents or catalysts to the electrochemical cell (Figure 3). For example, anodic oxidation of cortisone (**1b**) followed by addition of $NaBH_4$ to the undivided cell (Figure 3a) unlocked a simple and convenient one-pot protocol for the synthesis of 11-ketotestosterone (**4**), an important androgen.[19] Using a similar strategy and cortexolone (**1c**) as the substrate, 4-androstenediol (**5**), a testosterone precursor,[20] could be efficiently prepared in very good yield.

An open-pot two-step electrooxidative transformation for the synthesis of adrenosterone (**2b**) from hydrocortisone (**1a**) was also developed (Figure 3b). In this process, during the electrolysis of hydrocortisone **1a**, TEMPO was added to the cell as an electrocatalyst[21] after 4 F mol^{-1} had already been applied. Thus, the anodic generation of the 17-ketosteroid intermediate (**2a**) was immediately followed by electrocatalytic oxidation of the C11 hydroxyl group, leading to the 11-oxo derivative (**2b**). This transformation, which proved more challenging to achieve in one-pot without intermediate purification, required an optimization of the second electrooxidative step (see Table S2 in the Supporting Information). Ultimately, a high yield of **2b** (78%) was obtained by adding to the cell a combination of TEMPO (30 mol%) and an aqueous solution of Na_2CO_3 (1 equiv) to neutralize the glycolic acid present from the first step. TEMPO catalyzed anodic oxidations are favored by moderately basic pH.[21b] In an additional multistep transformation, following the hydroxyketone side chain cleavage of cortisone (**1b**), androstane-3,11,17-trione (**6**) was prepared by Pd/C catalyzed hydrogenation of the C4-C5 double bond (Figure 3c). In this case, once the electrolysis had ended, 10 mol% Pd/C was added to the electrochemical cell and the mixture stirred under H_2 atmosphere at room temperature for 2 h. Filtration of the reaction solution and extraction with distilled water or aqueous $NaHCO_3$/DCM provided an excellent yield (91%) of the reduced androgen **6**. Compound **6** is an important steroid with androgenic properties,[22] and an intermediate in the synthesis of deoxycholic acid[23] and other synthetic steroidal bile acids.[24]

The above successful preparation of androstane-3,11,17-trione (**6**), following a one-pot electrochemical side chain cleavage/catalytic hydrogenation sequence, led us to infer that the same transformation could probably be accomplished in a single electrochemical reaction. This is due to the fact that during the anodic side chain cleavage H_2 gas is produced at the cell cathode (the proposed reaction mechanism is depicted in Figure S1). Such synthetic strategy would result in a highly convenient and atom economic procedure for the synthesis of **6** and a number or related saturated androgens. To test this hypothesis, cortisone (**1b**) was electrolyzed under the optimal reaction conditions for the cleavage of the side chain in the presence of a suspension of 10 mol% Pd/C (Figure 4).

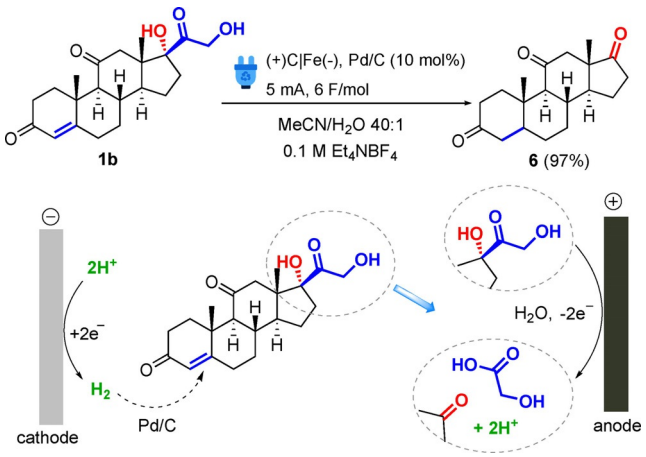


Figure 4. Simultaneous anodic removal of the C17 side chain and cathodic catalytic hydrogenation of **1 b**.

