Electronic Supplementary Information (ESI)

From Screening to Hectogram Scale: Sustainable and Scalable Electrochemical Synthesis of Mefenpyr-diethyl

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S1. General Information

Unless otherwise stated, all chemicals were purchased and used without further purification. Anhydrous solvents were either purchased or dried over standard drying agents and freshly distilled prior to use.
Reactions were monitored by TLC (Silica gel 60 F_{254}, *Merck KGaA*, Darmstadt, Germany), GC (GC-2025, *Shimadzu*, Kyoto, Japan, quartz capillary column HP-5MS, *Agilent Technologies*, Santa Clara, California, USA), GC-MS (GCMS-QP2010, *Shimadzu*, Kyoto, Japan, quartz capillary column HP-5MS, *Agilent Technologies*, Santa Clara, California, USA) and HPLC-MS (LC-20A Prominence, *Shimadzu Deutschland GmbH*, Duisburg, Germany, UV/VIS-detector SPD-20A/AV (*Shimadzu Deutschland GmbH*, Duisburg, Germany), LCMS-2020 Single Quadrupole (*Shimadzu Deutschland GmbH*, Duisburg, Germany) and an Eurospher II 100-5 C-18-Trennsäule column (*Knauer Wissenschaftliche Geräte GmbH*, Berlin, Germany, length 150 mm, diameter 4 mm, pore size 100 Å, particle size 5 µm).
Flash column chromatography was performed on Silica Gel 60 M (40–63 µm, *Machery-Nagel GmbH & Co.*, Düren, Germany) with a *Büchi* Sepacore system with *Büchi* Control Unit C-620, *Büchi* UV photometer C-635, *Büchi* fraction collector C-660 and two *Büchi* Pump Modules C-605 (*Büchi-Labortechnik GmbH*, Essen, Germany) or on a pre-packed PURIFLASH C18-HP 30 UM F0080 flash column (*Interchim*, Montluçon Cedex, France) with a *Büchi* Sepacore system in the same setup as described before.

^{1}H, ^{13}C, and 2D NMR spectra were acquired on a *Bruker* Avance III HD 300, Avance II 400 or Avance III HD 400 in $CDCl_3$, DMSO-d_6, CD_2Cl_2, CD_3CN, $(CD_3)_2CO$, or CD_3OD at 25 °C with the residual solvent peaks as internal reference for ^{1}H and ^{13}C NMR spectra. Mass spectra *via* electrospray-ionization (ESI+/-) or atmospheric pressure chemical ionization (APCI+/-) mass spectrometry were recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA).

Parameter screenings of the electrolytic conditions were performed using an *IKA* Screening System Package (*IKA-Werke GmbH & Co. KG*, Staufen, Germany, Figure S1 top) with electrodes the size of 70 mm × 10 mm × 3 mm. The apparatus and detailed construction information is reported in literature.[1]
The electrode surfaces were cleaned prior use. Isostatic graphite (C_{gr}, Sigrafine™ V2100, *SGL Carbon*, Bonn, Germany) was wet-polished with sandpaper (grade 1000 + 1200, Bosch, Stuttgart, Germany), rinsed with acetone and the abrasion was wiped off with a paper towel until the latter was not stained anymore. Glassy carbon electrodes (C_{gl}, SIGRADUR™ G, *HTW*, Thierhaupten, Germany) were rinsed with several solvents and wiped with a paper towel. Boron-doped diamond (BDD, DIACHEM™, 15 µm diamond layer on silicon support, *CONDIAS GmbH*, Itzehoe, Germany) was conditioned by electrolyzing as anode in 20% aqueous sulfuric acid (10 C cm², 10 mA cm²) and subsequently rinsed with water.

Constant current electrolyses for scale-up experiments were carried out in commercial (SynLectro™, *Merck KGaA*, Darmstadt, Germany, Figure S1, bottom left and middle)[2] or tailor-made (Figure S1, bottom, right)[3] beaker-type cells using TDK-Lambda Z+ series *(TDK-Lambda UK Limited*, Devon, UK) or multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) as power sources.

Figure S1: Top: schematic illustration of a screening block with undivided cells (left); undivided PTFE screening cell with BDD electrodes (right). Bottom: jacketed beaker-type cell, up to 50 mL reaction volume (left); beaker-type cell, up to 200 ml reaction volume (middle); jacketed beaker-type cell with 6 electrodes in a bipolar or stacked set-up, up to 1.5 L reaction volume (right).

S2. Calibration of Gas Chromatographic Yields

The evaluation of the GC yields was achieved by external calibration with 1,3,5-trimethoxybenzene as internal standard. The calibration factors *k* for each substance were determined according to equation (*1*).

$$\frac{n_{\text{analyte}}}{n_{\text{standard}}} = k\frac{A_{\text{analyte}}}{A_{\text{standard}}} \qquad (1)$$

S2.1. (*Z*)-Hydrazone 8a

Stock solutions of 1,3,5-trimethoxybenzene, (*Z*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8a**) and diethyl 1*H*-1-(2,4-dichlorophenyl)-4,5-dihydro-5-methylpyrazole-3,5-dicarboxylate (mefenpyr-diethyl, **1**) were prepared in ethyl acetate (Table S1). Different quantities of the stock solutions were transferred to GC vials (Table S2) and filled with acetonitrile to a total volume of 1.5 mL. Each vial was analysed three times and for each substance the mean value of the peak areas *A* from these three runs was used as a calibration point. The calibration curve can be found in Figure S2. The calibration factors *k* for each substance are listed in Table S3.

Table S1: Stock solutions for external calibrations using gas chromatography.

#	substance	*m* / mg	*n* / mmol	$V_{solvent}$ / mL	*c* / mM
stock 1	1,3,5-trimethoxybenzene	3038	18.06	100	181
stock 2	(*Z*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8a**)	39.8	0.152	5	30.5
stock 3	mefenpyr-diethyl (**1**)	63.6	0.170	5	34.1

Table S2: Calibration solutions for (*Z*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8a**) and mefenpyr-diethyl (**1**), internal standard: 1,3,5-trimethoxybenzene.

#	$V_{Stock\ 1}$ / µL	$V_{Stock\ 2}$ / µL	$V_{Stock\ 3}$ / µL
cal. 1	10	30	30
cal. 2	10	60	60
cal. 3	10	90	90
cal. 4	10	120	120
cal. 5	10	150	150
cal. 6	10	190	190
cal. 7	10	225	225

#	$V_{Stock\ 1}$ / µL	$V_{Stock\ 2}$ / µL	$V_{Stock\ 3}$ / µL
cal. 8	10	260	260
cal. 9	10	300	300
cal. 10	10	350	350
cal. 11	10	400	400
cal. 12	10	450	450
cal. 13	10	500	500

Table S3: Calibration factors for (*Z*)-hydrazone (**8a**) and mefenpyr-diethyl (**1**) used in the screening experiments.

substance	*k*
(*Z*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8a**)	5.152
mefenpyr-diethyl (**1**)	0.4713

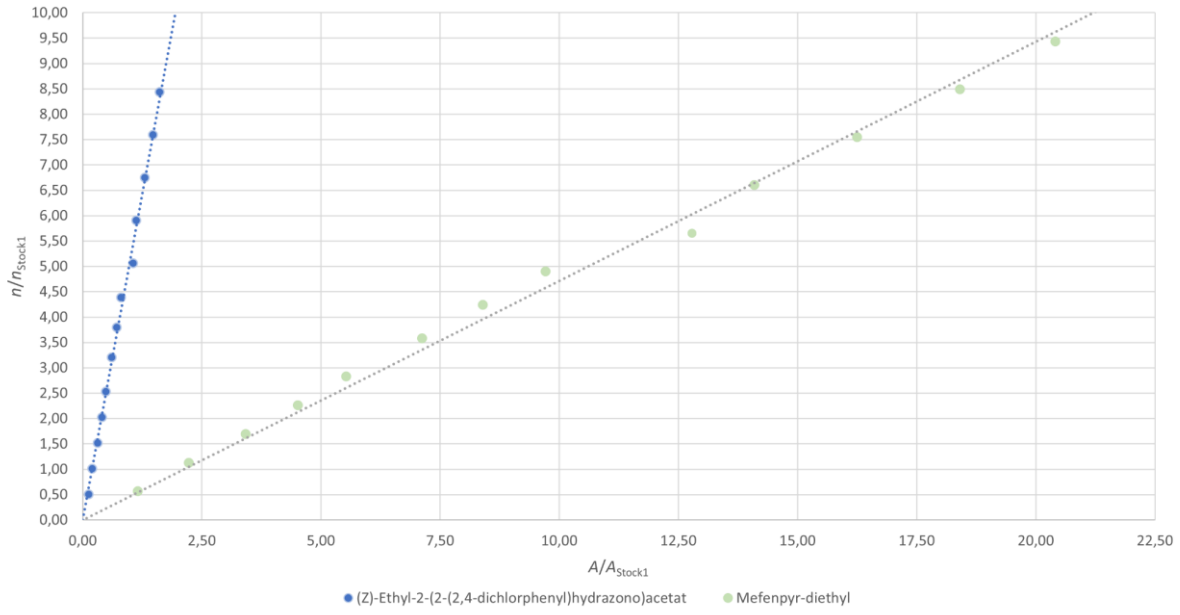


Figure S2: GC calibration for (*Z*)-hydrazone **8a** and mefenpyr-diethyl (**1**) used in the screening experiments (internal standard: 1,3,5-trimethoxybenzene).

S2.2. (*E*)-Hydrazone 8b

Stock solutions of 1,3,5-trimethoxybenzene, (*E*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8b**), and diethyl 1*H*-1-(2,4-dichlorophenyl)-4,5-dihydro-5-methylpyrazole-3,5-dicarboxylate (mefenpyr-diethyl, **1**) were prepared in ethyl acetate (Table S4). Different quantities of the stock solutions were transferred to GC vials (Table S5) and filled with acetonitrile to a total volume of 1.5 mL. Each vial was analysed three times and for each substance the mean value of the peak areas *A* from these three runs was used as a calibration point. The calibration curve can be found in Figure S3. The calibration factors *k* for each substance are listed in Table S6.

Table S4: Stock solutions for external calibrations using gas chromatography.

#	substance	*m* / mg	*n* / mmol	$V_{solvent}$ / mL	*c* / mM
stock 1	1,3,5-trimethoxybenzene	3038	18.06	100	181
stock 4	(*E*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8b**)	39.5	0.151	5	30.3
stock 5	mefenpyr-diethyl (**1**)	64.8	0.174	5	34.7

Table S5: Calibration solutions for (*E*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8b**) and mefenpyr-diethyl (**1**), internal standard: 1,3,5-trimethoxybenzene.

#	$V_{Stock\ 1}$ / µL	$V_{Stock\ 4}$ / µL	$V_{Stock\ 5}$ / µL
cal. 1	10	30	30
cal. 2	10	60	60
cal. 3	10	90	90
cal. 4	10	120	120
cal. 5	10	150	150
cal. 6	10	190	190
cal. 7	10	225	225

#	$V_{Stock\ 1}$ / µL	$V_{Stock\ 4}$ / µL	$V_{Stock\ 5}$ / µL
cal. 8	10	260	260
cal. 9	10	300	300
cal. 10	10	350	350
cal. 11	10	400	400
cal. 12	10	450	450
cal. 13	10	500	500

Table S6: Calibration factors for (*E*)-hydrazone **8b** and mefenpyr-diethyl (**1**) used in the screening experiments.

substance	*k*
(*E*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8b**)	0.7278
mefenpyr-diethyl (**1**)	0.4942

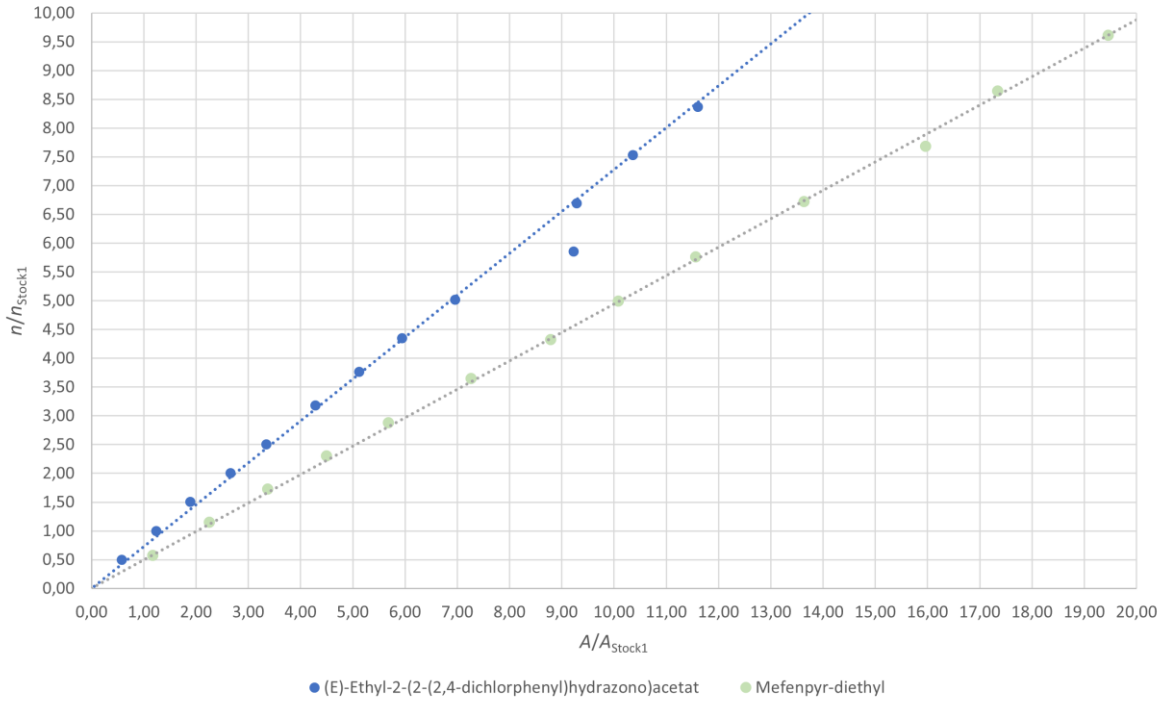


Figure S3: GC calibration for (*E*)-hydrazone **8b** and mefenpyr-diethyl (**1**) used in the screening experiments (internal standard: 1,3,5-trimethoxybenzene).

S3. Standard Operating Protocols (SOP)

SOP1: Screening for Suitable Electrolytic Conditions (Biphasic)

In 5 mL PTFE cells, the respective hydrazone and ethyl methacrylate were dissolved in 5 mL of a mixture of organic solvent and 1 M aqueous sodium halide solution at the given temperature under vigorous stirring (magnetic stirrer set to approx. 1000 rpm). The mixture was subjected to galvanostatic electrolysis using isostatic graphite plates as electrodes with a relevant surface area of 1.7 cm^2 (size: 70 × 10 × 3 mm, immersion depth 1.7 cm). The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. 1 mL of a solution of 1,3,5-trimethoxybenzene (3.000 g/100 mL ethyl acetate) was added as internal standard and the mixture shaken briefly. After separation of the layers, the organic fraction was dried over anhydrous magnesium sulfate and filtered. An aliquot was filtered through silica and subjected to GC analysis for quantitative analysis.

