Design of Experiments-Based Optimization of an Electrochemical Decarboxylative Alkylation using a Spinning Cylinder Electrode Reactor

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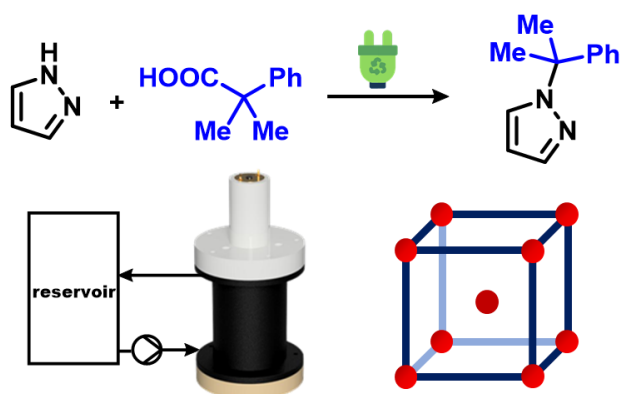
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ABSTRACT

A design of experiments model has been developed to optimize an electrochemical protocol for the decarboxylative N-alkylation of pyrazole in a spinning cylinder electrode reactor. The electrochemical reaction requires the incorporation of molecular sieves as an additive to ensure the absence of moisture and prevent potential electrode corrosion issues. The spinning cylinder electrode reactor proved to be an idea platform to scale up this transformation, involving a suspension of solid particles, to multigram scales. The reaction model, which showed an excellent fitting with the experimental data, provided insights on the effect of important electrolysis parameters unique to this reactor design, such as the electrode spinning speed, on the reaction conversion and selectivity. Furthermore, the design of experiments also supplied optimal electrolysis parameters for this complex multivariable reaction system, resulting in full conversion of the substrate and excellent selectivity for a 600 mL volume reaction in recirculation flow mode, with 94% isolated yield for the target N-alkylated product.

Keywords: design of experiments; electrochemical synthesis; sustainable chemistry; anodic oxidation; spinning cylinder electrode

INTRODUCTION

Preparation of organic compounds using electrochemical methods presents several advantages over conventional procedures that utilize conventional reagents.[1] Oxidizing agents, for example, are often hazardous materials that need to be handled with care due to their toxic and corrosive character. Oxidation reactions in organic synthesis are particularly problematic, as mixing oxidants with flammable solvents pose an inherent risk, which may be exacerbated on large scales.[2] In contrast, electrochemical synthesis achieves redox processes using electrical current instead of reagents and thus it is considered as an inherently safe technique.[3] Importantly, electrolysis can be scaled-up with relative ease from the laboratory scale to multi-100 g or kilogram amounts.[4,5] Due to these advantages, synthetic organic electrochemistry has gained significant attention over the past few years as a sustainable alternative to conventional synthetic technologies.[6]

The optimization of electrochemical processes is a relatively complex task. In addition to the typical reaction parameters of a conventional transformation, such as reaction temperature, concentration or reagent stoichiometry, other variables play a significant role on the reaction outcome, including the nature of the electrode materials, interelectrode gap, current density or the amount of charge passed through the mixture. Under these circumstances, simple "one-factor-at-a-time" optimizations may result in too large a number of experiments to achieve the best performing conditions, which often may not even be identified using this approach. In recent years, Design of Experiments (DoE) methods for the optimization of electrochemical processes have been applied by several groups,[7,8] providing a better understanding of complex multi-variable systems. An important aspect of DoE-based optimization of electrochemical processes is that, apart from locating optimal reaction parameters, it also provides an empirical model of the system, including the effect of the variables on the reaction outcome and any potential correlation between them.

