

Beyond Kolbe and Hofer–Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids

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Herein we report a conceptually new non-decarboxylative electrolysis of carboxylic acids to obtain their corresponding anhydrides as highly valuable reagents in organic synthesis. All carbon atoms of the starting material are preserved in the product in an overall redox-neutral reaction. In a broad substrate scope of carboxylic acids the anhydrides are gen-

erated with high selectivity, which demonstrates the versatility of the developed method. Beneficially, no dehydrating reagents are required in comparison to conventional methods and the synthesis is based on uncritical starting materials using graphite and stainless steel as very inexpensive and eco-friendly electrode materials.

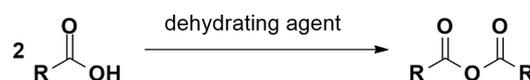
Introduction

Carboxylic acid anhydrides have been known for decades as versatile reagents and valuable reactive intermediates in organic synthesis.^[1] They demonstrate various advantages over their analogues, the carboxylic acid halogenides. The use of acid anhydrides does not free hydrogen halides as by-products which might interfere in the synthesis of complex structures, and the reaction is often rather mild in comparison with the corresponding acyl halogenide which facilitates more selective transformations. Carboxylic anhydrides are mainly used for the introduction of protective groups in natural product and active pharmaceutical ingredient (API) synthesis towards high-value esters and amides.^[2] Moreover, the anhydrides can also be employed as reagents to access a broad variety of different valuable structural motifs.^[3,4]

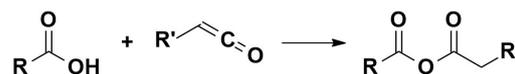
Their conventional synthesis is mostly performed starting from the corresponding carboxylic acids by addition of a dehydration agent; among others, highly toxic phosgene,^[5] thionyl chloride,^[6] phosphorus pentoxide,^[1] 1,2,3-triazines,^[7] or carbodiimides (Scheme 1) are routinely employed.^[8] Moreover, carboxylic acid anhydrides can be accessed using pre-functionalized substrates. The addition of carboxylic acids to ketenes and the oxidative cross-dehydrogenative coupling of aldehydes or alcohols are two of the possible routes.^[9] However, for these methods, non-commercial starting materials and toxic reagents

Synthesis of carboxylic acid anhydrides

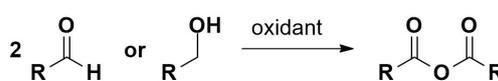
a) Dehydration of carboxylic acids



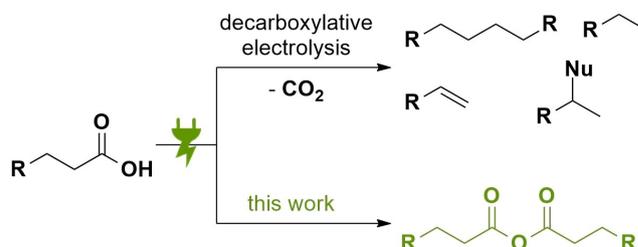
b) Addition to ketenes



c) Cross-dehydrogenative coupling



Electrolysis of carboxylic acids



Scheme 1. Conventional synthesis approaches of carboxylic acid anhydrides and electrolysis of carboxylic acids in organic media towards Kolbe, non-Kolbe, and Hofer–Moest products in comparison to this work.

are used, excessive thermal treatment is required, and low functional group tolerance is observed.^[9,10]

There is a recent, very acute and continuous urge for more sustainable synthetic methods which has led to a new dawn of organic electrosynthesis.^[11–15] In comparison to conventional synthesis, this method is highlighted by the means of economic and ecological benefits. The limitation of reagent waste by using electricity as a traceless activator obtained from renewable resources enables a sustainable synthesis protocol. With the use of carbon-based materials as electrodes, the synthesis can be performed metal-free which is of major interest in

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complex synthesis protocols of APIs.^[16] Moreover, the inherently safe character of an electrolysis should be also highlighted as no reaction can outrun when no current is applied. Additionally, using electricity has shown tremendous effects on the conversion of renewable resources toward the formation of valuable fine chemicals.^[17] In this case, carboxylic acids are important degradation components in the valorization of biomass to serve as sustainable reagent source.^[18–20]

