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Integration of high speed microwave chemistry and a statistical 'design of experiment' approach for the synthesis of the mitotic kinesin Eg5 inhibitor monastrol

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Abstract

The rapid preparation of the mitotic kinesin Eg5 inhibitor monastrol has been performed using multicomponent chemistry and combining microwave-assisted synthesis and a statistical design of experiments (DoEs) approach. By variation of the solvent, catalyst type and concentration, reaction time, and temperature a matrix of experiments for the DoE method was derived. As a result of 29 experiments with reaction times ranging from 10 to 30 min, an optimized procedure was derived that allowed the preparation of monastrol in 82%.

Keywords: Dihydropyrimidines; Multicomponent reaction; Design of experiments; Microwave irradiation; Heterocycles

1. Introduction

As statistical methods play an ever increasing important role in today's research programs, the so-called 'design of experiments' (DoEs) approach has become a valuable instrument in the hands of process and—more recently—of discovery oriented synthetic chemists.[1] After being implemented in praxis in the late 1950s,[2] DoE has further evolved so that today no in-depth knowledge of statistics is necessary for an organic chemist to succeed in applying these methods. By integrating statistical DoE protocols into sophisticated software packages,[3] this method has become easily accessible and a comfortable tool for reaction optimizations. Still, by tradition, chemists prefer to rely on their intuition whenever facing the issue of reaction optimization. Optimizing a reaction by randomly varying factors in a sequence (the so-called OVAT—'one variable at a time', or COST—'changing one separate factor at time') could be misleading, being one-dimensional, thus often missing the optimal set of conditions and/or leading to different implications. On the contrary, applying DoE provides the scientist with an organized approach concerning rational reaction variables' exploration, in multi-dimensional fashion additionally taking into account possible factor interactions. Another concern when using DoE can be the number of experiments needed in order to obtain a plausible model. However, this issue is easily resolved by the use of commercially available robotic synthesizers.

Microwave-assisted organic synthesis (MAOS) has emerged during the past two decades as another valuable technology for synthetic organic[4] and medicinal chemists.[5] Replacing the oil bath with a dedicated microwave reactor provides the opportunity to perform reactions in dramatically shortened time (more experiments and the corresponding data point generation from the statistical point of view) as well as increasing yields by using conditions not attainable under conventional heating.[4,5] Combining high speed microwave synthesis with a DoE approach, therefore, appears to be an ideal tool for obtaining truly optimized reaction conditions

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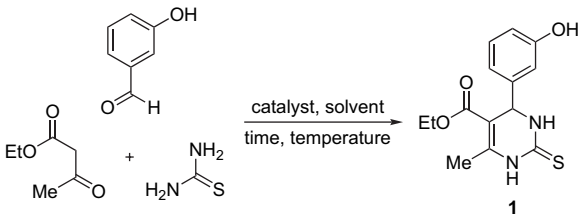
in a short period of time. Despite this fact, only a very limited number of publications so far have described applications using this attractive combination of enabling technologies.[1a,6] In this context, we herewith wish to report the use of a DoE approach in combination with automated sequential microwave synthesis for optimizing the Biginelli dihydropyrimidine synthesis.[7] Specifically, we have applied this technology for the synthesis of the mitotic kinesin inhibitor monastrol (Scheme 1, **1**),[8] a dihydropyrimidine derivative on which we have previously performed microwave-assisted optimization studies by the above mentioned conventional OVAT/COST method.[9,10]



Scheme 1. Biginelli three-component synthesis of monastrol.

