Supporting Information

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

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1 General Information

All **materials** were purchased from commercial suppliers. Formamidine acetate and Cyanamide F1000 were provided by *AlzChemAG*, Trostberg, Germany. Cyanamide was stored in the fridge at –30 °C. All chemicals were used without further purification. Anhydrous methanol was dried over sodium and distilled under argon atmosphere.

Mass spectra and high resolution mass spectra were obtained by using a *QTof Ultima 3* (*Waters*, Milford, Massachusetts) apparatus employing ESI+.

Melting points were determined with a Melting Point Apparatus *B-545* (*Büchi*, Flawil, Switzerland) and were uncorrected. The heating rate was 1°C/min.

^{1}H and ^{13}C **NMR spectra** were recorded at 25 °C by using a *Bruker Avance II 400* (400 MHz, 5 mm BBFO-SmartProbe with *z* gradient and ATM, *SampleXPress 60* sample changer, *Analytische Messtechnik*, Karlsruhe, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to traces of HDO (4.79 ppm for ^{1}H NMR, respectively) or DMSO (2.50 ppm for ^{1}H NMR and 40.0 ppm for ^{13}C NMR, respectively) in the corresponding deuterated solvent. Multiplicity of the signals is also indicated in brackets (s = singlet, bs = broad singlet). The spectra were treated by *MestReNova x64* Version 14.1.0 (*MestReLab*, Santiago de Compostela, Spain).

As **power source**, a Z60-3.5 device (*TDK Lambda*, Achern, Germany) with an output of 0–60 V (± 0.01 V) and 0–3.5 A (± 1 mA) was used. All electrolysis were carried out under galvanostatic conditions with a two-electrode set-up.

As **electrode materials** Ni (99.9%, *IKA Werke GmbH & Co. KG*, Staufen, Germany), graphite (isostatic, *Sigrafine®*, *SGL Carbon*, Wiesbaden, Germany), Ni/P foam (average pore size Ø 1.4 mm, *Aqua Titan*, Dortmund, Germany) and DSA / IrO_X on Ta (*DeNura*, Milano, Italy) were used.

As **separators** glass frits (porosity 4, 10–16 µm, *ROBU® Glasfilter-Geräte GmbH*, Hattert, Germany) and a Nafion™ N324 membrane (*DuPont*, Wilmington, United States) were used. Prior use thus have been swollen in electrolyte as reported.[1]

2 ^{1}H NMR analytics with internal standard

For the determination of the NMR yield, maleic acid (>99.0%, *TCI, Tokyo Chemical Industry,* Tokyo, Japan) was used as internal standard. The NMR spectra were recorded in D_2O. For quantitative NMR a delay time of t_1 = 30 s was used. All spectra were treated by phase and baseline correction.

The method was validated using commercial formamidine acetate (99.6%, *AlzChem AG,* Trostberg, Germany). Equimolar amounts of formamidine acetate (**2a**) and maleic acid (**4**) where weight out and dissolved in 0.5 mL of D_2O .

The amount of formamidine acetate n(**2a**) was determined using weight portion of maleic acid (**4**) by correlation of NMR integrals I with (EI). The calculated amount of **2a** was compared to the weight amount.

$$n(\mathbf{2a}) = n(\mathbf{4})\frac{2 \cdot I(\mathbf{2a})}{I(\mathbf{4})} \qquad \text{(EI)}$$