SOP2: Screening for Suitable Electrolytic Conditions (Homogeneous)

In 5 mL PTFE cells, the respective hydrazone, sodium halide, and ethyl methacrylate were dissolved in 5 mL of the given mixture of organic solvents at the given temperature. The mixture was subjected to galvanostatic electrolysis using isostatic graphite plates as electrodes with a relevant surface area of 1.7 cm^2 (size: size: 70 × 10 × 3 mm, immersion depth 1.7 cm). After the electrolysis, 1 mL of a solution of 1,3,5-trimethoxybenzene (3.000 g/100 mL ethyl acetate) was added as internal standard, the mixture was stirred briefly, and an aliquot was filtered through silica and subjected to GC analysis for quantitative analysis.

S4. Optimization of Pyrazoline Syntheses

S4.1. Synthesis from (*Z*)-Hydrazone 8a

S4.1.1. Solvent Optimization

(*Z*)-Ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8a**, **3.0 mmol, 783 mg, 1.0 eq.**) and ethyl methacrylate (**8.1 mmol, 925 mg, 2.7 eq.**) were placed in a jacketed 50 mL beaker-type cell, equipped with a cross-shaped magnetic stirring bar. Organic solvent (5 mL) and 1 M aqueous sodium iodide solution (20 mL) were added. Isostatic graphite plates with a relevant surface area of 5.4 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.7 cm) were used as anode and cathode. Constant current electrolysis was conducted at 25 °C (magnetic stirrer set to approx. 1000 rpm), with a current density of 35 mA cm^{-2} until 5.0 *F* (1447 C) was applied. The biphasic mixture was transferred to a separation funnel. The aqueous layer was additionally extracted with ethyl acetate (1 × 30 mL), the combined organic fractions were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield the crude product. Purification was performed by flash column chromatography over silica with cyclohexane/EtOAc (0% → 4% EtOAc). The results can be found in Table S7.

Table S7: Results of the initial solvent screening for the synthesis of mefenpyr-diethyl (**1**) from **8a**. Isolated yields.

Organic solvent	Yield / mg	Yield
MeO^{t}Bu	704	63%
EtOAc	820	73%
CH_2Cl_2	903	81%
PhCl	900	80%

S4.1.2. Optimization via Design of Experiments

Electrolysis was carried out according to SOP1 using (*Z*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8a, 0.60 mmol, 157 mg, 1.0 eq.**) and ethyl methacrylate (**1.79–3.21 eq.**). A mixture of 1 mL dichloromethane and 4 mL 1 M aqueous sodium iodide solution was used. Each data point was acquired thrice. The results can be found in Table S8.

A second screening was done since the extreme settings were reached for all parameters in the predicted optimum. Electrolysis was carried out according to SOP1 using (*Z*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8a, 0.60 mmol, 157 mg, 1.0 eq.**) and ethyl methacrylate (**1.79–3.21 eq.**). A mixture of 1 mL dichloromethane and 4 mL 1 M aqueous sodium iodide solution was used. Each data point was acquired twice. The results can be found in Table S9.

Table S8: First optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

#	*Q* / *F*	*j* / mA cm²	eq. ethyl methacrylate	*T* / °C	$m_{hydrazone}$ / mg	Yield[a]
1a	2.59	35.0	2.50	25	157	61%
1b	2.59	35.0	2.50	25	157	69%
1c	2.59	35.0	2.50	25	157	63%
2a	3.00	30.0	3.00	25	157	75%
2b	3.00	30.0	3.00	25	157	72%
2c	3.00	30.0	3.00	25	157	75%
3a	3.00	40.0	2.00	25	157	65%
3b	3.00	40.0	2.00	25	157	69%
3c	3.00	40.0	2.00	25	157	69%
4a	4.00	27.9	2.50	25	157	78%
4b	4.00	27.9	2.50	25	157	72%
4c	4.00	27.9	2.50	25	157	72%
5a	4.00	35.0	1.79	25	157	67%
5b	4.00	35.0	1.79	25	157	67%
5c	4.00	35.0	1.79	25	157	69%
6a	4.00	35.0	2.50	25	157	71%
6b	4.00	35.0	2.50	25	157	74%
6c	4.00	35.0	2.50	25	157	70%
7a	4.00	35.0	3.21	25	157	74%
7b	4.00	35.0	3.21	25	157	76%
7c	4.00	35.0	3.21	25	157	74%
8a	4.00	42.1	2.50	25	157	72%
8b	4.00	42.1	2.50	25	157	69%
8c	4.00	42.1	2.50	25	157	74%
9a	5.00	30.0	2.00	25	157	72%
9b	5.00	30.0	2.00	25	157	65%
9c	5.00	30.0	2.00	25	157	78%
10a	5.00	40.0	3.00	25	157	77%
10b	5.00	40.0	3.00	25	157	75%
10c	5.00	40.0	3.00	25	157	79%
11a	5.41	35.0	2.50	25	157	75%
11b	5.41	35.0	2.50	25	157	77%
11c	5.41	35.0	2.50	25	157	75%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

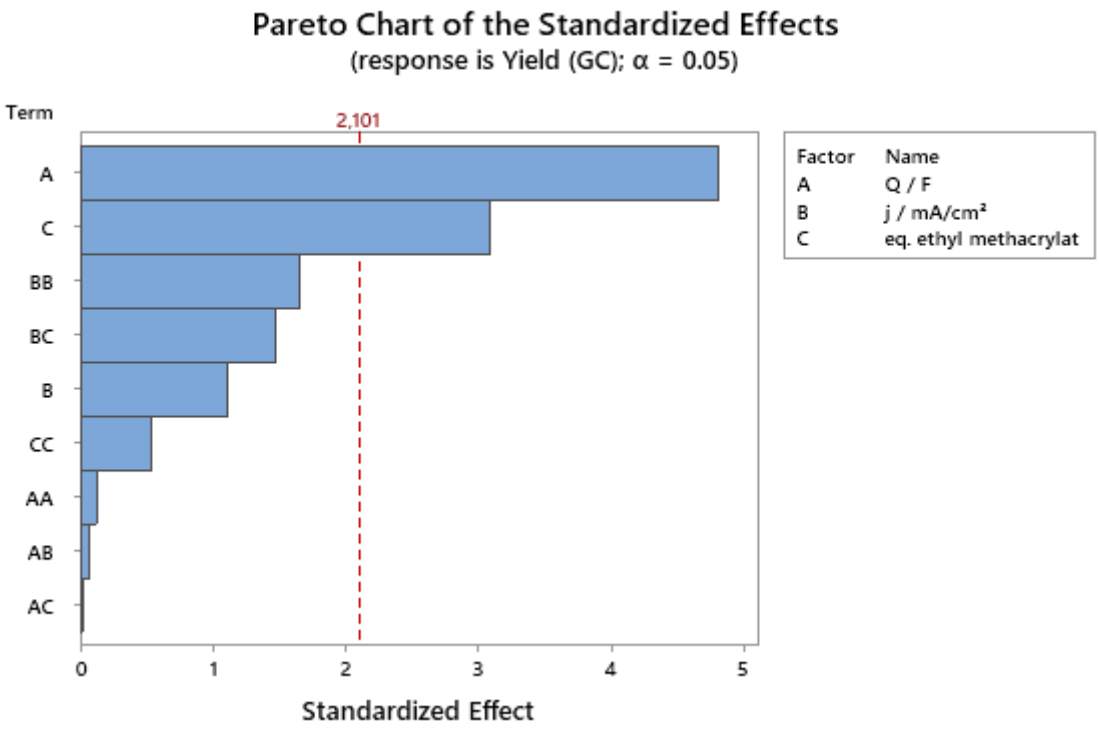


Figure S4: Pareto chart of the standardized effects for the first optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

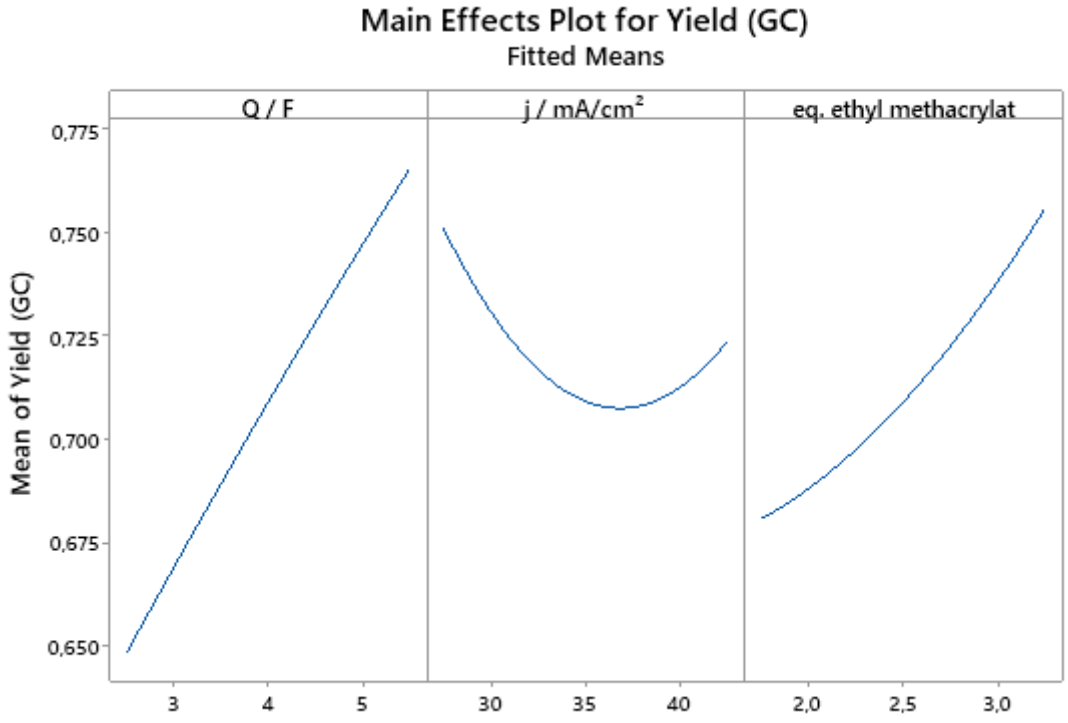


Figure S5: Main effects plot for the first optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

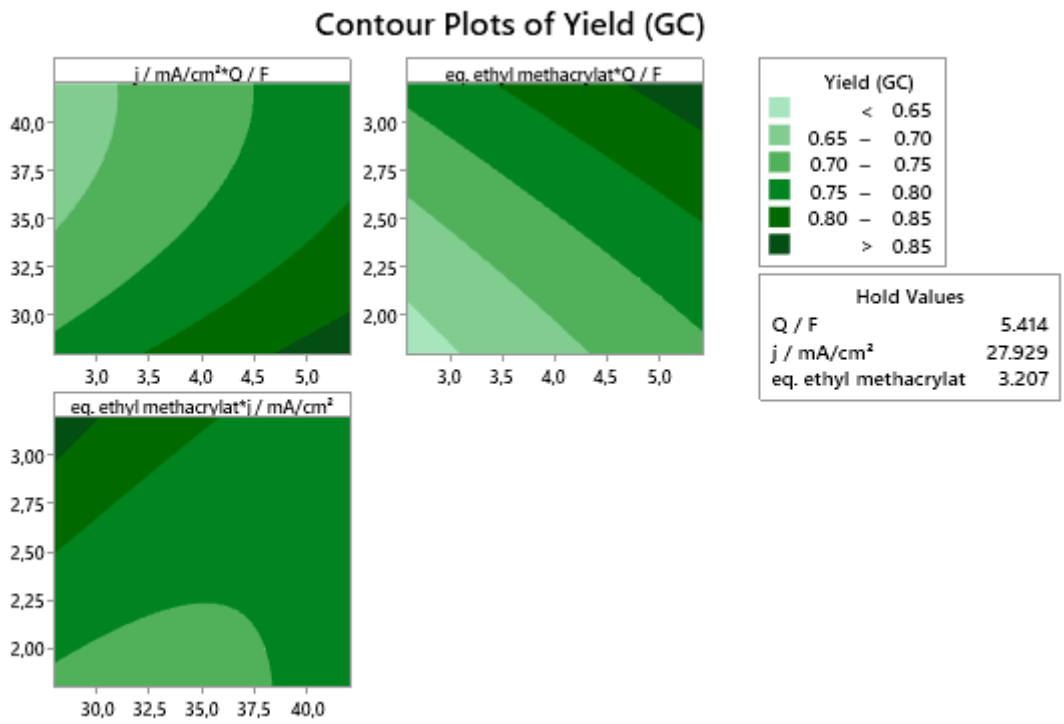


Figure S6: Contour plots for the first optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

Table S9: Second optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

#	*Q* / *F*	*j* / mA cm²	eq. ethyl methacrylate	*T* / °C	$m_{hydrazone}$ / mg	Yield[a]
1a	4.79	27.50	3.50	25	157	83%
1b	4.79	27.50	3.50	25	157	85%
2a	5.00	25.00	4.00	25	157	82%
2b	5.00	25.00	4.00	25	157	85%
3a	5.00	30.00	3.00	25	157	81%
3b	5.00	30.00	3.00	25	157	81%
4a	5.50	23.96	3.50	25	157	85%
4b	5.50	23.96	3.50	25	157	80%
5a	5.50	27.50	2.79	25	157	77%
5b	5.50	27.50	2.79	25	157	79%
6a	5.50	27.50	3.50	25	157	81%
6b	5.50	27.50	3.50	25	157	82%
7a	5.50	27.50	4.21	25	157	83%
7b	5.50	27.50	4.21	25	157	81%
8a	5.50	31.04	3.50	25	157	80%
8b	5.50	31.04	3.50	25	157	86%
9a	6.00	25.00	3.00	25	157	77%
9b	6.00	25.00	3.00	25	157	79%
10a	6.00	30.00	4.00	25	157	82%
10b	6.00	30.00	4.00	25	157	87%
11a	6.21	27.50	3.50	25	157	82%
11b	6.21	27.50	3.50	25	157	81%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

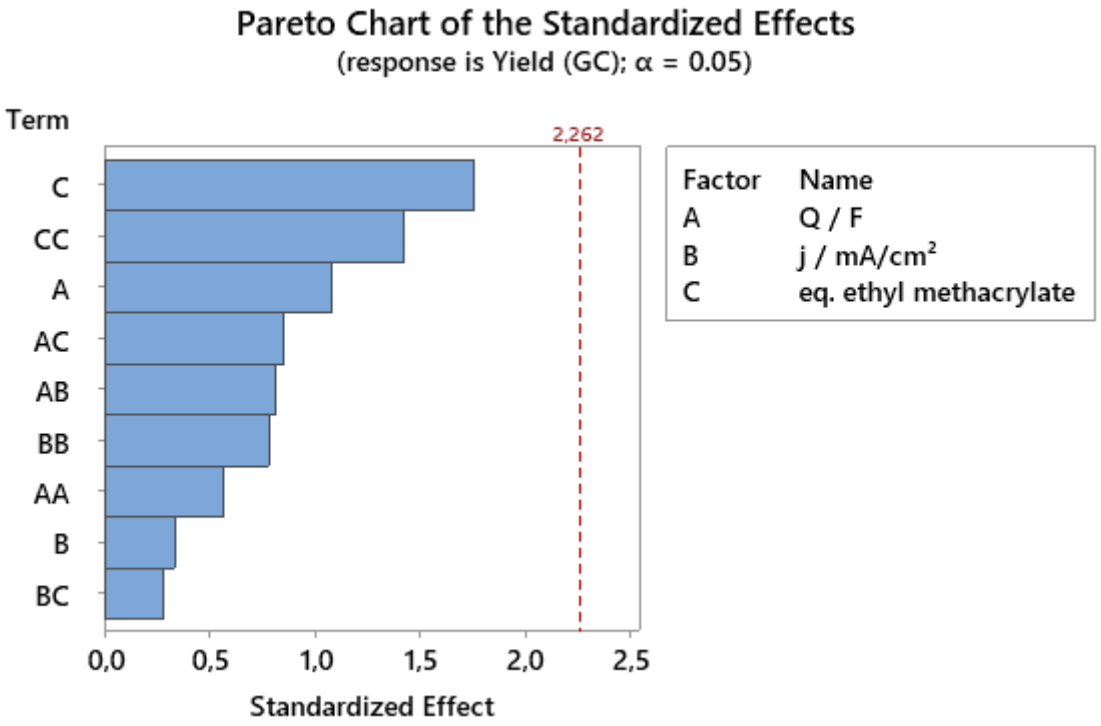


Figure S7: Pareto chart of the standardized effects for the second optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

