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# Electrochemically enabled oxidative aromatization of pyrazolines†

Silja Hofmann,‡[a] Martin Linden,‡[a] Julian Neuner,[a] Felix N. Weber[a] and Siegfried R. Waldvogel *[a,b]

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Pyrazoles are a very important structural motif widely found in pharmaceuticals and agrochemicals. An electrochemically enabled approach for the sustainable synthesis of pyrazoles *via* oxidative aromatization of pyrazolines is presented. Inexpensive sodium chloride is employed in a dual role as a redox mediator and supporting electrolyte in a biphasic system (aqueous/organic). The method is applicable to a broad scope and can be conducted in the simplest electrolysis set-up using carbon-based electrodes. Hence, the method allows for simple work-up strategies such as extraction and crystallization, which enables application of this green synthetic route on a technically relevant scale. This is underlined by demonstration of a multi-gram scale electrolysis without loss in yield.



## Introduction

Pyrazoles represent an important and common structural motif in modern pharmaceuticals due to their biological potency.[1] Depending on their substitution pattern and the functional groups attached to the pyrazole moiety, they have already found application in treatments for various diseases and have potential for further use.[2] One prominent example is sildenafil (**3**), a phosphodiesterase inhibitor for treatment of erectile dysfunction (Chart 1). Furthermore, pyrazoles exhibit metabolic,[3] cardiac,[4] and gastrointestinal effects,[5] antibacterial,[6] antipsychotic,[7] anti-inflammatory,[8] antinociceptive[9] properties and are promising candidates for the development of new anticancer drugs.[10] Pyrazoles are widely found in active compounds in agrochemicals, *e.g.* fungicides (pyraclostrobin, **2**)[11] or herbicides (benzofenap, **1**).[12]

Common synthetic strategies are summarized in Scheme 1. These involve condensations of 1,3-diketones[13] or ynones[14] with hydrazines. However, regioisomeric mixtures of the desired pyrazole are frequently obtained and the syntheses of these starting materials can be capricious. Hydroamination reactions followed by C–N couplings can be conducted in flow with inexpensive copper catalysts but are severely limited in scope.[15] Direct access to pyrazoles is possible by cyclization of readily available hydrazones with dipolarophiles.[16] Nonetheless, these methods largely require expensive transition metal catalysts[17] or additional oxidizers, *e.g.* oxygen[18] or peroxides,[19] or rely on costly nitro-olefins.[20] There are synthetic strategies which feature a two-step approach *via* initial formation of a pyrazoline from readily available starting materials and subsequent oxidation. For the latter step, oxidizing agents such as oxygen,[21] peroxides,[22] or halogens[23,24] in over-stoichiometric quantities are necessary, which typically necessitates a transition metal catalyst.[25] To name one example, the synthesis of pyraclostrobin (**2**) involves the oxidative aromatization of a pyrazolidinone as a key step. This reaction conventionally requires copper-, cobalt- or iron catalysts in combination with oxygen.[26] As modern chemistry moves towards greener methodologies, current synthetic strategies must fulfil the requirements of resource efficiency and sustainability as well as enhanced safety of the process. Electrochemistry aligns with these principles of green chemistry, as hazardous and often expensive redox reagents can be substituted with electric current.[27] This also facilitates inherently safe processes, allowing for precise control over the reaction as the electron transfer is initially constrained to the electrode surface.[28] In addition, the generation of reagent waste can be minimized as solvents and supporting electrolytes can be recycled.[29] The down-stream processing is often more costly than the electrochemical conversion and decisive for translation into large scale application.[30] The use of widely available and robust carbon-based electrode materials like boron-doped diamond (BDD) ensures low-maintenance set-ups.[31] In summary, the reaction can become almost waste- and pollutant-free if electricity from renewable resources is employed.

[a]*Department of Chemistry, Johannes Gutenberg University Mainz, Duesbergweg 10-14, Mainz, 55128, Germany. E-mail: waldvogel@uni-mainz.de; https://www.aksw.uni-mainz.de/prof-dr-s-r-waldvogel/*

[b]*Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS FMS), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany*

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‡The authors contributed equally to this work.