We became interested in the development of a scalable, multigram method for the N-alkylation of pyrazole (**1**). Baran and coworkers recently reported an electrochemical protocol that utilizes carboxylic acids such as **2** as alkylating reagents (Scheme 1). The method is based on the 2-electron oxidative decarboxylation of the aliphatic carboxylic acid, generating a carbocation intermediate which is trapped by pyrazole (i.e., a Hofer-Moest-type electrochemical reaction[10]). The process, which operates in DCM as the solvent, is highly moisture sensitive, as the carbocation generated can be trapped by water instead of the heterocycle, resulting in an alcohol side product. To alleviate this issue, the electrochemical protocol includes molecular sieves as an additive, resulting in a suspension of the solid in the liquid solution.

Scheme 1. Alkylation of pyrazole (**1**) via oxidative decarboxylation of **2**.
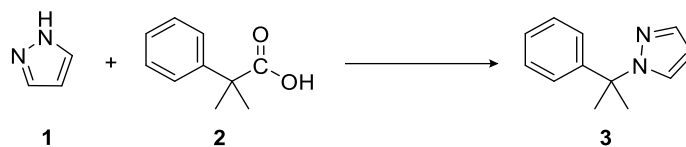
Scale up of electrochemical reactions involving solid-liquid heterogeneous mixtures can be challenging using traditional parallel-plate flow electrolysis cells. This type of reactor is characterized by very narrow interelectrode gaps (often below 1 mm), which provides very high electrode surface area to reactor volume ratios and thus very efficient electrolytic processes.[11] However, due the narrow interelectrode gap and static nature of the electrodes, the presence of solids can easily cause clogging of the reactor and electrode fouling. We have recently developed a scalable electrolysis cell that overcomes the main drawbacks of parallel plate flow reactors, including the processing of solid suspensions.[12,13] The cell features a moving cylindrical electrode, which spins around its axis and is concentrically inserted into a static pipe-shaped counter electrode.[12] The spinning cylinder electrode diameter is 10 mm narrower than the static counter electrode, providing an interelectrode gap of 5 mm. The rotating motion of the inner electrode, combined with a mixing unit attached to its bottom end, provides

excellent mixing and enables very efficient agitation of solids in suspension. Thus, we anticipated that such reactor platform would be suitable for the scale up of an electrolysis process involving suspensions of molecular sieves.

Notably, the use of a spinning cylinder electrochemical cell in flow mode adds further complexity to the optimization of the reaction conditions. Apart from all the reaction variables mentioned above for electrolysis processes (i.e., those involved in conventional chemistry plus current density and amount of charge), this system introduces two additional parameters that have a significant influence on the reaction outcome: the spinning speed of the working electrode and the flow rate with which the reaction mixture is processed. Moreover, it would be expected that several of the parameters are interconnected. For example, the spinning speed should influence the optimal current density and flow rate, etc.

Herein, we present the optimization of an electrochemical protocol for the N-alkylation of pyrazole in a spinning cylinder electrochemical reactor (SCER) using a DoE approach. Several reaction parameters, such as the electrode materials, were pre-screened in a small-scale batch vessel. Then, the process was transferred to the SCER in flow mode and fully optimized using a full-factorial DoE approach. The data was fitted to a model using multiple linear regression (MLR). The model revealed that the spinning speed and amount of charge were the most influential parameters for the reaction outcome, and that they influenced each other. The model also predicted optimal parameters for the electrolysis process, which resulted in an excellent isolated yield (94%) for the alkylation product in a multigram scale experiment. Notably, to the best of our knowledge, this study is the first to provide insights into the relation between several reactor parameters in spinning cylinder electrochemical reactors for synthetic organic electrochemistry.