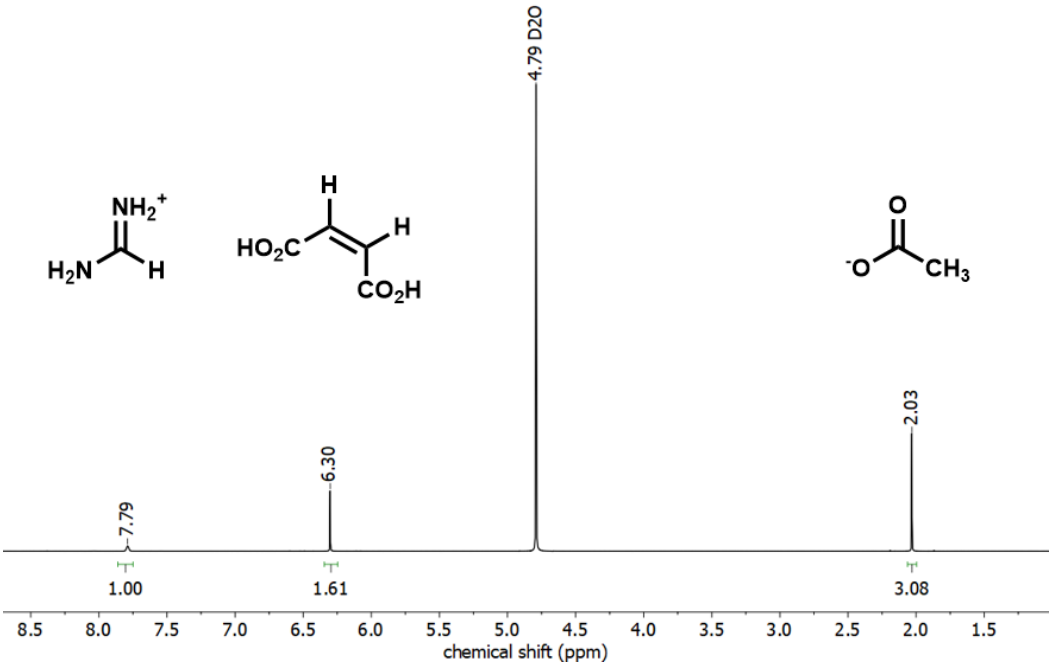


Figure S1. ^{1}H NMR of 2a and 4 for quantification of 2a.

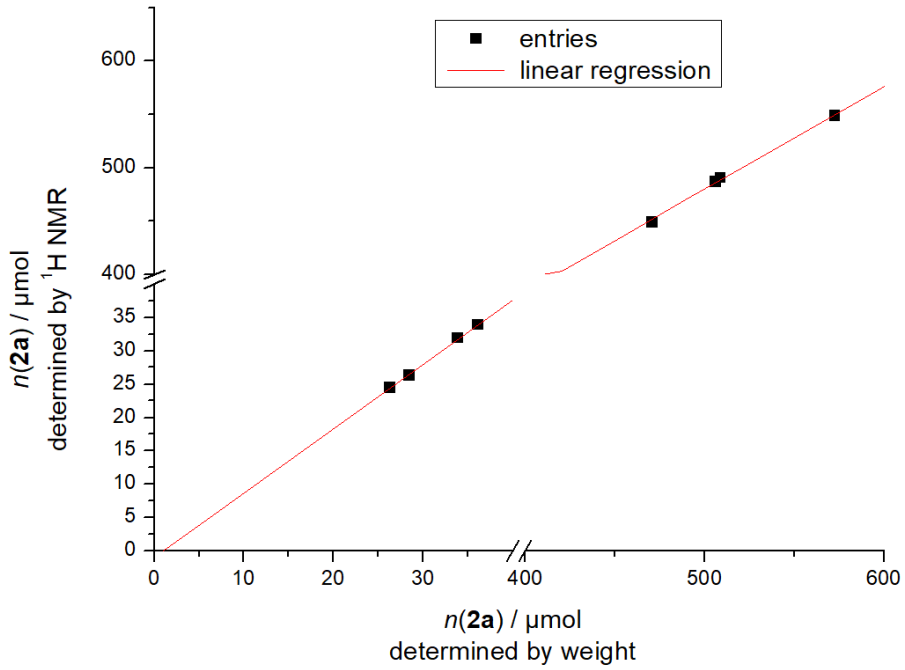


Figure S2. Amount of 2a determined over weight portion and calculated with internal standard 4.

Table S1. *n*(4) determined by weight and calculated *n*(2a) by correlation of NMR integrals vs. *n*(2a) determined by weight in the same sample.