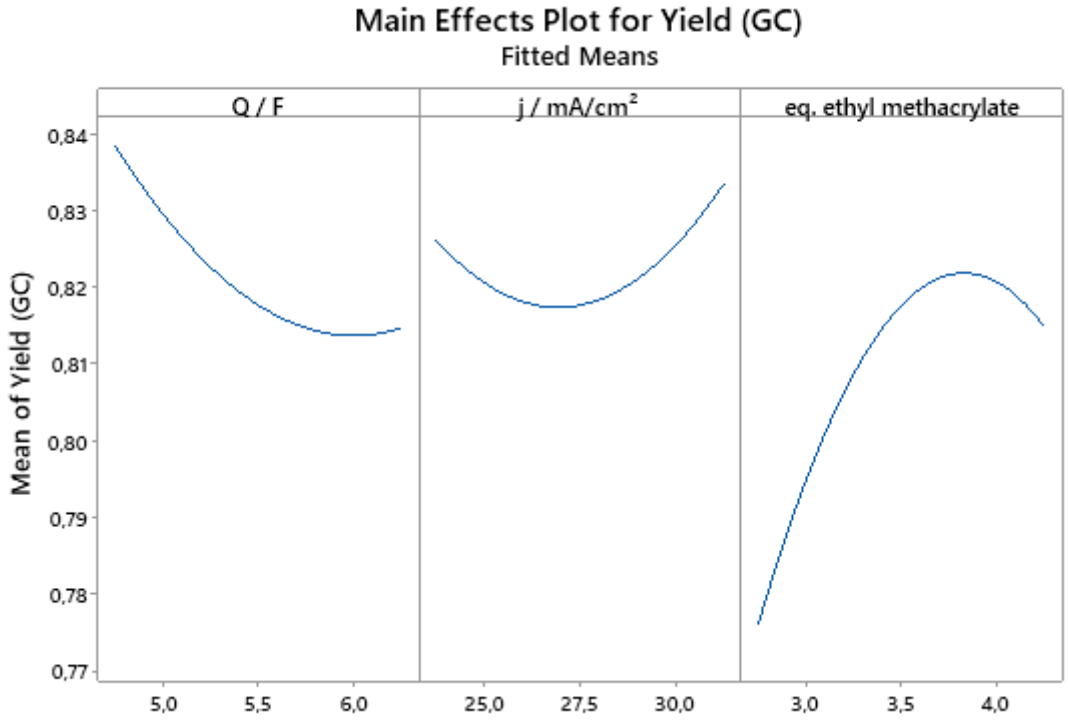


Figure S8: Main effects plot for the second optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

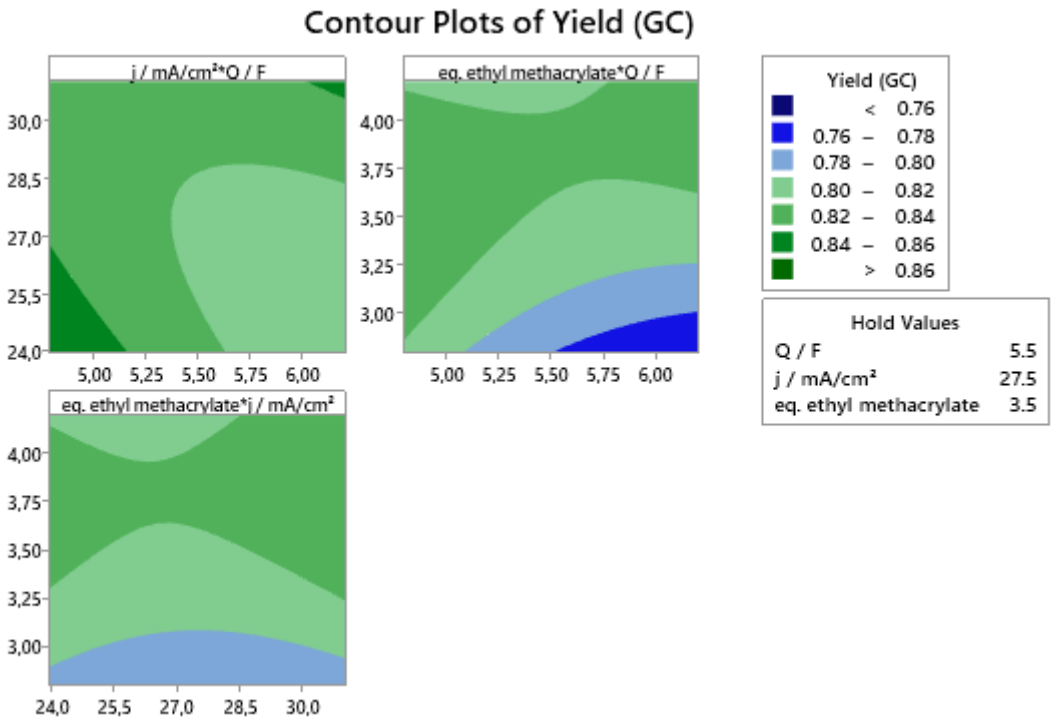


Figure S9: Contour plots for the second optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

S4.1.3. Comparison of the Predicted Optima

The predicted optima resulting from the DoE optimization were evaluated for determination of the optimum conditions.

Electrolysis was carried out according to SOP1 using (*Z*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8a, 0.60 mmol, 157 mg, 1.0 eq.**) and ethyl methacrylate (**3.21–4.21 eq.**). A mixture of 1 mL dichloromethane and 4 mL 1 M aqueous sodium iodide solution was used. The results can be found in Table S10.

Table S10: Comparison of the optima after optimization of the synthesis of mefenpyr-diethyl (**1**) from **8a** *via* DoE.

#	*Q* / *F*	*j* / mA cm²	eq. ethyl methacrylate	*T* / °C	$m_{hydrazone}$ / mg	Yield[a]
1	5.41	27.93	3.21	25	157	83%
2	6.21	31.04	4.21	25	157	80%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

S4.1.4. Concentration Screening and Temperature Optimization

The hydrazone concentration was optimized in a linear screening. According to SOP1 (*Z*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8a, 0.38–9.57 mmol, 100–2500 mg, 1.0 eq.**) and ethyl methacrylate (**3.21 eq.**) were dissolved in a mixture of 1 mL dichloromethane and 4 mL 1 M aqueous sodium iodide solution. Electrolysis was carried out at 25 °C with a current density of 27.9 mA cm^{-2} until an applied charge of 5.4 *F* was reached. The results can be found in Table S11.

Table S11: Linear screening of the concentration of hydrazone **8a**.

#	$m_{hydrazone}$ / mg	Yield[a]
1a	100	81%
1b	100	78%
2a	200	83%
2b	200	73%
3a	250	85%
3b	250	79%
4a	300	81%
4b	300	82%
5a	350	79%
5b	350	80%
6a	400	84%
6b	400	82%

#	$m_{hydrazone}$ / mg	Yield[a]
7a	450	80%
7b	450	82%
8a	500	79%
8b	500	80%
9a	600	85%
9b	600	87%
10a	700	88%
10b	700	86%
11a	850	89%
11b	850	91%
12a	1000	88%
12b	1000	89%

#	$m_{hydrazone}$ / mg	Yield[a]
13a	1250	84%
13b	1250	86%
14a	1500	84%
14b	1500	82%
15	2000	81%
16a	2500	82%
16b	2500	83%
17[b]	1000	88%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.
[b] Solvent-free conditions.

A comparison of biphasic and solvent-free synthesis of mefenpyr-diethyl (**1**) at different temperatures was done. (*Z*)-Ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8a**, **19.1 mmol, 5.0 g, 1.0 eq.**) and ethyl methacrylate (**61.5 mmol, 7.02 g, 3.21 eq.**) were placed in a jacketed 50 mL beaker-type cell, equipped with a cross-shaped magnetic stirring bar. 1 M aqueous sodium iodide solution (20 mL) and, if necessary, organic solvent (5 mL) were added. Isostatic graphite plates with a relevant surface area of 5.4 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.7 cm) were used as anode and cathode. Constant current electrolysis was carried out at the given temperature (magnetic stirrer set to approx. 1000 rpm), with a current density of 27.9 mA cm^{-2} until 5.4 *F* (9977 C) was applied. The biphasic mixture was transferred to a separation funnel. The aqueous layer was additionally extracted with ethyl acetate (1 × 30 mL), the combined organic fractions were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to yield the crude product. Purification was performed by flash column chromatography over silica with cyclohexane/EtOAc (0% → 5% EtOAc). The results can be found in Table S12.

Table S12: Final solvent and temperature optimization for the synthesis of mefenpyr-diethyl (**1**) from **8a**. Isolated yields.

Organic solvent	*T* / °C	Yield / g	Yield
CH_2Cl_2	25	6.03	84%
CH_2Cl_2	33	6.21	87%
None	25	6.02	84%
None	33	6.13	86%

S4.2. Synthesis from (*E*)-Hydrazone 8b

S4.2.1. Biphasic Mixture

S4.2.1.1. Solvent Optimization

According to SOP1 (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.38 mmol, 1.00 g, 1.0 eq.**) and ethyl methacrylate (**12.3 mmol, 1.40 g, 3.21 eq.**) were dissolved in a mixture of 1 mL organic solvent and 4 mL 1 M aqueous sodium halide solution. Electrolysis was carried out at 25 °C with a current density of 27.9 mA cm^{-2} until an applied charge of 5.4 *F* was reached. The results can be found in Table S13.

Table S13: Initial solvent and halide source optimization for the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b**.

Organic solvent	NaX	Org. solvent/halide solution (*v*/*v*)	Yield[a]
CH_2Cl_2	NaCl	1:4	4%
CH_2Cl_2	NaBr	1:4	*n/d*
CH_2Cl_2	NaI	1:4	6%
PhCl	NaI	1:4	15%
PhMe	NaI	1:4	28%
CyH	NaI	1:4	*n/d*
none	NaI	-	25%
MeO^{t}Bu	NaI	1:4	37%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

S4.2.1.2. Optimization via Design of Experiment

Electrolysis was carried out according to SOP1 using (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.60 mmol, 157 mg, 1.0 eq.**) and ethyl methacrylate (**2.32–5.68 eq.**). A mixture of 1 mL dichloromethane and 4 mL 1 M aqueous sodium iodide solution was used. Each datapoint was acquired thrice. The results can be found in Table S14.

A second screening was done to further optimize current density and reaction temperature. Electrolysis was carried out according to SOP1 using (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.60 mmol, 157 mg, 1.0 eq.**) and ethyl methacrylate (**2.68 mmol, 306 mg, 4.46 eq.**). A mixture of 1 mL dichloromethane and 4 mL 1 M aqueous sodium iodide solution was used. Each datapoint was acquired thrice. The results can be found in Table S15.

Table S14: First optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE

#	$m_{hydrazone}$ / mg	*j* /mA cm²	*Q* / F	*T* / °C	eq. ethyl methacrylate	Yield[a]
1a	157	28.0	4.00	20	4.00	34%
1b	157	28.0	4.00	20	4.00	19%
1c	157	28.0	4.00	20	4.00	23%
2a	157	23.0	3.00	25	3.00	12%
2b	157	23.0	3.00	25	3.00	8%
2c	157	23.0	3.00	25	3.00	7%
3a	157	23.0	5.00	25	5.00	20%
3b	157	23.0	5.00	25	5.00	17%
3c	157	23.0	5.00	25	5.00	16%

Table S14, continued.

#	$m_{hydrazone}$ / mg	j /mA cm^{-2}	Q / F	T / °C	eq. ethyl methacrylate	Yield[a]
4a	157	33.0	3.00	25	5.00	8%
4b	157	33.0	3.00	25	5.00	9%
4c	157	33.0	3.00	25	5.00	5%
5a	157	33.0	5.00	25	3.00	11%
5b	157	33.0	5.00	25	3.00	12%
5c	157	33.0	5.00	25	3.00	14%
6a	157	19.6	4.00	33	4.00	4%
6b	157	19.6	4.00	33	4.00	26%
6c	157	19.6	4.00	33	4.00	11%
7a	157	28.0	2.32	33	4.00	3%
7b	157	28.0	2.32	33	4.00	2%
7c	157	28.0	2.32	33	4.00	5%
8a	157	28.0	4.00	33	2.32	10%
8b	157	28.0	4.00	33	2.32	7%
8c	157	28.0	4.00	33	2.32	8%
9a	157	28.0	4.00	33	4.00	10%
9b	157	28.0	4.00	33	4.00	9%
9c	157	28.0	4.00	33	4.00	17%
10a	157	28.0	4.00	33	5.68	12%
10b	157	28.0	4.00	33	5.68	12%
10c	157	28.0	4.00	33	5.68	9%
11a	157	28.0	5.68	33	4.00	15%
11b	157	28.0	5.68	33	4.00	18%
11c	157	28.0	5.68	33	4.00	16%
12a	157	36.4	4.00	33	4.00	10%
12b	157	36.4	4.00	33	4.00	11%
12c	157	36.4	4.00	33	4.00	12%
13a	157	23.0	3.00	41	5.00	9%
13b	157	23.0	3.00	41	5.00	9%
13c	157	23.0	3.00	41	5.00	3%
14a	157	23.0	5.00	41	3.00	9%
14b	157	23.0	5.00	41	3.00	6%
14c	157	23.0	5.00	41	3.00	16%
15a	157	33.0	3.00	41	3.00	3%
15b	157	33.0	3.00	41	3.00	4%
15c	157	33.0	3.00	41	3.00	10%
16a	157	33.0	5.00	41	5.00	13%
16b	157	33.0	5.00	41	5.00	16%
16c	157	33.0	5.00	41	5.00	14%
17a	157	28.0	4.00	46	4.00	9%
17b	157	28.0	4.00	46	4.00	12%
17c	157	28.0	4.00	46	4.00	14%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