RESULTS AND DISCUSSION

Preliminary Optimization in a Small-Scale Beaker Cell. Prior to attempting the electrochemical reaction in a spinning cylinder electrode reactor, it was first evaluated in a small-scale undivided cell (5 mL IKA ElectraSyn 2.0 vial). The purpose of this preliminary study was to screen for reaction conditions that are reactor-independent, such as the optimal electrode material. More importantly, we wanted to assess whether any small amount of corrosion or fouling occur on the surface of the working electrode, as such an undesired effect could have a more severe impact on a larger scale system, particularly in flow mode. The decarboxylative coupling of pyrazole (**1**) and 2-phenylisobutyric acid (**2**) was selected as a model reaction (Table 1). This transformation has been reported to perform well in DCM as the solvent and 2,4,6-collidine as the base using graphite and nickel as the anode and cathode materials, respectively.[9] Based on the original work, no attempts to modify the solvent system, base or supporting electrolyte were made. When the standard conditions were applied, the reaction performed very well in terms of conversion and selectivity (Table 1, entry 1), but visible corrosion of the surface of the graphite anode was observed (Figure S1). This effect could be ascribed to the fact that the reaction mixture can penetrate the porous graphite material and react a few micrometers below the surface, detaching electrode particles as CO_2 bubbles are generated (graphite is made of sintered particles).[14] Indeed, no corrosion was observed under the same conditions when the standard graphite was substituted by non-porous resin-filled impervious graphite (Table 1, entry 2). A three-dimensional electrode, graphite felt, was also tested. The felt provided diminished selectivity compared to solid graphite (entry 3). Importantly, although conversion and selectivity were not affected when the molecular sieves were omitted (entry 4), corrosion of the anode was again observed. In this case, the corrosion could be due to water oxidation, which generates CO_2 in combination with graphite, consuming part of the electrode surface.[15] This experiment confirmed that the addition of molecular sieves is critical to ensure that electrodes remain unaffected under the reaction conditions, an essential feature for flow experimentation. Notably, technical grade DCM could be used as well for this

transformation, as the presence of molecular sieves ensured that any traces of water are removed from the solution (entry 5). A reduction of the supporting electrolyte loading to 0.025 M did not have, in principle, a negative effect on the reaction outcome (entry 6). However, a significant increase in the cell voltage from 7 V to 12 V was observed, which could lead to increased electrolysis temperatures on large scale. Thus, the concentration of nBu_4NPF_6 remained 0.05 M in subsequent experiments. Modification of the amount of base or carboxylic acid **2** (entries 7 and 8) decreased the conversion and selectivity. Increase of the current density to 10 mA/cm^2 slightly decreased the selectivity (entry 9), while further increase to 13 mA/cm2 resulted in rapid degradation of the anode surface (entry 10).

Table 1. Small scale optimization of the reaction conditions for the electrochemical alkylation of 1 with 2.[a]
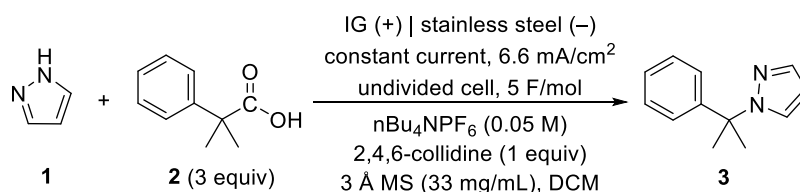
entry	deviations from scheme	conv (%)[b]	select (%)[c]	anode corrosion/fouling
1	graphite cathode	99	99	yes
2	none	99	99	no
3	graphite felt anode	99	86	no
4	no molecular sieves	99	99	yes
5	DCM tech. grade	99	99	no
6	0.025 M nBu_4NPF_6	99	99	no
7	0.5 equiv 2,4,6-collidine	79	89	yes
8	2 equiv **2**	99	94	no
9	10 mA/cm^2	99	98	no
10	13 mA/cm^2	-	-	yes

Transfer of the Electrochemical Decarboxylative Alkylation to the Spinning Cylinder Electrode Reactor and Design of Experiments Model Generation. The spinning cylinder electrode design, which has been described in detail in a previous publication,[12] features an interelectrode gap of 5 mm, which is the same distance as in the undivided IKA ElectraSyn 2.0 vials. Thus, the reaction conditions pre-optimized as described above could be readily transferred to the system. A reactor featuring a 94 cm^2 working electrode was selected for this transformation. The electrochemical reactor setup was operated in flow recirculation mode (see Figure S2). In a typical electrolysis procedure, a reaction mixture of 600 mL volume was placed in a stirred reservoir. Good stirring was maintained both in the reservoir and the electrochemical cell at all times to avoid settling of the molecular sieve particles during operation.