2. Results and discussion

As we have previously demonstrated, monastrol (**1**) can be easily synthesized using a sealed vessel microwave protocol employing the Biginelli cyclocondensation of ethyl acetoacetate, 3-hydroxybenzaldehyde, and thiourea, promoted by the use of $Yb(OTf)_3$ in MeCN as solvent.[9] This approach shortens the reaction time required by conventional heating methods from hours to a few minutes. These reaction conditions were specifically optimized for the preparation of monastrol although similar conditions are applicable for preparing other dihydropyrimidine-2-thione derivatives.[10] Since the original 1999 report, numerous procedures have been reported in which different mediators and solvents have been introduced for the preparation of monstrol.[11,12]

To fully optimize the dihydropyrimidine-2-thione formation, we have now examined a number of experimental variables using a statistical DoE software package (MODDE8 from Umetrics)[3] in combination with an automated single mode microwave reactor, which allowed unattended processing of reaction vessels.[4,5] For the initial screening, we focused our attention on a few Lewis acid catalysts—$Cu(OTf)_2$, $CuBr_2$, $LaCl_3$, and $Yb(OTf)_3$, and few standard organic solvents—acetonitrile, ethanol, dichloromethane, and tetrahydrofuran. For this initial screening, we decided to apply the previously optimized[9] microwave conditions—continuous irradiation for 30 min at 120 °C of 1.5 equiv of ethyl acetoacetate, 1 equiv of 3-hydroxybenzaldehyde, 1 equiv of thiourea, 0.1 equiv of the catalyst, and 1 mL of solvent, as a starting point. Using the DoE software package, a Full Factorial Design (mixed) was chosen, where catalysts and solvents were selected as qualitative factors and conversion and purity were the desired responses, providing 16 main experiments plus 3 center points (center points serve to give measure of the reproducibility of the results and allow for more reliable statistical modeling), where the main effects and all interactions are not confounded. One advantage of the DoE software packages is the possibility for graphical representation of the results by automatically generated plots. Hence, an interaction plot with the results (Fig. 1) was produced, showing that both $LaCl_3$ and $Yb(OTf)_3$ in acetonitrile indeed perform very well as catalysts in terms of conversion and purity (in contrast to $CuBr_2$).

From the data shown in Figure 1, it was determined that in this case the solvent of choice clearly is ethanol, in particular in combination with $LaCl_3$ or $Yb(OTf)_3$ as a Lewis acid. It should be noted that previous empirical optimizations have found acetonitrile to be a suitable solvent.[9] Based on a price analysis[13] of $LaCl_3$ and $Yb(OTf)_3$, we have decided to use

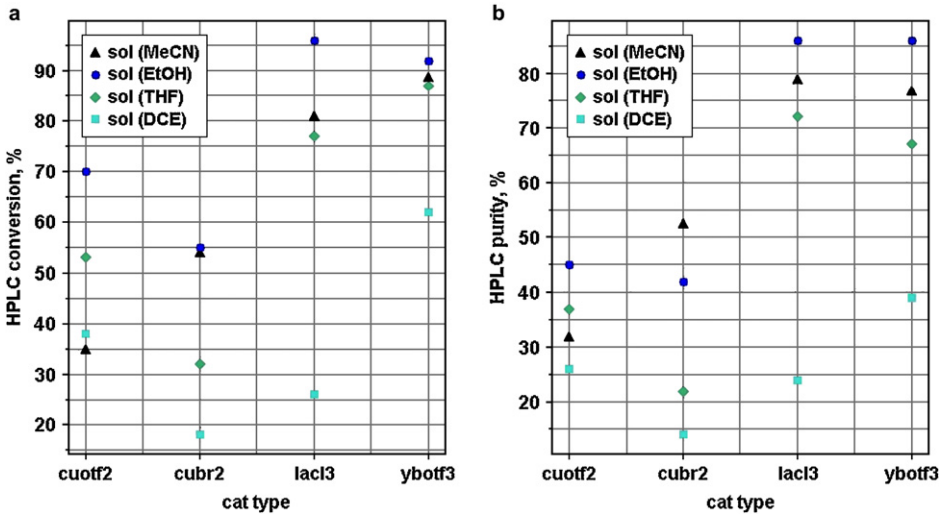


Figure 1. Interaction effects plot of the catalyst/solvent screening for the optimized synthesis of monastrol for (a) conversion and (b) purity. This type of plot enables the effect of both solvent and catalyst to be visualized simultaneously. Clearly the result in terms of conversion and purity is highly dependent on both the choice of solvent and catalyst.