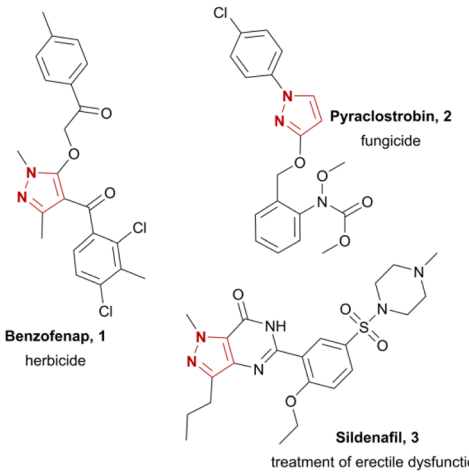
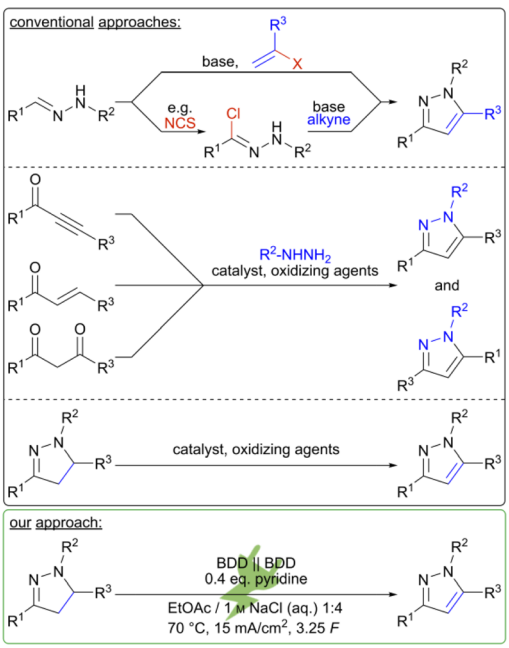



**Chart 1** Representative examples of pharmaceutically and agrochemically important pyrazoles.



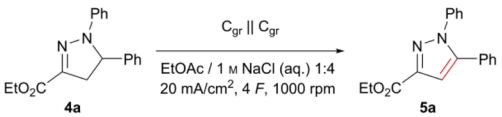

**Scheme 1** Conventional and electrochemical approaches for the synthesis of pyrazoles.

Electrochemical reactions of pyrazoles have been of scientific interest for decades;[32] in particular, the functionalization of pyrazoles at position 4 have been studied. Besides electrochemical chlorination,[33,34] bromination[34,35] or even iodination reactions,[36] a methodology for an electrochemical selenylation has also been established.[37] Additionally, electrochemical *N*-arylation reactions of unsubstituted or 4-nitro-substituted pyrazoles have been studied.[38] Furthermore, the iodide-mediated synthesis of highly sulfonylated pyrazoles from sulfonylhydrazines in an undivided electrolysis cell has been reported.[39] An intramolecular approach to the pyrazole moiety uses hypervalent iodine-mediated C–N-coupling of α,β-unsaturated hydrazones granting access to 1,3,5-substituted pyrazoles. However, this requires electron-withdrawing substituents on the nitrogen.[40] Electrosynthesis to pyrazole derivatives including N–N bond formation usually does not provide the hetero-aromatic system.[41] Remarkably, the oxidation of pyrazolines to their corresponding pyrazoles is less common. Potentiostatic oxidation of both 3-aminopyrazoline[42] and 1,3,5-triphenylpyrazoline[43] led to dimerization as well as the formation of the corresponding pyrazoles. An electrochemical iodide-mediated approach for the synthesis of pyrazolines and pyrazoles from readily available hydrazones gave access to a library of pyrazolines in up to excellent yields.[44] Application of a redox mediator enhances selectivity and suppresses side reactions, *e.g.* polymerizations or over-oxidations.[45] However, using alkynes as dipolarophiles yielded the corresponding pyrazoles in rather poor yields. We have developed an electrochemical method for the oxidation of pyrazolines to their corresponding pyrazoles using inexpensive sodium chloride in a double role as supporting electrolyte and mediator. BDD was chosen as electrode material in an environmentally friendly solvent system of water and ethyl acetate, allowing for facile work-up.[46] The synthesis was performed under the simplest conditions: an undivided beaker-type electrolysis cell using a constant current set up. These are all prerequisites for operation in multi-gram scale.