A design of experiments was performed using the software package Modde® to build a reaction model, with the objective of assessing the effect of several reaction variables on the reaction outcome and locating the optimal reaction conditions. For this purpose, several of the optimal parameters that had been pre-screened in small scale were kept constant (i.e., reaction stoichiometry, solvent, electrode materials). Thus, the experimental design focused on the electrolysis parameters that are specifically relevant to the use of the spinning cylinder electrode reactor, namely spinning speed (rpm), amount of charge (F/mol), flow rate (mL/min) with which the mixture is recirculated, and current density (mA/cm^2). Then, a design space containing center points as well as a high and low value for each of the 4 parameters was created (Table 2). The center points for the current density and the amount of charge were based on the small-scale experiments (6.6 mA/cm^2 and 4 F/mol, respectively). For the electrode spinning speed and pump flow rate, the selected center points were based on previous experience with the system.[12,13]

Table 2. Low, center and high values used for each of the parameters used for the optimization of the electrochemical reaction in a spinning cylinder reactor in flow mode.[a]

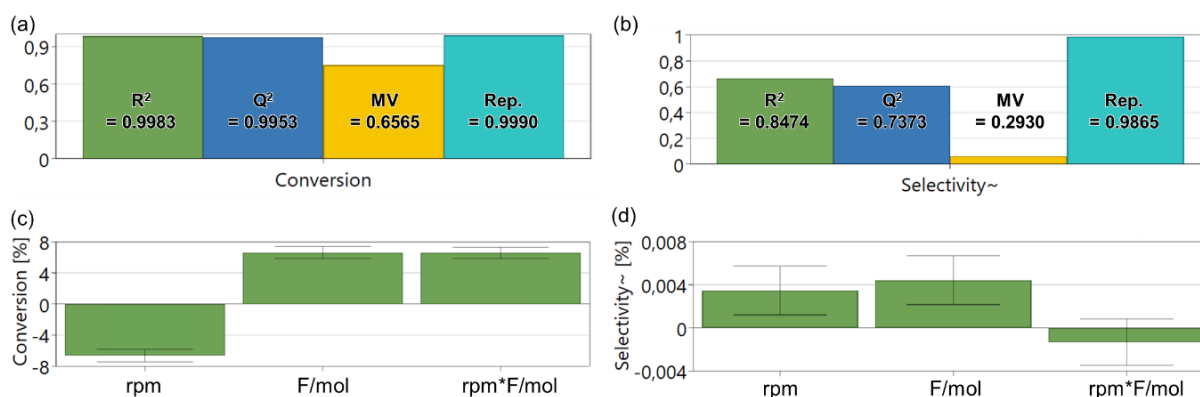| Parameter	-1	0	1
spinning speed (rpm)	300	600	900
charge (F/mol)	2	4	6
flow rate (mL/min)	50	100	150
current density (mA/cm^2)	3.3	6.6	9.9

[a] Conditions: 80 mmol **1**, 600 mL reaction mixture. 94 cm^2 surface area working electrode reactor, constant current.

A full factorial design with 4 factors and 2 levels for each factor (2^4 experiments) with 3 center points was generated giving a total of 19 experiments. Each of the 19 experiments was performed on a 600 mL scale in flow mode. Once the electrolysis time had been elapsed, the power supply was turned off and 1,3,5-trimethoxybenzene was added to the reservoir as an internal standard. The pumps and the mixing were maintained for 5 min to ensure homogenization of the standard in the reaction mixture. Then, an aliquot of the mixture was analyzed by crude ^{1}H NMR. Crude ^{1}H NMR monitoring was selected to minimize sample manipulation and increase the robustness of the data. The results of the experiments are collected in Table S1.