$LaCl_3$ for all further optimization studies as this is less expensive. With this information in hand, we decided to next examine the effects of temperature, time, and catalyst concentration on the monastrol synthesis using $LaCl_3$/ethanol as the reaction medium. A second experimental design was devised. In this model, the effects and interactions between the reaction temperature and the reaction time were investigated. These two parameters were selected as quantitative factors for the design. A three level factorial design was selected using 100–120–140 °C for the temperature variation and 10–20–30 min for the time variation. The design consisted of eight runs plus two center point experiments (Table 1).

Table 1
Three level factorial design and results for a temperature–time dependence study of the Biginelli reaction (Scheme 1)[a]

Exp	Temp (°C)	Time (min)	Conversion[b] (%)	Purity[c] (%)
1	100	10	67	51
2	140	10	86	68
3	100	30	84	64
4	140	30	94	74
5	100	20	77	60
6	140	20	95	79
7	120	10	78	60
8	120	30	96	71
9	120	20	89	69
10	120	20	85	66

[a] Software-generated set of experiments including 8 main experimental points and 2 center points (experiments 9 and 10). For details on experimental conditions, see main text.
[b] HPLC conversion (peak area percent, 215 nm) based on 3-hydroxybenzaldehyde and product peak integration.
[c] HPLC purity (peak area percent, 215 nm), unreacted starting materials are considered as impurities.

As in the first design the molar ratio of ethyl acetoacetate/3-hydroxybenzaldehyde/thiourea/$LaCl_3$ was kept at 1.5/1.0/1.0/0.1, the mixture being dissolved in 1 mL pure ethanol. After microwave heating of the reaction mixtures 1–10 under the defined conditions (Table 1), the model was fitted with the values obtained for conversion and purity. The summary plot of the model displayed acceptable values for R^2 and Q^2 for both conversion (0.91 and 0.71) and purity (0.96 and 0.70) representing the model as good for our studies, which was also confirmed by 'Lack-of-Fit' and ANOVA plots (data not shown).[14] Figure 2 shows a plot for the coefficients of the model. As it can be seen, both temperature and time are significant (error bars small relative to the size of the bar) and have a positive impact on both conversion and purity. The additional square and interaction terms are not highly significant (error bars are large and span the axis), however, they are required to give a good model. It should be noted that the influence of these terms, particularly the time×time term differs for each of the responses. The contour plot (Fig. 3) shows a 'map' of the reaction space based on the results obtained by experimental design assessing temperature and time effects on the monastrol synthesis. Due to the presence of a slight curvature in the response for purity it can be predicted that at elevated temperatures (>140 °C) and prolonged reaction time (30 min) the product purity will drop.

The fact that higher reaction temperatures (>120 °C) in microwave-assisted Biginelli reactions using protic solvents such as ethanol will lead to reduced dihydropyrimidine product purities has been experimentally demonstrated previously and can be rationalized by partial decomposition of the urea/thiourea components.[10,15] With this information in hand, we decided to perform one additional experimental design to optimize the catalyst concentration. For this purpose another experimental matrix was assembled. In this model the effects and interactions between the reaction temperature and the quantity of catalyst employed in the reaction were studied.

These two parameters were selected as quantitative factors for the design, and conversion and purity were depicted as responses. For the variation of the factors, we selected 100–120–140 °C steps for the temperature variation and 5–10–15 mol % for the catalyst concentration. Again, we selected a three level factorial design to efficiently explore the reaction space. The set of suggested experiments contained eight design runs plus three center points (Table 2). The reagent ratio and amount of solvent were kept identical as in the previous design.