Entry	$n(\mathbf{4})$ / µmol by weight	$\frac{I(\mathbf{2a})}{I(\mathbf{4})}$	$n(\mathbf{2a})$ / µmol by NMR	$n(\mathbf{2a})$ / µmol by weight
1	23.4	1.38	33.9	36.1
2	25.9	1.62	31.9	33.9
3	24.0	1.96	24.5	26.3
4	23.3	1.77	26.3	28.4
5	444.7	1.62	549.0	572.7
6	415.3	1.85	449.0	470.7
7	478.5	1.95	490.7	508.7
8	484.5	1.99	486.9	506.1

The linear regression trough to measurements was used for validation of NMR yields. It was assumable that the total yield of formamidine **2a** could be determined from NMR yield using equation (EII).

$$(96.2\% \pm 0.2\%)\, n_{\text{weight}}(\mathbf{2a}) = n_{\text{NMR}}(\mathbf{2a}) \qquad \text{(EII)}$$

3 *Typical protocols*

3.1 Electrochemical screening - batch

For the electrochemical screening of batch reactions a screening system designed by WALDVOGEL *et al*. was used.[2] This setup is commercially available as *IKA Screening Package (divided)* from *IKA Werke GmbH & Co. KG*, Staufen, Germany.

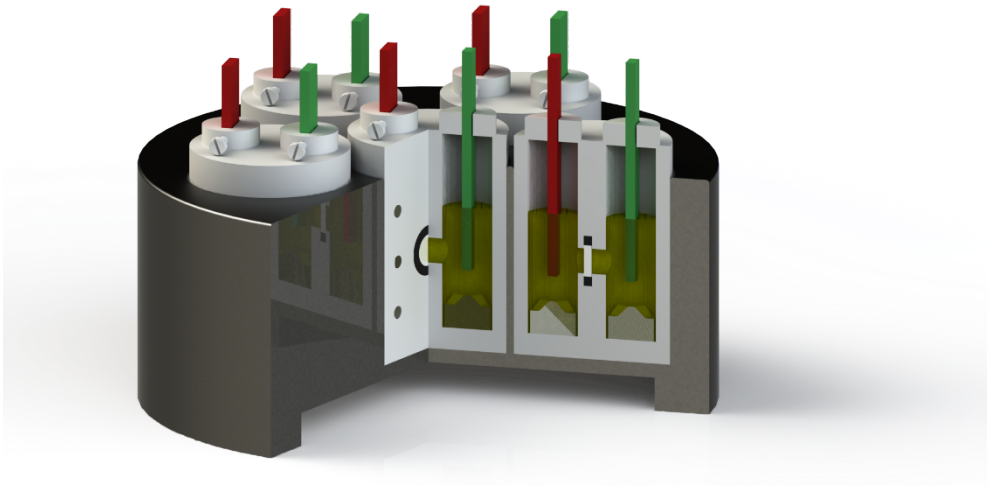
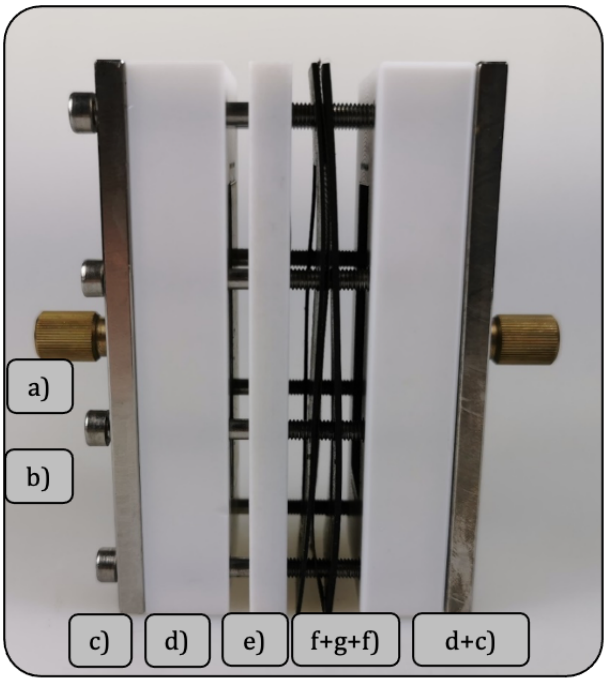


Figure S3. Screening setup employed with divided cells.