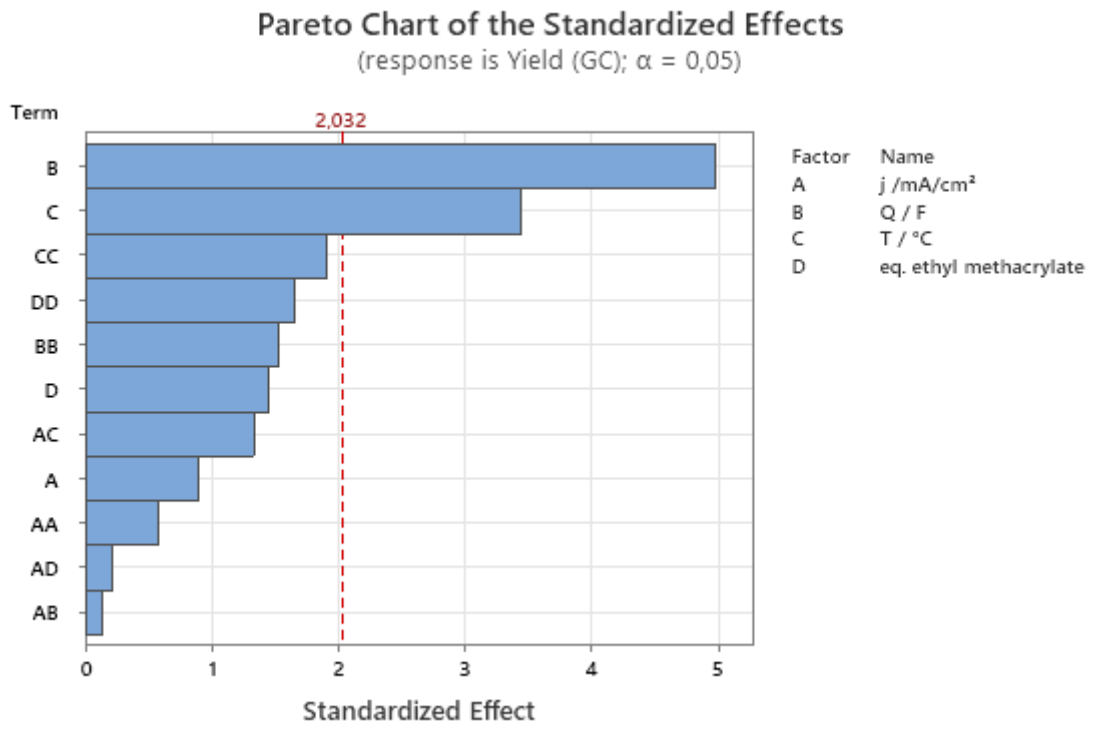


Figure S10: Pareto chart of the standardized effects for the first optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

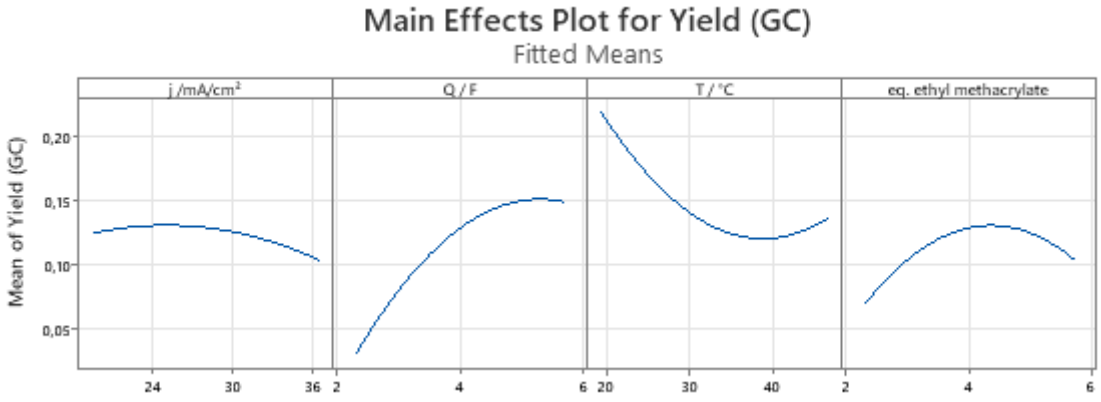


Figure S11: Main effects plot for the first optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

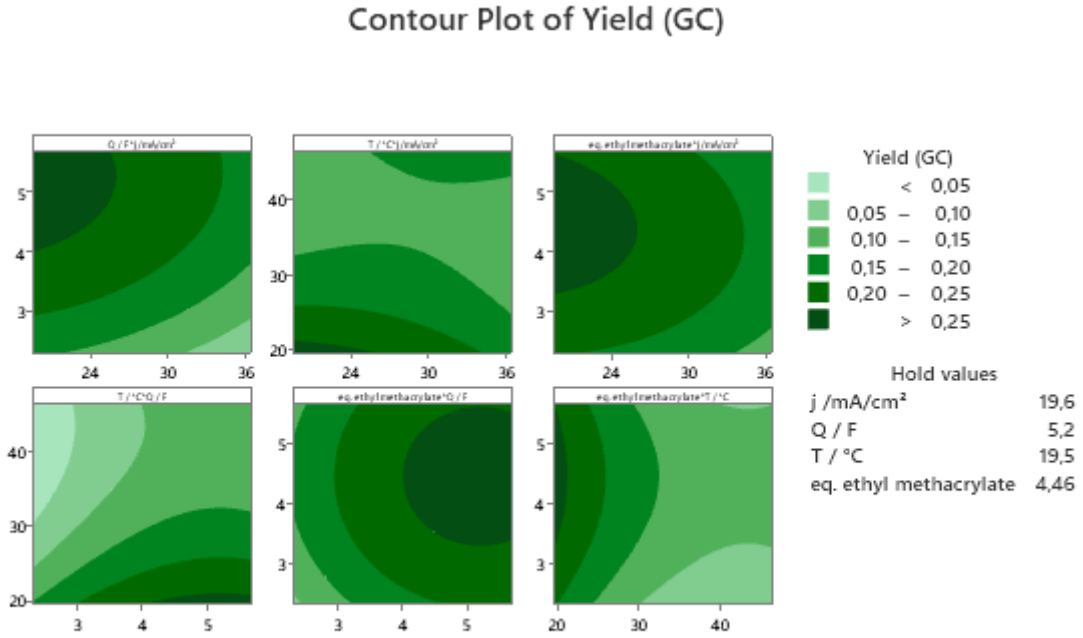


Figure S12: Contour plots for the first optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

Table S15: Second optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

#	$m_{hydrazone}$ / mg	*j* /mA cm^{-2}	*Q* / F	*T* / °C	eq. ethyl methacrylate	Yield[a]
1a	157	15.0	5.20	8	4.46	22%
1b	157	15.0	5.20	8	4.46	7%
1c	157	15.0	5.20	8	4.46	20%
2a	157	10.0	5.20	10	4.46	7%
2b	157	10.0	5.20	10	4.46	13%
2c	157	10.0	5.20	10	4.46	14%
3a	157	20.0	5.20	10	4.46	6%
3b	157	20.0	5.20	10	4.46	23%
3c	157	20.0	5.20	10	4.46	22%
4a	157	7.93	5.20	15	4.46	17%
4b	157	7.93	5.20	15	4.46	11%
4c	157	7.93	5.20	15	4.46	6%
5a	157	15.0	5.20	15	4.46	10%
5b	157	15.0	5.20	15	4.46	20%
5c	157	15.0	5.20	15	4.46	18%
6a	157	22.1	5.20	15	4.46	16%
6b	157	22.1	5.20	15	4.46	13%
6c	157	22.1	5.20	15	4.46	6%
7a	157	10.0	5.20	20	4.46	6%
7b	157	10.0	5.20	20	4.46	18%
7c	157	10.0	5.20	20	4.46	14%

Table S15. continued.

#	$m_{hydrazone}$ / mg	j /mA cm^{-2}	Q / F	T / °C	eq. ethyl methacrylate	Yield[a]
8a	157	20.0	5.20	20	4.46	11%
8b	157	20.0	5.20	20	4.46	17%
8c	157	20.0	5.20	20	4.46	14%
9a	157	15.0	5.20	22	4.46	15%
9b	157	15.0	5.20	22	4.46	19%
9c	157	15.0	5.20	22	4.46	18%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

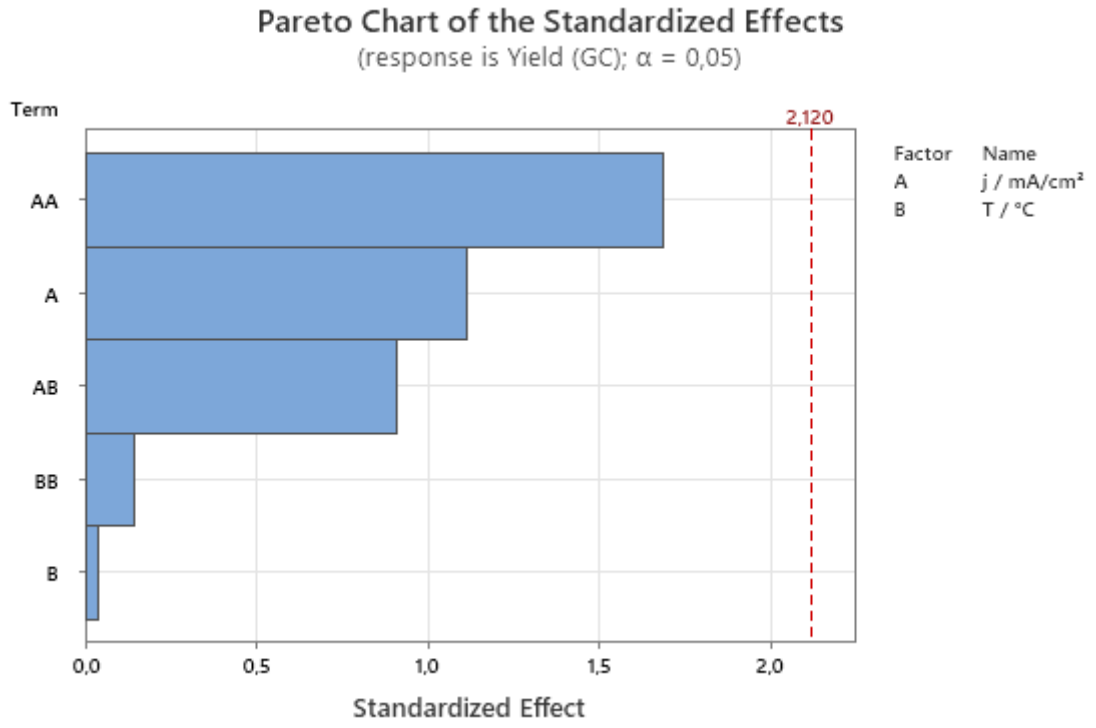


Figure S13: Pareto chart of the standardized effects for the second optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

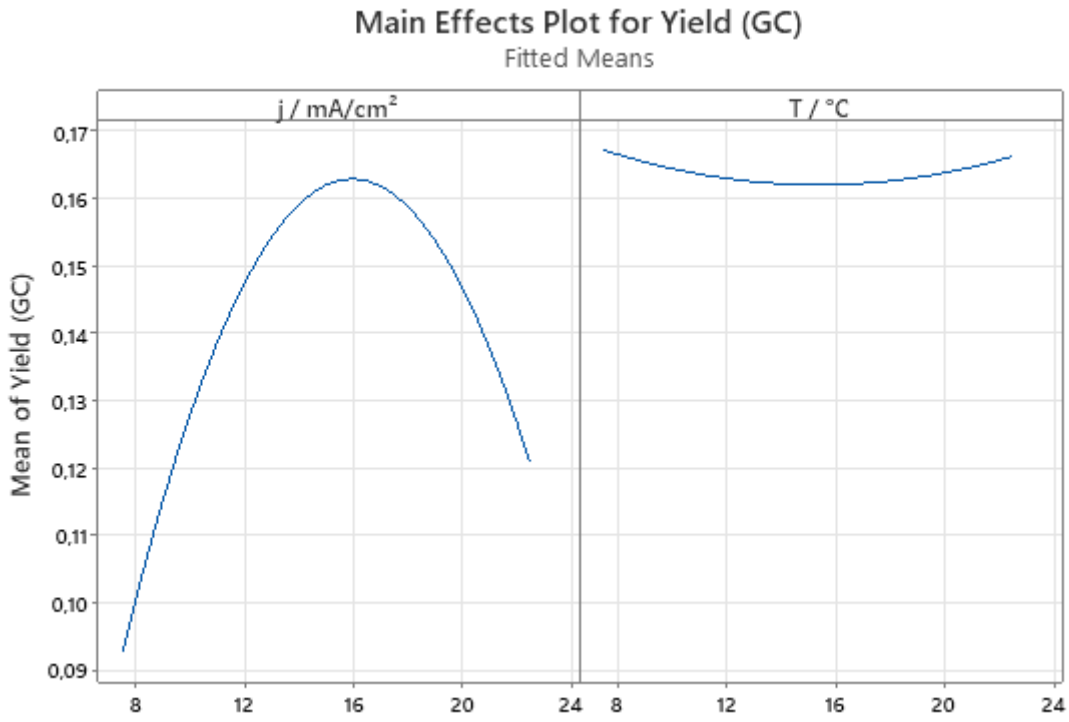


Figure S14: Main effects plot for the second optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

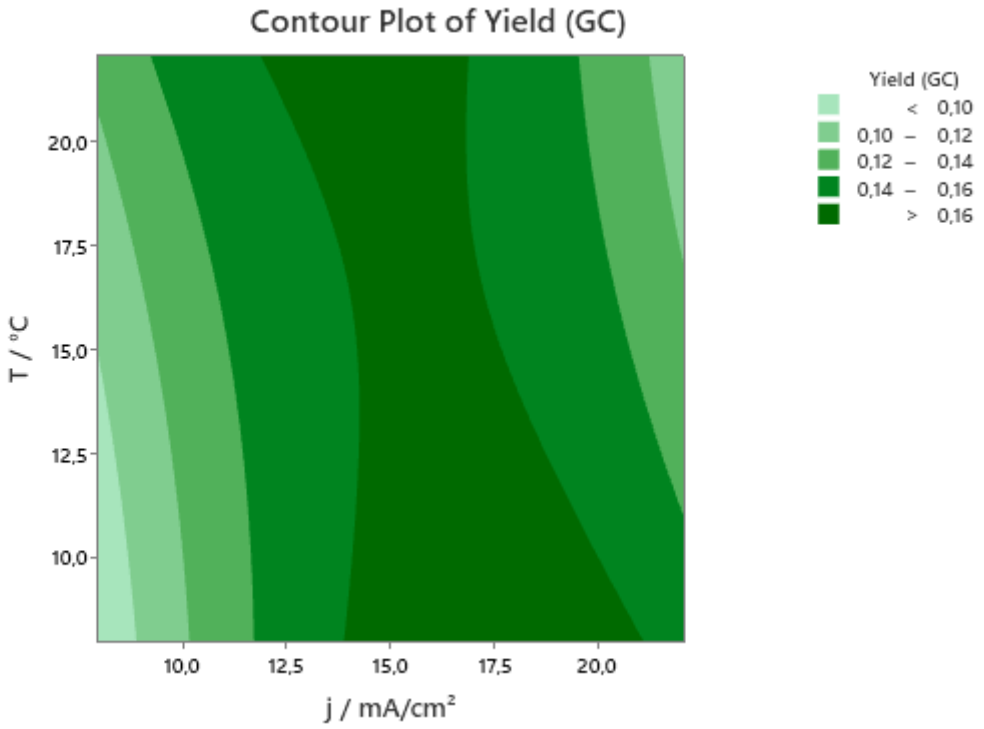


Figure S15: Contour plots for the second optimization of the biphasic synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

S4.2.2. Homogenous System

S4.2.2.1. Preliminary Optimization

Electrolysis was carried out according to SOP2 using (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.60 mmol, 157 mg, 1.0 eq.**) and ethyl methacrylate (**2.68 mmol, 306 mg, 4.46 eq.**). Electrolysis was carried out 25 °C with 17 mA cm^{-2} until a charge of 5.2 *F* (301.7 C) was applied. The results can be found in Table S16.

