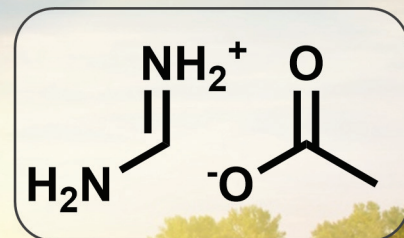
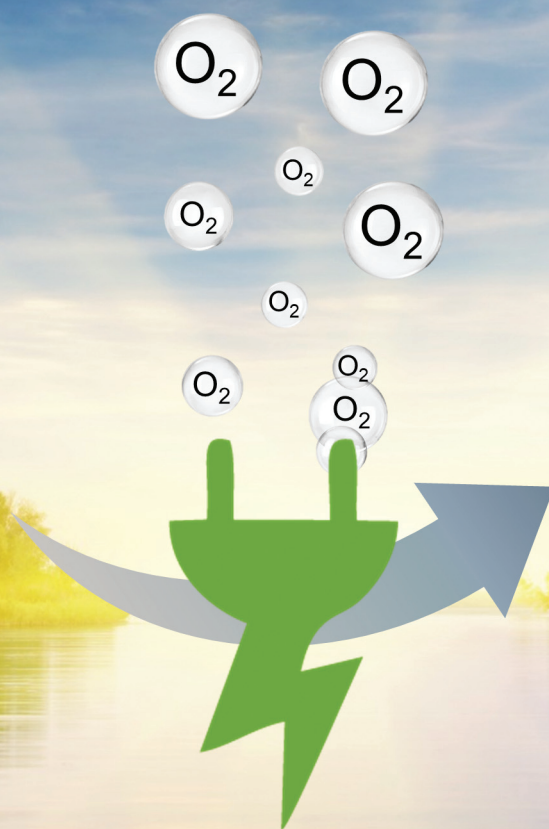
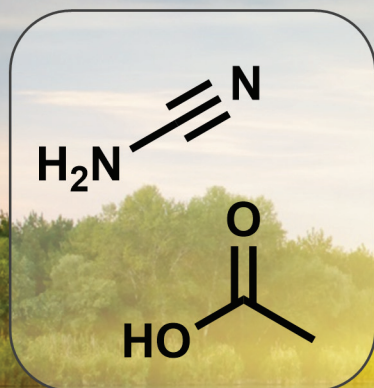


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Sustainable and cost-efficient electro-synthesis of
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electrolyte



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Sustainable and cost-efficient electro-synthesis of formamidine acetate from cyanamide in aqueous acidic electrolyte†

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Formamidine represents a versatile building block in synthetic organic chemistry. We developed a new electrochemical synthesis of formamidine acetate by cathodic reduction of cyanamide in an aqueous electrolyte and in high yield. The crude product could be used for further conversions, such as to pyrimidines without purification. Compared to established synthetic routes neither prior processing of cyanamide was necessary, nor precious transition-metal catalyst were required, nor any reagent waste was produced, and only biocompatible and sustainable solvents were employed for this process, following the requirements of *green chemistry*.

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Introduction

Formamidine salts are one of the most versatile building blocks for the synthesis of heterocycles involving an *NCN*-motif *e.g.* pyrimidines,^{1,2} imidazoles,³ and 1,3,5-triazines.⁴ It can also be used as ligand in several perovskite-type solar cells.^{5–8} As a free base, formamidine is not stable. Therefore, the only synthetic approaches are applicable with formamidine salts.^{4,9,10} Formamidine acetate is the most attractive derivative in technical processing due to its non-hygroscopic and good crystallizing properties,¹¹ whereas sulfate or chloride salts are not easy to handle. The acetate can also be used in several condensation reactions without prior liberation of the free base.¹¹