In a divided cell for electrochemical screening (Figure S3) equipped with a glass frit or a Nafion membrane as separator, every half-cell was filled with the same base electrolyte (7 mL). The cell, if temperature-controlled, was stirred for a half hour with the electrolyte inside, to reach a constant reaction temperature. Afterwards the cyanamide (**1**) was dissolved into the catholyte. The electrodes were immersed into electrolyte (electrode surface A = 3.6 cm^2) and the electrolysis was conducted.
After the electrolysis was finished, the electrodes were removed, rinsed with water and the reaction mixture was transferred into a flask (if a Nafion membrane was used as separator, just the catholyte was transferred). The solvent was removed at reduced pressure. Maleic acid (**4**) was added as internal standard and the residue was dissolved in H_2O/D_2O (1:1). 0.5 mL of the mixture were used to determine the yield of **2a** by NMR spectroscopy.

3.2 Electrochemical screening - flow

The electrochemical screening in a flow electrolysis cell was carried out in a screening cell designed by WALDVOGEL *et al*.[3,4] This setup is also commercially available as *IKA ElectraSyn flow* from *IKA Werke GmbH & Co. KG*, Staufen, Germany. The cell was modified with a Ni foam casing, which was previously reported.[4]



a)	contact for power supply
b)	screws
c)	metal-plate
d)	teflon half cell with electrode (2 x 6 cm^2)
e)	Ni foam casing (2 x 6 x 0.3 cm^3)
f)	EPDM spacer
g)	Nafion membrane

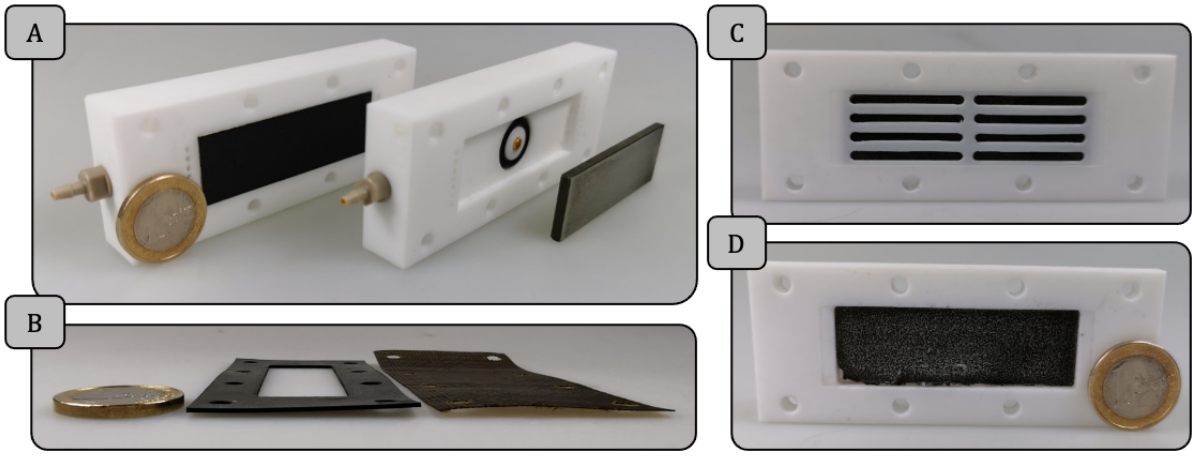


Figure S4. Schematic setup of modular flow electrolysis cell (up). Separated components of the flow electrolysis cell. A: Teflon blocks with electrodes (DSA, left/Ni, right) and in/outlet of electrolyte. B: EPDM spacer (left) and Nafion N 324 membrane (right). C: Casing for Ni foam (front, facing to anode). D: Casing for Ni foam (back, connected to Ni cathode).[4] 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.

A solution of cyanamide (**1**, *C* = 20 g/L) in solvent and supporting electrolyte was freshly prepared before every screening. By using a peristaltic pump *Ismatec® Reglo Digital MS-2/12* by *Cole-Parmer GmbH*, Wertheim, Germany. Anolyte and catholyte were pumped and collected separately.