## Results and discussion

Initially, the electrochemical oxidation of pyrazolines was investigated using ethyl 1*H*-4,5-dihydro-1,5-diphenylpyrazole-3-carboxylate **4a** as test substrate. First, the influence of halide, organic solvent, electrode material, and temperature were tested (Table 1). Initial reactions were performed using con-

**Table 1** Initial reaction optimization targeting halide source, concentration, and reaction temperature




| Deviation from standard conditions | *T*/°C | Yield[a] |
|---|---|---|
| None | 25 | 26% |
| 1 M NaBr | 25 | 0% |
| 1 M NaI | 25 | 0% |
| None | 65 | 38% |
| 2.5 M NaCl | 65 | 34% |
| None | 70 | 59% |
| **BDD \|\| BDD** | **70** | **62%** |
| $C_{gl}$ \|\| $C_{gl}$ | 70 | 0% |
| DSA ($IrO_2$ on Ta) \|\| $C_{gr}$ | 70 | 43% |
| DSA (Ru–Ir mixed oxide on Ta) \|\| $C_{gr}$ | 70 | 57% |
| DSA (Ru–Ir mixed oxide on Ta) \|\| VA1.4571 | 70 | 49% |
| DSA (Ru–Ir mixed oxide on Ti) \|\| $C_{gr}$ | 70 | 55% |

Screening reactions performed in 5 mL Teflon cells. *n*(Pyrazoline) = 0.34 mmol. [a] Yield determined using GC analysis with 1,3,5-trimethoxybenzene as internal standard after external calibration.

ditions based on previous work on the mediated electrochemical synthesis of pyrazolines.[44] Here, graphite electrodes and a biphasic solvent system (ratio of the layers organic/aqueous 1 : 4), with a sodium halide concentration of 1 M with respect to the aqueous phase was used along with high stirring speed (1000 rpm). The concentration of the test substrate **4a** was set to 0.34 mmol (concentrations of pyrazolines are given relative to the organic layer). At 25 °C, among all tested halides, only sodium chloride yielded the desired pyrazole **5a** in 26%. The yield for **5a** increased with elevated temperature, and hit a maximum yield of 59% at 70 °C. Within the tested electrode materials (graphite ($C_{gr}$), glassy carbon ($C_{gl}$), BDD, and various dimension stable anodes (DSA)), BDD gave **5a** in highest yield of 62%. Alteration of the counter electrode to stainless steel did not improve product formation.[47] Further reaction optimization with regards to temperature, current density, and amount of charge was conducted using a Design of Experiments (DoE) approach. This enables fast and precise investigation of the reaction process, while interactions between the factors and outliers are considered for the statistical analysis of the results.[48] A fractional factorial design was chosen ($2^{4-1}$ resolution of III with central point and rotatable axis points, each data point run in triplicate). Target optimization led to the following reaction conditions: BDD electrodes, EtOAc/1 M NaCl (aq.) 1 : 4 (v/v), 70 °C, 15 mA $cm^{-2}$ current density, and an applied charge of 2.5 *F*, which yielded **5a** in 73% (calibrated GC yield). Next, the addition of tetraalkylammonium chlorides as co-supporting electrolytes to the electrolysis mixture (maintaining a total chloride concentration of 1 M) was investigated. Employing tetrabutylammonium chloride in the electrolysis showed almost no beneficial effect. Use of ammonium salts with shorter alkyl chains (Me or Et) proved to be detrimental (see Table S8, ESI†).