The most common used synthetic access to formamidine salts is represented by condensation reaction of triethyl-*ortho*-formiate with gaseous ammonia¹¹ or the reduction of (thio-)urea¹² or cyanamide^{9,13} at transition-metal catalysts (Scheme 1). A technical relevant synthesis of formamidine acetate is the catalytic hydrogenation of cyanamide in aqueous acetic acid in high yields, using inexpensive starting materials. A tremendous disadvantage of this approach is, technical cyanamide contains traces of several catalyst poisons like thiourea, sulfides and cyanides.¹⁴ Thus, high loadings of cata-

lyst are required and it has to be expensively reactivated after the process. Based on the tremendous increase of the palladium costs over past years, the reaction became economically less reasonable. The reluctant use of transition-metal catalysts and the avoidance of reagent waste by using atom economic processes also became more and more interesting for the past few decades.¹⁵ Direct electro-organic processes could fulfill this by using electrons as oxidizing or reducing agents.^{16–18} In combination with the application of biocompatible and sustainable solvents, in particular water, this leads to ultra-sustainable processes with only hydrogen or oxygen evolution as by-products. Electro-organic synthesis has experienced recently a renaissance.^{19,20} Organic electrosynthesis is being adopted in both, academia and industry as the 21st century's synthetic technique that can help to reach the goals imposed by climate change.^{16,21,22} The use of electric current as a reagent-less way to drive chemical reactions will be crucial to establish more sustainable synthetic processes.^{23–25} Having gained recently experience in cathodic reduction of nitrogen substrates,^{26–31} we were prompted to focus on this challenge.

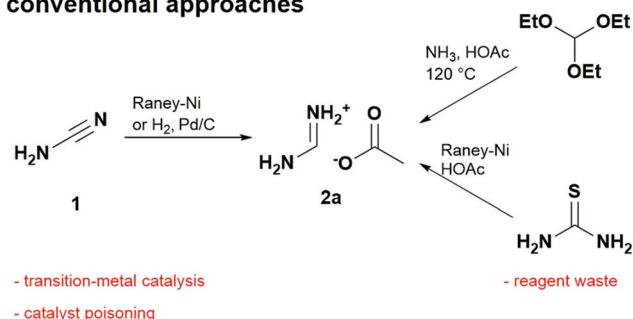
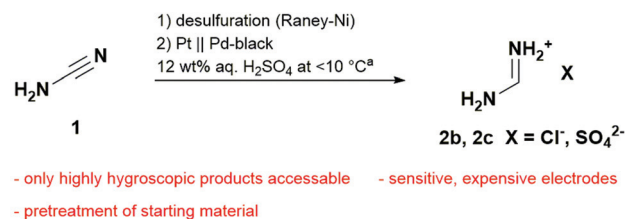
In 1960s Odo *et al.* investigated the electrochemical reduction of several nitriles in aqueous acidic electrolytes.^{32,33} They were able to design an electrolysis for the reduction of cyanamide to formamidine in aqueous acidic media in good yield leading almost pure compound. A preceding complete desulfuration of starting material using RANEY®-Ni was necessary due to sensitive cathode material.^{32,33} In addition, the instability of cyanamide in combination with strong mineral acids^{14,34,35} and the generation of very hygroscopic salt caused, that this electrochemical process did not experience further technical interest.

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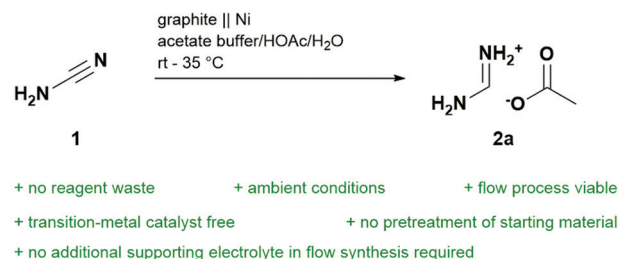
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conventional approaches

electrochemical reduction (Odo *et al.*)

this work



Scheme 1 Synthetic strategies leading to formamidinium salts (2). ^aFor chloride salt 6 wt% aq. HCl was used as electrolyte.