The data for the optimization (Table S1) were fitted using the software package MODDE® (version 11, Umetrics).[16] Models were obtained using multiple linear regression (MLR), including main and interaction terms. Terms with a potential contribution to the overall response of zero were removed from the model. Additionally, as suggested by the software

using the Tukey's test, one of the 19 data points was removed from the model fitting as it provided an anomalous result, probably due to experimental error (experiment 14, Table S1). Removal of the datapoint resulted in a significantly improved overall fit (R^2).

The model fitting coefficients for the conversion (Figure 1a) and selectivity (Figure 1b) revealed high correlation for the two outputs ($R^2 > 0.7$ in both cases) as well as good predictive capability ($Q^2 > 0.5$). Notably, a model validity (MV) coefficient of 0.29 was obtained for the selectivity (Figure 1b). Full details on the model coefficients are collected in Tables S2 and S3. This value was ascribed to the good replicates observed. Interestingly, the spinning speed (rpm) showed a negative effect when analyzed as an independent factor on the reaction conversion (Figure 1c). It is not clear why this effect was observed. Indeed, reaction data (Figure S1) showed excellent conversions at 300 rpm and 600 rpm, but poor conversion values at 900 rpm. On the other hand, the spinning speed had a positive effect on the reaction selectivity (Figure 1d) due to the enhanced mixing, which was an anticipated outcome. Furthermore, as expected, the amount of charge (F/mol) significantly influenced the conversion in a positive manner. The effect on the selectivity was also positive (Figure 1d). This was a surprising outcome, as generation of intermediates is not expected in this transformation. The electrode spinning speed and amount of charge showed a positive combined effect on the conversion (Figure 1c), i.e., at high conversions, when larger amounts of charge had been applied, increases of the spinning speed had a positive effect, again due to enhanced mass transfer. The combined effects of the spinning speed and the amount of charge on the conversion and selectivity are depicted in Figure 2.

Figure 1. Summary of the model fitting data for the conversion (a) and selectivity (b) values for the electrochemical alkylation of pyrazole (**1**) and effect of the relevant reaction parameters on the reaction outcome (c, d). R^2: coefficient of determination; Q^2: predictive capability. MV: model validity; Rep.: reproducibility.
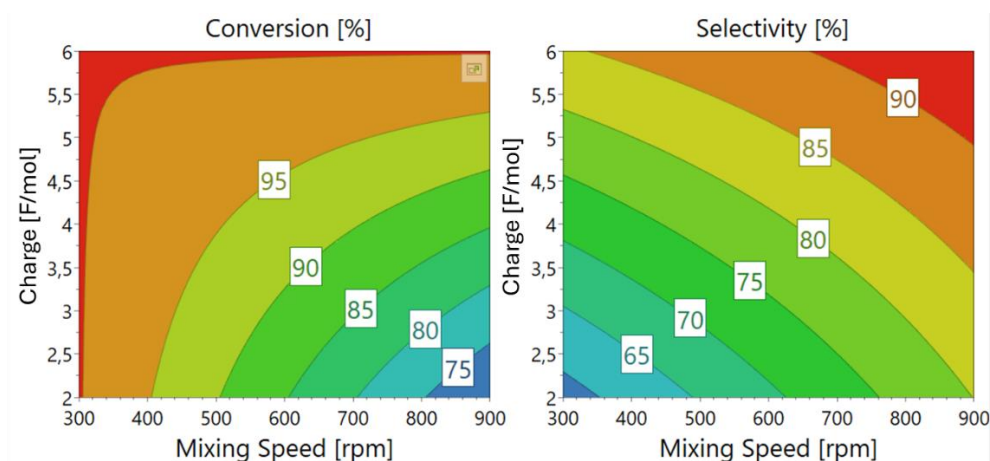
Figure 2. Model contour plots for the conversion and selectivity vs mixing speed (rpm) and amount of charge (F/mol).

