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Electrocatalytic Hydrogen Evolution Reaction Enabling Cyanation of Electron-poor Carbons with Acetone Cyanohydrin

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The Pt-cathode hydrogen evolution reaction (Pt-HER) of acetone cyanohydrin provides an alternative method for introducing the cyano group onto electrophilic carbons of imines and chalcones. The synthesis of α-aminonitriles and β-cyano ketones has been achieved smoothly with a small excess of cyanating agent (2 equivalent), catalytic amount of supporting electrolyte and low electricity consumption (0.02 F/mol). Besides demonstrating a general atom economy, the high Faradaic efficiency, allows for a scale-up with low-demanding electrochemical design and short electrolysis times.

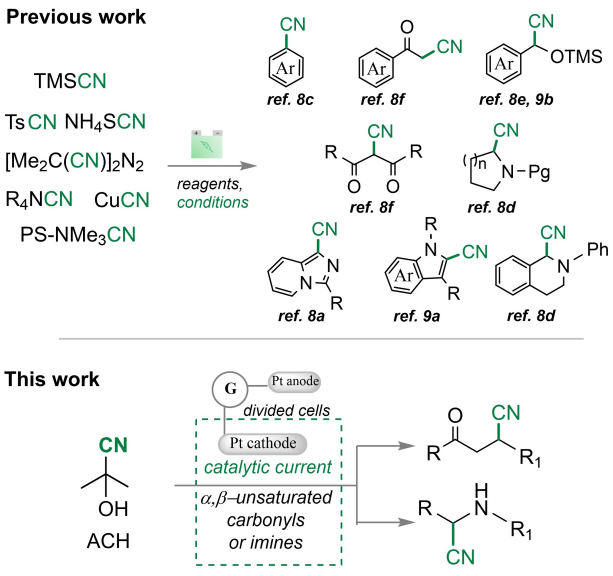
Introduction

Cyanation reactions[1] play a pivotal role in organic chemistry, enabling rapid structural diversification through the straightforward transformation of the nitrile group in various other functionalities such as amides, α-amino acids, amines, carbonyls and heterocycles like oxazoles, oxazolines, tetrazoles etc.[2] Moreover, the presence of a nitrile functionality may provide added value *per se*, also allowing the further functionalization in adjacent positions.[3] However, the inherent toxicity and volatility of hydrogen cyanide (HCN) poses significant challenges in practical applications, prompting organic chemists to explore more manageable synthetic equivalents and surrogates.[4] Concurrently, there are ongoing efforts to develop safer, more efficient processes utilizing alternative techniques such as mechanochemical methods,[5] continuous flow,[6] photocatalysis,[7] electrocatalysis,[8] and combined electrochemical/continuous flow strategies.[9] These latest approaches are particularly valuable as they also enabled the employment of *"non-CN"* source and/or the cyanation of unactivated C–H.

Among the 3rd generation nucleophilic cyanide source, acetone cyanohydrin (ACH) stands out as one of the most convenient options, due to its liquid state, stability, ready availability and cost-effectiveness. Consequently, this reagent has found many useful applications, most notably in the Strecker reaction,[10] Mitsunobu reaction,[11] and Michael-type addition.[12]

Base, metal and phase transfer catalysis have been traditionally used to activate ACH, however, to the best of our knowledge, there are no electrochemical studies focusing on this cyanating agent.

Following a long-standing research program of one of us on cathodic activation of nucleophiles using sub-stoichiometric/catalytic electricity and similarly reduced amount of supporting electrolyte,[13] we here report an electrochemically-induced CN addition to α,β-unsaturated ketones or imines using ACH as CN source (Scheme 1).



Scheme 1. Reagents used in electrochemical cyanation with accessible products, and this work.

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Results and Discussion

As reported in Table 1, we started our investigation on the electrochemically-induced CN addition to α,β-unsaturated ketones, by screening the electrochemical parameters and reaction conditions on the model compound **1 a** (Scheme 2).

Although ACH do not show any voltametric peak both in DMF/$TBABF_4$ and CH_3CN/$TBABF_4$, from the data of Table 1 (entry 1–3, 5, 7 and 10), the following insights emerge: i) the reaction is initiated by a cathodic reduction process, then progresses chemically until the consumption of **1 a** is completed, furnishing the expected product **2 a** in high isolated yield; ii) although the whole process proceeds even *"ex-cell"* after the pre-electrolysis of ACH with catalytic current (0.02–0.04 F/mol of **1 a**), the separation of the two redox half-reactions is mandatory for the attainment of the product; iii) the utilization of Pt as the cathode is crucial for enhancing the process efficiency (entry 10).