In this work, a robust method for synthesis of formamidinium acetate (2a) is reported under cost-efficient and sustainable conditions. The aqueous acetic acid electrolyte system could be easily reused and only water is consumed in the course of electrolysis with oxygen evolution as counter reaction. In the flow synthesis the addition of supporting electrolyte was obsolete, resulting in a very simple work up of crude product. Therefore, we developed a method, which is fully in line with the requirements of *green chemistry*.¹⁵

Results and discussion

Elucidation of suitable electrolysis conditions was established within an electrochemical screening approach (see ESI†).³¹ Anodic side reactions by oxidizing 1 or 2 and also reactions with anodically generated oxygen were suspected, so the reduction was performed in a divided cell setup. A glass frit and a Nafion membrane were investigated as separator materials. Interestingly the Nafion membrane provided a

better conductivity in the setup. It is noteworthy to mention, that the necessity of a divided set-up could lead to some drawbacks in industrial applications, hence the separation of two electrolyte circuits is more elaborate and there is a voltage drop by the separator. The processes are also limited to the stability and performance of the separator material. As this is the most limiting factor, most industrial processes using divided set-ups are limited to proton exchange membranes, like Nafion we used. Such separators exhibit outstanding stability and high current density capability. Therefore, the most technical relevant synthesis known using divided cell set-up is chlor-alkali electrolysis in membrane cells. This also exhibits the advantage, that both side-stream gases (hydrogen and oxygen) were synthesized in divided compartments, so they could be used as technical gases. In an undivided set-up, they will be mixed (oxyhydrogen), which would lead to inherent safety issues.

Future perspective research on the development of membrane materials with high ionic selectivity and conductivity, by mechanical stability, although being thin could make divided set-ups more attractive for further use in industrial synthesis.

As initial conditions, protic solvents with a pH < 7 were investigated, in order to prevent a dimerization of cyanamide (1) to dicyandiamide.^{14,34,35} One of the major challenges was to overcome the instability of cyanamide (1) at low or high pH, in combination with uptake of stoichiometric amounts of protons during reaction and the poor conductivity of acetic acid as weak electrolyte system. For the initial investigations 1 M NaOAc had been added as supporting electrolyte, to overcome the weak conductivity of aqueous acetic acid. With concentrations below 0.5 M NaOAc the yield of formamidinium (2) remarkably decreased by an increase of inner ohmic resistance of the cell (Table 1, entries 4–8). An excess of acetic acid (10 to 20 eq. referring to 1) was necessary to achieve the target compound 2a upon electrolysis.

Protons were consumed in the course of electrolysis to stabilize the formamidinium (2) as cationic species. If less acetic acid was employed, a loss of 2a due to the generation of the hydrolyzed products such as formamide or formiate was observed.

Table 1 Impact of supporting electrolyte onto the reduction of cyanamide (1)

Entry	Supporting electrolyte	Concentration [M]	Yield ^a [%]
1	KOAc	1.00	68
2	NH ₄ OAc	1.00	65
3	NaCl ^b	1.00	68
4	NaOAc	1.00	78
5	NaOAc	0.50	75
6	NaOAc	0.25	50
7	NaOAc	0.10	47
8	None		14

^a ¹H NMR yield calculated with maleic acid as internal standard.
^b Chlorine evolution in anolyte. Electrolytic conditions: C_{gr} (+) || Ni (-), 1.4 M aq. HOAc, supporting electrolyte, 4 F, 5 mA cm⁻², 20 °C, 1 mmol of 1 in 7 mL electrolyte (C = 6 g L⁻¹), glass frit.

Table 2 Impact of cathode material onto the reduction of cyanamide (1)

Entry	Cathode	Yield ^a [%]
1	Co	22
2	Pd	5
3	Ni, planar	79
4	Ni, porous	87
5	Zn	0
6	CuSn ₇ Pb ₁₅ (leaded bronze)	0

^a ¹H NMR yield calculated with maleic acid as internal standard. Electrolytic conditions: C_{gr} (+) || cathode (-), 1.0 M aq. HOAc, 1.0 M NaOAc; 4 F, 5 mA cm⁻², 20 °C, 1 mmol of 1 in 7 mL electrolyte (C = 6 g L⁻¹), glass frit.