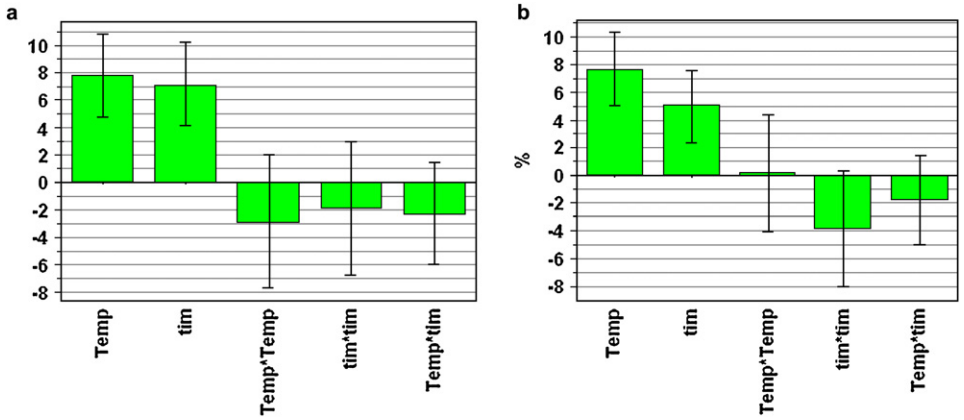


Figure 2. Coefficient plot for temperature–time effect screening for (a) conversion and (b) purity. Each plot contains the terms used in the statistical model. Positive bars indicate a positive impact of the term on the measured response. Negative bars indicate a negative effect. The significance of each term in the model is determined by the size of the bar relative to the error bar. Non-significant terms are small and have an error bar, which spans the axis.

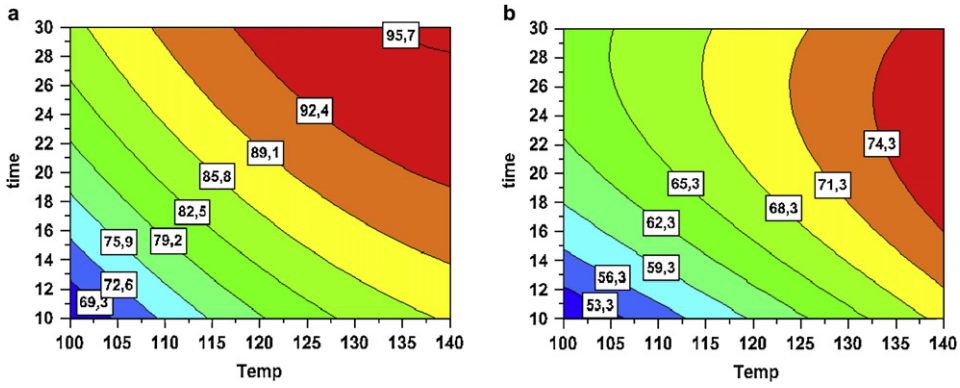


Figure 3. Response surfaces for (a) conversion and (b) purity in dependence of temperature and time. Each contour line indicates a level of the response, e.g., conversion for a given combination of the variables, in this case temperature and time. Blue areas indicate a low response and red areas indicate a high response, thus the optimal regions are red in these plots. Curvature of the lines indicates that the response is non-linear with respect to one or both of the factors. The purity response is strongly curved on the time axis, which is consistent with the significant time×time term in the model.

After microwave heating the reaction mixtures using the defined conditions, the model was fitted with the values obtained for conversion and purity. However, fitting the results gave a rather poor model with a low Q^2 value and poor reproducibility. To solve this problem the choice was either to attempt a more sophisticated type of design or to improve the prediction capability of the existing model by complementing the model with additional runs. Since the main purpose of DoE is to optimize a reaction with minimal effort and maximal efficiency, we opted for the second possibility. Using the MODDE8 software capabilities design was complemented with five additional runs (experiments 12–15, Table 2). As anticipated, inclusion of the results from the additional five experiments and re-fitting the optimized model, we were able to get somewhat better results. Still, the complemented model was not able to adequately describe the studied response. In the MODDE8 software the so-called 'Normal Probability Plot of Residuals' is available as part of the model analysis tools, which display the distribution of the responses on a double log scale. On this plot it is possible to detect obvious 'outliers', which do not fit well within the distribution of responses. By examining the Normal Probability Plot of Residuals for the results from experiments six and seven were depicted as strong outliers. Exclusion of these results and re-fitting of the model substantially improved the values for R^2 and Q^2 for both conversion (0.92 and 0.74) and purity (0.92 and 0.76), the validity and reproducibility of the model were correspondingly above 87%.

