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Electrochemistry

# Electrochemical Synthesis of Pyrazolines and Pyrazoles via [3+2] Dipolar Cycloaddition

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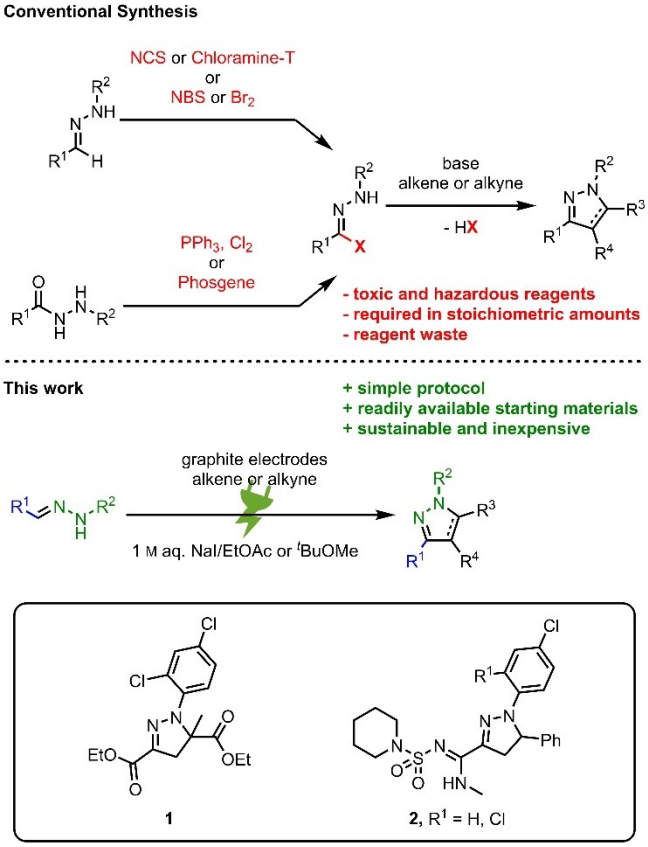
**Abstract:** Pyrazolines and pyrazoles are common and important motifs of pharmaceutical agents and agrochemicals. Herein, the first electrochemical approach for their direct synthesis from easily accessible hydrazones and dipolarophiles up to decagram scale is presented. The application of a biphasic system (aqueous/organic) even allows for the conversion of highly sensitive alkenes, wherein inexpensive sodium iodide is employed in a dual role as supporting electrolyte and mediator. In addition, mechanistic insight into the reaction is given by the isolation of key step intermediates. The relevance of the presented reaction is underlined by the synthesis of commercial herbicide safener mefenpyr-diethyl in good yields.

## Introduction

Among the biggest challenges imposed on preparative chemistry currently is the demand for resource-efficient and environmentally benign techniques.[1] In addition, the safety of chemical conversions and processes is of high concern.[2–4] Electrochemistry helps to fulfill these demands, as electricity substitutes expensive and often hazardous redox reagents for substrate conversion.[2–4,5] The precise control over the reaction, as the initial electron transfer is confined to the electrode surface, facilitates inherently safe processes.[6,7] Furthermore, vast amounts of reagent waste, which usually have to be taken into account, are avoided. In general, solvents and supporting electrolytes are unaffected by the transformations and can be recycled.[8] Inexpensive, sustainable, and eco-friendly carbon-based electrode materials like graphite, glassy carbon, or boron-doped diamond (BDD)[9] are widely available, and the latter is especially low in maintenance. Thus, when employing electricity from renewable sources, the reaction becomes practically waste- and pollutant-free.[1,7]

The structural motifs of pyrazoles and pyrazolines are widely found in the fields of pharmaceutical and agricultural chemistry due to their outstanding biological activity. Their widespread applications cover fields of antimicrobials featuring suppression of multidrug resistance,[10] anti-cancer agents[11] as well as pesticides and insecticides.[12] For example, mefenpyr-diethyl (**1**, Scheme 1, bottom)[13] is produced as an herbicide safener on industrial scale.[14–16] In addition, pyrazoline **2** is a key intermediate in the synthesis




***Scheme 1.*** Top: Approaches for the synthesis of pyrazolines and pyrazoles starting from hydrazones. Bottom: Important and representative structures for agrochemically (mefenpyr-diethyl, **1**) and pharmaceutically (**2**) active pyrazolines.

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of various potent cannabinoid $CB_1$ receptor antagonists used in the treatment of obesity and its accompanying risks, as well as cancer, inflammatory diseases, and their implications.[17,18]

Conventionally, pyrazole and pyrazoline synthesis can be achieved by condensation of 1,3-diketones or α,β-unsaturated ketones,[19] with hydrazines. [3+2] dipolar cycloadditions of nitrile imines and alkenes or alkynes also enable access to these compounds.[20,21] Mostly, nitrile imines are formed by elimination of hydrogen chloride from hydrazonoyl chlorides (Scheme 1, top).[22] However, in the synthesis of hydrazonoyl halides hazardous chemicals like *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS),[21,23] or phosphorous-reagents[24] have to be employed for oxidation of the corresponding hydrazones. More recently, a sustainable electrochemical oxidation of hydrazones, granting access to diazo compounds, was presented by Lam et al.[25] Electrochemical reactions of pyrazolines and pyrazoles have been studied since the 1970s, including dehalogenations[26] as well as halogenation and dimerization reactions.[27] Furthermore, an electrochemical intramolecular cyclization reaction for pyrazole synthesis has been reported, but relies on rather complex starting materials.[28]