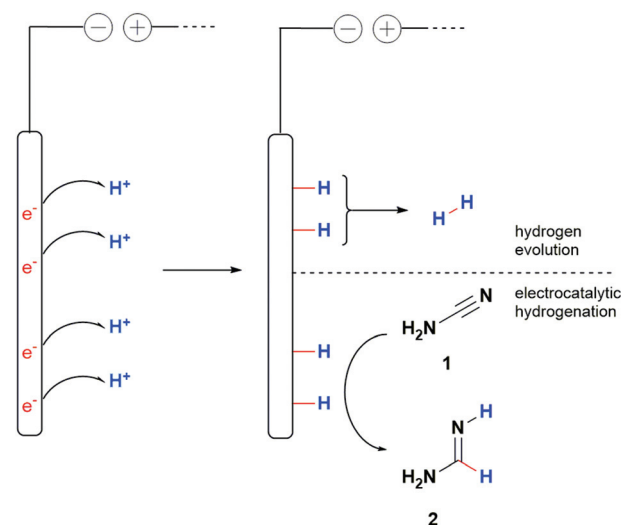
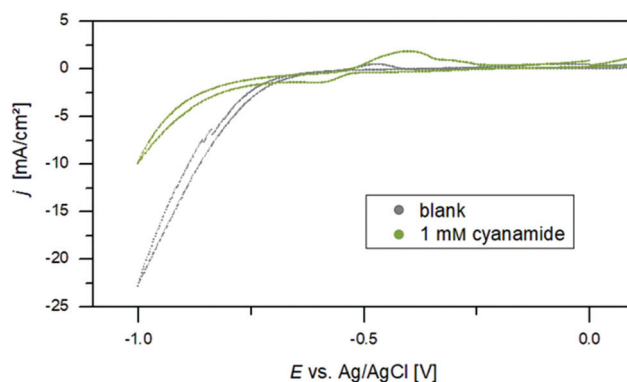
For the cathodic reduction, several electrode materials were investigated (Table 2). Therefore, 1 M HOAc/NaOAc buffer was used, as these conditions gave the highest yield in prior screening. 2 should only be detected by reduction using cathode materials exhibiting a high negative over-potential for hydrogen evolution reaction.³⁶ As anode, carbon electrodes were preferably used (glassy carbon or graphite).

Cobalt and palladium did not lead to satisfactory yields (Table 2, entries 1 and 2). The use of an inexpensive Ni cathode provided the best yields. A higher surface of the electrode leads to systemically better yields, than the planar geometry (Table 2, entries 3 and 4). The product was synthesized in good yields with up to 87%.

Using cathode materials with outstandingly high over-potentials for the hydrogen evolution reaction, such as lead or leaded bronzes,^{27,31,37-40} failed completely in this transformation. The good yields corresponding to higher surface of the electrode and the necessity of cathode materials with a moderate negative over-potential for hydrogen evolution led to the conclusion that reduction is carried out by electrocatalytic hydrogenation on the electrode surface (Scheme 2). To further investigate the mechanistic pathway of the reduction, CV (cyclic voltammetry, Fig. 1) measurements were carried out.

Indeed, no signal for a SET (single electron transfer) was indicated by measurement. A shift of the decomposition voltage of the electrolyte was also observed. Both are suitable indicators for a surface activation by hydrogen and a subsequent hydrogenation of cyanamide.⁴¹ This mechanism is underpinned by observation of hydrogen evolution at cathode surface and the over-stoichiometric amount of applied charge, which is necessary to achieve full conversion of 1.