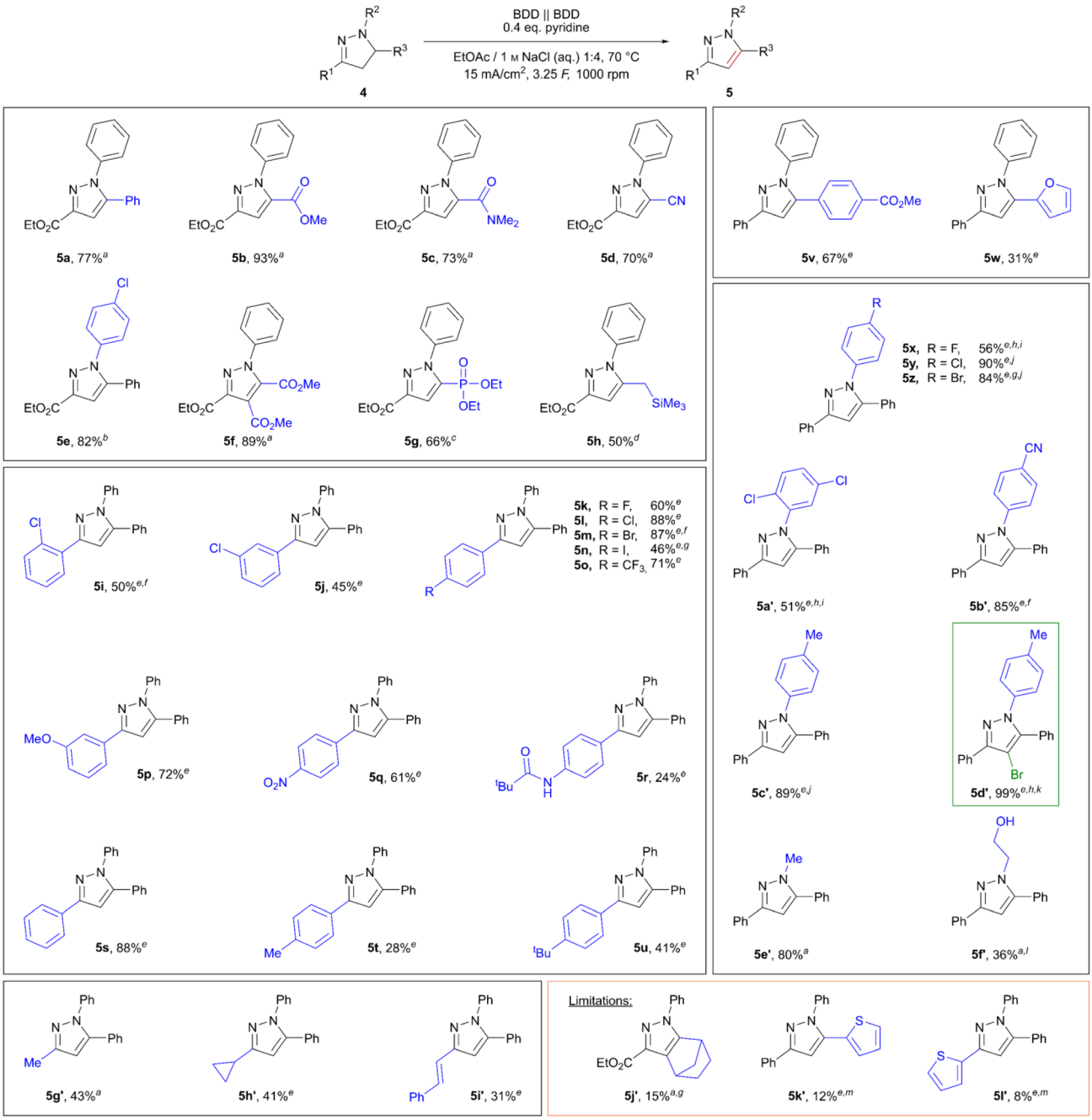
Previous work has shown the importance of finely dispersed emulsions for efficient conversion in biphasic systems;[44] therefore, the set-up was changed to 25 mL jacketed beaker-type cells with more powerful cross-shaped stirring bars to allow for more efficient mixing. Within the first scale-up experiment (1.7 mmol pyrazoline **4a**) it was discovered full conversion of the substrate was possible at 3.25 *F* instead of 2.5 *F*, providing **5a** in 69% yield. Therefore, the optimum amount of charge was adjusted for further experiments to reflect this discovery. To yield the corresponding pyrazole, elimination of hydrogen halide must take place. Thus, small amounts of different bases were used within the reaction.