In general, the presented approach is analogous to the synthesis of isoxazoles, and isoxazolines from aldoximes.[29] The synthesis of nitriles, isoxazolines and isoxazoles can be achieved by electrolysis via nitrile oxides as key intermediates.[30–34] These reactions have been investigated since the late 1980s when Shono et al. published the halogen-mediated synthesis of nitriles from oximes.[30,31] However, the use of $Cl^-/Cl^+$ as mediator in combination with precious platinum electrodes leads to severe corrosion.[35] This was circumvented by Waldvogel et al., who established an electrochemical protocol for direct synthesis of nitriles from oximes employing inexpensive graphite anodes.[32,36] Recently, the anodic oxidation of highly lipophilic betulin aldoxime to its nitrile oxide and subsequent formation of isoxazole conjugates has been demonstrated.[33] Based on these processes, a new electro-organic synthesis for 1,3,5-substituted pyrazolines and pyrazoles from readily available hydrazones was developed. Herein, a protocol allowing for synthesis of pyrazolines up to decagram scale is described. The scale-up is robust without any loss in yield, and is applicable even with highly sensitive dipolarophiles like styrene. This is achieved through application of a biphasic system for protection of such sensitive dipolarophiles from undergoing side reactions, e.g., polymerizations, during the electrolysis. Furthermore, it allows for a facile and inexpensive workup that contributes to the feasibility of electro-organic synthesis on a technically relevant scale.[37]

## Results and Discussion

For the initial investigation, ethyl glyoxylate phenylhydrazone (**3**) was chosen as a test substrate with styrene as dipolarophile. In general, statistically driven optimization strategies like Design of Experiments (DoE) allow for a time and resource efficient optimization process. Furthermore, a variation in yield for one parameter setting can easily be taken into account by weighting of this datapoint.[38] To enable reaction optimization via DoE, preliminary parameters needed to be set. Therefore, influence of electrode material, alkali metal halide source, organic solvent and phase ratio were studied using 5 mL Teflon cells. Quantification was performed using gas chromatography (GC) analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard. To our delight, within the carbon-based electrode materials screened, BDD, glassy carbon, and graphite ($C_{gr}$), the latter and most inexpensive material gave superior results. Commercially available sodium chloride, bromide, and iodide were tested as electrolytes and phase ratios of organic to aqueous phase from 1:4 to 4:1 (*v*/*v*) were employed. Besides ethyl acetate, dichloromethane and *tert*-butyl methyl ether were investigated as organic solvents. Environmentally benign ethyl acetate as organic solvent and 1 M aqueous