Table 2
Complemented three level factorial design for a temperature–catalyst concentration dependence study in the Biginelli reaction (Scheme 1)[a]

Exp	Temp (°C)	Catalyst (mol %)	Conversion[b] (%)	Purity[c] (%)
1	100	5	88	77
2	140	5	91	86
3	100	15	93	77
4	140	15	92	90
5	100	10	91	77
6[d]	140	10	88	86
7[d]	120	5	92	79
8	120	15	93	86
9[e]	120	10	93	82
10[e]	120	10	93	81
11[e]	120	10	93	85
12[f]	100	5	87	73
13[f]	140	5	93	91
14[f]	100	15	93	78
15[f]	140	15	95	91
16[f]	120	10	92	83

[a] Software-generated set of experiments including eight main experimental points, two center points, and five complementing experimental points. For details on experimental conditions, see main text.
[b] HPLC conversion (peak area percent, 215 nm) based on 3-hydroxybenzaldehyde and product peak integration.
[c] HPLC purity (peak area percent, 215 nm), unreacted starting materials are considered as impurities.
[d] Strong outliers excluded from the model.
[e] Center points.
[f] Complementing runs.

From the coefficient plot (Fig. 4) the pronounced temperature effect was evident, in particular on purity. The squared terms have a much greater impact on the conversion (large bars) than they do on the purity (small bars and large error bars). This suggests that the conversion is non-linear with respect to both temperature and catalyst concentration. The 2D surface plot (Fig. 5) represented the dependence of the conversion and purity of monastrol formation on the temperature and catalyst concentration. As it is evident from the plot, the purity has an almost linear dependence of the catalyst concentration and temperature variation (consistent with the coefficient plot shown in Fig. 4b). However, in the case of conversion we observe a strong curvature in the response particularly with respect to the catalysts concentration (this is again consistent with the coefficient plot shown in Fig. 4a). These plots taken together suggest that optimal performance in the synthesis of monastrol (in terms of purity) is predicted when the catalyst concentration and temperature are at a maximum—140 °C and 15 mol % of $LaCl_3$ (Fig. 5b), but the best results in terms of conversion could be achieved at around 125 °C and 10 mol % $LaCl_3$.

The final optimized conditions for the synthesis of monastrol (Scheme 1) were determined using the MODDE8 sweet-spot function (Fig. 6). We targeted maximum conversion and purity (conversion being more important). However, the sweet-spot region for the temperature–catalyst design was