The electrochemical parameters for the reduction were optimized to increase the yield of target compound 2a at elevated concentration of starting material compared to first investigations, to ensure a technical application (Table 3). Low current densities were beneficial (entries 1-3) and an excess of charge (two times the theoretical amount) was applied to achieve the best yields (entries 2 and 4). The yield was highly depending on the temperature of the electrolysis. In contrast to expectations, higher temperature leads to better yields with a decrease over 40 °C due to partially degradation of starting

**Scheme 2** Postulated mechanism for the reduction of 1 in aqueous acidic electrolyte.**Fig. 1** Cyclic voltammetry (CV) for the reduction of cyanamide. Working electrode: Ni; counter electrode: glassy carbon; reference electrode: Ag/AgCl in 3 M KCl; electrolyte: 2 M aq. HOAc; 0.5 M NaOAc at 20 °C.**Table 3** Investigation of electrochemical parameters and the temperature on the reduction

Entry	<i>j</i> [mA cm ⁻²]	<i>Q</i> [F ref to 1]	<i>T</i>	Yield ^a [%]
1	2	4	Rt	79
2	5	4	Rt	75
3	10	4	Rt	51
4	5	2	Rt	49
5	5	4	10 °C	54
6	5	4	40 °C	82
7	5	4	50 °C	77
8	0	(19 h)	Rt	0
9 ^b	5	4	Rt	25

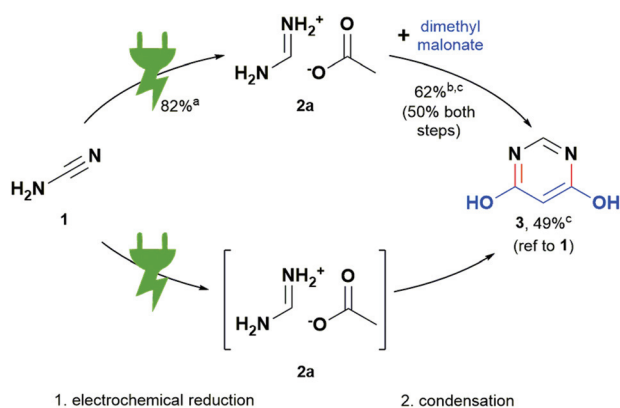
^a ¹H NMR yield calculated with maleic acid as internal standard.
^b Undivided cell (5 mL). Electrolytic conditions: C_{gr} (+) || Ni (-), 4.8 M aq. HOAc, 0.5 M NaOAc, 2-4 F, 2-10 mA cm⁻², 10-50 °C, 3.3 mmol of 1 in 7 mL electrolyte (C = 20 g L⁻¹), Nafion membrane.

material **1**. Without the application of current (entry 8) no formation of formamidine acetate (**2a**) was detected. The utilization of an undivided cell led to a strong decrease in yield because of anodic side reactions (entry 9).

The desired compound **2a** could be synthesized in good yields. Nevertheless, the large amount of NaOAc as supporting electrolyte makes this reaction less relevant for industrial applications. Both salts **2a** and NaOAc, show a similar solubility pattern. This prevents a quantitative isolation of pure target compound **2a** using only technically applicable steps for purification (*e.g.* extraction or crystallization). However, the supporting electrolyte as contamination of formamidine (**2a**) did not significantly affect the yield of further conversions, like in the synthesis of 4,6-dihydropyrimidine (**3**). Consequently, the electrochemically generated **2a** can be easily used in telescoped sequences (Scheme 3).

The best electrolytic conditions, determined by screening, were used for a scale-up of the reaction. Both, concentration of starting material **1** and the expansion of electrolytic setup into a modular H-type cell (see ESI†) were investigated (Table 4).^{31,42}

The electrochemical scale-up by increasing the concentration of **1** did only slightly reduce the yield of **2a**.



Scheme 3 Further conversion of formamidine acetate (**2a**) to 4,6-dihydropyrimidine (**3**). ^a¹H NMR yield calculated with maleic acid as internal standard. ^b Reaction was carried out with purified **2a**. ^c Isolated yield.