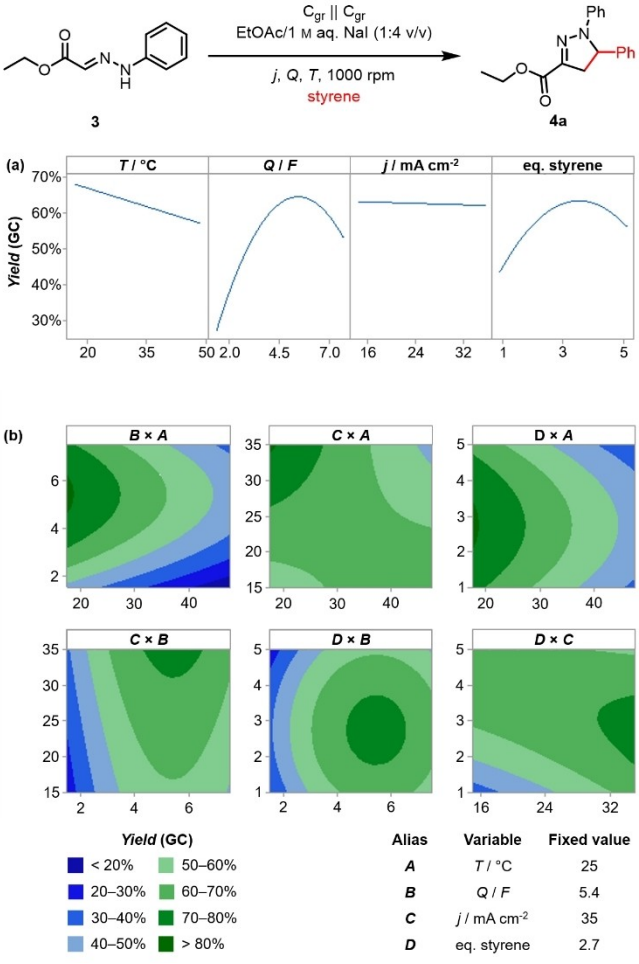
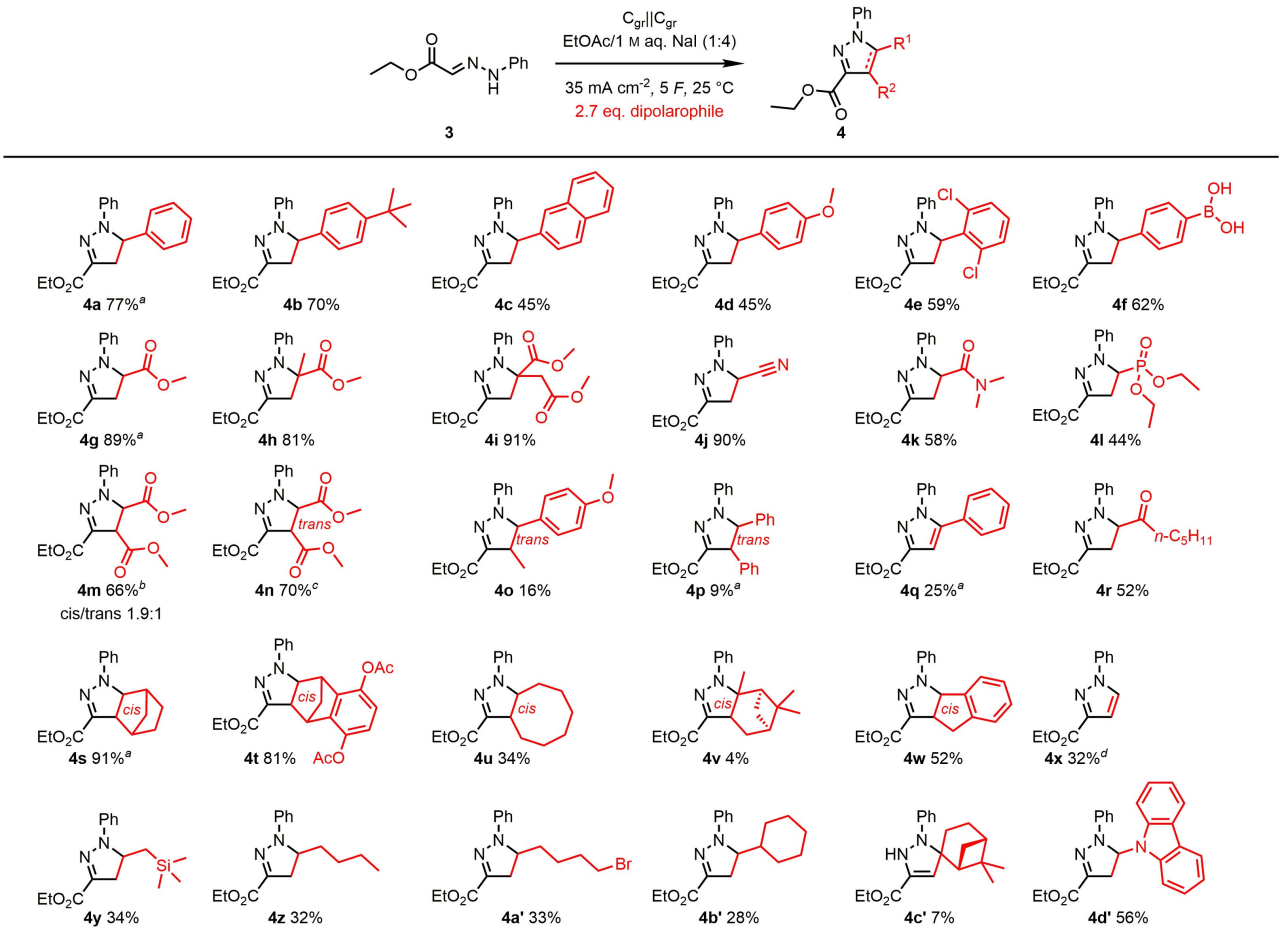



***Figure 1.*** Optimization of the synthesis of ethyl 1*H*–4,5-dihydro-1,5-diphenyl-pyrazole-3-carboxylate (**4a**) via DoE after backwards elimination ($\alpha = 0.05$). 0.52 mmol scale. a) Main effect diagram. b) Contour plots. Yield (GC) determined with 1,3,5-trimethoxybenzene as an internal standard after external calibration.

sodium iodide with a phase ratio of 1:4 (v/v) was chosen as the superior electrolyte.