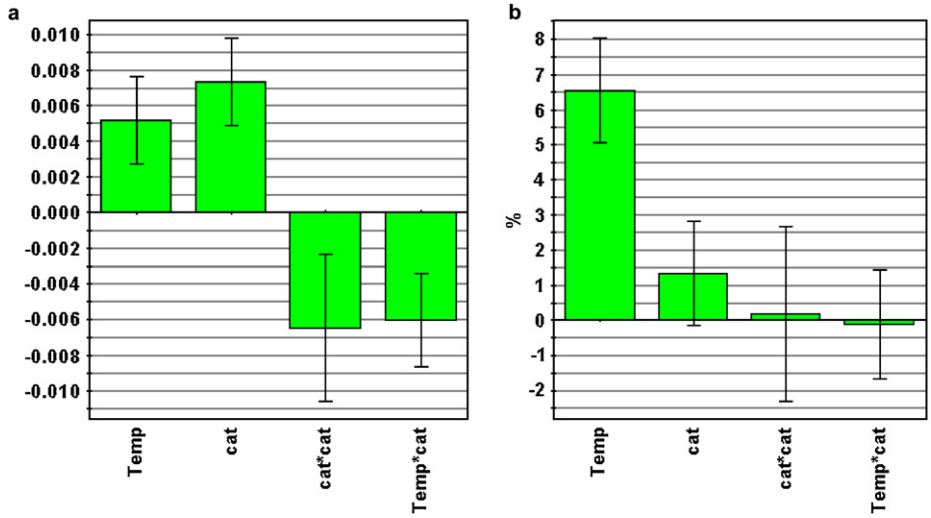


Figure 4. Coefficient plot for temperature–catalyst amount effect screening: for (a) conversion and (b) purity. Each plot contains the terms used in the statistical model. Positive bars indicate a positive impact of the term on the measured response. Negative bars indicate a negative effect. The significance of each term in the model is determined by the size of the bar relative to the error bar. Non-significant terms are small and have an error bar, which spans the axis.

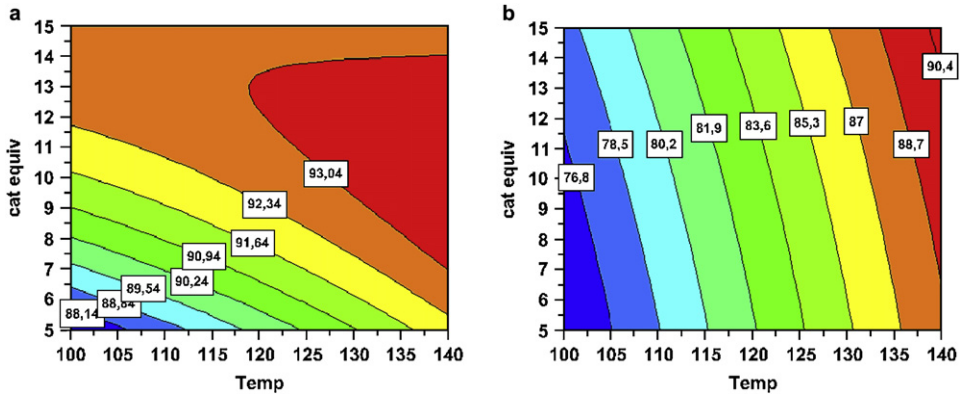


Figure 5. Response surfaces for (a) conversion and (b) purity in dependence of temperature and catalyst concentration.

narrower than the one for the temperature–time model (still including the desired area from the first one—Fig. 6b), as a result the temperature–catalyst sweet spot was selected as the one of higher importance. A sweet spot corresponding to 140 °C and 12 mol % $LaCl_3$ was selected from Figure 6a as the optimal set of conditions for the reaction. For the duration of the microwave irradiation 30 min were considered as optimum. The response for conversion was predicted to be 93% and the obtained response was 94%, leading to 82% isolated yield after chromatographic work-up.

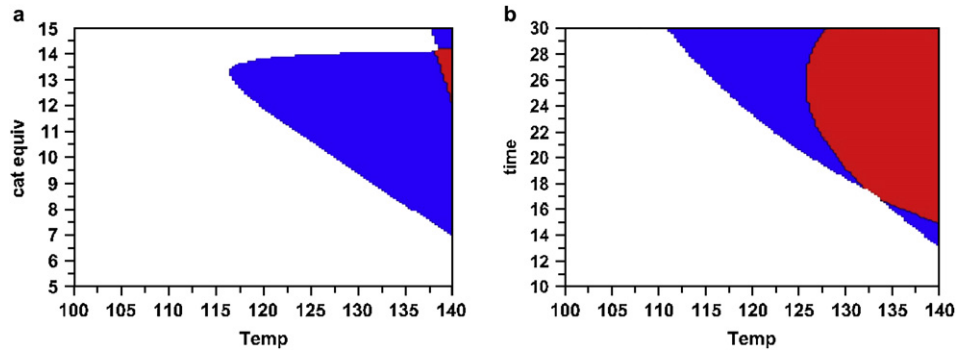


Figure 6. Sweet-spot prediction plots for (a) temperature versus catalyst amount (the set desired values for conversion are in the range 93–95% and 90–100% for purity), and (b) temperature versus time (the set desired values for conversion are in the range 90–96% and 72–80% for purity). Areas in red meet both given criteria, areas in blue meet one of the criteria and in the white area no criteria is met.