Single-pass flow electrolysis

For the flow electrolysis 5 mL of catholyte and anolyte were prepared. The electrolyte was pumped through the flow electrolysis cell. The electrolysis was conducted, as the electrolyte reached the outlet of the flow cell. The forerun of the catholyte (1 mL, ca. 2 half cell volumes) was discarded. The product mixture was collected (about 2 to 3 mL). For the analysis of the concentration of **2a** in the catholyte, a part (1 mL) was transferred into a flask. Maleic acid (**4**) was added as internal standard. The solvent was removed at reduced pressure and the residue was dissolved in H_2O/D_2O (1:1). 0.5 mL of the mixture were used to determine the amount of formamidine acetate (**2a**) by NMR spectroscopy.

Flow electrolysis (cycling mode)

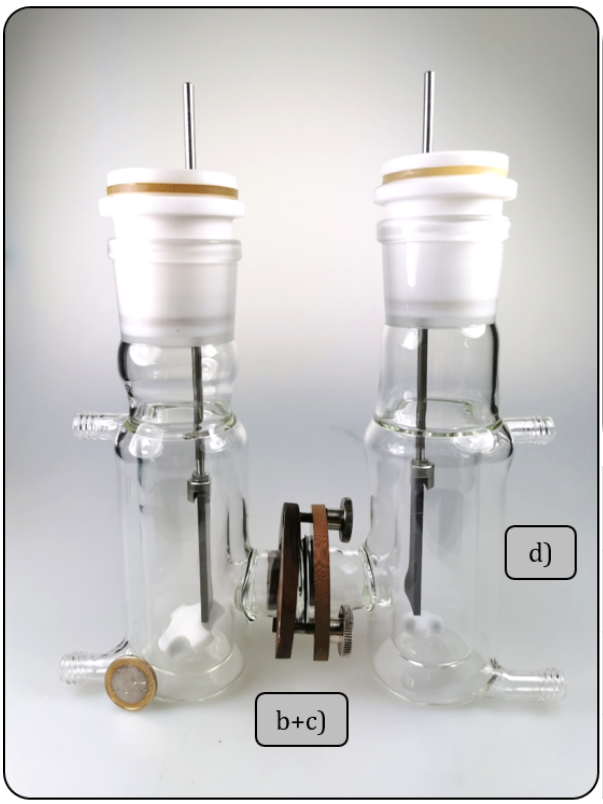
For the flow electrolysis in cycling mode 3 mL of catholyte and anolyte were prepared. While stirring, those were pumped through the cell and were collected back in the same flask. The electrolysis was conducted, when the electrolyte was pumped back into flask. After the electrolysis was finished, the electrolytes were pumped another 15 minutes through the system to achieve a homogeneous concentration of formamidine acetate (**2a**) in the catholyte. 0.5 mL of the catholyte were removed, diluted by D_2O (0.5 mL) and maleic acid (**4**) was added as internal standard. 0.5 mL of the mixture were used to determine the amount of formamidine acetate (**2a**) by NMR spectroscopy.

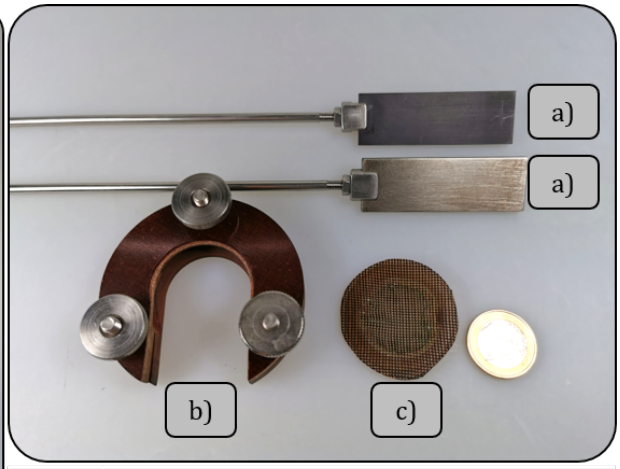
Flow electrolysis (Ni foam, cycling mode)