Of the tested bases sodium carbonate, triethylamine, and pyridine, addition of 0.4 eq. pyridine allowed for an increase in yield of **5a** to 75% (see Table S9, ESI†). Lastly, the influence of substrate concentration on the reaction was tested. Fortunately, the reaction proceeded smoothly in the concentration range of 0.34 M (75% **5a**) and 0.75 M (77% **5a**), while lower concentrations of 0.25 M proved detrimental, yielding 55%. Employing even higher concentrations of pyrazoline (1 M **4a**) also resulted in a drop in yield, likely due to poor solubility of the starting material in the organic layer. The scope of the reaction was investigated, and different pyrazoles could be obtained in moderate to excellent yields. The results are summarized in Scheme 2. In particular, it was found that pyrazolines bearing an ester group in the 3-position were oxidized smoothly, yielding pyrazoles **5a–5h** in 50–93% yield, including 4,5-disubstituted pyrazole **5f** (89%). In contrast, 4,5-disubstituted pyrazole **5j′** was only obtained in poor yield of 15%, likely due to enhanced ring strain of the condensed norbornene. Furthermore, the influence of different substituents in the positions 1, 3, and 5 was investigated. The *N*-methyl analogue **5e′** was obtained in 80% yield, and even the *N*-(2-hydroxethyl)-substituted pyrazoline was converted successfully yielding 36% of the corresponding pyrazole **5f′**. In addition, the tolerance of aliphatic and styryl substituents in position 3 was demonstrated in yields up to 43% (**5g′–5i′**). Interestingly, the cyclopropyl-substituted pyrazole **5h′** (41%) was obtained in a yield comparable to the methyl-substituted analogue **5g′** (43%) with no side products or products indicating opening of the cyclopropyl ring.

The applicability of the more substituted 1,3,5-triarylpyrazolines was then tested under these conditions. Although 1*H*-4,5-dihydro-1,3,5-triphenylpyrazole was converted smoothly using optimized reaction conditions, yielding the corresponding pyrazole **5s** in 88%, the chosen substrate concentration of 0.75 M (relative to the organic layer) proved too high for the three fold substituted 1*H*-1,3,5-triaryl-4,5-dihydro-pyrazolines used. Therefore, the concentration of substituted 1*H*-1,3,5-triaryl-4,5-dihydro-pyrazolines was lowered to 0.3 M. Variation of the 3-position on the aryl ring showed some general trends. Whilst 1*H*-1,3,5-triphenylpyrazole (**5s**) was obtained in a good yield of 88%, the yields dropped with increasing electron-donating character of the *para* substituents: *p*-methyl (**5t**, 28%), *p*-pivaloylamino (**5r**, 24%). As an exception, the *p-tert*-butyl derivative **5u** was obtained in 41% yield, most likely due to steric aspects. In contrast, substrates bearing electron-donating groups in *meta*-position undergo the reaction well, as shown by pyrazole **5p** (72%). Furthermore, electron-withdrawing substituents in *para*-position gave satisfying yields of 61% and 71% for *p*-$NO_2$ (**5q**) and *p*-$CF_3$ (**5o**), respectively. For chloro-substituted pyrazoles **5i–5l** a general trend for the increase in yield for *meta* (**5j**, 45%) < *ortho* (**5i**, 50%) < *para* (**5l**, 88%) was observed. To our delight, *para*-fluoro (**5k**, 60%), *para*-bromo (**5m**, 87%), and even *para*-iodo (**5n**, 46%) derivatives were obtained; the iodo derivative result was especially pleasing as it is prone to undergo side reactions resulting from oxidation of the iodoarene.[49] Limitations of the method were found for 3- and 5-thien-2-yl-substituted pyrazoles **5l′** (8%) and **5k′** (12%), whereby degradation of the substrates was predominantly observed. Interestingly, conversion of a 5-furan-2-yl substituted pyrazoline was successful, giving 31% of the corresponding pyrazole **5w**.