Design of Experiments – Model Validation and Parameter Optimization. Once the reaction model was obtained as described above, it was validated by comparing predicted reaction data with experimental results. In particular, the predicted reaction parameters needed to obtain 85% conversion and 85% selectivity were outputted from the model (Figure 3a). We were interested in experimentally validating our model by selecting a response in a design space region that would be most sensitive to a change in the reaction conditions. Thus, we used the optimizer

(target objective) in MODDE® to predict conditions that were estimated to give this result.. The reaction parameters suggested by the model to achieve these results were a spinning speed of 854 rpm, an amount of charge passed through the reaction mixture of 3.8 F/mol with a current density of 4.9 mA/cm^2 and recirculation of the electrolyte at 69 mL/min. Gratifyingly, when a 600 mL reaction mixture was processed under these conditions, 86% conversion and 90% selectivity was obtained (^{1}H NMR data with 1,3,5-trimethoxybenzene as internal standard), which confirms an excellent fit between predicted values and experimental data.
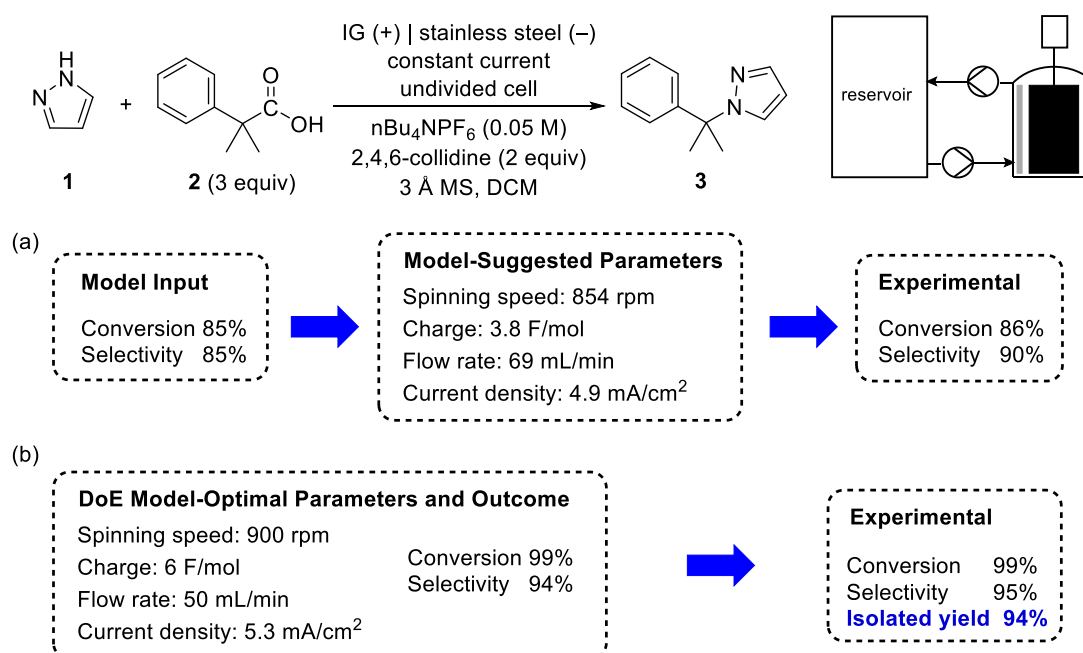
Figure 2. (a) Validation of the DoE-based model by comparing the experimental and an inputted predicted outcome and (b) optimal electrolysis parameters obtained from the model.

The DoE-based reaction model was also utilized to locate the optimal reaction parameters (Figure 3b). For this purpose the software package MODDE utilizes the Nelder-Mead method (also known as the downhill simplex method) on the fitted response surface.[17] Full conversion of the starting material and an excellent 94% selectivity was predicted at an electrode spinning speed of 900 rpm, a charge of 6 F/mol using a current density of 5.3 mA/cm^2 and a recirculation flow rate of 50 mL/min. Processing of a 600 mL reaction mixture under

these conditions provided full conversion of the substrate and a selectivity of 95%, which is an excellent fit with the model-predicted outcome. A fraction of the crude reaction mixture (10% of the total volume) was purified by column chromatography, providing 698 mg of pure product **3** (94% isolated yield) (6.98 g in total).