Table S16: Preliminary optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b**.

Solvent mixture	Halide source	Yield[a]
EtOH (p.A.)/H_2O, 1:4 (*v*/*v*)	NaI, 6.7 eq.[b]	6%
EtOAc/EtOH (p.A.)/H_2O, 3:1:1 (*v*/*v*/*v*)	NaI, 1.7 eq.[b]	12%
MeOH	NaI, 1.0 eq.	16%[c]
MeOH	NaI, 2.0 eq.	19%[c]
MeOH	NaI, 3.0 eq.	24%[c]
EtOH (denaturated)	NaI, 2.0 eq.	11%
EtOH (p.A.)	NaI, 2.0 eq.	21%
^{i}PrOH	NaI, 2.0 eq.	13%
EtOH (p.A.)	NaI, 3.0 eq.	29%[d]
MeCN/EtOH (p.A.), 1:3 (*v*/*v*)	NaI, 3.0 eq.	28%
MeCN/EtOH (p.A.), 1:2 (*v*/*v*)	NaI, 3.0 eq.	28%
MeCN/EtOH (p.A.), 1:1 (*v*/*v*)	NaI, 3.0 eq.	30%
MeCN/EtOH (p.A.), 2:1 (*v*/*v*)	NaI, 3.0 eq.	19%
MeCN/EtOH (p.A.), 3:1 (*v*/*v*)	NaI, 3.0 eq.	19%
MeCN/EtOH (p.A.), 1:1 (*v*/*v*)	NaBr, 3.0 eq.	17%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard. [b] Employed as 1 M aqueous solution. [c] Methyl ester was partially formed. [d] Applied charge 4.0 *F*.

S4.2.2.2. Optimization *via* Design of Experiment

Electrolysis was carried out according to SOP2 using (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.43–0.77 mmol, 113–201 mg, 1.0 eq.**), sodium iodide (**0.32–3.68 eq.**), and ethyl methacrylate (**3.16–4.84 eq.**) 25 °C. A mixture of acetonitrile and ethanol, p.A., (1:1, *v*/*v*) was used. The results can be found in Table S17.

A second screening was done to further optimize current density and the amounts of iodide and ethyl methacrylate. Electrolysis was carried out according to SOP2 using (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.57 mmol, 149 mg, 1.0 eq.**), sodium iodide (**2.79–4.21 eq.**), and ethyl methacrylate (**3.79–5.21 eq.**) 25 °C. A mixture of acetonitrile and ethanol, p.A., (1:1, *v*/*v*) was used. The results can be found in Table S18.

Table S17: First optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

#	$m_{hydrazone}$ / mg	*j* / mA cm^{-2}	*Q* / *F*	eq. ethyl methacrylate	eq. NaI	Yield[a]
1	113	17.50	3.50	4.00	2.00	25%
2	131	15.00	2.50	4.50	3.00	30%
3	131	15.00	4.50	4.50	1.00	31%
4	131	20.00	2.50	3.50	1.00	26%
5	131	20.00	4.50	3.50	3.00	21%
6	157	13.30	3.50	4.00	2.00	35%

Table S17, continued.

#	$m_{hydrazone}$ / mg	j / mA cm^{-2}	Q / F	eq. ethyl methacrylate	eq. NaI	Yield[a]
7	157	17.50	1.82	4.00	2.00	24%
8	157	17.50	3.50	3.16	2.00	31%
9	157	17.50	3.50	4.00	0.32	41%
10a	157	17.50	3.50	4.00	2.00	27%
10b	157	17.50	3.50	4.00	2.00	36%
10c	157	17.50	3.50	4.00	2.00	33%
11	157	17.50	3.50	4.00	3.68	33%
12	157	17.50	3.50	4.84	2.00	35%
13	157	17.50	5.18	4.00	2.00	24%
14	157	21.70	3.50	4.00	2.00	23%
15	183	15.00	2.50	3.50	3.00	26%
16	183	15.00	4.50	3.50	1.00	19%
17	183	20.00	2.50	4.50	1.00	28%
18	183	20.00	4.50	4.50	3.00	22%
19	201	17.50	3.50	4.00	2.00	26%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

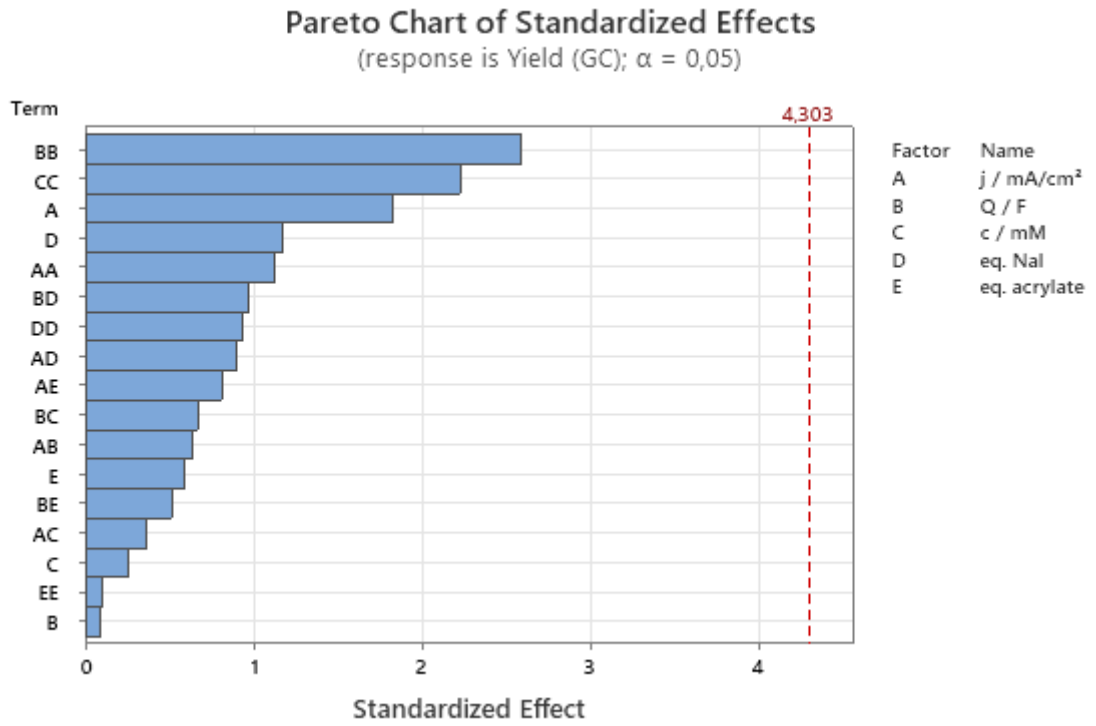


Figure S16: Pareto chart of the standardized effects for the first optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

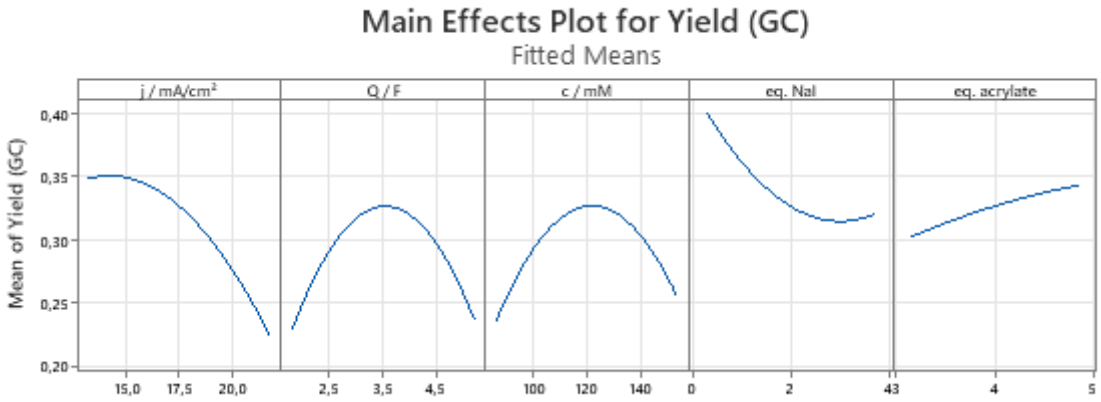


Figure S17: Main effects plot for the first optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

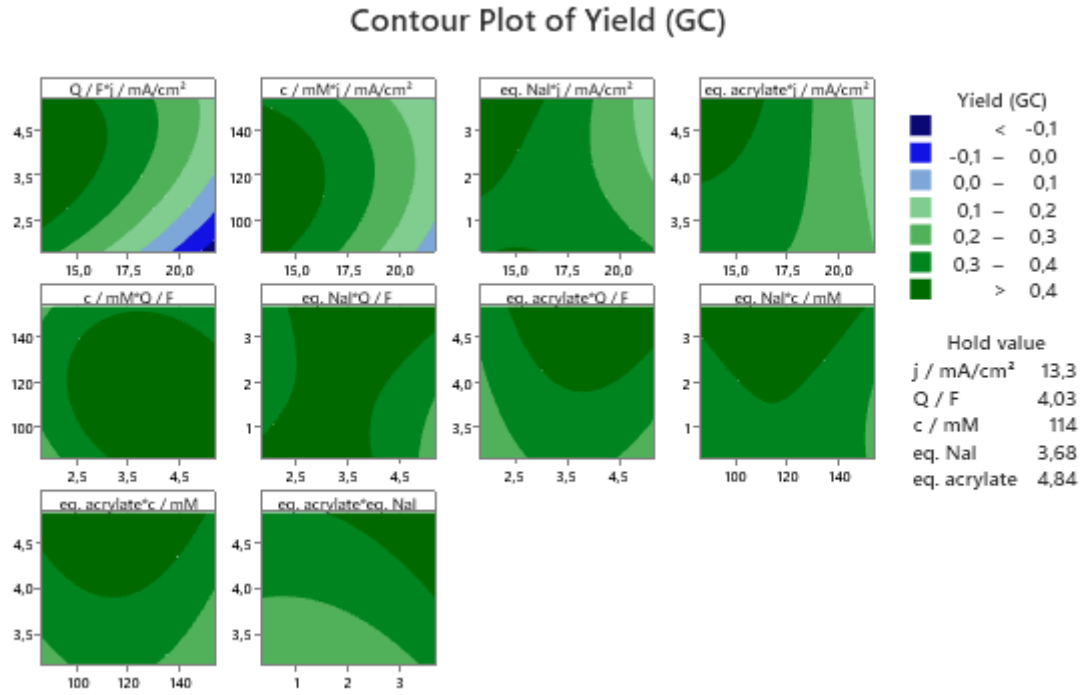


Figure S18: Contour plots for the first optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

Table S18: First optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

#	$m_{hydrazone}$ / mg	*j* / mA cm^{-2}	*Q* / *F*	eq. ethyl methacrylate	eq. NaI	Yield[a]
1	149	8.96	4.03	4.50	3.50	34%
2	149	10.00	4.03	4.00	4.00	35%
3	149	10.00	4.03	5.00	3.00	43%
4	149	12.50	4.03	3.79	3.50	32%
5	149	12.50	4.03	4.50	2.79	32%
6a	149	12.50	4.03	4.50	3.50	22%
6b	149	12.50	4.03	4.50	3.50	39%
6c	149	12.50	4.03	4.50	3.50	36%
7	149	12.50	4.03	4.50	4.21	23%
8	149	12.50	4.03	5.21	3.50	25%
9	149	15.00	4.03	4.00	3.00	27%
10	149	15.00	4.03	5.00	4.00	28%
11	149	16.04	4.03	4.50	3.50	24%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

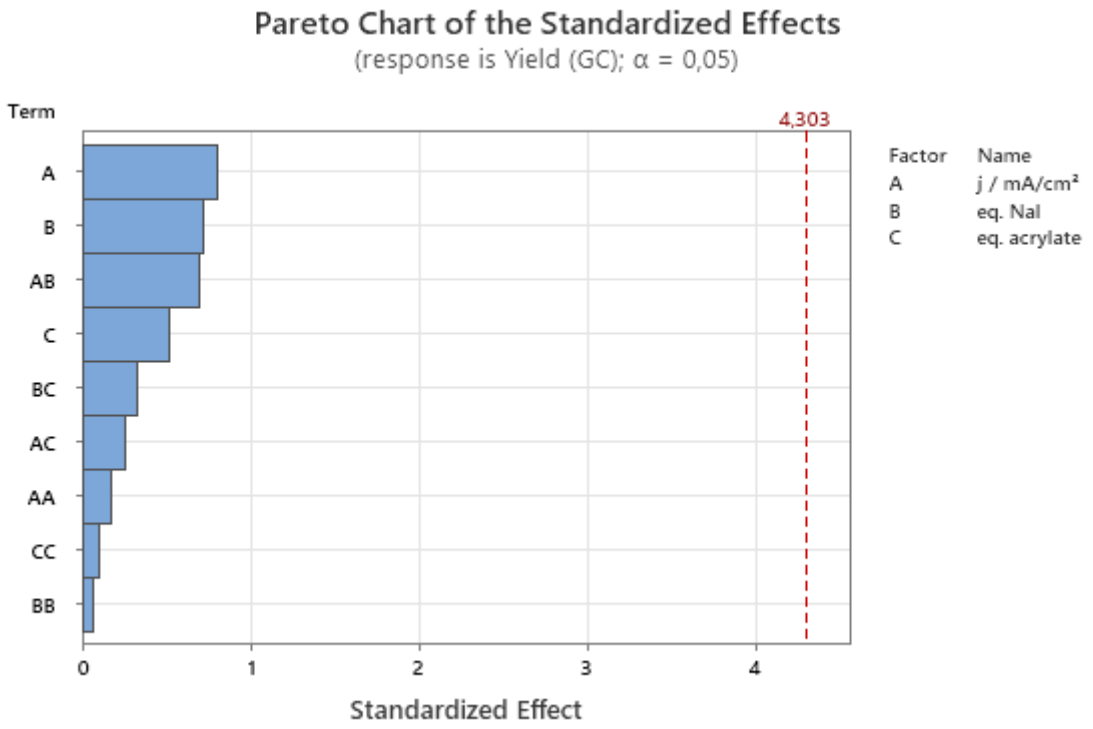


Figure S19: Pareto chart of the standardized effects for the second optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

