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Use of a Design of Experiments approach for the optimisation of a microwave assisted Ugi reaction

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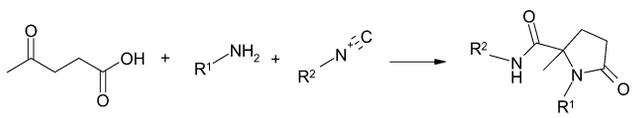
The utility of a Design of Experiments (DoE) approach for the rapid and efficient optimisation of a microwave assisted Ugi 3cc reaction of levulinic acid is demonstrated. DoE methods have also been applied to the assessment of the reaction scope for a range of amine and isonitrile substrates. The optimal procedure developed using this approach has enabled the preparation of lactam derivatives in moderate to excellent yields (17–90%) in a reaction time of only 30 min compared to the conventional methodology which required up to 48 h.

In recent years the use of microwave irradiation to accelerate reactions has become increasingly popular.[1] The availability of single mode microwave reactors which enable the fine control of temperature and pressure during microwave reactions has further enhanced the use of this technique in organic synthesis.[2] One key advantage of using microwaves is the flash heating effect, which often leads to much reduced reaction times from hours down to minutes. To make the most of this feature it is essential that an efficient optimisation protocol is followed to rapidly identify the optimal conditions for the microwave assisted reaction.

In the course of our studies we have found that the use of a Design of Experiments (DoE) approach allows for the efficient determination of optimal conditions for microwave assisted reactions. DoE has been extensively used in process research for the optimisation of large scale chemistries however it can be readily applied to reactions on any scale.[3–5] As part of our ongoing investigations into multi-component reactions[6,7] we report here on the use of DoE to identify optimal conditions for an Ugi 3cc reaction and to explore the scope of this reaction for a range of substrates.

The Ugi 3cc reaction of levulinic acid **1** with an amine **2** and an isonitrile **3** has been reported to proceed at room temperature in methanol solvent to give the lactam derivatives **4** in moderate yields over a period of 48 h.[8] We sought to find a microwave assisted protocol for this reaction to provide the desired adducts in a short time period (ideally less than 30 minutes) and in acceptable yields. Using the MODDE 7™ DoE software from Umetrics[9] we designed a set of screening reactions to determine the factors which had a significant effect on the yield of the reaction (Scheme 1).

The factors we decided to investigate were equivalents of amine, concentration, imine pre-formation time,[10] microwave reaction time and microwave temperature. We employed a two level fractional factorial design (resolution IV, allowing interaction effects to be modelled) giving 18 experiments plus two centre points. The reactions were carried out in a CEM Discover microwave using 10 ml reaction vessels sealed with pressure caps. The extent of conversion was determined by HPLC analysis with integration of the UV peak area of product relative to an internal standard (dimethyl bromoterephthalate).



Scheme 1 Ugi reaction of levulinic acid **1** to form lactams **4a**–**h**.

The data was fitted in MODDE 7™ using partial least squares fitting (PLS) giving a model in which R^2 (the goodness of fit of the model) and Q^2 (the goodness of prediction of the model) were 0.82 and 0.57 respectively.[11] The model was considered to be good enough for screening purposes. The low level of Q^2 is due to the non-linear response to microwave temperature requiring a squared term to be included in the model.[12] The effect of the factors on the response is represented by the coefficient plot (Fig. 1). The sign of the coefficient determines whether the factor should be high or low, the size of the bar indicates the importance of that factor in the model. In cases where the bar is much smaller than the confidence interval it is likely that the factor is not very significant. From Fig. 1 the key factors can be identified as microwave reaction time (+), microwave temperature (+), concentration (−), amine equivalents (small +). It was thought likely that the imine pre-formation was insignificant. This was confirmed by comparing the contour plots for 0 min and 30 min imine pre-formation showing optimal conversions of 60 and 67% respectively (Fig. 2 a and b).