3. Conclusion

In summary, combining the advantages of automated high speed microwave synthesis and a statistical design of experiments (DoEs) approach has allowed the rapid screening for an optimum catalyst/solvent system and for temperature–time–catalyst concentration conditions for the synthesis of the mitotic kinesin Eg5 inhibitor monastrol. The now proposed $LaCl_3$/ethanol catalyst/solvent system was demonstrated to be as effective as the more traditionally employed $Yb(OTf)_3$/acetonitrile combination. As a final remark it should be mentioned that these statistically driven studies required a set of 29 experiments in total. By using HPLC as rapid analytical tool, the full set of optimizations could be performed in a very short time span.

4. Experimental

4.1. General

Microwave-assisted reactions were performed on a Discover (CEM Corporation) single mode microwave instrument at 2450 MHz controlled irradiation using standard sealed microwave glass vials. For the statistical model generation and evaluation of the responses, MODDE8 (Umetrics) software was used. Reaction temperatures were monitored by an IR sensor on the outside wall of the reaction vials. Reaction times refer to hold times at the selected set temperature, not to total irradiation times. ^{1}H NMR spectra were recorded on a Bruker AMX 360. Low resolution mass spectra were obtained in the atmospheric pressure chemical ionization (positive or negative APCI mode). Analytical HPLC analysis was carried out on a LiChrospher 100 C18 reversed-phase analytical column (119×3 mm, 5 μm particle size) at 25 °C, using mobile phase A (water/MeCN 9/1 (v/v)+0.1% TFA) and phase B (MeCN+0.1% TFA), with linear gradient from 30% B to 100% B in 8 and 2 min with 100% phase B. Chromatographic product purification was performed as previously described.[9] Melting points were recorded on a GALLENKAMP melting point apparatus.

4.2. Experimental procedure for design 1 (catalyst/solvent optimization/full factorial design—mixed)

The design matrix consists of 19 runs (16 main runs plus 3 center points), automatically generated by the MODDE8 software. These were performed in a random fashion in accordance to the software-generated worksheet table. The screening runs were performed as follows: in a 10 mL Pyrex microwave vial, 3-hydroxybenzaldehyde (100 mg, 0.82 mmol, 1 equiv), ethyl acetoacetate (157 μL, 1.23 mmol, 1.5 equiv), thiourea (60.7 mg, 0.82 mmol, 1 equiv), and the corresponding catalyst—$LaCl_3$ (24.5 mg, 0.082 mmol, 0.10 equiv), $Cu(OTf)_2$ (29.7 mg, 0.082 mmol, 0.12 equiv), $CuBr_2$ (18.3 mg, 0.082 mmol, 0.12 equiv), or $Yb(OTf)_3$ (50.9 mg, 0.082 mmol, 0.12 equiv) were added to 1 mL ethanol, tetrahydrofuran, dichloroethane, or acetonitrile. After magnetic stirring for 2 min, the vial was closed, placed in the microwave cavity, and irradiated at 140 °C for 30 min (fixed hold time). After the reaction was completed, an aliquot sample of the reaction mixture was taken and subjected to HPLC analysis (215/254 nm) in order to determine the conversion/purity for the corresponding run.