Based on these results, further reaction optimization with regards to current density ($j$), amount of charge ($Q$), temperature ($T$), hydrazone concentration, and styrene equivalents was performed using DoE. A $2^{5-1}$ fractional factorial design was chosen (resolution V with central point and rotatable axial points, each datapoint acquired twice, analysis by backwards elimination, $\alpha = 0.05$). Accordingly, the amount of charge was identified to be the most influential parameter of the reaction. Furthermore, styrene equivalents and temperature have a significant impact on the reaction outcome (Figure 1). Maintaining the electrolysis temperature at 25 °C allows for a higher optimum current density of 35 mA cm$^{-2}$ and, consequently, shorter reaction times, as dissipation of the reaction heat prevents the hydrazone as well as the formed nitrile imine intermediate from decomposing. An excess of styrene is required to ensure sufficient conversion of the in situ formed nitrile imine to the corresponding pyrazoline. However, styrene related by-products are not observed and as a result, excess unreacted styrene can therefore be recovered from the reaction mixture (see below). Subsequent target optimization led to the following conditions: graphite electrodes, EtOAc and 1 M aqueous NaI solution as solvents (1:4 ($v/v$)), 25 °C, 35 mA cm$^{-2}$ current density, amount of charge of 5.4 $F$ and 2.7 eq styrene yielding 63 % (GC) of pyrazoline **4a**. Subsequently, the maximum hydrazone concentration was investigated in a linear screening. As expected, the hydrazone concentration in the organic layer has no significant impact on pyrazoline formation, since the initial oxidation takes place in the aqueous phase. Therefore, it was not covered by the calculated model. Indeed, the reaction was found to proceed smoothly and without any effect to the yield from low concentrations of 260 mM (50 mg mL$^{-1}$) to concentrations as high as 1040 mM (200 mg mL$^{-1}$) in the organic solvent. Solubility issues at even higher concentrations resulted in a drop in yield. Sodium iodide concentrations and addition of different tetraalkylammonium iodides were also investigated. Decreasing the sodium iodide concentration to 0.75 mM or below whilst the other optimized conditions were unchanged resulted in a drop in yield. Use of tetraalkylammonium salts in combination with NaI (to a total iodide concentration of 1 M) proved detrimental. Short chain tetraalkylammonium salts such as tetramethyl- or tetraethylammonium iodide expectably did not affect the reaction. When moving on to longer carbon chains (propyl, butyl), the yield of the desired pyrazoline decreased with

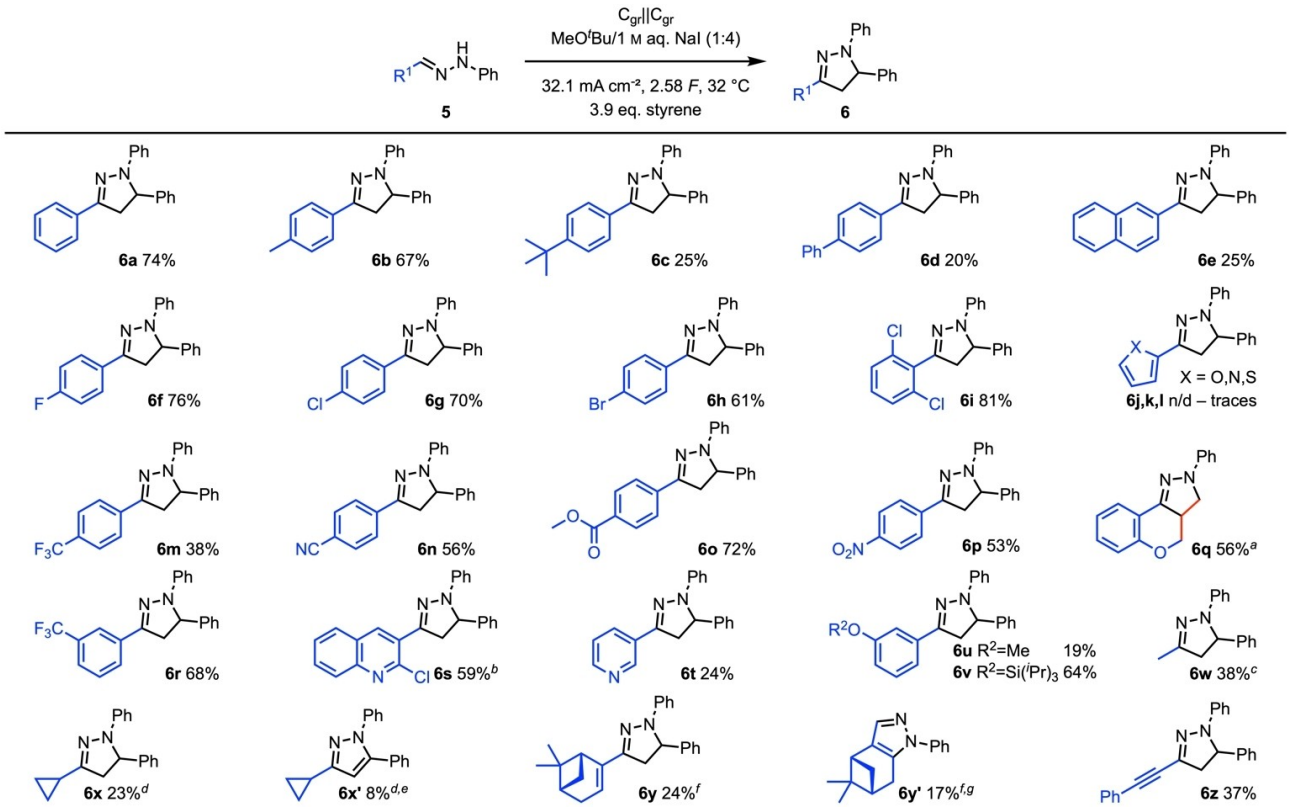



***Scheme 2.*** Scope of dipolarophiles. 3 mmol scale. [a] 3.9 mmol scale, 5.4 $F$; [b] dimethyl maleate as dipolarophile; [c] dimethyl fumarate as dipolarophile; [d] vinyl acetate as dipolarophile.