With respect to using carboxylic acids in electro-organic synthesis, seminal experiments have been performed by Kolbe in the 19th century, demonstrating the successful decarboxylation of such acids by application of electricity.^[21,22] Besides the well-known character of such recombined radical products, commonly denoted as Kolbe products, the non-Kolbe pathway includes a further subsequent anodic oxidation with an elimination leading to unsaturated products (Scheme 1). The intermediates in the latter pathway were trapped with the addition of nucleophiles like hydroxides as shown by Hofer and Moest.^[23] This results in a possible functionalization of the decarboxylated products with *O*-nucleophiles to enable access to a variety of compounds.^[24–27]

In this work we demonstrate a conceptually different outcome in the electrolysis of carboxylic acids towards the generation of their corresponding anhydrides without the observation of decarboxylated (non-)Kolbe products and without the requirement for additional dehydration agents.

Results and Discussion

The mechanism of the Kolbe reaction was studied extensively for more than a century.^[28] Surprisingly, even though carboxylic anhydrides were discussed as potential intermediates already at the end of the 19th century,^[29] neither any experimental evidence, nor the anhydrides themselves have ever been observed in the electrolysis of carboxylic acids. Our current study shows that Kolbe and non-Kolbe pathways can be completely suppressed, and carboxylic anhydrides are obtained instead. The formation of carboxylic anhydrides became evident for the first time when pivalic acid (**1i**) was electrolyzed at 100 mA cm⁻² in acetonitrile using an undivided cell, graphite electrodes, and tetraethylammonium tetrafluoroborate (TEABF₄) as the supporting electrolyte. Intrigued by this result, we investigated several reaction parameters (for details, see the Supporting Information). Notably, throughout our studies, no decarboxylated products were found with the exception of *N*-*tert*-butylacetamide, which was formed as a side-product in the electrolysis of pivalic acid (**1i**). Isobutyric acid (**1h**) was then chosen as an appropriate model substrate for the investigation of the parameter set for electrolysis. Testing of electrode materials revealed graphite and stainless steel as the best anode and cathode materials, respectively. The influence of the anode material on the anhydride yield is low. Besides graphite, glassy carbon, boron-doped diamond (BDD),^[30] iridium-titanium mixed metal oxide (DSA[®]), and platinum, which is the material of choice for Kolbe electrolysis,^[31,32] gave similar yields (Table 1 entry 11, see Supporting Information). Graphite, as the most

Table 1. Optimization and control experiments.

#	Deviation from standard conditions ^[a]	Yield 2h [%] ^[b]
1	None	58
2	No current	0
3	$j = 10 \text{ mA cm}^{-2}$	25
4 ^[c]	$j = 100 \text{ mA cm}^{-2}$	39
5 ^[c]	$j = 200 \text{ mA cm}^{-2}$	36
6 ^[d]	Inert conditions	40
7 ^[e]	TEABF ₄ instead of KSCN	15
8 ^[e]	LiClO ₄ instead of KSCN	18
9	$c(\text{KSCN}) = 0.05 \text{ M}$	37
10	$Q = 1.5 \text{ F}$	44
11	Pt stainless steel	52
12	$T = 313 \text{ K}$	42
13 ^[f]	$c(\text{isobutyric acid}) = 1.0 \text{ M}$	45
14	$c(\text{isobutyric acid}) = 0.4 \text{ M}$	29
15 ^[g]	<i>i</i> -PrCN instead of MeCN and EMIMSCN instead of KSCN	33

[a] Reaction conditions: undivided cell, under air, 298 K, 0.7 M isobutyric acid (**1h**) in 5.0 mL MeCN, 0.10 M KSCN, 1.1 F, 50 mA cm⁻², graphite anode, stainless steel cathode; [b] quantification by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; [c] cell temperature not controlled; [d] 7.0 mmol scale; [e] BDD anode; [f] quantification by GC-FID with dibutyl fumarate as internal standard; [g] conductivity with KSCN was too low to perform the experiment.

economic choice, gives the highest yields but gets severely degraded when supporting electrolytes other than thiocyanates are used in acetonitrile. However, in the presence of thiocyanate, fouling can be suppressed. On the cathodic side, stainless steel, platinum, niobium, and nickel provide the highest yields, while copper, graphite, and glassy carbon show significantly lower yields. At 50 mA cm⁻² in the presence of KSCN, platinum cathodes in acetonitrile show obvious corrosion^[31–33] in contrast to inexpensive stainless steel.