Table 4 Experiments for the scale-up of the reaction

Entry	<i>m</i> (1) [g]	<i>C</i> (1) [g L ⁻¹]	Yield ^a [%]	Cell type
1	0.14	20	78	Screening cell (7 mL)
2	0.21	30	69	
3	0.28	40	65	
4	0.35	50	67	
5	1.00	20	52	

^a ¹H NMR yield calculated with maleic acid as internal standard. Electrolytic conditions: C_{gr} (+) || Ni (-), 4.8 M aq. HOAc, 0.5 M NaOAc, 4 F, 5 mA cm⁻², 35 °C, Nafion membrane.

Unfortunately, the scale-up approach in divided cell setup faced some drawbacks by decreased surface-to-volume-ratio of electrodes and membrane and also by an increased inter-electrode gap.

To overcome these issues it was favorable to carry out the reduction of **1** an electrochemical flow cell.^{43–47} A narrow gap between the electrodes in combination with the enhanced surface-to-volume-ratio from membrane to flow compartments, led to an enhanced conductivity of electrolyte system.^{43,47,48} Therefore, the addition of high amounts NaOAc as supporting electrolyte was circumvented, in order to obtain pure **2a** by crystallization.

Starting from the optimized batch electrolyte system, a flow cell was employed that was designed in our group but can also be commercially purchased (see ESI†).^{43,49}

The modular flow cell we used (Fig. 2), can be equipped with a casing, which is loadable with metal or carbon-based foams and felts. The electrolyte flows through this porous material, which is connected to a planar electrode of same material.⁴⁹

The formation of hydrogen as a major side reaction displaced the electrolyte at cathode-surface by flushing the electrolyte and the starting material **1** out of reactor, so a yield of only 26% was achieved (Scheme 4). To avoid the side reaction and maintain a constant flow of electrolyte, the flow rate was increased. By the way, the yield of **2a** decreased by a decrease of applied charge. However, the current efficiency was increased by an increase of flow rate. Hence, the application of

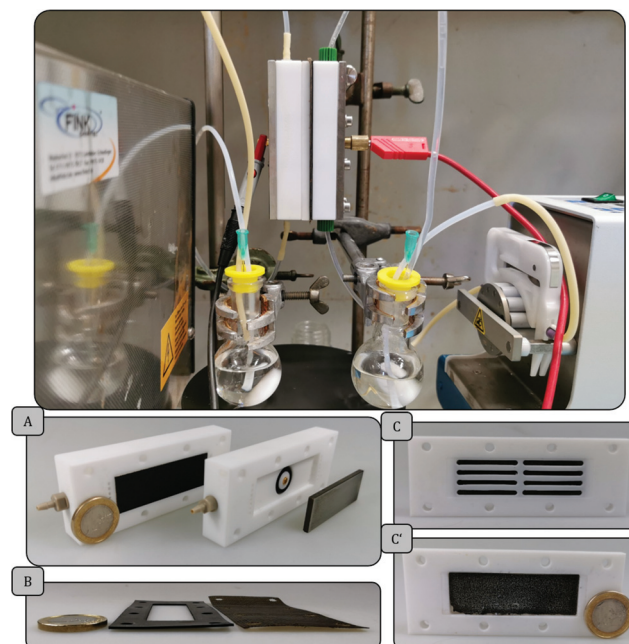
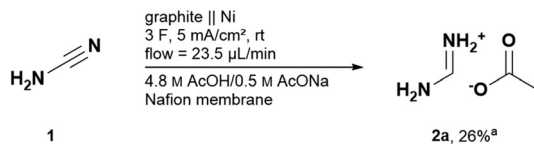


Fig. 2 Modular flow cell used for electrochemical reduction of cyanamide, connected to separated pumps and reservoirs (top) and its components (A–D). (A) Teflon blocks with electrodes (DSA, left/Ni, right). (B) EPDM spacer (left) and Nafion N 324 membrane (right). (C) Ni foam casing (front, facing to anode). (C') Ni foam casing (back, connected to Ni cathode). As comparison a 1 € coin is depicted with a diameter of 23.25 mm/0.915 inch and a thickness of 2.33 mm/0.092 inch.