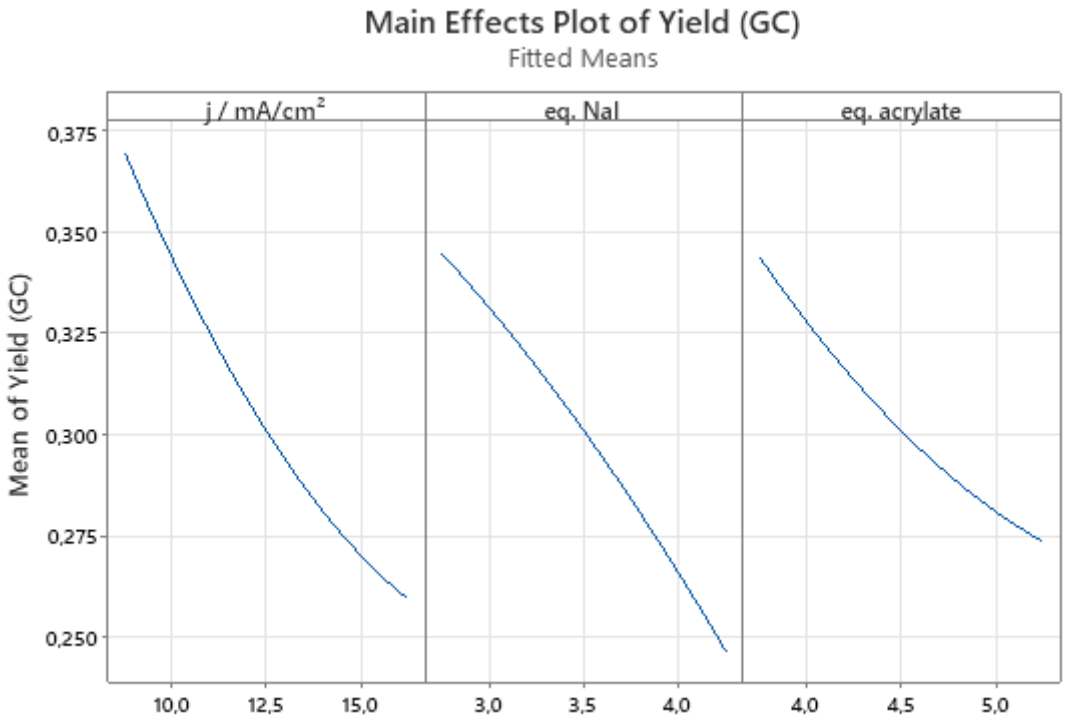


Figure S20: Main effects plot for the second optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

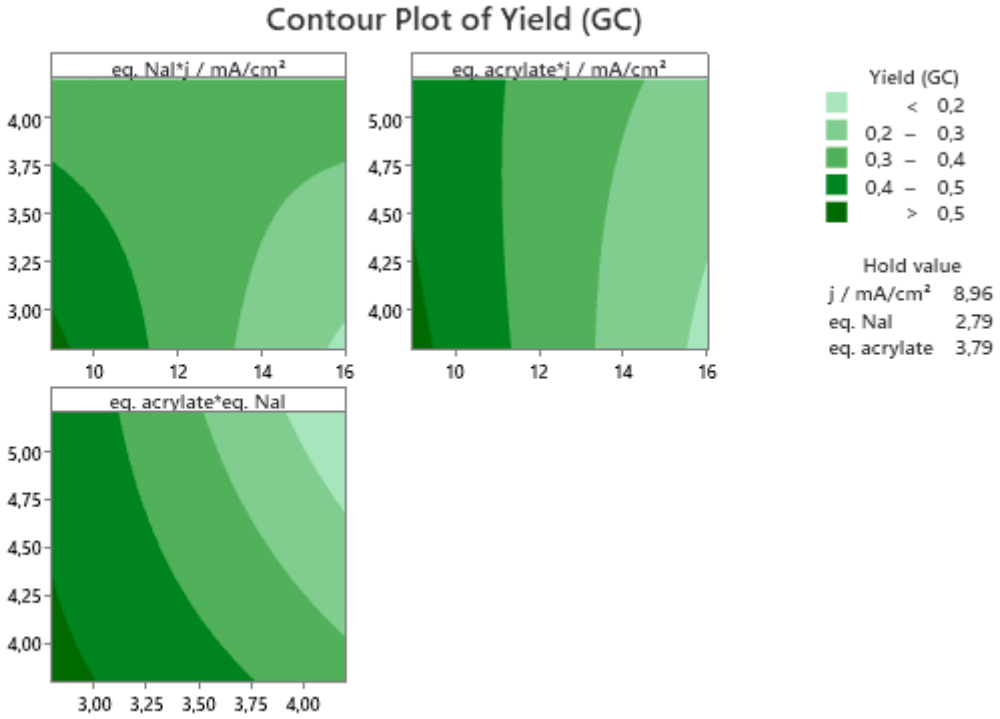


Figure S21: Contour plots for the second optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b** *via* DoE.

S4.2.2.3. Comparison of the Predicted Optima

The predicted three best settings resulting from the DoE optimization were evaluated for determination of the optimum conditions.

Electrolysis was carried out according to SOP2 using (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.57 mmol, 149 mg, 1.0 eq.**), sodium iodide (**2.79–3.48 eq.**), and ethyl methacrylate (**3.79–5.21 eq.**) at 25 °C. A mixture of acetonitrile and ethanol, p.A., (1:1, *v*/*v*) was used. The results can be found in Table S19.

Table S19: Comparison of the optima after optimization of the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b**.

#	$m_{hydrazone}$ / mg	*j* / mA cm^{-2}	*Q* / *F*	eq. ethyl methacrylate	eq. NaI	Yield[a]
1	149	8.96	4.03	3.79	2.79	33%
2	149	8.96	4.03	5.21	2.79	14%
3	149	9.38	4.03	3.79	3.48	30%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

S4.2.2.4. Linear Screening of the Current Density

The current density was further optimized in a linear screening. According to SOP2 (*E*)-ethyl glyoxylate-2,4-dichlorophenylhydrazone (**8b, 0.57 mmol, 149 mg, 1.0 eq.**), sodium iodide (**1.59 mmol, 239 mg, 2.79 eq.**), and ethyl methacrylate (**2.16 mmol, 247 mg, 3.79 eq.**). Electrolysis was carried out at 25 °C in a mixture of acetonitrile and ethanol, p.A., (1:1, *v*/*v*) until a charge of 4.03 *F* was applied. The results can be found in Table S20.

Table S20: Linear optimization of the current density for the homogenous synthesis of mefenpyr-diethyl (**1**) from **8b**.

#	*j* / mA cm^{-2}	Yield[a]
1	1.0	39%
2	2.0	45%
3	4.0	46%

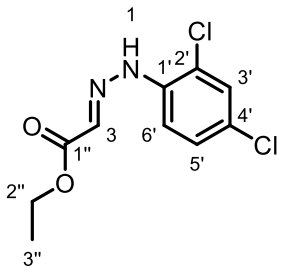
#	*j* / mA cm^{-2}	Yield[a]
4	6.0	35%
5	8.0	37%
6	10.0	30%

#	*j* / mA cm^{-2}	Yield[a]
7	12.0	33%

[a] Determined using GC analysis after external calibration with 1,3,5-trimethoxybenzene as internal standard.

S5. Substrate Synthesis

S5.1. (*Z*)-Ethyl glyoxylate-2,4-dichlorophenylhydrazone (8a)



Decagram Scale:

In a 250 mL round bottom flask, 2,4-dichlorophenylhydrazine hydrochloride (**46.8 mmol, 10.0 g, 1.0 eq.**) was dissolved in THF (75 mL) and chilled to 0 °C. Triethylamine (**56.2 mmol, 5.68 g, 1.2 eq.**) was added dropwise, the mixture was stirred for 15 min, filtered, and the residue washed with THF (25 mL). To the filtrate, ethyl glyoxylate (**46.8 mmol, 4.78 g, 1.0 eq.**) in toluene (1:1 *w*/*w*) was added dropwise at 0 °C. Afterwards, the mixture was stirred for 5 h, while reaching room temperature. The solvent was removed under reduced pressure and the residue recrystallized from cyclohexane/ethyl acetate (2:1 *v*/*v*) to yield the product as a light-yellow solid (**37.6 mmol, 9.82 g, 80%**).

Hectogram Scale:

In a 4 L three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel 2,4-dichlorophenylhydrazine hydrochloride (**0.937 mol, 200 g, 1.0 eq.**) was suspended in THF (1.5 L). Triethylamine (**0.984 mol, 99.5 g, 1.05 eq.**) was added dropwise under vigorous stirring. After the addition was finished, the mixture was stirred for 20 min, filtrated and the residue washed with THF. The combined filtrates were concentrated under reduced pressure and the free hydrazine was dissolved in ethanol (1.5 L).

In a 6 L three necked round bottom flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel, ethyl glyoxylate (**2.34 mol, 239g, 2.5 eq.**, technical grade) in toluene (1:1 *w*/*w*) was dissolved in ethanol (2 L) and the mixture was chilled to 0 °C in an ice bath. The hydrazine solution was added dropwise under vigorous stirring, while maintaining the temperature well below 5 °C. Afterwards the mixture was stirred at 0–5 °C until full conversion was reached as monitored by TLC (approx. 1 h). The mixture was concentrated under reduced pressure to an approx. volume of 750 mL and chilled at -18 °C for 4 days. The product was obtained after filtration without any further purification as a light-yellow solid (**0.587 mol, 153.3 g, 63%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 8.68 (s, 1H, *H*–1), 7.57 (d, *J* = 8.9 Hz, 1H, *H*–3'), 7.30–7.22 (m, 2H, *H*–3, 6'), 7.20 (dd, *J* = 8.9, 2.4 Hz, 1H, *H*–5'), 4.31 (q, *J* = 7.1 Hz, 2H, *H*–2''), 1.35 (t, *J* = 7.1 Hz, 3H, *H*–3''). **^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm:** 163.6, 137.6, 129.1, 128.9, 128.3, 126.9, 118.5, 116.4, 61.3, 14.3.
HRMS (ESI+), *m/z*: calculated for $C_{10}H_{10}{}^{35}Cl_2N_2O_2$ + H^+ 261.0192 [*M*+H]$^+$, found 261.0192; calculated for $C_{10}H_{10}{}^{35}Cl^{37}ClN_2O_2$ + H^+ 263.0164 [*M*+H]$^+$, found 263.0164; calculated for $C_{10}H_{10}{}^{37}Cl_2N_2O_2$ + H^+ 265.0138 [*M*+H]$^+$, found 265.0137.
Known compound, spectral data correspond to literature.[4]
LC-MS analysis: water (5vol% MeCN, 0.1vol% formic acid)/MeCN (50 → 100vol% MeCN in 10 min, 10 min 100vol% MeCN), λ = 254 nm: t_R = 9.190 min.

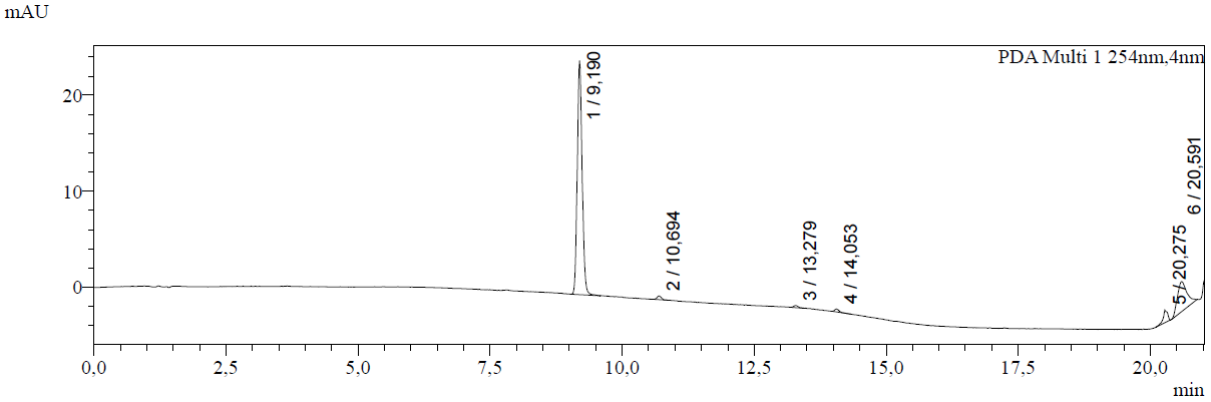
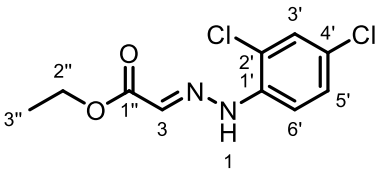


Figure S22: HPLC chromatogram of (*Z*)-hydrazone **8a**.

S5.2. (*E*)-Ethyl glyoxylate-2,4-dichlorophenylhydrazone (8b)

In a 2 L round bottom flask, ethyl glyoxylate (**0.79 mol, 80.7 g, 1.05 eq.**) in toluene (1:1 *w*/*w*) and 2,4-dichlorophenylhydrazine hydrochloride (**0.75 mol, 160.1 g, 1.0 eq.**) were dissolved in ethanol (750 mL). Glacial acetic acid (**0.75 mol, 45.0 g, 1.0 eq.**) was added, and the mixture was refluxed overnight. After crystallization of the product at -30 °C, the product was filtered off, and the residue washed with water. The product was obtained without further purification as orange needles (**0.67 mol, 174.5 g, 89%**).



^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 12.58 (s, 1H, *H*-1), 7.54 (d, *J* = 8.9 Hz, 1H, *H*-6'), 7.33 (d, *J* = 2.3 Hz, 1H, *H*-3'), 7.22 (dd, *J* = 8.9, 2.3 Hz, 1H, *H*-5'), 6.75 (s, 1H, *H*-3), 4.29 (q, *J* = 7.1 Hz, 2H, *H*-2''), 1.36 (t, *J* = 7.1 Hz, 3H, *H*-3'').

^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 163.5, 138.5, 129.1, 128.2, 127.0, 121.6, 119.6, 115.4, 61.0, 14.3.

Known compound, spectral data correspond to literature.[5]

LC-MS analysis: water (5vol% MeCN, 0.1vol% formic acid)/MeCN (50 → 100vol% MeCN in 10 min, 10 min 100vol% MeCN), λ = 254 nm: t_R = 14.049 min.

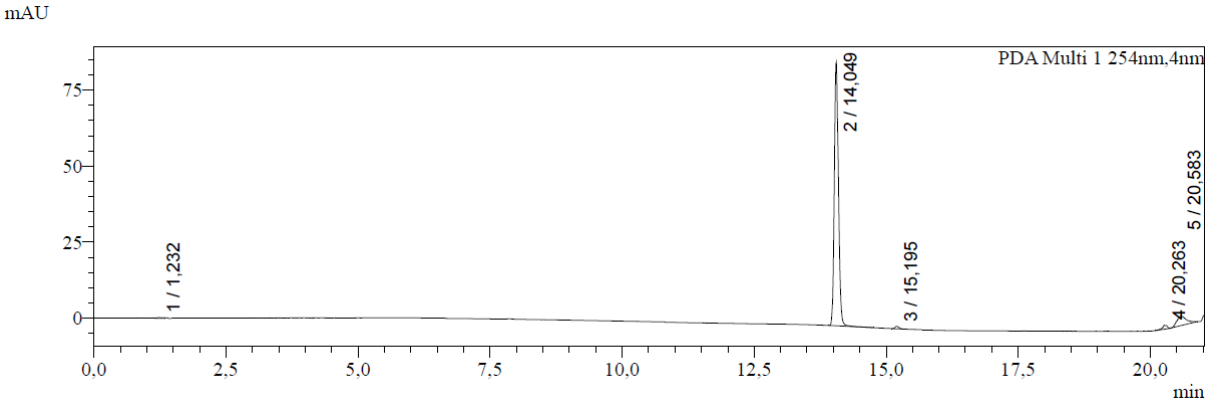
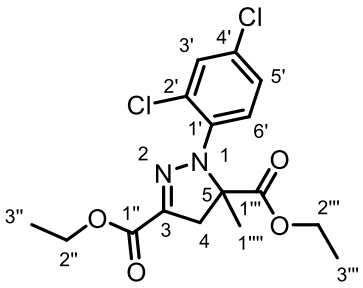


Figure S23: HPLC chromatogram of (*E*)-hydrazone 8b.

