

Pyrazolidin-3,5-diones

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Access to Pyrazolidin-3,5-diones through Anodic N–N Bond Formation

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Abstract: Pyrazolidin-3,5-diones are important motifs in heterocyclic chemistry and are of high interest for pharmaceutical applications. In classic organic synthesis, the hydrazinic moiety is installed through condensation using the corresponding hydrazine building blocks. However, most *N,N'*-diaryl hydrazines are toxic and require upstream preparation owing to their low commercial availability. We present an alternative and sustainable synthetic approach to pyrazolidin-3,5-diones that employs readily accessible dianilides as precursors, which are anodically converted to furnish the N–N bond. The electroconversion is conducted in a simple undivided cell under constant-current conditions.

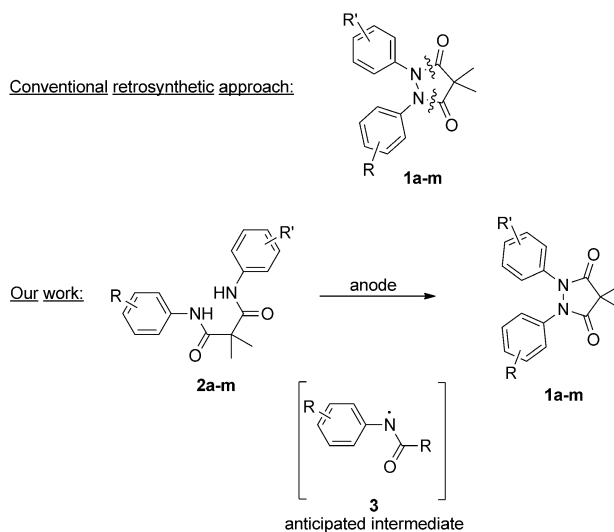
The discovery of pyrazolidin-3,5-diones dates back to Emil Fischer, who identified them as condensation products of malonic acid and phenylhydrazine in the late 19th century.^[1] After a more detailed study on synthetic routes and expansion of the scope in the first decade of the 20th century, their physiological effects were described in 1940 by Hans Ruhkopf, a pharmaceutical chemist.^[2] He pointed out the similarity of their biological profile to that of pyrazolones, which were already known as analgesic, anti-inflammatory, and antipyretic substances.^[3] This research led to the broad application of *N,N'*-diarylpyrazolidin-3,5-dione derivatives as analgesic drugs, with phenylbutazon as the most prominent drug for rheumatism. Even though the market for these compounds has decreased in the last decades owing to undesired side effects, they still play a major role in veterinary medicine. Moreover, possible applications for derivatives of pyrazolidin-3,5-diones are still a hot topic in contemporary research.^[4] Consequently, novel methods for a modular access to such heterocyclic systems are highly desired.

The retrosynthetic approach to pyrazolidin-3,5-diones is based on an activated malonic acid derivative and an *N,N'*-diarylhydrazine.^[5] Although this can be an effective approach for the synthesis of simple substrates, this approach exhibits two major drawbacks. First, most hydrazine building blocks are highly carcinogenic.^[6] Therefore, extra safety arrangements are required and up-scaling is problematic. Second, only simple hydrazine derivatives are commercially available and the use of derivatives with more-complex substitution

patterns can require upstream steps with negative effects on yield and efficiency.^[7]

Recently, electroorganic chemistry has experienced a renaissance in the field of preparative organic methodology.^[8] Conventional chemical oxidizers or reducing agents are replaced by electric current as an inexpensive and sustainable reagent. The generation of reagent waste can be avoided, leading to improved atom economy. By combining these advantages with long-lasting electrode materials, this method can generally be considered as “green chemistry”.^[9] Moreover, electrochemistry enables extraordinary reaction pathways that are not easily realized by conventional methods.^[10] Electroorganic conversions have also been established for the generation of heterocyclic compounds.^[11]