Further investigation into the influence of different substituents on the aryl ring at the 1-position was conducted. Analogous to the results for *para*-substituted arenes in the 3-position, electron-withdrawing groups proved beneficial for the oxidation of pyrazolines. Therefore, *para*-cyano functionalization gave pyrazole **5b′** in a very good yield of 85%. Again, *para*-halogenated derivatives gave moderate to very good yields (pyrazoles **5x–5z**, F 56% < Br 84% < Cl 90%). Indeed, the yields




**Scheme 2** Optimized reaction conditions and scope of the oxidative aromatization of pyrazolines. Isolated yields. [a] 3.75 mmol scale; [b] 3.06 mmol scale, 5 F; [c] 2.62 mmol scale; [d] 2.94 mmol scale; [e] 1.5 mmol scale; [f] 4 F; [g] 4.5 *F*; [h] 1 M NaBr (aq.); [i] 2 *F*; [j] 1 M NaX (aq., $X^- = Cl^-/I^-$ (1 : 1)); [k] 5 *F*; [l] 2.5 *F*; [m] 6.5 *F*.

and findings are in accordance with those obtained for the *para*-halo substituted arenes in the 3-position. However, for successful conversion of these halogenated pyrazolines a change of the supporting electrolyte was necessary. Whilst fluorinated pyrazole **5x** as well as 2,5-dichloro substituted pyrazole **5a′** (51%) gave the best results when 1 M NaBr (aq.) was used, a 1 : 1 mixture of NaCl (aq.) and NaI (aq.) with respect to a total halide concentration of 1 M had to be employed for chloro (**5y**) and bromo (**5z**) derivatives. The influence of different supporting electrolytes was investigated for the conversion of 1-(*p*-methylphenyl) substituted pyrazoline **4c′**. Although the application of solely sodium chloride led to side product formation and degradation of the starting material, the corresponding pyrazole **5c′** was obtained in a very good yield of 89% when the mixed aqueous supporting electrolyte NaCl/NaI (1 : 1, total halide concentration 1 M) was employed. To gain insight into the influence of halogen species in this specific oxidation, experiments with elemental iodine and

iodine monochloride were carried out. Pyrazole **5c′** was only obtained in 57% (NMR yield) when iodine was directly used. However, application of iodine monochloride gave pyrazole **5c′** in 92% (NMR yield), which is indeed comparable to the 89% isolated yield achieved using our electrolysis technique. Hence, we propose that the use of the mixed NaCl/NaI electrolyte results in the *in situ* formation of iodine monochloride, which then serves as the oxidizing agent. Additionally, the application of 1 M NaBr (aq.) in the electrolysis was investigated. Interestingly, after 3.25 *F* both the desired pyrazole as well as the monobrominated compound **5d′** were obtained. Furthermore, **5d′** was obtained selectively in 99% yield after 5 *F* of charge was applied. A control experiment employing elemental bromine yielded both the pyrazole **5c′** (55% NMR yield) and the monobrominated compound **5d′** (35%). The electrochemical bromination of pyrazoles using aqueous sodium bromide electrolytes has also been reported in literature.[34,35] Hence, our results are in accordance with literature findings and the presented method could also be extended to electrochemical bromination reactions of pyrazoles.

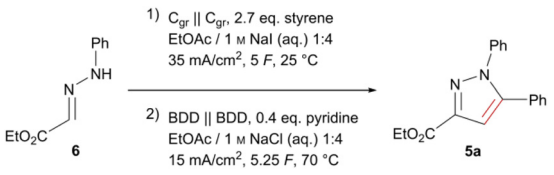
### Sequential anodic synthesis from hydrazones and scale-up

To emphasise the application potential of the presented reaction, a telescoped synthesis of pyrazole **5a** starting from ethyl glyoxylate phenyl hydrazone (**6**) was carried out (Scheme 3). In the first step, the corresponding pyrazoline was synthesized according to a recently published protocol.[44] After the first electrolysis, styrene and excess iodine were removed and the crude product was subjected to a second electrolysis step: oxidative aromatization of the obtained pyrazoline. To our delight, when using a telescoped two-step electrosynthesis we obtained pyrazole **5a** in 60% yield. Furthermore, when each step was conducted with product isolation both steps gave 77% yield, with an identical overall yield of 60%. Hence, pyrazoles can be obtained *via* this two-step sequential electrolysis, wherein isolation of intermediate pyrazolines is not required.