It is also worth noting that the reliance on catalytic current quantity is especially beneficial in this scenario, where inherently electroactive substrates like α,β-unsaturated ketones could undergo to cross-coupling,[14] or unwanted side-reactions. Indeed, a control experiment conducted in absence of ACH, demonstrated the complete disappearance of **1 a**, upon passing a sub-stoichiometric quantity of electricity (0.7 F/mol), under standard conditions. However, in such a case, no significant selectivity towards specific products was observed on the TLC plate.

With the optimal set of conditions in hand, we tested the generality of the electrochemical cyanation using various α,β-unsaturated carbonyls, as shown in Scheme 3.

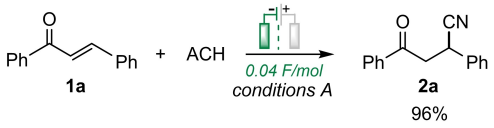
The electrochemical cyanation of various chalcones bearing alkyl, halogen, and methoxy substituents on either aromatic ring proceeded smoothly, leading to the corresponding β-ketonitriles in 84–96% isolated yields. High yield, with the selective formation of the double cyanation product **2 m** as diastereoisomer mixture was also obtained with benzylideneacetone. Under similar conditions, substrate **1 n** and **1 o** exhibited slightly reduced reactivity/selectivity, resulting in the formation of the corresponding products **2 n** and **2 o** with isolated yields of 51% and 52%, respectively.

Instead, stringent limitations were encountered with the substrates **1 p–t** which have been recovered mostly unreacted upon varying several electrolysis/reaction conditions such as current quantity, temperature, and reaction time. It is worth noting that, despite exhibiting minimal reactivity under standard electrolysis conditions, nitrostyrene **1 p** underwent substantial hydrodimerization when subjected to undivided-cell electrolysis with a stoichiometric quantity of current (Scheme 3).[15] Consequently, in an effort to reduce potential side-reactions of sensitive functionalities, the cyanation of the challenging functionalized α,β-unsaturated amide **1 t** was tested under *"ex-cell"* conditions with a slight increase in current quantity. However, analysis *via* ^{1}H NMR of the crude mixture

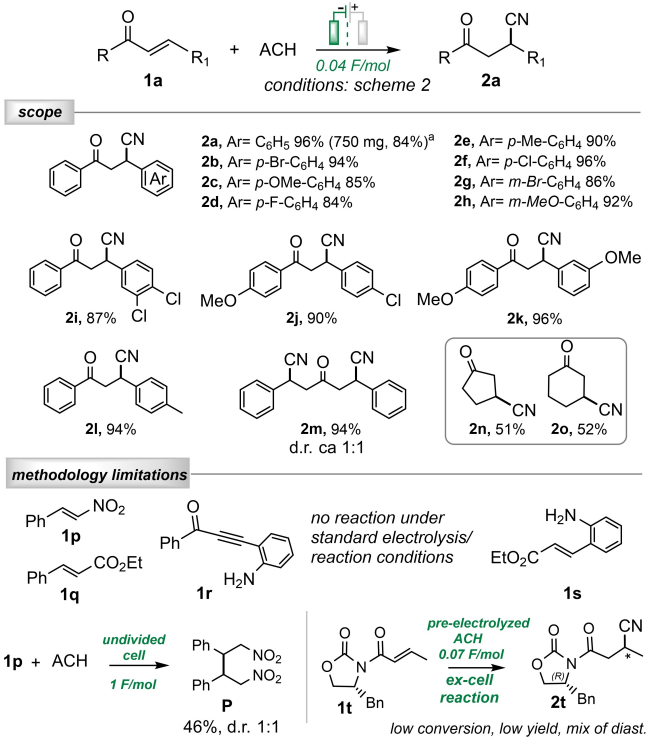
Table 1. Optimization of the electrochemical cyanation of **1 a** with ACH.[a]

Entry[b]	Deviation from standard conditions	Yield[c]
1	None	96%
2	No electricity	–
3	Undivided cell	–
4	DMF instead of CH_3CN	90%
5[d]	*ex-cell* reaction	82%
6	Electrolysis/reaction at r.t.	92%
7[e]	Solvent-free, ACH (15 eq.)	30%
8[e]	0.02 F/mol, CH_3CN (1.5 ml)	72%
9[e]	0.02 F/mol, CH_3CN (1.5 ml), ACH (3 eq.)	65%
10	GC as cathode	18%
11[2]	0.02 F/mol, CH_3CN (1 ml)	53%

[a] Other optimization data are reported in reported in S.I., Table S1. [b] For electrolysis using divided cell, the potential is ranging from 9 to 30 V. [c] Isolated yield. [d] **1 a** was added post-electrolysis of ACH in CH_3CN. [e] Both electrolysis and reaction were conducted at r.t.