The reaction was then repeated, in the absence of internal standard, under the optimal conditions indicated in the screen. The reaction mixture was made up in the microwave tube using 1.5 equivalents of amine **2a** at 0.2 M concentration in methanol. The tube was then sealed and irradiated at 100 °C for 30 min in the Discover microwave. The desired product **4a** was isolated in 90% yield (100% purity) after column chromatography. This was considered to be a satisfactory result for our purposes and no further optimisation was carried out.

The next phase of the investigation was to determine how applicable this procedure was to a range of substrates. Again we chose to use a DoE approach using a D-optimal design which can accommodate multiple levels of qualitative factors.

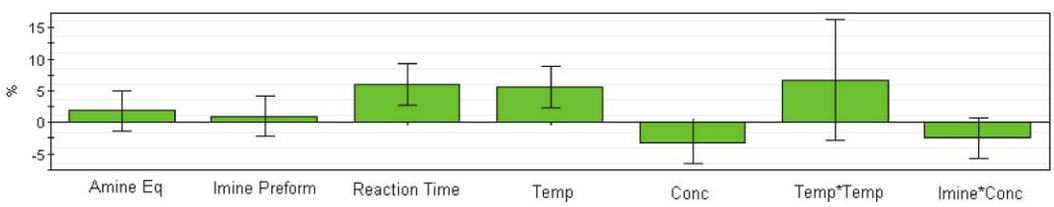


Fig. 1 Coefficient plot for the initial screening experiments.

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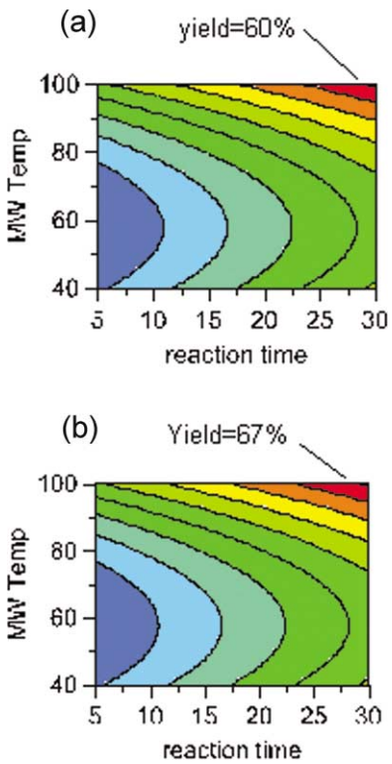

Fig. 2 (a) Contour plot for 1.5 eq amine, 0.2 M concentration and 0 min imine preformation. (b) Contour plot for 1.5 eq amine, 0.2 M concentration and 30 min imine preformation.

MODDE 7™ was used to generate a design of 16 runs in which each experiment was replicated twice to assess the reproducibility of the procedure. The substrates were chosen to reflect the different reactivity of the amines and isonitriles (Fig. 3).

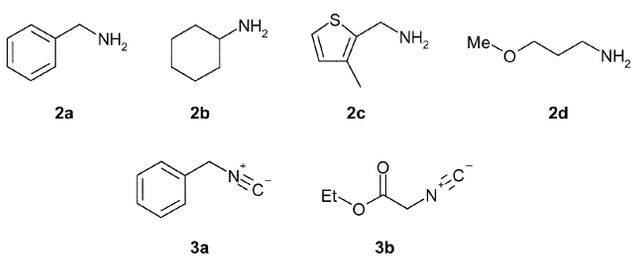

Fig. 3 Amine and isonitrile substrates used in the scoping study.

The reactions were carried out using the optimal procedure (in the case of the ethyl isocyanoacetate substrate ethanol was used as solvent to avoid problems with transesterification). The conversion was determined by NMR analysis of the crude reaction mixture and the products isolated after purification using column chromatography (Table 1). In most cases the reproducibility of the procedure was good. The interaction plot (Fig. 4) shows how the conversion varied across the range of substrates. In general all of the amines performed well in combination with benzyl isonitrile **3a** (>80%) however the results with ethyl isocyanoacetate **3b** were quite varied (39–88%). In the context of using this chemistry for the synthesis of a library of Ugi adducts this variability would not be satisfactory and further optimisation for the ethyl isocyanoacetate substrate would be required.