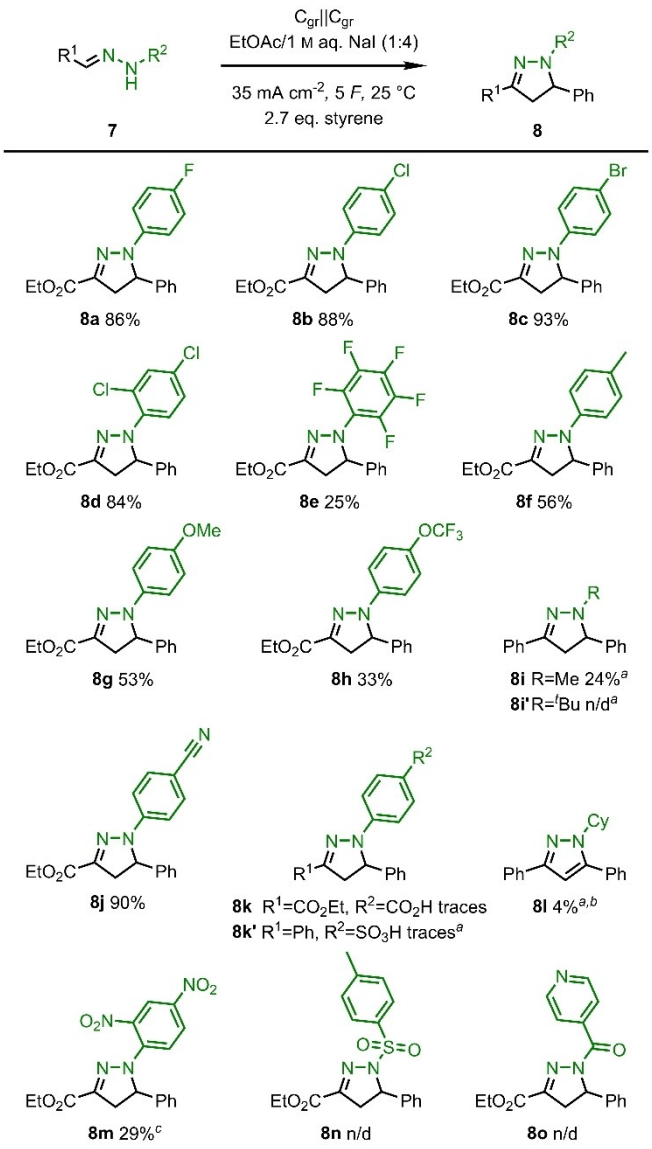
increasing chain length. At the same time, formation of by-products seemed to be promoted, as indicated by GC analysis. This led to the conclusion that the occurring accumulation of the electrogenerated oxidizing agent in the organic layer promotes side reactions rather than accelerating pyrazoline formation. High stirring speeds of 1000 rpm proved to be crucial for achieving sufficient conversion of the hydrazones and high yields of the corresponding pyrazoline. Therefore, the reaction can be assumed to be highly affected by formation of a finely dispersed emulsion of organic droplets in the aqueous layer and, hence, that the actual hydrazone oxidation occurs at the interface and not within the organic layer.

Surprisingly, benzaldehyde-derived hydrazones could not be converted successfully using the system described above. This was readily circumvented by changing the organic solvent from ethyl acetate to *tert*-butyl methyl ether. Further optimization of the adjusted system via DoE was performed with benzaldehyde phenylhydrazone (**5a**) as a second test substrate on 0.51 mmol scale. Optimum conditions were determined to be 2.58 *F*, 32.1 mA cm$^{-2}$, 32 °C and 3.9 eq styrene. However, contrary to the results from the experiments with ethyl glyoxylate phenylhydrazone (**3**), a linear concentration screening for hydrazone **5a** revealed a clear maximum in yield at 637 mM (125 mg mL$^{-1}$) hydrazone in the organic layer. The ascending trend between 75 mg mL$^{-1}$ and 125 mg mL$^{-1}$ can be assigned to an elongated time span between nitrile imine formation and [3+2] cycloaddition, caused by low concentrations of the reaction partners. Thus, the nitrile imine shows a higher risk of undergoing decomposition. On the other hand, higher decomposition rates were seen in hydrazone as its concentration was increased due to the prolonged electrolysis duration. Nonetheless, decomposition of benzaldehyde hydrazones by auto-oxidation is commonly known in literature.[39]

By altering the dipolarophile and the hydrazone, a broad variety of pyrazolines was synthesized (Scheme 2–4). Diverse functional groups and substitution patterns were tolerated. Among the dipolarophiles (Scheme 2), acrylates were converted most successfully (**4g** 89 %, **4h** 81 %, **4i** 91 %, **4j** 90 %), which is likely due to the enhanced reactivity of electron-deficient alkenes.[40,41] Comparable results were obtained for 1,2-disubstituted alkenes. However, it is clearly evident that these olefins (**4m–p**) exhibit lower reactivity than their monosubstituted analogues (**4a**, **d**, **g**). Strained systems like norbornenes can compensate for this effect by release of their strain during the cycloaddition (**4s** 91 %, **4t** 81 %), in accordance with previous reports.[41] Less strained alkenes consequently result in a lower yield (**4u** 34 %, **4w** 52 %). Boronic acids (**4f** 62 %) and phosphonates (**4l** 44 %) are tolerated as well as heterocyclic alkenes (**4d′** 56 %), which demonstrated the broad applicability of the method. Furthermore, it is shown for pyrazole **4x** (32 %) that leaving group-bearing alkenes like vinyl acetate can be used as acetylene surrogates on laboratory scale.