It should be emphasized that the DoE optimization revealed reaction conditions that provided excellent results which would not have been found using a traditional "one variable at a time" approach. For example, screening of the spinning speed using a charge of 2 F/mol in each experiment would have resulted in the conclusion that high spinning speeds (i.e., 900 rpm) are detrimental to the reaction conversion. However, the DoE-based model showed that high spinning speeds are favorable when combined when larger amounts of charge passed through the reaction mixture. Thus, this work exhibits the importance of model-based optimization approaches for multi-parameter systems in which the variables may be interconnected.

CONCLUSIONS

In summary, we have developed a multi-gram procedure for the electrochemical N-alkylation of pyrazole in a spinning cylinder electrode reactor in flow recirculation mode. The reaction significantly benefits from the use of molecular sieves as an additive, providing both improved selectivity and, importantly avoiding any corrosion of the graphite electrodes. As the molecular sieves form a suspension in the reaction mixture, the spinning cylinder electrode reactor technology is suitable for processing large reaction mixtures, as it can readily handle solids in suspension without the potential clogging issues of traditional parallel plate reactors. Throughout this work, several 600 mL volume reaction mixtures were processed in a 54 mL reactor in flow mode without issues. To study the connections between the different electrolysis parameters and obtain optimal results, the electrochemical reaction was optimized using a design of experiments-based model. While the effect of some of the reaction parameters was

expected, such as improved selectivity at high spinning speed, other factors were revealed by the model. For example, a correlation between the spinning speed and the amount of charge passed through the mixture was found, whereby high spinning speeds in combination with high amounts of charge provide excellent conversion and selectivity. The reaction model permitted the identification of optimal reaction parameters that provided 94% isolated yield of the alkylation product in a multi-gram experiment.

EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR spectra were recorded on a 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. For HPLC analysis, the separation was carried out on a Macherey-Nagel Nucleodur C18 HTec column (150 mm × 4.6 mm, particle size 5 μm) at 37 °C using mobile phase A (H_2O/acetonitrile (9+1 v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 0.6 mL min^{-1}. The following gradient was applied: hold 5% of B for 2 minutes, then linear increase from 5% B to 20% B in 6 min, followed by a linear increase from 20% B to 100% B in 1 min, then hold 100% B for 1 min, followed by column equilibration time at 5% B for 5 min. The detection of compounds was accomplished by diode array detector. All chemicals were obtained from standard commercial vendors and were used without any further purification. Small scale electrochemical reactions were carried out in 5 mL IKA ElectraSyn 2.0 vials. Stainless steel electrodes for small scale experimentation were acquired from IKA. The spinning electrode reactor static electrode, used as the counter electrode, was made of 316 stainless steel, purchased from Hubs. Impervious graphite for small scale experimentation were purchased from Graphtek LLC (FC-GR grade, SKU: GT001735).

Impervious graphite cylinders for the spinning electrode reactor were acquired from GAB Neumann. Graphite felts AvCarb G280A was obtained from the Fuel Cell Store.

Caution: the electrochemical oxidations described herein produce stoichiometric amounts of H_2 gas as byproduct. Appropriate dilution of the gas generated with N_2 to a concentration below the explosion limit is highly recommended, especially during multigram experimentation.

Preliminary Optimization of the Electrochemical Synthesis of 3 in a 5 mL Beaker Cell (Table 1). Pyrazole (**1**) (14 mg, 0.2 mmol) and the corresponding amounts of 2-methyl-2-phenylpropanoic acid (**2**), 2,4,6,trimethylpyridine, nBu_4NPF_6 and powdered 3 Å molecular sieves were placed in a 5 mL undivided IKA ElectraSyn 2.0 vial and mixed with 3 mL of DCM. Then, the mixture was electrolyzed under constant current with a stirring of 900 rpm until the desired amount of charged had been passed. When electrolysis was completed, a 50 μL aliquot of the reaction mixture was diluted with MeCN and analyzed by HPLC.