S6. Pyrazoline Synthesis

S6.1. Mefenpyr-diethyl (1) from (*Z*)-hydrazone 8a



Preparative Scale:

In a jacketed 50 mL beaker-type cell, (*Z*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8a, 19.1 mmol**, **5.0 g**, **1.0 eq.**) and ethyl methacrylate (**61.5 mmol**, **7.02 g**, **3.21 eq.**) were dispersed in 1 M aqueous sodium iodide (20 mL). Isostatic graphite plates (size: 60 × 20 × 3 mm) were used as anode and cathode with an immersion depth of 2.7 cm, a relevant anode surface area of 5.4 cm^2, and an interelectrode gap of 5 mm. Constant current electrolysis was carried out at 33 °C and 1000 rpm, with a current density of 27.9 mA cm^{-2} until an amount of charge of 5.4 *F* was applied. The biphasic mixture was transferred to a separation funnel for separation. The aqueous layer was additionally extracted with ethyl acetate (1 × 30 mL), the combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield the crude product. After flash column chromatography over silica with cyclohexane/EtOAc (0% → 4% EtOAc) mefenpyr-diethyl was obtained as an orange oil (**16.4 mmol, 6.13 g, 86%**).

^{1}H NMR (400 MHz, $CDCl_3$), *δ*/ppm: 7.41(d, *J* = 2.1 Hz, 1H, *H*-3'), 7.25–7.19 (m, 2H, *H*-5', *H*-6'), 4.33 (qd, *J* = 7.2, 1.7 Hz, 2H, *H*-2''), 4.19 (q, *J* = 7.2 Hz, 2H, *H*-2'''), 3.73 (d, *J* = 17.7 Hz, 1H, (*H*-4)'), 3.12 (d, *J* = 17.7 Hz, 1H, (*H*-4)''), 1.46 (s, 3H, *H*-1''''), 1.35 (t, *J* = 7.1 Hz, 3H, *H*-3''), 1.24 (t, *J* = 7.1 Hz, 3H, *H*-3''').

^{13}C NMR (101 MHz, $CDCl_3$), *δ*/ppm: 171.5, 162.3, 140.1, 138.0, 133.6, 133.4, 130.5, 130.2, 127.5, 73.6, 62.3, 61.5, 45.1, 22.1, 14.5, 14.1.

HRMS (ESI+), *m/z*: calculated for $C_{16}H_{18}{}^{35}Cl_2N_2O_4 + H^+$ 373.0716 $[M+H]^+$, found 373.0718; calculated for $C_{16}H_{18}{}^{35}Cl^{37}ClN_2O_4 + H^+$ 375.0690 $[M+H]^+$, found 375.0692; calculated for $C_{16}H_{18}{}^{37}Cl_2N_2O_4 + H^+$ 377.0669 $[M+H]^+$, found 377.0674.
Known compound, spectral data correspond to literature.[4]

Decagram Scale:

(*Z*)-Hydrazone **8a** (**100 mmol, 26.1 g, 1.0 eq.**) and ethyl methacrylate (**321 mmol**, **36.6 g 3.21 eq.**) were placed in 200 mL beaker-type cell, equipped with a magnetic stirring bar with stabilizing ring. 1 M aqueous sodium iodide solution (105 mL) was added. Isostatic graphite plates (size: 80 × 35 × 5 mm) with an immersion depth of 5 cm, a relevant surface area of 17.5 cm^2, and an interelectrode gap of 5 mm were used as anode and cathode. Constant current electrolysis was carried out at 33 °C, with a current density of 27.9 mA cm^{-2} until 5.4 *F* (52102 C) was applied. The biphasic mixture was transferred to a separation funnel and ethyl acetate (300 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (1 × 100 mL). The combined organic fractions were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield the crude product. Excess ethyl methacrylate was removed by vacuum distillation. The resulting oil was filtered through silica (0% → 25% → 50% EtOAc in cyclohexane). Mefenpyr-diethyl **1** was obtained as a dark-orange oil (**88.2 mmol, 32.92 g, 88%**).

Hectogram Scale:

(*Z*)-Hydrazone **8a** (**0.800 mol, 209 g, 1.0 eq.**) and ethyl methacrylate (**2.57 mol**, **293 g 3.21 eq.**) were placed in a jacketed 1.5 L beaker-type cell, equipped with a magnetic stirring bar with stabilizing ring. 1 M aqueous sodium iodide solution (836 mL) was added. A sandwich-type electrode pack consisting of six isostatic graphite plates (size: 220 × 70 × 5 mm; 3 anode plates, 3 cathode plates) was used with an immersion depth of 11.5 cm, a relevant surface area of 402.5 cm^2, and interelectrode gaps of 5 mm. Constant current electrolysis was carried out at 33 °C, with a current density of 27.9 mA cm^{-2} until 5.4 *F* (417055 C) was applied. The biphasic mixture was transferred to a separation funnel and ethyl acetate (1000 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (1 × 400 mL). The combined organic fractions were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield the crude product. The mixture was diluted with *p*-xylene (250 mL) and excess ethyl methacrylate was removed by vacuum distillation. The resulting oil was filtered through silica (0% → 12.5% EtOAc in cyclohexane). Mefenpyr-diethyl **1** was obtained as a dark-orange oil (**0.528 mol, 196.9 g, 66%**).

The aqueous phase from the extraction was freeze-dried to recover sodium iodide (**0.543 mol, 81.4 g, 0.68 eq.**).

Synthesis from (*Z*)-Hydrazone **8a** under the Conditions Optimized for (*E*)-Hydrazone **8b**:

In a jacketed 50 mL beaker-type cell, (*Z*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8a, 2.85 mmol**, **745 mg**, **1.0 eq.**), sodium iodide (**7.96 mmol, 1.19 g, 2.79 eq.**), and ethyl methacrylate (**10.8 mmol**, **1.23 g**, **3.79 eq.**) were dissolved in acetonitrile (12.5 mL) and ethanol, p.A., (12.5 mL). Isostatic graphite plates (size: 60 × 20 × 3 mm) were used as anode and cathode with an immersion depth of 2.7 cm, a relevant anode surface area of 5.4 cm^2, and an interelectrode gap of 5 mm. Constant current electrolysis was carried out at 25 °C with a current density of 4.0 mA cm^{-2} until an amount of charge of 4.03 *F* (1109 C) was applied. The mixture was evaporated to dryness under reduced pressure. The crude was purified by filtration through a pad of silica with cyclohexane/EtOAc (0% → 50% EtOAc). Mefenpyr-diethyl (**1**) was obtained as an orange oil (**1.75 mmol, 653 mg, 61%**).

S6.2. Mefenpyr-diethyl (1) from (*E*)-hydrazone 8b

Preparative Scale:

In a jacketed 50 mL beaker-type cell, (*E*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8b, 2.85 mmol**, **745 mg**, **1.0 eq.**), sodium iodide (**7.96 mmol, 1.19 g, 2.79 eq.**), and ethyl methacrylate (**10.8 mmol**, **1.23 g**, **3.79 eq.**) were dissolved in acetonitrile (12.5 mL) and ethanol, p.A., (12.5 mL). Isostatic graphite plates (size: 60 × 20 × 3 mm) were used as anode and cathode with an immersion depth of 2.7 cm, a relevant anode surface area of 5.4 cm^2, and an interelectrode gap of 5 mm. Constant current electrolysis was carried out at 25 °C with a current density of 4.0 mA cm^{-2} until an amount of charge of 4.03 *F* (1109 C) was applied. The mixture was evaporated to dryness under reduced pressure. The crude was purified by filtration through a pad of silica with cyclohexane/EtOAc (0% → 50% EtOAc). Mefenpyr-diethyl (**1**) was obtained as an orange oil (**2.03 mmol, 757 mg, 71%**).

Gram Scale:

In a jacketed 200 mL beaker-type cell, (*E*)-ethyl glyoxylate 2,4-dichlorophenylhydrazone (**8b, 22.8 mmol**, **5.96 g**, **1.0 eq.**), sodium iodide (**63.7 mmol, 9.54 g, 2.79 eq.**), and ethyl methacrylate (**86.5 mmol**, **9.87 g**, **3.79 eq.**) were dissolved in acetonitrile (100 mL) and ethanol, p.A., (100 mL). Isostatic graphite plates (size: 80 × 35 × 5 mm) were used as anode and cathode with an immersion depth of 6.5 cm, a relevant anode surface area of 32.5 cm^2, and an interelectrode gap of 5 mm. Constant current electrolysis was carried out at 25 °C with a current density of 4.0 mA cm^{-2} until an amount of charge of 4.03 *F* (8876 C) was applied. The mixture was evaporated to dryness under reduced pressure. The crude was purified by filtration through a pad of silica with cyclohexane/EtOAc (0% → 50% EtOAc). Mefenpyr-diethyl (**1**) was obtained as an orange oil (**14.9 mmol, 5.59 mg, 66%**).

Decagram Scale:

(*E*)-Hydrazone **8b** (**161 mmol, 42.0 g, 1.0 eq.**), ethyl methacrylate (**610 mmol**, **69.6 g 3.79 eq.**), and sodium iodide (**449 mmol**, **67.3 g**, **2.79 eq.**) were placed in a jacketed 1.5 L beaker-type cell, equipped with a magnetic stirring bar with stabilizing ring. Ethanol (700 mL) and acetonitrile (700 mL) were added. A bipolar electrode pack consisting of six isostatic graphite plates (size: 220 × 70 × 5 mm) was used with an immersion depth of 13 cm, a relevant surface area of 455 cm^2, and interelectrode gaps of 5 mm. Constant current electrolysis was carried out at 25 °C, with a current density of 4 mA cm^{-2} until 4.03 *F* (62547 C) was applied. The solvent was removed under reduced pressure and the mixture was taken up in ethyl acetate (500 mL) and water (500 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (250 mL) three times. The combined organic layers were washed with water (250 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield the crude product. Excess ethyl methacrylate was removed by vacuum distillation. The resulting oil was filtered through silica (12.5% → 25% EtOAc in cyclohexane). Mefenpyr-diethyl (**1**) was obtained as a dark orange oil (**101 mmol, 37.8 g, 63%**).

The aqueous phase from the extraction was freeze-dried to recover sodium iodide (**0.400 mol, 59.9 g, 2.48 eq.**).

S7. References

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5 J.-N. Zhu, W.-K. Wang, J. Zheng, H.-P. Lin, Y.-X. Deng and S.-Y. Zhao, *J. Org. Chem.*, 2019, **84**, 11032.

S8. NMR Spectra

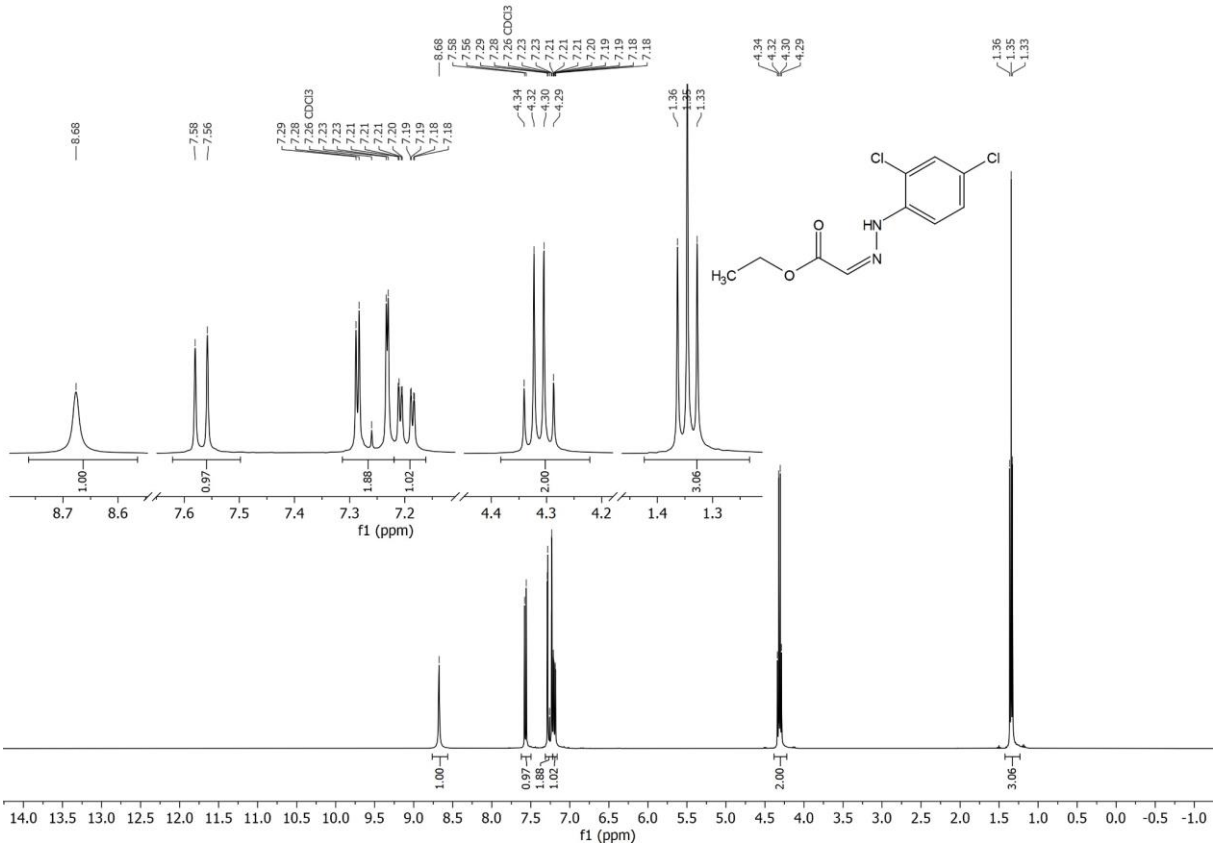

Figure S24: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8a**.