We present a preparative electroorganic route to 1,2-diarylpyrazolidin-3,5-diones using an undivided cell equipped with a very simple two-electrode arrangement. The reaction is based on an oxidative cyclization reaction between the two aryl-substituted nitrogen atoms of malonic dianilide derivatives (Scheme 1). Therefore, an amidyl radical (**3**) as an intermediate can be anticipated. The structure and reactivity of amidyl radicals have been broadly investigated in the past decades. They have mainly been explored in relation to rearrangements and intramolecular hydroamination reactions of alkenes.^[12] As a challenge for the chemical community, the efficient formation of these reactive intermediates has always been of great interest. Especially in the past 15 years, much work has focused on the conversion of non-activated amides or relatives thereof.^[13] Recently, the first electrochemical approaches to amidyl radicals have been reported, either as



Scheme 1. The conventional approach to pyrazolidin-3,5-diones and our novel approach.

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direct oxidation or as a ferrocene-mediated process.^[14] We were able to use these electrogenerated intermediates for an innovative and effective synthesis of pyrazolidin-3,5-diones. Only few comparable coupling reactions of nitrogen moieties are known for the electrochemical formation of alkyl hydrazines, tetrazenes, and thiaziridine-1,1-dioxides, and the anodic dimerization of carbazole derivatives.^[10c,15] The starting materials can be easily prepared in high yields starting from malonyl chloride and the corresponding aniline derivatives.^[16] In contrast to *N,N'*-diarylhydrazines, a broad variety of anilines is commercially available. To facilitate successful conversion, 2,2-dimethylmalonyl dianilides (**2a–m**) were used. The Thorpe–Ingold effect means that the smaller angle between the coupling moieties facilitates the cyclization tendency of these groups.^[17]

The electrochemical oxidation of amides and related substances is primarily known in the context of a Shono-type oxidation. This reaction is well explored and is mainly used for amidoalkylation reactions.^[18] For *N*-aryl amides with no abstractable hydrogen, several degradation reactions, which are strongly dependent on the substitution pattern on the aromatic ring, have been observed.^[19]

In initial screening experiments, several dianilides, solvents, and electrode materials were evaluated. For a time-efficient screening process, small undivided screening cells made of Teflon were employed.^[20] 2,2-Dimethyl-*N,N'*-di-(4-methylphenyl)malonic diamide (**2a**) served as test substrate for elaboration of the electrolysis conditions. Important electrolysis parameters are current density, anode material (graphite, boron-doped diamond, glassy carbon, or platinum), cathode material (platinum, leaded bronze, graphite, or nickel), and solvents, as well as supporting electrolytes at different concentrations (TBABF₄, TBAPF₆, TBAClO₄, triethylmethylammonium methyl sulfate, and LiClO₄; TBA = tetrabutylammonium). First optimization studies were performed in methanol, since it showed a favorable side-product profile. However, high amounts of charge were necessary and only low yields of under 10% were realizable in this system. Moreover, most dianilides are poorly soluble in methanol. After exploring various combinations of different dianilides, solvents, and electrode materials, the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) delivered promising yields and a good solubility. In electroorganic studies, this particular fluorinated solvent turned out to be outstandingly stable.^[21] The optimized electrolysis conditions are displayed in Scheme 2.

The optimization process revealed some interesting features of the conversion. Low current densities of

0.5 mA cm⁻² provided the best yields, and even slightly elevated current density had a tremendous effect onto the yield (Table 1). Interestingly, a low concentration of 0.01 M of the supporting electrolyte was beneficial and led to a slight increase in yield (Table 2). These low concentrations of

Table 1: Influence of the current density on the yield of derivative **1a**.^[a]

Entry	Current density [mA cm ⁻²]	Yield ^[b] [%]
1	0.5	70
2	1	57
3	2	30

[a] 0.01 M TBAPF₆, anode: graphite, cathode: platinum. [b] ¹H NMR yield, standard: 2,4,6-triiodophenol.