The supporting electrolyte has significant impact on the anhydride yield. Thiocyanate, a rather unusual anion for a supporting electrolyte, stands out from the others (Table 1, entries 7 and 8, see Supporting Information). Importantly, the formation of anhydrides is not limited to SCN⁻ but occurs with most conventional supporting electrolytes, albeit in lower yields. In some experiments with SCN⁻ as supporting electrolyte, the formation of an orange solid was observed (see Supporting Information), insoluble in common organic solvents and water. The infrared spectrum indicates the presence of parathiocyanogen (SCN)_x, an inorganic polymer,^[34] is formed from oxidation of SCN⁻ and subsequent polymerization.^[35] Lowering the amount of potassium thiocyanate for optimized atom and cost efficiency does however not increase the yield of the desired product (Table 1, entry 9).

A variation of the applied current density revealed a maximum yield of the carboxylic anhydride **2h** at 50 mA cm⁻² (Table 1, entry 3–5). Neither increasing the temperature of the reaction (Table 1, entry 12) nor a variation of the concentration

of the carboxylic acid (Table 1, entries 13 and 14) result in an increased yield of the desired product. However, with respect to the applied charge, a maximum was observed at 1.1 F with decreasing yields for higher amounts of charge (Table 1, entry 10; for detailed studies, see the Supporting Information). However, in these experiments we observed that the acid was not completely consumed at the end of the electrolysis. Corresponding control experiments with both the carboxylic acid and the corresponding anhydride present in the reaction mixture show that only up to 70% yield of additional anhydride is formed in the cell. Therefore, we postulate a depletion of the anhydrides at low concentrations of the carboxylic acids to take place.

The promising results in the reaction with isobutyric acid (1h) were then used to explore the scope of the reaction. The variety of investigated aliphatic carboxylic acids gave the

corresponding anhydrides with high selectivity (Figure 1). Notably, the NMR spectra and gas chromatograms of the crude reaction mixtures do not show any by-products (see Supporting Information).

Several functional groups, including double bonds (2l, 2m, 2w, 2x) and halogen atoms (2n, 2o, 2p, 2u, 2v, 2y) are tolerated. This valuable functional group tolerance is of high interest for subsequent functionalization in complex synthesis protocols. The low solubility of some longer-chain carboxylic acids in acetonitrile at room temperature was overcome by increasing the temperature to 313 K or by addition of EtOAc. With KSCN as the supporting electrolyte, caprylic acid (1f) and longer linear carboxylic acids quickly form a thick layer of potassium carboxylate on the cathode impeding electrical conductivity. With 1-ethyl-3-methylimidazolium thiocyanate (EMIMSCN) as the supporting electrolyte, no corrosion was visible at the