For this flow electrolysis a *Dosierpumpe Ritmo R 033* (*Fink Chem+Tec GmbH & Co.KG*, Leinfelden-Echterdingen, Germany) was used. The base electrolytes (4.8 M aq. HOAc) were pumped through the flow electrolysis cell. As the catholyte reached the outlet of the cell, a current of 25 mA (j = 2.3 mA/cm^2, geometrical current density) was applied. A suitable amount of electrolyte (approx. 20 mL) was pumped through the cell with a flow rate of 10 mL/min. In order to remove Ni ions, which were dissolved from cathode, while no current was applied, this forerun was discarded.

Afterwards reservoirs of cyanamide (**1**, 500 mg, 11.9 mmol) in 4.8 M aq. HOAc (25 mL) as catholyte and 4.8 M aq. HOAc (25 mL) as anolyte were connected to the flow electrolysis cell and flow rate was decreased to 3 mL/min. Henceforth, the electrolysis was conducted at 25 mA (j = 2.3 mA/cm^2, geometrical current density). A charge of 2–4 F was applied. 0.5 mL of the catholyte were removed, diluted by D_2O (0.5 mL) and maleic acid (**4**) was added as internal standard. 0.5 mL of the mixture were used to determine the amount of formamidine acetate (**2a**) by NMR spectroscopy.

3.3 H-type cell





a)	electrodes 2 x 6 cm² graphite || Ni
b)	wood-flange for connenction of half cells
c)	Nafion membrane
d)	50 mL half cell with cooling jacket, stirring bar and teflon plug

Figure S5. Picture and description of the 100 mL H-type divided cell for electrochemical synthesis. Further information of use and features of this H-type cell are reported.[1,5,6] As comparison a 1 € coin is depicted with a diameter of 23.25 mm/0.915 inch.

In each half cell (Figure S5), 0.5 M NaOAc in 4.8 M aq. HOAc were presented (50 mL each). The cells were brought to 35 °C by a heating jacket with a thermostat. Cyanamide (**1**, 1.00 g, 23.8 mmol, 1 eq.) was dissolved in the catholyte. The electrodes were immersed 4 cm into the solution so that the electrode area was 8 cm². The electrolysis was conducted with the following parameters:

anode || cathode:	graphite || Ni
current density:	j = 5 mA/cm²
electron equivalents	4 F
temperature:	T = 35 °C
separator:	Nafion membrane

After completion of the electrolysis, the catholyte was transferred into a flask and the solvent was removed at reduced pressure at 40 °C. The residue was triturated with Et_2O to start crystallization. The solid was filtered off, dried in vacuum and weighed (10.208 g). An aliquot (0.247 g) was taken from the crude product and the yield of formamidine acetate (**2a**, 52%, 1.287 g, 12.4 mmol) was determined by NMR means as described above.

4 *Separation of formamidine acetate from sodium acetate by extraction*

^{1}H NMR analysis of salt mixtures

About 50 mg of the analyte were dissolved in D_2O (0.5 mL) and the ratio of formamidine ions to acetate ions *r* was investigated by ^{1}H NMR spectroscopy by correlation of the integrals. Since the integral of the acetate ions $I(OAc^-)$ has 3 protons and the integral of formamidine $I(FA^+)$ only 1 proton, the molar ratio *r* of formamidine per acetate was determined according to equation (SIII).

$$r = \frac{n(\mathrm{FA^+})}{n(\mathrm{OAc^-})} = \frac{3 \cdot I(\mathrm{FA^+})}{I(\mathrm{OAc^-})} \qquad \text{(SIII)}$$

Representation of the salt mixture

Formamidine acetate (10.40 g, 0.1 mol) and sodium acetate (8.20 g, 0.1 mol) were dissolved in 4.8 M aq. HOAc (250 mL). The solvent was removed at reduced pressure and the molar ratio was investigated as described above. The molar ratio *r* of the salt mixture was *r* = 0.49.