***Scheme 3.*** Scope of aldehyde phenylhydrazones. 3.2 mmol scale. [a] without styrene; [b] solvent: dichloromethane; [c] 3 mmol scale, 5 *F*, 2.7 eq styrene, solvent: EtOAc, 25 °C; [d] 3 mmol scale, 2 *F*, 2.7 eq styrene, solvent: EtOAc, 25 °C; [e] by overoxidation of **6x**; [f] 25 °C; [g] side reaction of **6y**.

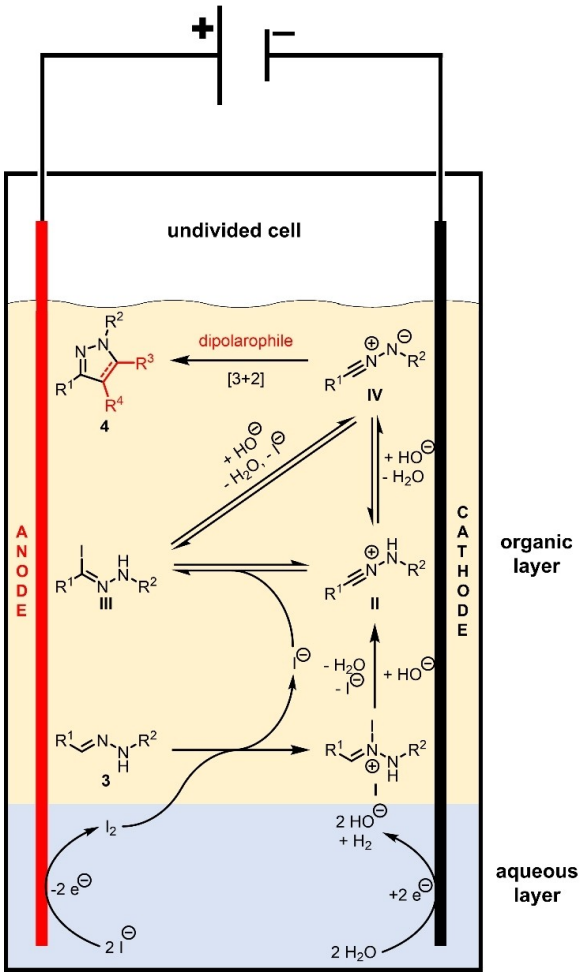



***Scheme 4.*** Scope of hydrazine components. 3 mmol scale. [a] 3.2 mmol scale, 2.58 *F*, 32 mA cm$^{-2}$, 32 °C, 3.9 eq styrene, solvent: *tert.*-butyl methyl ether; [b] by overoxidation of the corresponding pyrazoline; [c] solvent: dichloromethane.

Hydrazones of various aldehydes were converted in moderate to very good yields of up to 81 % (Scheme 3) Within the investigated substrates, 2,6-dichlorobenzaldehyde phenylhydrazone (**5i**) gave an impressive pyrazoline yield of 81 %. The *p*-halogenophenyl-substituted pyrazolines **6f–h** showed a clear trend of decreasing yields for the higher homologues (F 76 %, Cl 70 %, Br 61 %). Hydrazones of electron-deficient aldehydes were converted smoothly, whereby pyrazolines **6m–p** show increasing yields with increasing electron-withdrawing effect of the substituents. An analogous trend is seen for pyrazolines derived from *meta*-substituted hydrazones **6r–v**. In this case, even electron-rich hydrazones were converted successfully (**6u** 19 %, **6v** 64 %). This as well as the good results from the conversions of hydrazone **3** clearly indicates a beneficial effect of electron-withdrawing moieties on the C-terminus of the hydrazones. Despite the electrochemical sensitivity of the nitro[42] and pyridine moiety, examples **6p** and **6t** were obtained in slightly decreased yields of 53 % and 24 %, respectively. A quinoline as protected pyridine analogue was easily converted (**6s** 59 %).

A similar behavior was seen for the influence of the hydrazine component on the pyrazoline formation (Scheme 4). In general, halogen substituents on the hydrazine moiety were observed to be very beneficial for the pyrazoline formation. The *para*-halophenyl pyrazolines **8a–c** were obtained in excellent yields of 93 % (Br), 88 % (Cl) and 86 % (F). The surprisingly decreased yield for perfluorophenyl-substituted pyrazoline **8e** (25 %) may be explained by the excessive fluorination and an adjacent fluorophobic effect. Furthermore, the rather electron-deficient *p*-cyano-substituted derivative **8j** gave an excellent yield of 90 %, while methoxy or trifluoromethoxy substitution led to good to moderate yields (**8g** 53 %, **8h** 33 %). Again, the low yield of the nitro-substituted derivative **8m** (26 %) can be explained by the instability of nitro groups under electrochemical conditions. The loss of stabilization by an aromatic substituent led to a drop to moderate pyrazoline yields (**8i**, **8i′**, **8l**). Steric stabilization by a bulkier aliphatic group (methyl < cyclohexyl < *tert*-butyl) was not observed. Therefore, we concluded, that *N*-alkyl substituted hydrazones might be prone to undergo side-reactions or decomposition in the transition state, which apparently cannot be compensated by the increased steric stabilization of the *N*-alkyl nitrile imine. Similarly, attempts of intermediate stabilization by application of an acyl group or heteroanalogous moieties were also not successful. In the case of pyrazoline **8n** this can be explained by the leaving group characteristics of the tosylate preventing nitrile imine formation and, consequently, failure to form the pyrazoline. This leads to decomposition of the substrate similar to Bamford-Stevens type reactions.[43] In a similar way, acyl-substituted pyrazoline **8o** is not accessible using this method. The hydrazone can undergo oxidative cyclization to an azomethine imine intermediate, which is then subjected to further reactions.[44]