Scheme 2. Electrochemical cyanation of chalcone with ACH. Conditions A: divided cells by a glass frit 5G. Pt spirals as anode and cathode. Catholyte: **1 a** (0.5 mmol), ACH (1 mmol), CH_3CN (0.5 ml), $TBABF_4$ (0.02 mmol). Anolyte: CH_3CN (0.5 ml), $TBABF_4$ (0.2 mmol). Current intensity: 6 mA, T = 50 °, reaction time after the electrolysis, 12 h.



Scheme 3. Scope and limitations of the electrochemical cyanation of α,β-unsaturated carbonyls. Unless otherwise indicated, electrolyses were conducted under the conditions reported in Scheme 2. [a] Large scale cyanation on 3.6 mmol of **1 a**.

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revealed only partial conversion of **1t**, with the detection of **2t** as a diastereoisomeric mixture (H NMR of the crude is reported in Supporting Information).

Subsequently, the generality of the electrocatalytic activation of ACH was further examined for its applicability in the cyanation of imines aiming to produce α-aminonitriles, which are valuable intermediates in the synthesis of α-aminoacids.

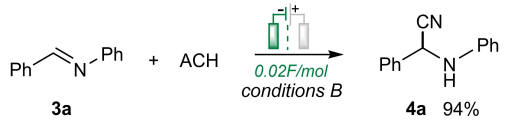
In order to optimize the reaction, a series of experiments similar to those outlined in Table 1 were conducted, using imine **3a** as the reference compound (all these data are collected in S.I., Table S2).

In comparison to the protocol previously established for chalcones, an even lower amount of electricity (0.02 F/mol), supporting electrolyte and ACH loading, achieved the transformation of imine **3a** into the corresponding 2-phenyl-2-(phenylamino)acetonitrile **4a**, in a good 94% yield (Scheme 4).

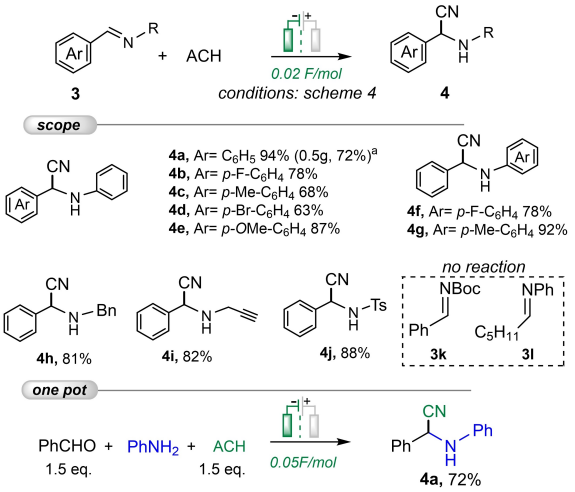
Consistently, this electrochemical protocol facilitated the cyanation of several imines **3a–j** derived from differently substituted aromatic aldehydes and N-aryl protecting groups, with yields ranging from 63% to 94% (Scheme 5).

Benzyl (**3h**), propargyl (**3i**) and tosyl (**3j**) protecting groups were also well tolerated, while the reaction failed with Boc-protected imine **3k** and the alkyl derivative **3l**.

Significantly, the electrochemical activation could also be exploited for a one-pot process directly leading to **4a**, by electrolyzing ACH in the presence of benzaldehyde and aniline, with 72% yield (one pot, Scheme 5).



Scheme 4. Electrochemical cyanation of imine **3a** with ACH. Conditions B: divided cells by a glass frit 5G. Pt spirals as anode and cathode. Catholyte: **3a** (0.25 mmol), ACH (0.38 mmol), CH_3CN (0.8 ml), $TBABF_4$ (0.015 mmol). Current Intensity: 6 mA. T = r.t.; reaction time after the electrolysis: 18 h.



Scheme 5. Scope of the electrocatalytic cyanation of imines. [a] Large scale cyanation on **3a**. One pot reaction: Benzaldehyde (0.32 mmol), aniline (0.21 mmol), ACH (0.32 mmol) in CH_3CN (0.67 mL), $TBABF_4$ (0.006 mmol) were electrolyzed using standard conditions B. Current quantity (0.05 F/mol).