4.3. Experimental procedure for design 2 (temperature–time optimization/three level factorial design)

The design matrix consists of 10 runs (8 main runs plus 2 center points, see Table 1), automatically generated by the MODDE8 software. These were performed in a random fashion in accordance to the software-generated worksheet table. The screening runs were performed as follows: in a 10 mL Pyrex microwave vial, 3-hydroxybenzaldehyde (100 mg, 0.82 mmol, 1 equiv), ethyl acetoacetate (157 μL, 1.23 mmol, 1.5 equiv), thiourea (60.7 mg, 0.82 mmol, 1 equiv), and 10 mol % $LaCl_3$ (24.5 mg, 0.082 mmol, 0.10 equiv) were added to 1 mL ethanol. After magnetic stirring for 2 min, the vial was closed, placed in the microwave cavity, and irradiated at 100, 120, or 140 °C for 10, 20, or 30 min (fixed hold time). After the reaction was finished, an aliquot sample of the reaction mixture was taken and subjected to HPLC analysis (215/254 nm) in order to determine the conversion/purity for the corresponding run.

4.4. Experimental procedure for design 3 (temperature–catalyst amount optimization/three level factorial design)

The design matrix consists of 11 runs (8 main runs plus 3 center points, see Table 2), automatically generated by the MODDE8 software. These were performed in a random fashion in accordance to the software-generated worksheet table. The screening runs were performed as follows: in a 10 mL Pyrex microwave vial, 3-hydroxybenzaldehyde (100 mg, 0.82 mmol, 1 equiv), ethyl acetoacetate (157 μL, 1.23 mmol, 1.5 equiv), thiourea (60.7 mg, 0.82 mmol, 1 equiv), and $LaCl_3$—5 mol % (10.1 mg, 0.041 mmol, 0.05 equiv), 10 mol % (24.5 mg, 0.082 mmol, 0.10 equiv), or 15 mol % (30.1 mg, 0.123 mmol, 0.15 equiv)—were added to 1 mL ethanol. After magnetic stirring for 2 min, the vial was closed, placed in the microwave cavity, and irradiated at 100, 120, or 140 °C for 30 min (fixed hold time). After the reaction is finished, an aliquot sample of the reaction mixture was taken and subjected to HPLC analysis (215/254 nm) in order to determine the conversion/purity for the corresponding run. Five more experimental runs were performed for complementing the design after the first fitting (see Table 2). These were automatically generated and added to the previous set by the MODDE8 software. They were performed in a random fashion in accordance to the software-generated worksheet table and include the following experimental points: 100 °C with 5 mol % $LaCl_3$, 140 °C with 10 mol % $LaCl_3$, 100 °C with 15 mol % $LaCl_3$, 140 °C with 15 mol % $LaCl_3$, and 120 °C with 10 mol % $LaCl_3$. The five complementary runs were analyzed in the manner described above.

*4.5. Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (monastrol, **1**): optimized protocol*

In a 10 mL Pyrex microwave vial, 3-hydroxybenzaldehyde (100 mg, 0.82 mmol, 1 equiv), ethyl acetoacetate (157 μL, 1.23 mmol, 1.5 equiv), thiourea (60.7 mg, 0.82 mmol, 1 equiv), and $LaCl_3$ (24.5 mg, 0.082 mmol, 0.10 equiv) were added to 1 mL anhydrous ethanol. After magnetic stirring for 2 min, the vial was closed, placed in the microwave cavity, and irradiated at 140 °C for 30 min (fixed hold time). After the reaction was finished, the solvent was removed under reduced pressure and the residue subjected to silica gel chromatography (chloroform/acetone=5/1), resulting in the isolation of the pure product in 82% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.12 (t, J=6.9 Hz, 3H), 2.27 (s, 3H), 4.02 (q, J=6.6 Hz, 2H), 5.51 (d, J=1.44 Hz, 1H), 6.61–6.70 (m, 3H), 7.06–7.17 (m, 1H), 9.44 (s, 1H), 9.60 (s, 1H), 10.29 (s, 1H). Mp 183–185 °C (MeCN), lit.[9] mp 184–186 °C.

Acknowledgements

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14. R^2 is a statistical parameter, which defines the goodness of fit of the model. The closer to 1 this value is the better the fit. Q^2 defines the goodness of prediction of the model. Again this should be as close to 1 as possible. Only a model with good R^2 and Q^2 can be reliably used in a predictive sense.
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