Investigation of solvents and temperatures for extraction

The salt mixture (500 mg) was weighed into a glass frit (porosity 4). Solvent (5 mL) was added and the suspension was stirred with a glass rod (1 min). The solvent was then filtered by reduced pressure. The filtrate was concentrated at reduced pressure at 40 °C and the molar ratio *r* of the filtrate was analyzed as described above. Ethyl acetate, diethyl ether and toluene were analysed in the same way. Indeed, neither formamidine acetate or sodium acetate were not extracted with any of these solvents.

Table S2. Molar ratio *r* of formamidinium *n*(FA^+) per acetate *n*(OAc^-) after extraction from a salt mixture with *r* = 0.49.

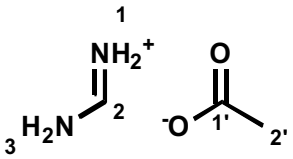
molar ratio $r = \frac{n(\mathrm{FA^+})}{n(\mathrm{OAc^-})}$		Solvent			
		H_20	MeOH	EtOH	^{i}PrOH
	4 °C	0.49[a]	0.34	0.52	0.64
T	25 °C	0.50[a]	0.38	0.54	0.70
	boiling	0.47[a, b]	0.47	0.55	0.75

[a] complete solution of both salts. [b] detection of formamide in filtrate

5 Synthesis of the authentic reference compounds

5.1 Formamidine acetate (2a) by catalytic hydrogenation

5%-Pd on activated carbon (25.3 mg, 0.24 mmol, 1 mol%, unreduced) was placed in a flask and suspended in water (8.5 mL) and acetic acid (1.5 mL, 26.2 mmol, 1.1 eq.). The flask was sealed and transferred under H_2 atmosphere. The suspension was stirred vigorously for 30 min to completely reduce the catalyst. Afterwards a solution of cyanamide (**1**, 1.0 g, 23.8 mmol, 1.0 eq.) in water (10 mL) was added, while continuing intense stirring. The reaction mixture was stirred until the starting material was consumed (TLC, 3.5 h). The catalyst was filtered off, washed with water and the solvent was removed at reduced pressure. The resulting crude product (**2a**, 1.5 g, 14.9 mmol, 63%) was recrystallized from hot MeOH.[7]



Characterization:

Colorless, crystalline solid.

Melting point: 151–152 °C (MeOH).

^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.66 (s, 3H, *H*-2'), 3.43 (bs, 2H, NH_2), 7.76 (s, 1H, *H*-2), 9.80 (bs, 2H, NH_2^+) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 24.9 (*C*-2'), 158.5 (*C*-2), 176.1 (*C*-1') ppm.

HR-MS (ESI, Pos. Mode): m/z for $CH_5N_2^+$ $[M]^+$ calculated: 45.0447

found: 45.0447

5.2 Formamidine acetate (2a) by electrochemical reduction

The base electrolytes (4.8 M aq. HOAc) were pumped through the flow electrolysis cell. As the catholyte reached the outlet of the cell, a current of 25 mA (j = 2.3 mA/cm^2, geometrical current density) was applied. A suitable amount of electrolyte (approx. 50 mL) was pumped through the cell with a flow rate of 10 mL/min for catholyte and 3.0 mL/min for anolyte. In order to remove Ni ions, which were dissolved from cathode, while no current was applied. This forerun was discarded.
Afterwards reservoirs of cyanamide (**1**, 500 mg, 11.9 mmol) in 4.8 M aq. HOAc (25 mL) as catholyte and 4.8 M aq. HOAc (25 mL) as anolyte were connected to the flow electrolysis cell and flow rate was decreased to 3 mL/min. Henceforth, the electrolysis was conducted at 25 mA (j = 2.3 mA/cm^2, geometrical current density). A charge of 4 F was applied. The addition of a part of catholyte (two drops) to a 1 M solution of $AgNO_3$ in 10% *aq*. NH_3 (0.4 mL), showed a nearly complete conversion of starting material (no yellow precipitate).