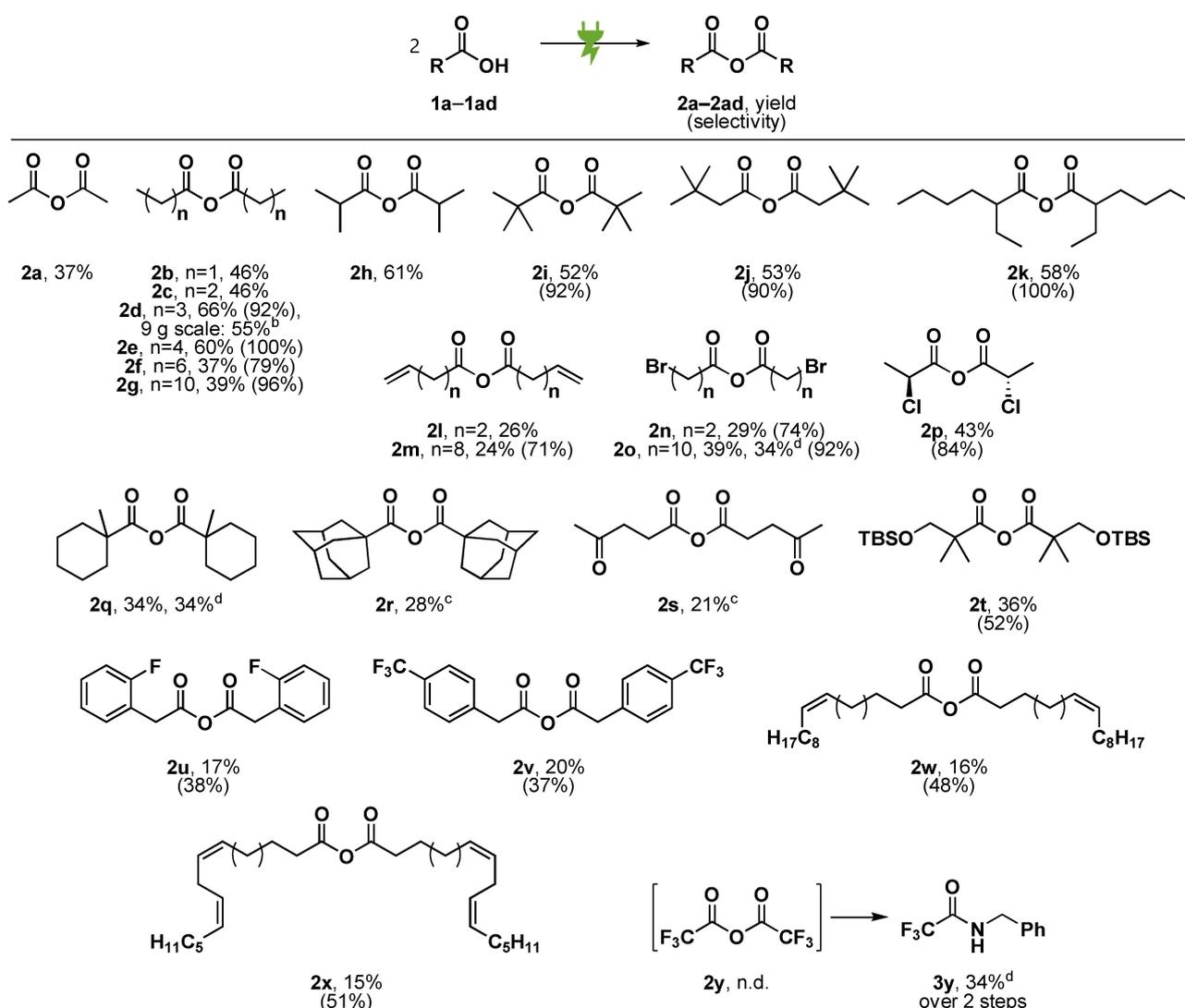
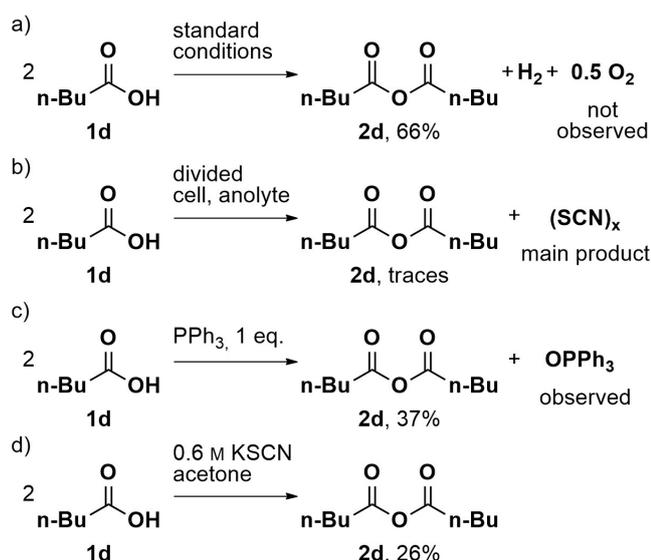


Figure 1. Electrochemically generated carboxylic anhydrides; [a] reaction conditions: undivided cell, under air, 298 K, 0.7 M carboxylic acid **1** in 5.0 mL MeCN, 0.10 M KSCN, 1.1 F, 50 mA cm⁻², graphite anode, stainless steel cathode; quantification by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; selectivity = yield/conversion; for individual deviations from standard conditions see Supporting Information; [b] quantification by GC-FID with dibutyl fumarate or dibromomethane as internal standard; [c] quantification by inverse-gated ¹³C NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; [d] isolated yield.