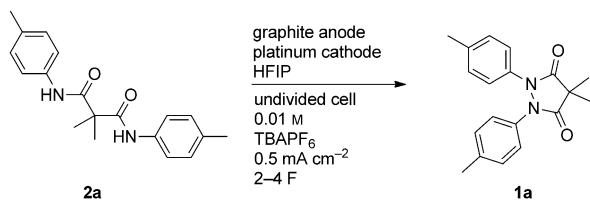
Table 2: Influence of the supporting electrolyte concentration on the yield of derivative **1a**.^[a]

Entry	Supporting electrolyte concentration [mol L ⁻¹]	Yield ^[b] [%]
1	0.1	69
2	0.01	70

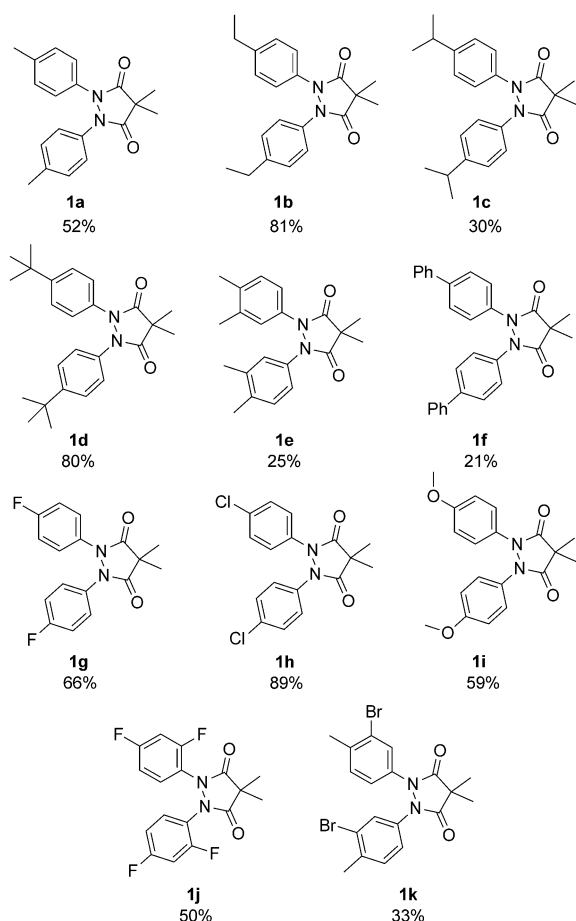
[a] TBAPF₆, anode: graphite, cathode: platinum, current density: 0.5 mA cm⁻². [b] ¹H NMR yield, standard: 2,4,6-triiodophenol.

supporting electrolyte facilitate the workup and lead to a more sustainable atom economy. The solvent is quantitatively recycled by distillation to minimize the fluorine footprint. The cathode material exhibits significant influence onto the anodic process. In comparison to graphite, platinum as a cathode required a much lower applied charge for full conversion to be reached. Additionally, only undivided cells enabled this conversion, thus supporting the crucial role of the cathode within the system. This beneficial effect is found when the counter reaction or species generated facilitate the overall transformation.^[10d] Here, the specific nature of both the solvent and the cathode material play a role: HFIP provided the best results in combination with platinum cathodes. The acidic character of HFIP (*pK_a* = 9.3)^[21d] in combination with the low overpotential for hydrogen evolution at platinum cathodes leads to the generation of alcoholate anions. This basic milieu facilitates the anodic oxidation of amide nitrogen through prior deprotonation.