Furthermore, the multi-gram scale synthesis of pyrazole **5a** was performed to an excellent yield of 89% (6.82 g, 23.3 mmol; Table 2). This clearly demonstrates the robustness of the established electrochemical conversion and indicates its application potential for synthesis on technically relevant scales.

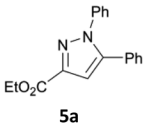
### Application in the synthesis of pyraclostrobin

The oxidation of pyrazolinone **4m′** as a key step in the synthesis of pyraclostrobin (**2**) (BASF SE, sales volume 735 million. US$ (2009)[51]) was chosen to illustrate a potential application of




Scheme 3 Telescoped double electrochemical conversion of hydrazones to pyrazoles.

Table 2 Scale-up of the synthesis of pyrazole **5a**

| Pyrazole | | |
|---|---|---|
|  |  |  |
| 5a | 77%[a] 845 mg 2.89 mmol | 89%[b] 6.82 g 23.3 mmol |

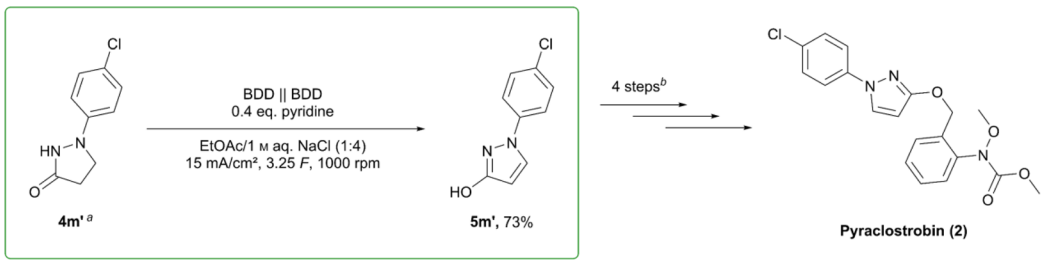
[a] 3.75 mmol scale. 25 mL beaker-type cell. [b] 7-Fold scale-up, 26.3 mmol scale, 200 mL beaker-type cell. Isolated yields given.

the presented reaction. On 3.75 mmol scale, the reaction was shown to proceed smoothly, yielding 73% of the desired pyrazole **5m′** (Scheme 4). Together with the observed robustness in scale-up, this emphasises the relevance of this set-up for further investigation and extension towards technical or industrial scale. Due to the simple work-up and usage of widely employed techniques such as distillation and crystallization, it is easy to see this process as transferrable to and used on larger scales.