platinum surface. Changing to EMIMSCN as the supporting electrolyte restores conductivity and, furthermore, enables the conversion of long-chain fatty acids and carboxylic acids with dominating alkyl moieties (**2f**, **2g**, **2m**, **2o**, **2q**, **2r**, **2w**, **2x**). Due to its low boiling point, trifluoroacetic anhydride (**2y**) was not isolated but directly converted to *N*-benzyltrifluoroacetamide (**3y**). This demonstrates the in situ applicability of the generated carboxylic acid anhydrides in subsequent transformations. The electrolysis of valeric acid (**1d**) was successfully scaled up to 9 g (88 mmol), resulting in 55 % yield of **2d**.

In our hands, the carboxylic anhydrides could not be purified by chromatography on silica without the sacrifice of losing most or all the material. However, aqueous work-up with saturated NaHCO_3 and subsequent distillation, or filtration over silica and K_2CO_3 , gave analytically pure samples. The isolated yields match the yields determined by NMR quantification (**2o**, **2q**).

Peculiarly, no by-products were found in the crude reaction mixtures, as mentioned before. Acetamide, the obvious by-product from solvent oxidation, was not found in any experiment. The heterogeneous electron transfer from the electrode to the electrolyte, and vice versa, as well as the absence of any literature precedent render coming up with precise mechanistic model for the electrochemical formation of carboxylic anhydrides difficult at this point. Control experiments and experimental observations rule out some potential reaction pathways (Scheme 2). During electrolysis, gas evolution is observed at the cathode but not at the anode. Quick verification tests indicate hydrogen evolution but no oxygen evolution. These rule out water as stoichiometric by-product. However, at this time, the oxygenated species yet remains unidentified. We are confident that no O_2 is formed in the electrolysis (see mechanistic studies in the Supporting Information).



Scheme 2. Control experiments with deviations from standard conditions; Yields determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; standard conditions: undivided cell, under air, 298 K, 0.70 M carboxylic acid in 5.0 mL MeCN, 0.10 M KSCN, 1.1 F, 50 mA cm^{-2} , graphite anode, stainless steel cathode.

Cyclic voltammetry (see Supporting Information) confirms the irreversible oxidation of SCN^- to $(\text{SCN})_x$ formed in trace amounts only, but does not provide any other insights.^[36] However, when the electrolysis is performed in the anode chamber of a divided cell, $(\text{SCN})_x$ is the main product, and the anhydride is only found in traces (Scheme 2b). In the presence of 1 equiv. PPh_3 , the yield of the anhydride is lowered to 37 % but formation of triphenylphosphine oxide is observed (Scheme 2c).^[37] Since there is no other source of oxygen present, it has to derive from the acid. We note that another mechanism might be active in this case and has to be investigated in further studies. With high probability, acetonitrile and KSCN can be ruled out as oxygen acceptors as compounds pointing in this direction could not be observed (Scheme 2d). Albeit in lower yields, anhydride **2d** is also formed in acetone, even in the absence of KSCN. Again, another mechanism might be at work here, but that notwithstanding, the reaction is unprecedented. Despite careful experimental analysis, we did not find an oxygenated by-product. The control experiments suggest that neither the solvent nor the supporting electrolyte are crucial for the anhydride formation, although thiocyanate has major influence on the yields of the products. Studies on the mechanism of the demonstrated transformation are ongoing in our laboratories, aiming to deepen our insight into this conceptually novel transformation.

Conclusion

In summary, we have discovered a conceptually new reaction pathway in the electrolysis of carboxylic acids, which enables the synthesis of carboxylic anhydrides without the need for a dehydrating agent. The use of thiocyanates as unusual supporting electrolytes is crucial to obtain the carboxylic anhydrides in reasonable yields. Products of Kolbe and non-Kolbe pathways have not been observed in the transformation of 25 different carboxylic acids under our conditions, potentially due to the absence of base. The direct electrochemical synthesis of carboxylic anhydrides from carboxylic acids can be expected to open broad applications in the valorization of carboxylic acids derived from renewable resources.

Experimental Section

Detailed information on reaction optimization, general procedures, and detailed product characterization can be found in the Supporting Information, including NMR spectra and GC chromatograms.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carboxylic acids · carboxylic anhydrides · electrochemistry · electrosynthesis · sustainable chemistry

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