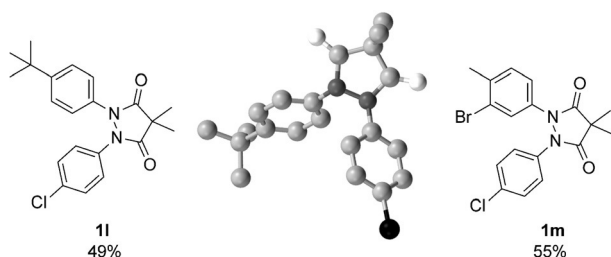
The elaborated electrolysis conditions were adapted to a variety of substituted 2,2-dimethylmalonic dianilides, leading to a wide substrate scope for this novel electroorganic transformation. (Scheme 3). The results indicate the general nature of the method regarding the substitution pattern on the aromatic ring. Most substrates could be converted in good to excellent yields, and several heterofunctionalized substitutions were tolerated, for example, fluoro (**1g**, **1j**), chloro (**1h**, **1i**), bromo (**1k**) and methoxy (**1i**) substituents. Moreover, the reaction also tolerates the introduction of an additional aromatic system to give a biphenyl substitution pattern (**1f**). Another interesting result is the successful conversion of two non-symmetric substrates (**1l** and **1m**) as a further argument for the diversity of the method (Scheme 4). In particular, the introduction of the bromo substitution (**1m**) broadens the



Scheme 2. Anodic cyclization to 2,2-dimethyl-*N,N'*-(4-methylphenyl)-pyrazolidin-3,5-dione.



Scheme 3. Substrate scope of the electrochemical N–N coupling to give symmetrical pyrazolidin-3,5-diones.



Scheme 4. Successfully synthesized non-symmetric pyrazolidin-3,5-diones. Center: molecular structure of derivative **1l** by X-ray analysis.

scope for regioselective follow-up reactions. The exact molecular structures of the derivatives were determined by the substituents on the aromatic ring. While the planarity of the heterocycle in substrates **1e**, **1i**, and **1l** is distorted, the pyrazolidin-3,5-dione system of derivative **1f** is planar. Interestingly, one of the two biphenyl motifs of molecule **1f** is propeller twisted, while the other one is not, thus leading to an interesting packing pattern (the detailed structure is shown in the Supporting Information).

Nevertheless, a tremendous effect of the substitution pattern of the aromatic ring on the yield was observed.

Unexpectedly, activation of the aromatic ring does not correlate with a more effective conversion. Specific stabilization of the *para* position and the influence of oxidizable benzylic positions seems to be more important. Substrates with an unsubstituted benzylic position showed lower yields in comparison to those with heteroatom-functionalized or quaternary carbon atoms. The negative effect of additional or more-stabilized benzylic positions is apparent from molecules **1a**, **1c**, **1e**, and **1k**. For derivative **1k**, the bromo substitution seems to have a further negative effect. Interestingly, ethyl substitution (**1b**) increased the yield to 81 % in comparison to methyl substitution (**1a**, 52 % yield) and 2-methylethyl substitution (**1c**, 30 % yield). A possible rationale in this particular case is competition between steric effects and stabilized benzylic positions.

Regarding the mechanism, two potential routes can be postulated (see the Supporting Information). In accordance with previous postulations for anodic oxidations, subsequent oxidation and deprotonation of the amidic nitrogen atom is conceivable.^[14] In basic media, the presence of deprotonated amide functionalities can be assumed at equilibrium. In addition to oxidation at the anode, intramolecular nucleophilic attack of the other amide function is thereby facilitated. A second option is the formation of a diamidyl radical species, which forms the pyrazolidin-3,5-dione through recombination. The thermal homolytic cleavage of *N,N'*-diarylhydrazines is an equilibrium process.^[22] This indicates an analogous backward reaction between two amidyl radicals.

Dianilides with an unsubstituted *para* position or an *ortho* methyl group failed under a broad spectrum of different conditions owing to unselective degradation or oligomerization. The fact that a change in the conditions had no effect on the negative outcome of these reactions suggests a substrate-induced obstacle. In most other solvents, only traces of product were detectable and the dianilides were badly soluble.

In conclusion, we established a novel access to 1,2-diarylpyrazolidin-3,5-diones without the need for toxic hydrazine building blocks. Combining the sustainability of electrochemical conversions with easily accessible and inexpensive starting materials, this approach is a favorable alternative to the conventional methods. A broad substitution pattern is tolerated and non-symmetric substrates can also be converted. Naturally, further work needs to be done to elucidate the mechanism.

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