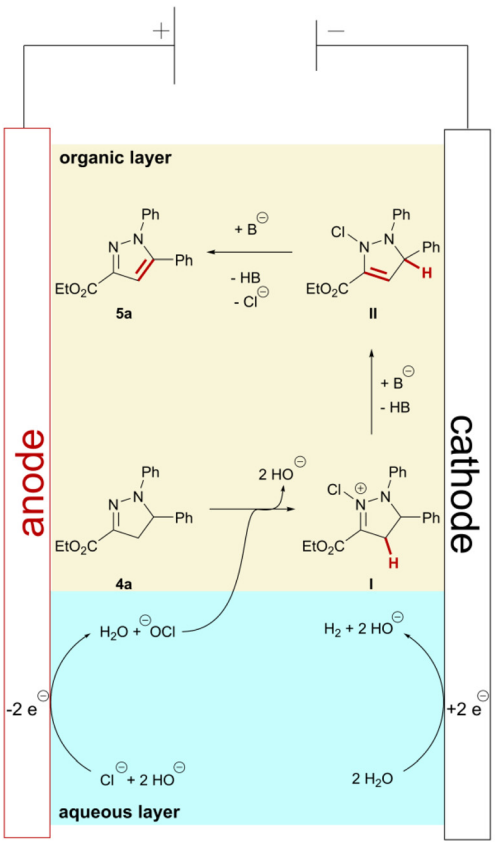
### Mechanistic considerations

As a result of the broad functional group tolerance and previous investigations into biphasic electrochemical reactions involving halogens as mediators,[44] we propose an ionic reaction mechanism (Scheme 5). In the aqueous layer, anodic oxidation of chloride ions initially forms adsorbed or dissolved chlorine. In aqueous media, further reaction with water occurs immediately, forming hypochlorite. However, further oxidation to chlorine species in higher oxidation states, *e.g.* chlorate, is possible.[52] Fast stirring and sufficient mixing of organic and aqueous layer proved key for successful conversion of the pyrazolines. Thus, chlorination of pyrazoline **4a** at the nitrogen in position 2 occurs most likely at or close to the phase boundary, forming positively charged intermediate **I**. This is also supported by the observation that addition of tetraalkylammonium salts with longer carbon chains had no effect on the pyrazole formation. Subsequent base-promoted proton elimination results in chlorinated intermediate **II**. Formal elimination of HCl in the final step results in aromatization and, consequently, formation of pyrazole **5a**. As hydrogen evolution serves as the cathodic counter reaction, stoichiometric amounts of hydroxide ions are formed during the reaction. However, addition of sub-stoichiometric amounts of pyridine (0.4 eq.) to the reaction mixture promoted product formation and improved the yields. Therefore, we assume that the addition of pyridine as a base supports the proton elimination and, as a result, the product formation in the beginning of the reaction. Additionally, pyridine may also interact with intermediates **I** and **II** within the organic layer and not just at the phase boundary, thereby promoting a fast conversion to the corresponding pyrazole. Chlorinated pyrazolines, *e.g.*, in 5-position, were never observed by any analytical method, even




**Scheme 4** Electrochemical key step in the synthesis of pyraclostrobin (**2**). [a]Synthesis of **4m′** from 4-chlorophenylhydrazine hydrochloride and methyl acrylate, MeOH, NaOMe, Δ. [b] (1) base, 2-nitrobenzyl chloride; (2) $H_2$/Pt; (3) methyl chloroformate; (4) base, dimethyl sulfate.[50,51]




**Scheme 5** Postulated reaction mechanism. Hydroxide or pyridine both may serve as the base (B).

when the organic layer was subjected to GC-MS analysis before the theoretical amount of charge (2 *F*) was applied. As a consequence, we propose the oxidative aromatization occurs *via* initial chlorination at the nitrogen in 2-position in accordance with the literature.[24,34,53]

## Conclusions

A new method for the synthesis of pharmaceutically and agrochemically relevant pyrazoles was established. Starting from readily available pyrazolines, *e.g.*, by condensation of chalcones with hydrazines, more than 35 examples were synthesized in moderate to excellent yields up to 93%.

The reaction features a broad functional group tolerance and was demonstrated to be perfectly scalable to multi-gram scale. Ubiquitous and inexpensive sodium chloride was used in a double role as redox mediator and supporting electrolyte. This allows for facile work-up strategies and simplifies solvent recovery as well as waste management, since sodium chloride is commonly tolerated in sewage. Moreover, a sequential electrochemical synthesis from hydrazones without intermittent work-up and no loss in yield was performed. This allows for telescoped electrosynthetic approaches by switching the aqueous layers. Relevance of the demonstrated reaction was further underlined by a key step oxidation in the synthesis of the industrially relevant fungicide pyraclostrobin (**2**). In addition, the established system can be extended to oxidative aromatization and *in situ* bromination, as shown by the synthesis of a 4-brominated pyrazole in quantitative yield. Therefore, the reaction can potentially be used to access building blocks for coupling reactions. Finally, carefully chosen control experiments allowed the proposal of a convincing reaction mechanism which is in agreement with literature findings.

Due to the simple experimental set-up featuring sustainable carbon-based electrode materials, inexpensive and environmentally benign solvents and electrolytes, the demonstrated reaction is a viable green alternative to previous conventional approaches for pyrazoline oxidation.

## Author contributions

S. H. and M. L. contributed equally to this work. S. H. and M. L. established the reaction, analysed experimental data, and performed scope and scale-up reactions. S. H. and J. N. conducted the experiments for initial reaction optimization and DoE. M. L., S. H., and F. N. W synthesized starting materials and carried out batch-type electrolyses. S. H., M. L., and S. R. W. wrote the manuscript. All authors discussed the results and agreed to the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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