Table 1 Results of scoping experiments based on the D-optimal design

Amine	Isonitrile	Product	Conversion (%)	Yield (%)
2a	**3a**	**4a**	97, 98	90
2b	**3a**	**4b**	82, 84	68
2c	**3a**	**4c**	80, 82	89
2d	**3a**	**4d**	94, 94	49
2a	**3b**	**4e**	76, 81	33
2b	**3b**	**4f**	39, 45	24
2c	**3b**	**4g**	88, 81	43
2d	**3b**	**4h**	56, 72	17

In conclusion we have demonstrated the utility of a DoE approach for the rapid and efficient optimisation of microwave assisted reactions. We have further shown that DoE methods can assist with the assessment of the scope of the microwave assisted reaction when applied to a range of substrates. The outcome of this study has been the elucidation of a microwave assisted procedure for the Ugi 3cc reaction of levulinic acid yielding lactam products in moderate to excellent yield after only 30 min of reaction compared to the conventional procedure which required a 48 h reaction period.

Experimental

To a 10 ml microwave tube was added MeOH (1 ml), levulinic acid (23 mg, 0.2 mmol), benzylamine **2a** (33 μL, 0.3 mmol), and benzylisonitrile **3a** (24 μL, 0.2 mmol) with stirring at room temperature. The tube was sealed with a pressure cap and placed in the microwave cavity. The sample was irradiated for 30 min at 100 °C and then allowed to cool to room temperature. The reaction solvent was evaporated and the residue dissolved in dichloromethane and washed with ammonium chloride solution (sat. aq.) followed by sodium hydroxide solution (2 M). The organic layer was then dried over sodium sulfate, filtered and the solvent evaporated. Purification by column chromatography on silica gel eluted with 9 : 1 ethyl acetate–hexane gave the desired product **4a** (58 mg, white solid) in 90% yield. δ_H (400 MHz; $CDCl_3$) 7.3–7.2 (8H, m), 7.15–7.05 (2H, m), 6.3 (bs, 1H, NH), 4.58 (1H, d, J_{AB} 15), 4.35 (1H, dd, J_{AB} 15, J_{AX} 6), 4.29 (1H, d, J_{AB} 15), 3.99 (1H, dd, J_{AB} 15, J_{BX} 5), 2.5–2.4 (2H, m), 2.4–2.3 (1H, m), 2.0–1.9 (1H, m), 1.45 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 176.2 (C=O), 173.1 (C=O), 137.9 (C), 137.7 (C), 128.8 (CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 67.7 (C), 44.7 (CH_2), 43.7 (CH_2), 33.5 (CH_2), 29.5 (CH_2), 23.1 (CH_3); *m/z* (ES^+) 323 (M + 1, 100%).

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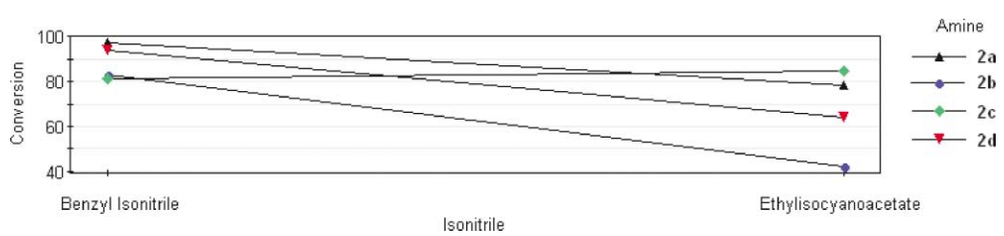

Fig. 4 Interaction plot for the scoping study using a D-optimal design.

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9 www.umetrics.com.
10 Many protocols for performing Ugi 4cc and 3cc reactions employ an imine pre-formation step.
11 A good model has R^2 and Q^2 values close to 1. For screening purposes $R^2 > 0.8$ and $Q^2 > 0.5$ is desirable.
12 Experimental designs which support non-linear responses are generally of the central composite type requiring a larger number of experiments to be carried out.