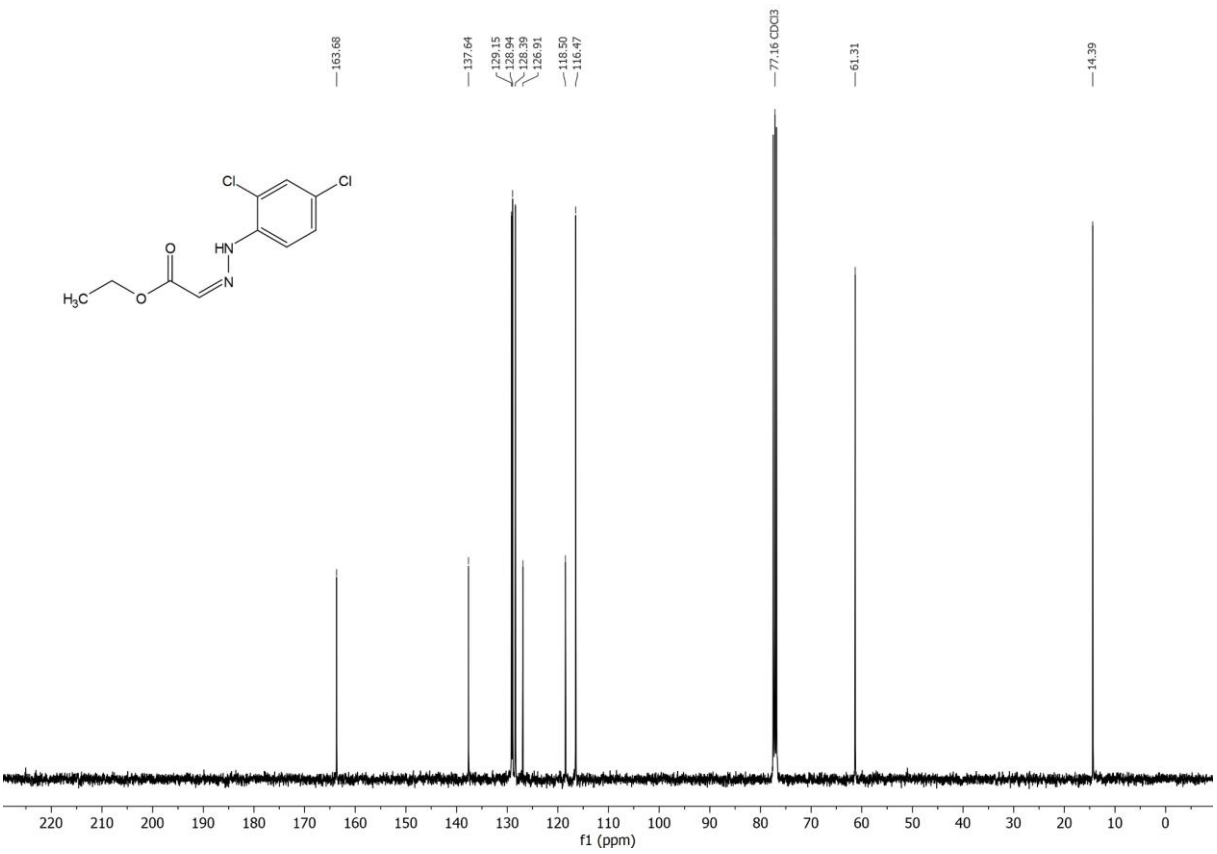

Figure S25: ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **8a**.

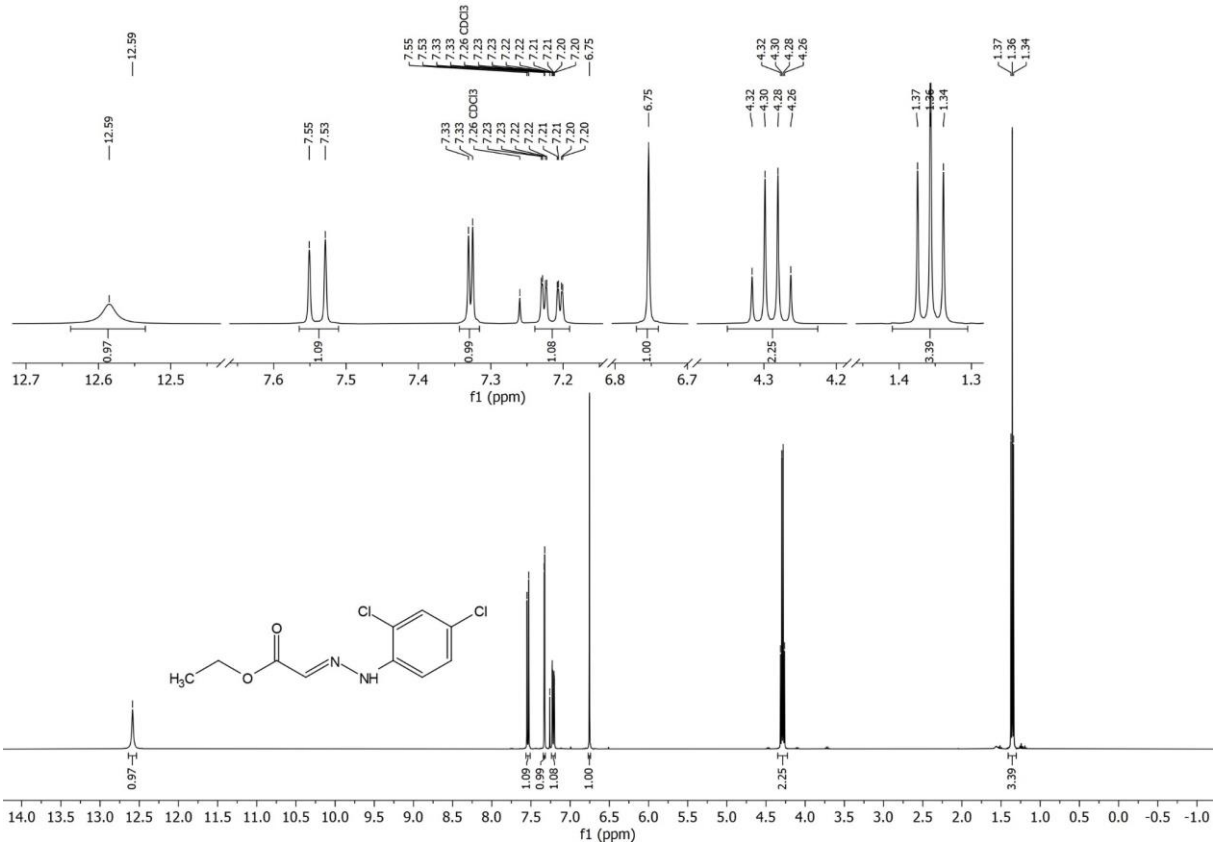

Figure S26: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8b**.

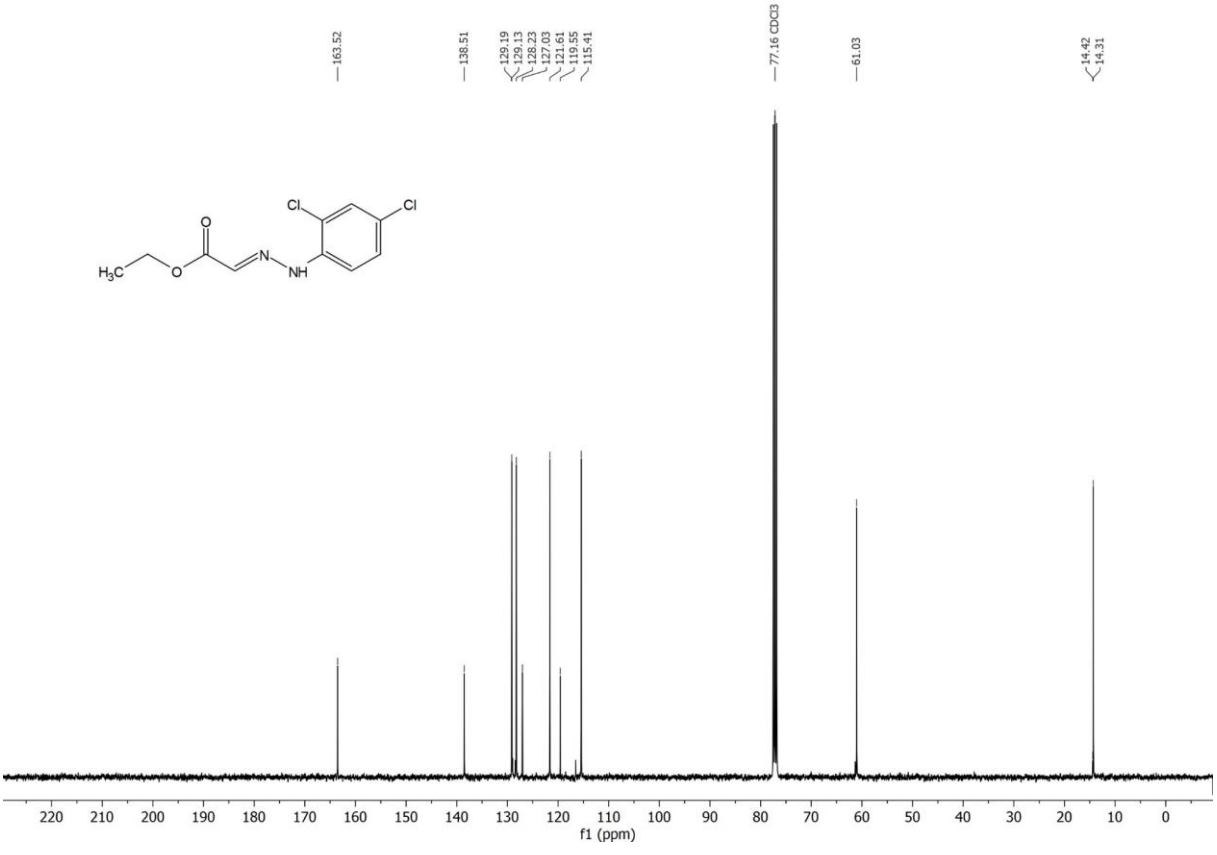

Figure S27: ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **8b**.

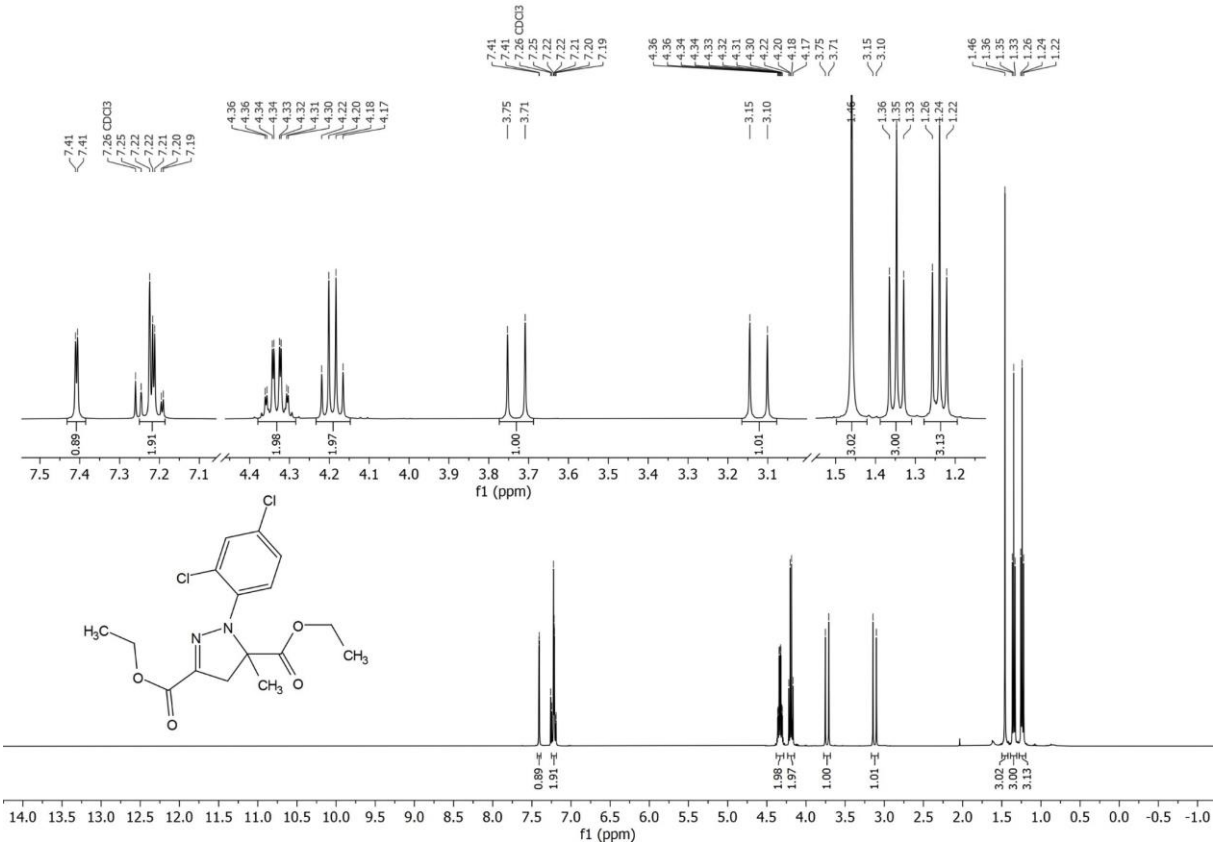

Figure S28: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1**.

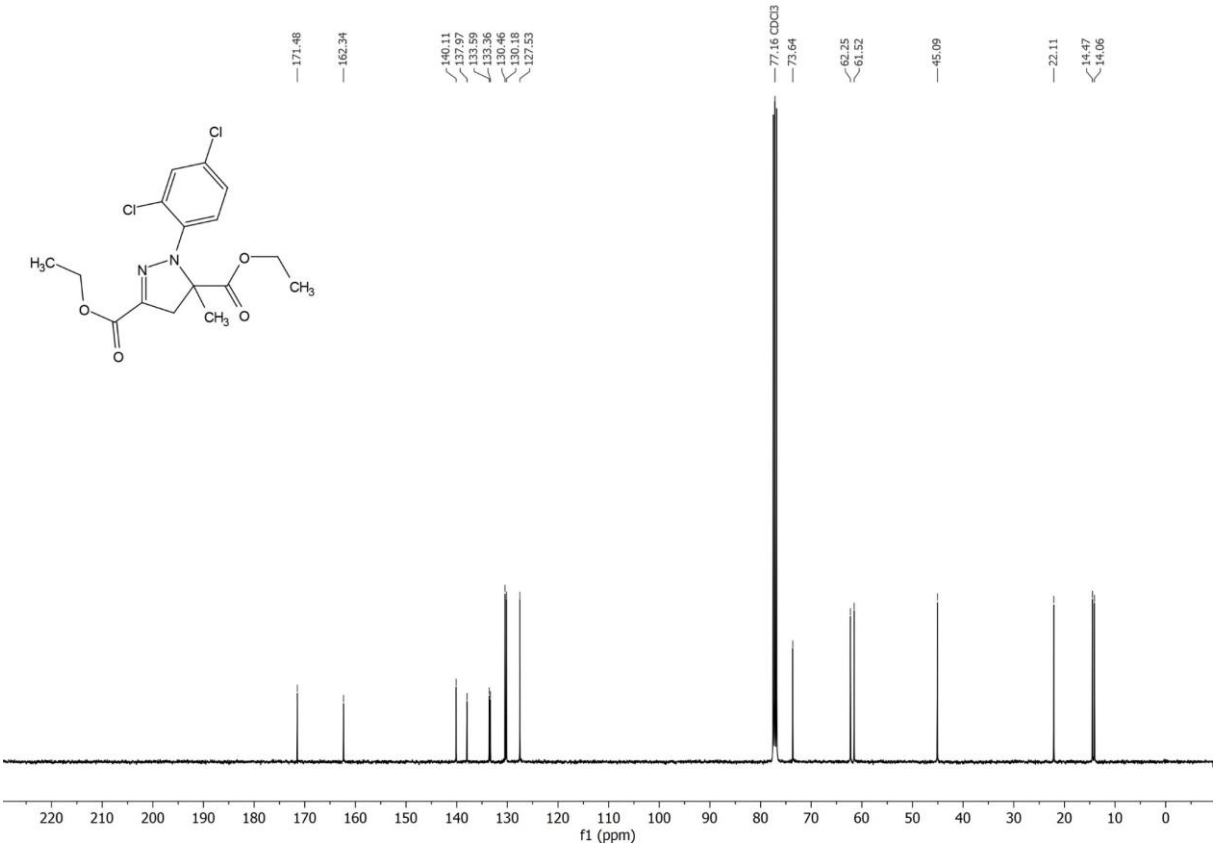

Figure S29: ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of **1**.