After the electrolysis was finished, the catholyte was transferred in a flask. The cathodic compartment of the cell was washed with water (about 25 mL). The washings and the catholyte were combined and the solvent was removed at reduced pressure. As MeOH (0.5 mL) and Et_2O (25 mL) were added, the crude formamidine acetate (**2a**, 1.056 g, purity of 91wt%) precipitates.
Recrystallisation from hot EtOH (2.4 mL) at 2 °C gave pure formamidine acetate (**2a**, 659 mg, 6.3 mmol, 54%).

Characterization:

Precipitated (91wt%, NMR analysis).[A]

Melting point: 135–137 °C (MeOH/Et_2O).

Recrystallized.

Melting point: 156–158 °C (EtOH).

5.3 4,6-Dihydroxypyrimidine (3)

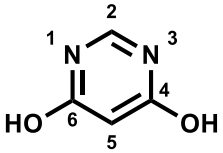
Classical chemical route
Formamidine acetate (**2a**, 500 mg, 4.8 mmol, 1.00 eq.) was charged under Ar atmosphere in a round bottom flask. The starting material was suspended in anhydrous MeOH (2 mL). The suspension was chilled to 0 °C. While stirring and cooling, 30% NaOMe solution (1.8 mL, 9.6 mmol, 2.00 eq.) in MeOH was added. The solution was stirred for 5 min and dimethyl malonate (0.6 mL, 5.1 mmol, 1.06 eq.) was added. The solution was stirred at 0 °C for 1 h, then at room temperature for 2 h, and then under reflux for 2 h. The reaction mixture was chilled to 0 °C and 15% aqueous HCl (2.2 mL, 9.6 mmol, 2.00 eq.) was slowly added. The suspension was stirred at 0 °C for 1 h and the product **3** (333 mg, 3.0 mmol, 62%) was filtered off, washed with ice-cold water, EtOH and Et_2O and dried in vacuum.

Electrochemical route
According to typical procedure for electrochemical screening in batch, 2 cells were employed for electrochemical screening with 0.5 M NaOAc in 4.8 M aq. HOAc and heated to 30 °C. Cyanamide (**1**, 140 mg, 3.3 mmol, 0.50 eq.) was dissolved into each catholyte. The electrolysis was conducted according to the parameters listed below.

anode || cathode:	graphite || Ni
current density:	j = 5 mA/cm^2
electron equivalents:	4 F
temperature:	T = 30 °C
separator:	Nafion membrane

[A] The content of formamidine in crude product was determined by ^{1}H NMR using maleic acid as internal standard.

After completion of the electrolysis, both catholytes were transferred to a flask and the solvent was removed at reduced pressure. The residue was suspended in Et_2O (20 mL). The solid was filtered off and extracted twice by ^{i}PrOH (10 mL) at 50 °C. The filtrate was concentrated to dryness at reduced pressure. The flask was brought into inert conditions and the solid suspended in anhydrous MeOH (3 mL). The suspension was chilled to 0 °C and 30% NaOMe (2.5 mL, 13.3 mmol, 2.00 eq.) in MeOH was slowly added. After stirring for 5 min, dimethyl malonate (0.8 mL, 7.1 mmol, 1.06 eq.) was added. The solution was stirred at 0 °C for 1 h, then at room temperature for 2 h, and then under reflux for 2 h. The reaction mixture was chilled to 0 °C and 15% aqueous HCl (3.0 mL, 13.3 mmol, 2.00 eq.) was slowly added. The suspension was stirred at 0 °C for 1 h and the product **3** (367 mg, 3.3 mmol, 49%) was filtered off, washed with ice-cold water, EtOH and Et_2O and dried in vacuum.



Characterization:

Colorless, crystalline solid.

Melting point: >260 °C (degr.).

^{1}H NMR (300 MHz, DMSO-d_6) δ = 5.22 (s, 1H, *H*-5), 8.01 (s, 1H, *H*-2), 11.74 (bs, 2H, O*H*) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 90.1 (*C*-5), 150.0 (*C*-2), 166.2 (*C*-4, *C*-6) ppm.

HR-MS (ESI, Pos. Mode): m/z for $C_4H_5N_2O_2^+$ $[M+H]^+$ calculated: 113.0346

found: 113.0345

6 References

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