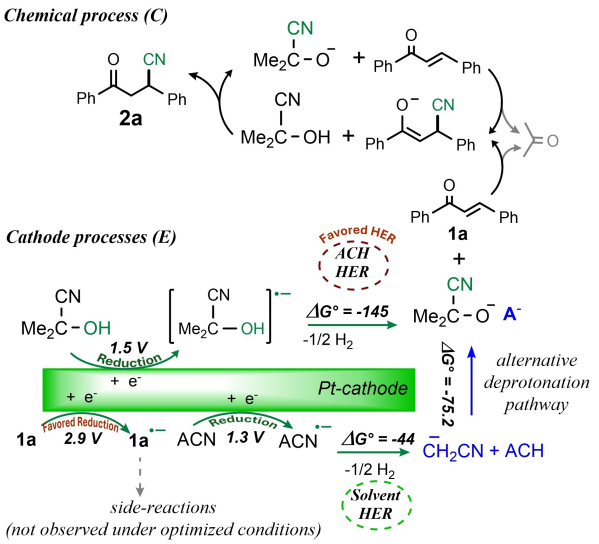
Based on the results reported in Table 1 and DFT computations of the standard free energies and the redox potentials, we can outline an electrochemical-chemical (EC) pathway starting with the cathodic reduction of ACH. Its subsequent thermodynamically thermodynamically highly favored HER ($\Delta G^\circ = -145$ kJ/mol) generates the deprotonated species **A**. The reaction should then evolve chemically by 1,4-addition of CN^- to the α,β-unsaturated carbonyls (or 1,2-addition to the imine) reaching completion (Scheme 6).

Accordingly with the experimental data,[14] DFT calculations predicted **1a** as the more reducible species in our system; however, side-reactions resulting from its electro-activation are only observed when ACH is absent, when undivided-cell electrolysis is performed, or when the HER of ACH is disfavoured because of electrode materials having higher overpotentials with respect to the Pt cathode (Table 1, entry 10).

It is also worth to note that the reduction and subsequent HER of acetonitrile (ACN), while less favored compared to the direct activation of the cyanating agent ($\Delta V = 1.3$ V, $\Delta G^\circ = -44$ kJ/mol of ACN *vs.* $\Delta V = 1.5$ $\Delta G^\circ = -144$ kJ/mol of ACH), can concurrently initiate the reaction *via* acid-base reaction (in blue in Scheme 6).[16]

Despite the vigorous gas evolution at the Pt-cathode as the galvanostatic electrolysis began, cyclic voltammetry experiments failed in identifying the reduction peak of ACH. As a result, direct production of $[ACH]^{\bullet-}$ may be expected for sure only in solvent-free conditions (Table 1, entry 7).

Thus, to gain a more comprehensive understanding of the reaction pathway, we also investigated alternative channels for the indirect electrochemical ACH activation using DFT calculations (Scheme 7). Based on these results, the only plausible alternative involves the solvent used for the electrolysis (Scheme 7, Equation 3).



Scheme 6. Proposed EC pathway for the electrochemical cyanation process. Standard free energies (ΔG° (kJ/mol)) are calculated at 25 °C. ΔV are calculated excluding the reference electrode absolute redox potential. Free energy values of other plausible reactions or involving the reduction of other species such as **1a**, $TBABF_4$ or solvents (DMF) are reported in S.I., Table S3.

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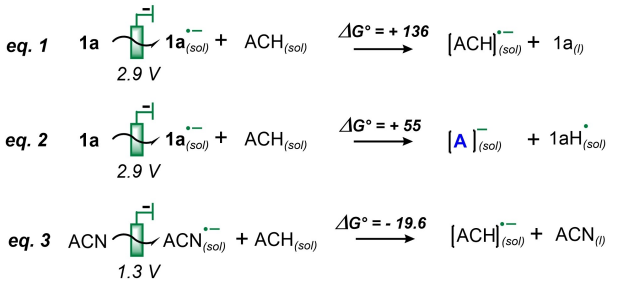

Scheme 7. Thermodynamics for indirect electrochemical activation of ACH. Standard free energies (ΔG° (kJ/mol)) are calculated at 25 °C. ΔV are calculated excluding the reference electrode absolute redox potential.

Conclusions

In summary, the electrochemically-induced synthesis of α-aminonitriles and β-cyano ketones has been successfully accomplished using 2 equivalents of ACH as cyanating agent and remarkably low electricity consumption (0.02 F/mol). Mechanistic insights based on DFT calculations, suggest the involvement of a Pt-cathode hydrogen evolution reaction of the ACH. Besides demonstrating a general atom economy, the high Faradaic efficiency, calculated at 5000 %, appears to be promising for straightforward scale-up with short electrolysis times and minimal demands on electrochemical equipment.

Experimental Section

Detailed experimental procedures, electrochemical design and electrolysis conditions are reported in supporting information. Starting materials **1 a**, **1 m**–**q**, and **3 j**–**k** are commercially available and were used without any further purification. Starting materials **1 b**–**l**[17a] **1 r**,[17b] **1 s**[17c], **1 t**[17d] and **3 a**–**i**[18] were prepared as reported in the literature.

Supporting Information

The authors have cited additional references within the Supporting Information.[19–34]

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Conflict of Interests

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: α-aminonitriles · β-cyanoketones · acetone cyanohydrin · catalytic current · electrochemical cyanation

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