In this experiment, the reaction vial was tightly closed to ensure that the H_2 generated at the cathode could not easily escape the cell. To our delight, HPLC monitoring of the reaction mixture revealed disappearance of both the starting steroid **1 b** and the 17-ketosteroid intermediate **2 b**. Compound **6**, generated by simultaneous anodic oxidation and cathodic catalytic hydrogenation of **1 b** was obtained in nearly quantitative yield (97 %). It should be emphasized that, while examples of „ex-cell" exploitation of the H_2 generated in electrochemical reactions have been reported,[25] in situ utilization „in-cell" for the catalytic reduction of a molecule that is simultaneously being oxidized is unprecedented.

The synthetic usefulness of the electrochemical protocol was further demonstrated by performing a multigram scale experiment (9 mmol). The side chain cleavage of cortisone (**1 b**), leading to 17-ketosteroid **2 b**, was selected as model (Figure 5). For this experiment, a cell with higher electrode area was employed to increase the productivity and avoid the prolonged electrolysis times that would be needed with the standard IKA cell (see Supporting Information for details). Thus, while keeping constant the current density with respect to the small-scale

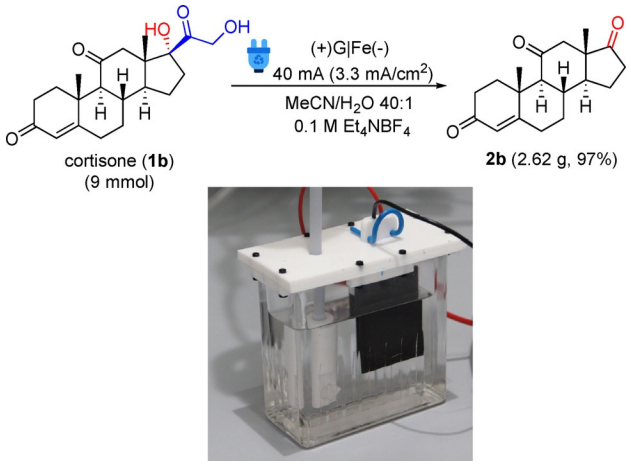


Figure 5. Multigram scale electrochemical synthesis of 17-ketosteroid **2 b**.

experiments (3.3 mA cm^{-2}), the cell current could be increased to 40 mA by immersing ca. 12 cm^2 of electrode surface into the reaction mixture. Gratifyingly, application of the optimal electrolysis conditions for small scale (cf. Figure 2 a) with 40 mA to a 90 mL solution resulted excellent conversion and selectivity toward **2 b**. Simple extractive workup resulted in 97 % isolated yield (2.62 g) of the pure 17-ketosteroid (Figure 5).

The proposed mechanism for the C17 side chain cleavage might involve direct oxidation of the hydroxyketone moiety or initial formation of a hydrate intermediate (Figure 6 a). Formation of a hydrate would result in a C–C bond cleavage similar to that of a 1,2-diol, which is known to be relatively facile under electrochemical conditions.[26] Indeed, cyclic voltammetry of hydrocortisone **1 a** in the absence and the presence of water (Figure 6 b) revealed that the oxidation is easier when water is present. Additionally, the reaction performed best with water as additive compared with other less nucleophilic protic solvents (H_2O > MeOH > EtOH) (Table S1). In both cases, the cleavage is a 2-electron process in which glycolic acid is re-