Scheme 4 Initial parameters for electrochemical screening in flow electrolysis. ^a¹H NMR yield calculated with maleic acid as internal standard.

the charge was carried out by pumping the electrolyte solution several times through the system in a so called cycling electrolysis reaction. For this setup the addition of NaOAc as supporting electrolyte was omitted, due to the narrow gap of the flow electrolysis cell. This facilitates the down-stream processing even further. This beneficial effect of the narrow gap electrolysis cell to work supporting electrolyte free was previously observed for other conversions only in undivided cells.

High flowrates with different current density were investigated on the outcome on current efficiency for the process (Table 5). The theoretical amount of charge was applied and the concentration of formamidinium-ions (2) were determined by NMR.

By an increase of the flow rate, the yield of 2a also increased. A flowrate of at least 0.4 mL min⁻¹ was necessary, since the electrolyte was not constantly flowing due to massive hydrogen evolution. There was no markedly increase of yield using flow rates higher 1.4 mL min⁻¹ (entries 1–3). Lower current densities were beneficial (entries 4 and 5). The application of higher amounts of charge did not significantly increase the yield of product (entries 6 and 7) at planar electrode. For the flow electrolysis a graphite or a tantal-based DSA (IrO_x) anode were used. Graphite anodes gave better current efficiencies (entries 7 and 8). The DSA anode showed less by-products but a decrease in current efficiency, resulting in less cell voltage. Later on a Ni foam electrode previously reported was used,⁴⁹ in combination with a scale-up of the reaction.

Table 5 Investigation of parameters for cathodic transformation of cyanamide 1 in a continuous flow electrolyzer

Entry	Anode	<i>I</i> [mA]	Flow rate [mL min ⁻¹]	<i>Q</i> [F ref to 1]	<i>C</i> of 2a [g L ⁻¹] (yield ^a [%])
1	Graphite	50	0.5	2	13.2 (27)
2	Graphite	50	1.0	2	17.2 (35)
3	Graphite	50	1.4	2	19.5 (38)
4	Graphite	25	1.4	2	20.1 (40)
5	Graphite	75	1.4	2	15.0 (30)
6	Graphite	25	1.4	4	21.3 (43)
7	Graphite	25	1.4	6	17.6 (35)
8	DSA	25	1.4	4	15.8 (32)
9 ^b	DSA	25	3.0	2	22.6 (46)
10 ^b	DSA	25	3.0	4	30.2 (61, 54 ^c)

^a¹H NMR yield calculated with maleic acid as internal standard. ^b DSA (+) || Ni foam (-), 11.9 mmol of 1 in 25 mL electrolyte (*C* = 20 g L⁻¹). ^c Isolated yield. Electrolytic conditions: anode (+) || Ni (-), 4.8 M aq. HOAc, 2–4 F, 25–75 mA, 0.5–3.0 mL min⁻¹, 20 °C, 1.5 mmol of 1 in 3 mL electrolyte (*C* = 20 g L⁻¹), Nafion membrane.

This led to a former increase in yield of 2a, by a non-laminar flow of electrolyte and an enhanced electrode surface (entries 9 and 10).

A maximum concentration of 2a with *C* = 30.2 g L⁻¹ was achieved, which is a total yield of 61% referred to 1. The work-up of crude product 2a was very easy after flow electrolysis, by a distillation of solvent, which could be recovered and reused in subsequent electrolysis after addition of acetic acid and cyanamide. The crude formamidinium acetate (2a) could be simply recrystallized from hot ethanol, which gave pure target compound in 54% yield.

Conclusions

We could establish a novel method for the electrochemical reduction of cyanamide by using only cost-efficient and sustainable conditions. The designed batch electrolysis provided the target compound in good yield, but was not easy scalable in batch. However, redesigning the electrolysis transferring it to a supporting electrolyte-free flow electrolysis in a narrow gap cell provided significant progress. The down-stream processing became very simple, leading to a crude product being suitable for subsequent condensation reactions. Noteworthy, this leads to a very potent technical process, which is inherently safe towards a controlled synthesis and can prevent the usage of Pd as catalyst and avoids prior processing of starting material.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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