The reported findings regarding the substituent stabilization of the nitrile imines are in concordance with literature. DFT calculations by Ananikov et al. indicate that substituents even in *para*-position of the C-terminus can cause a tremendous change in the conformation and electronic structure of the nitrile imine and, thus, its reactivity.[45] These results could also offer an explanation for our observations, as for most hydrazones originating from an electron-rich aldehyde only traces of product could be observed. One exception is the formation of **6q** via intramolecular [3+2] cycloaddition in 56 % yield. This suggests that the pre-organization in this system prevents the decomposition of the intermediary formed nitrile imine due to faster cycloaddition. As it was observed within the dipolarophile scope (Scheme 2), the reaction with dimethyl fumarate as dipolarophile yielded the 4,5-*trans*-substituted pyrazoline **4n** exclusively. In contrast, the reaction of dimethyl maleate resulted in a mixture of the derived *cis*- and *trans*-substituted

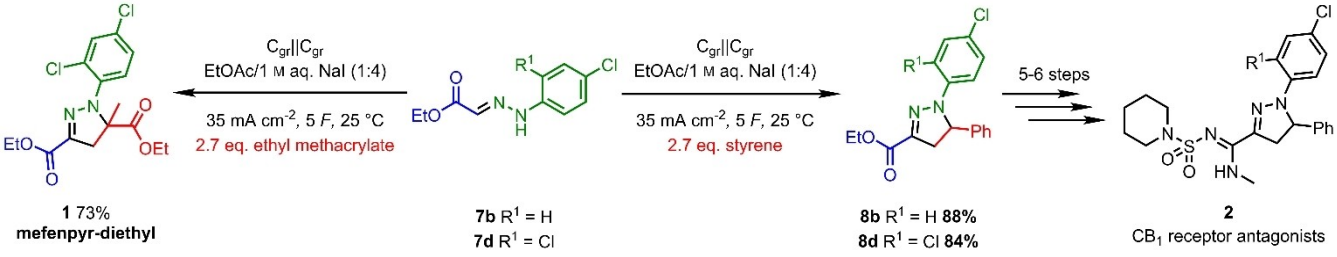



***Scheme 5.*** Proposed mechanism of the pyrazoline formation.

product **4m** (1.9:1 *cis*/*trans* ratio, as determined by $^1$H NMR). This gave rise to questions about the reaction mechanism. First, the electrolysis of dimethyl maleate alone or in the presence of ethyl pyruvate phenylhydrazone as oxidation inhibited analogue of hydrazone **3** was investigated. However, none of these conditions led to formation of the corresponding fumarate. Assuming a nitrile imine is formed in situ, the mechanism should follow the principle of a classic 1,3-dipolar cycloaddition and therefore provide stereoconservative characteristics as is seen for 1,2-*trans*-disubstituted alkenes. Employing cyclic alkenes resulted in *cis*-pyrazolines selectively, which further supports the theory of the formation of pyrazolines via classical 1,3-dipolar cycloaddition. In accordance with that, a hydrazonoyl iodide **III** (Scheme 5; e.g., **3a**: $R^1 = CO_2Et$, $R^2 = Ph$) was isolated from the reaction mixture, which allows nitrile imine **IV** formation via elimination of hydrogen iodide, comparable to conventional base promoted nitrile imine formation from hydrazonoyl chlorides. The importance of traces of base in the formation of the nitrile imine from the hydrazonoyl iodide as well as the hydrazonoyl iodide itself is easily demonstrated by performing the reaction in a divided cell, where no conversion was achieved.

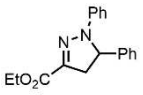
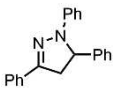
Generally, the role of nitrile imines in 1,3-dipolar cycloadditions and the reaction mechanisms thereof still attract attention. In particular, the theoretical aspects are not yet fully understood, as occurring violations of regioselectivity seem to support the formation of radical intermediates.[46] However, the successful synthesis of the cyclopropyl-substituted pyrazoline **6x** rather supports a non-radical mechanism, as it is unlikely to be accessible via radical pathways. Furthermore, computational approaches suggest a concerted cycloaddition that may allow for asynchronous bond formation depending on electronic as well as steric effects of the substituents.[47] A hydrazone comparable to **3** showed shorter C–C bond length than C–N bond length for the new bonds formed in the transition state, implying the formation of the C–C bond occurs first.[48] In the case of maleate as a dipolarophile, the reported asynchronous bond formation would explain the observed partial isomerization, as it enables formation of the energetically more favorable *trans*-state. Therefore, an oxidation of the hydrazone to the nitrile imine followed by a [3+2] dipolar cycloaddition (Scheme 5) is proposed in accordance with the studies on the conventional synthesis of pyrazoles from hydrazones via oxidation with NCS by Kobayashi and Togo.[49]