Experimental Design Optimization of the Electrochemical Synthesis of 3 in a in a 54 mL Spinning Cylinder Electrode Cell (Tables S1 and 2). A jacketed stirred vessel was loaded with pyrazole (**1**) (2.72 g, 40 mmol), 2-methyl-2-phenylpropanoic acid (**2**) (19.7 g, 120 mmol), 2,4,6-trimethylpyridine (5.3 mL, 40 mmol), nBu_4NPF_6 (11,6 g, 30 mmol), powdered 3 Å molecular sieves (10 g) and DCM (600 mL). The reaction mixture was pumped to the cell, which was equipped with a 94 cm^2 impervious graphite electrode, using a peristaltic pump (Masterflex L/S). The flow rate of the pump was set according to Table S1. Simultaneously, an outlet tube, connected to a second pump, was introduced into the cell via a top port. The second pump was set to a flow rate slightly larger than the input pump, to ensure a constant level of liquid within the reactor. The outlet line was connected back to the solution reservoir. Once the system had been filled with liquid and recirculation of the electrolyte was established, spinning of the electrode was initiated (Table S1) as well as electrolysis under constant current. When the desired amount of charge had been passed, the power supply was turned off. Then, 1,3,5-

trimethoxubenzene was added to the reservoir, and the mixture recirculated for at least 5 min to homogenize it. An aliquot of the crude mixture was analyzed by ^{1}H NMR.

Electrochemical Synthesis of 3 in a in a 54 mL Spinning Cylinder Electrode Cell under Optimal Conditions. A jacketed stirred vessel was loaded with pyrazole (**1**) (2.72 g, 40 mmol), 2-methyl-2-phenylpropanoic acid (**2**) (19.7 g, 120 mmol), 2,4,6-trimethylpyridine (5.3 mL, 40 mmol), nBu$_4$NPF$_6$ (11,6 g, 30 mmol), 3 Å molecular sieves (10 g) and DCM (600 mL). The reaction mixture was pumped to the cell, which was equipped with a 94 cm^2 impervious graphite electrode, using a peristaltic pump (Masterflex L/S) with a flow rate of 50 mL/min. Simultaneously, an outlet tube, connected to a second pump, was introduced into the cell via a top port. The second pump was set to a flow rate slightly larger than the input pump, to ensure a constant level of liquid within the reactor. The outlet line was connected back to the solution reservoir. Once the system had been filled with liquid and recirculation of the electrolyte was established, spinning of the electrode was initiated at a rate of 900 rpm as well as electrolysis under a constant current of 503 mA (5.3 mA/cm^2). When 6 F/mol of charge had been passed the power supply was turned off. The input pump was reversed to return all the reaction mixture to the solution reservoir. A fraction of the crude mixture corresponding to 10% of the total volume was evaporated under reduced pressure. The residue was extracted in DCM/aqueous NaHCO$_3$. The organic phase was dried over Na$_2$SO$_4$, evaporated, and the residue further purified by column chromatography, yielding 698 mg of the pure product **3** (94% isolated yield, 6.98 g extrapolated to the complete crude mixture). ^{1}H NMR(300 MHz, Chloroform-d) δ 7.62 (d, J = 1.5 Hz, 1H), 7.51 (m, 1H), 7.35–7.31 (m, 1H), 7.30–7.23 (m, 2H), 7.06 – 7.03 (m, 2H), 6.33-6.31 (m, 1H), 2.01 (s, 6H). ^{13}C NMR(75 MHz, Chloroform-d) δ 146.8, 138.8, 128.4, 127.7, 127.2, 125.0, 105.2, 63.5, 29.8. These data agree with those previously reported in the literature.[9]

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Supplementary pictures and tables, ^{1}H-NMR and ^{13}C-NMR spectra of the prepared product.

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