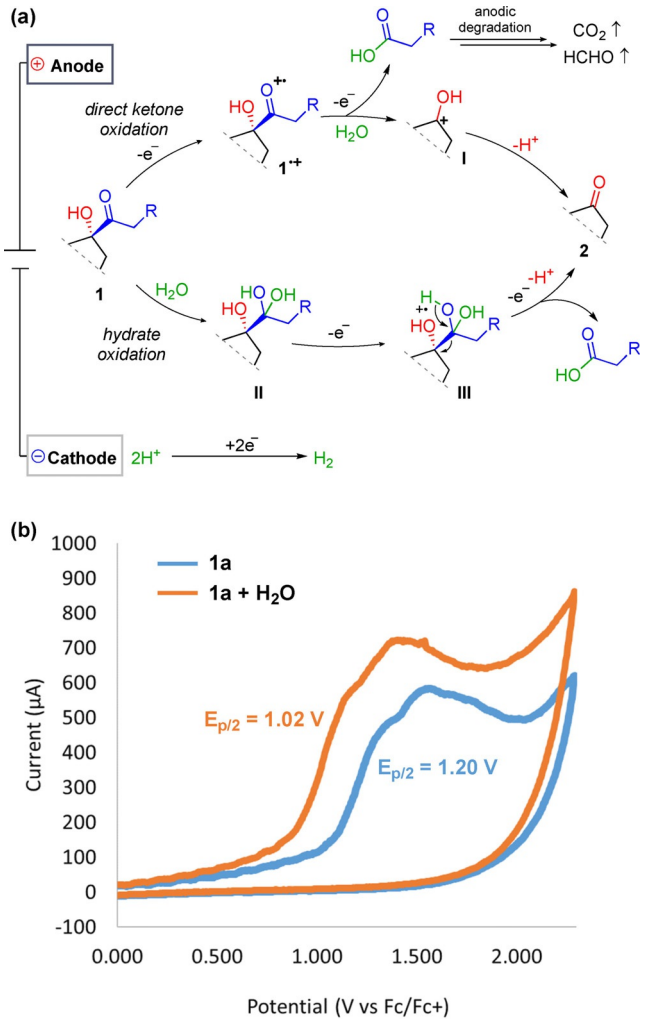


Figure 6. (a) Suggested mechanism for the electrochemical side chain cleavage and (b) cyclic voltammetry of hydrocortisone **1 a** in the presence and the absence of water.

leased as byproduct. Notably, when a ^{13}C NMR spectrum of a crude reaction mixture was recorded after partial evaporation of the solvent, no glycolic acid could be observed (Figure S1). In fact, no other carbons in addition to the reaction product, the supporting electrolyte and the solvent were present. This was ascribed to further electrochemical oxidation of glycolic acid under the electrolysis conditions to gaseous products (probably CO_2 and formaldehyde), which would explain that more than 4 F mol^{-1} are always needed to obtain full conversion of the steroid starting material. This hypothesis could be confirmed by electrolyzing a sample of glycolic acid under the standard reaction conditions. Thus, NMR monitoring of a reaction mixture containing glycolic acid as substrate showed complete disappearance of this material under electrolysis (Figure S2). In addition, cyclic voltammetry of glycolic acid (Figure S3) showed that this compound can indeed by oxidized under the same potentials as the steroid substrates.

To put the electrochemically-enabled, one pot procedure for the synthesis of C19-androgen steroids described herein into perspective, it was compared with the standard side chain cleavage using the $NaBH_4/NaIO_4$ method.[9b] Notably, the two-step $NaBH_4/NaIO_4$ side chain cleavage system requires more than 4 g of reagents per gram of 17-ketosteroid generated. Then, the intermediate needs to be purified via two or more workup steps before it can be further processed, which is detrimental to the overall yield and sustainability of the synthesis. Our electrochemical protocol provided quantitative yields for many 17-ketosteroids **2**, and their direct functionalization without the need of intermediate purification was demonstrated with several examples (Figures 3 and 4). From the economical viewpoint, the electrochemical methodology also provides significant advantages with respect to the conventional reagents. The cost of electricity is practically insignificant with respect to the stoichiometric amounts of $NaBH_4$ and $NaIO_4$ required in the conventional method and, importantly, the supporting electrolyte can be readily reutilized, as it could be recovered essentially pure by evaporation of the aqueous phase after the extractive workup.

Conclusions

In summary, we have developed a safe and sustainable electrochemical procedure for the synthesis of C19 androgen steroids based on the anodic oxidative removal of the C17 side chain from corticosteroids. This clean and high yielding method has enabled several one-pot multistep transformations for the preparation of important androgens, without isolation of the 17-ketosteroid intermediate. In addition, a procedure for the simultaneous anodic removal of the C17 side chain cleavage and cathodic catalytic hydrogenation of the C4-C5 double bond of corticosteroids has been demonstrated. This remarkable example of paired electrolysis is arguably the methodology for the synthesis of saturated androgens with the highest possible atom economy.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anodic oxidations · electroorganic synthesis · one-pot reactions · steroids · sustainable chemistry

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