As going from 0.78 mmol to 3.9 mmol scale increased the yield of pyrazoline **4a** by 14 % resulting in 77 % isolated yield, the system was tested for scale-up robustness. Impressively, it was possible to run the synthesis of pyrazoline **4a** in a twelve-fold scale-up in a bipolar cell on 47 mmol scale (9 g hydrazone **3**, 10.6 g pyrazoline **4a**, 77 %) without detriment to yield (Table 1). Likewise, scale-up experiments were conducted for pyrazoline **6a**. Changing from 0.64 mmol to 3.2 mmol scale increased the yield by 26 % giving an isolated yield of 74 %. Further scale-up to 38 mmol scale (7.5 g hydrazone) still yielded 69 % (7.89 g) of pyrazoline **6a**. In this context, it was demonstrated that the workup




***Scheme 6.*** Synthesis of mefenpyr-diethyl (**1**, left) and $CB_1$ receptor antagonists (**2**, right). 3 mmol scale.

***Table 1:*** Scale-up of the syntheses of pyrazolines **4a** and **6a** from screening to decagram scale.

| batch-type electrolysis cell |  **4a** |  **6a** |
|---|---|---|
|  | 63 %[a]<br>0.49 mmol | 48 %[a]<br>0.31 mmol |
|  | 77 %[b]<br>3.02 mmol<br>0.890 g | 74 %[b]<br>2.36 mmol<br>0.704 g |
|  | 77 %[b]<br>36.0 mmol<br>10.6 g | 69 %[b]<br>26.4 mmol<br>7.89 g |

[a] GC yield determined with 1,3,5-trimethoxybenzene as an internal standard after external calibration. [b] isolated yield.

procedure can be changed from reverse-phase column chromatography to technically relevant recrystallization. The improved yields and the robustness of scale-up can be attributed to using more powerful cross-shaped stirring bars. In contrast to the ones used on small scale, the former enabled far better mixing and therefore, formation of a more finely dispersed emulsion. Moreover, the above results indicate that this transformation is extraordinarily robust and well suited for further scale-up. In parallel, recyclability of dipolarophile and supporting electrolyte were investigated for the formation of pyrazoline **6a**. On 38 mmol scale, it was possible to reisolate 2 eq of styrene by distillation of the crude product which means an effective consumption of only 1.9 eq styrene during the reaction. Freeze-drying of the aqueous phase yielded a quantitative amount of inorganic solid which was reused for synthesis of pyrazoline **4a** on a 3 mmol scale with a very good yield of 80 %. This is comparable to the obtained yield with fresh sodium iodide (77 %). Furthermore, this shows the exquisite efficiency of the simple workup, as the direct re-use of the recovered sodium iodide did not interfere with further conversions even of another substrate.

Moreover, the technical relevance of the presented reaction was demonstrated by synthesis of pharmaceutically and agrochemically relevant compounds. Pyrazoline **8d**, a key inter-mediate for the synthesis of a class of pharmaceutically active pyrazolines (see above)[18] was successfully synthesized in a very good yield of 84 %. Likewise, pyrazoline **8b**, a key intermediate for a comparable class of APIs, was also obtained in a very good yield of 88 % (Scheme 6). Finally, to demonstrate this reaction's application potential, the agrochemical mefenpyr-diethyl (**1**, Bayer CropScience), a pyrazoline of industrial relevance,[14–16] was synthesized in a very good yield of 73 % (Scheme 6) Moreover, the two-step synthesis relies on widely available platform chemicals with simple and facile workup strategies. Contrary to current conventional synthetic approaches, the use of hazardous chemicals can largely be avoided. Solvents and other adjuvants can be easily recycled by well-known processes such as distillation. As a result, the overall process was improved in terms of time-, reagent- and cost-efficiency, resulting in enhanced environmental sustainability.

## Conclusion

In summary, a facile strategy for the synthesis of agrochemically relevant and pharmaceutically interesting 1,3,5-trisubstituted 1*H*-4,5-dihydropyrazoles from readily available platform chemicals is presented.

The synthesis of more than 60 derivatives in moderate to excellent yields is demonstrated. The reaction features outstanding regioselectivity and allows the application of even sensitive alkenes under electrochemical conditions. Carefully chosen substrates as well as isolation of intermediates enabled the proposal of a profound reaction mechanism.

The successful synthesis of a commercially relevant agrochemical as a potential application manifested the relevance of the presented process. Implementation of a biphasic system minimized the workup to common, broadly applicable purification strategies, such as crystallization. Moreover, the recycling of the excess dipolarophile and the mediator was demonstrated with great success. The sodium iodide was quantitatively recovered and reused. The reaction was found to be extraordinarily robust towards scale-

up. Overall, the simple experimental set-up, use of graphite as a sustainable electrode material, application of green solvents as well as readily available and inexpensive electrolytes facilitates modern, ecologically, and economically benign synthetic processes for pyrazoline synthesis.

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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 Supporting Information of this article.

**Keywords:** Cycloaddition · Electrochemistry · Hydrazones · Oxidation · Pyrazolines

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