

Report

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Reports

Reproducibility Across Microwave Instruments: Preparation of a Set of 24 Compounds on a Multiwell Plate under Temperature-Controlled Conditions

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Introduction. High-speed microwave synthesis has drawn a considerable amount of attention in recent years.¹ The application of microwave heating technology to the preparation of compound libraries has attracted the interest of the medicinal chemistry community as a powerful tool for rapid analogue synthesis while carrying out drug discovery. The blending of microwave heating technology and parallel synthesis is a logical consequence of the significant rate enhancements and higher product yields associated with the use of microwave ovens and the increase in productivity afforded by combinatorial chemistry techniques.² In general, two approaches have been used for microwave assisted parallel and combinatorial chemistry: On one hand, series of compounds are prepared sequentially in an automated single-mode instrument, allowing for control of temperature and pressure in each reaction independently. On the other hand, compounds are prepared in parallel arrays using a multimode instrument. The use of a single-mode instrument offers the advantage of full control of each reaction. However, in this case, all reactions must be processed sequentially, and this could provide a bottleneck in productivity, especially for large series of compounds. Multimode instruments offer the possibility to perform multiple reactions in one irradiation experiment, but reactions are usually

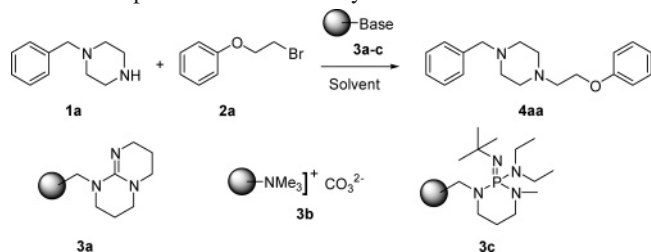
performed without an appropriate control of the temperature, which limits the reproducibility of the experiments, especially when unmodified domestic ovens are used.³

While irradiating multiwell polypropylene plates using household microwave ovens, some researchers have reported problems in connection with the thermal instability of the polypropylene material and temperature gradients developing between individual wells upon microwave heating.^{2a} To overcome these problems, Nüchter and Ondruschka⁴ recently described a reactor system⁵ that improves heating efficiency and enhances thermal stability and generally provides a better performance when compared to the classical polypropylene-based system. One key advantage to the Nüchter and Ondruschka system is that the temperature of the block is controlled with a fiber-optic sensor underneath the reaction vessel. Grieco et al. recently demonstrated the utility of this system by preparing six peptides on solid support.⁶ Despite these findings, the application of this system for the preparation of series of compounds using microwave irradiation has not been reported.

One of the key issues when carrying out microwave chemistry is reproducibility when going from one type of instrument to another. Obviously, it is desirable to obtain consistent results when switching instruments. Examining the reproducibility between microwave ovens has been recently reported, but the focus of these programs related to challenges associated with changing the scale of the reactions when going from a single-mode to multimode ovens.^{7,8} In this report, comparison of results between single-mode and multimode microwave ovens, when applying these instruments to preparing sets of compounds, is described. The results of these experiments validate the use of multiwell plates under microwave irradiation as an alternative to speed up parallel synthesis.

Results and Discussion. To compare the results between both instruments, N-alkylation was used as a model reaction. The initial experiments were designed to optimize temperature, equivalents of the alkylating reagent **2a**, time, base,

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Table 1. Optimization of N-Alkylation

entry	<i>T</i> (°C)	2a (equiv)	<i>t</i> (min)	base	solvent	<i>Y</i> (%) ^a
1	100	1.2	5	3a	NMP	81
2	120	1.2	5	3a	NMP	85
3	140	1.2	5	3a	NMP	88 (1) ^b
4	150	1.2	5	3a	NMP	88 (3) ^b
5	150	1.2	5	3a	DMF	86 (3) ^b
6	150	1.2	5	3a	DMSO	83 (5) ^b
7	150	1.2	5	3b	NMP	46 ^c
8	150	1.2	5	3c	NMP	55 ^c
9	140	1.2	10	3a	NMP	86 (4) ^b
10	140	1.3	5	3a	NMP	89 (1) ^b
11	140	1.5	5	3a	NMP	87 (3) ^b

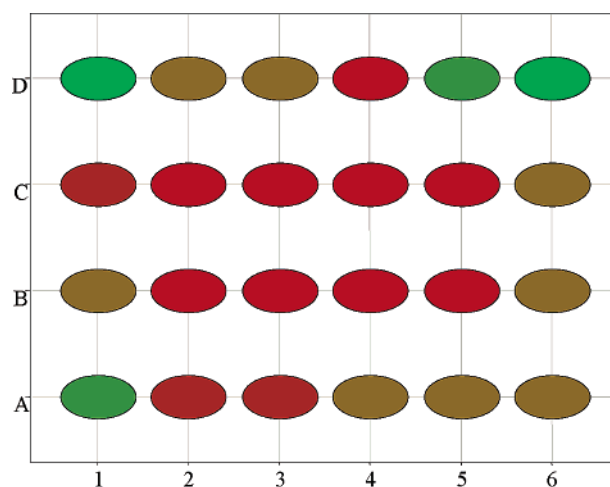
^a Percentages are based on the product peak area by LC/MS.

^b In parentheses, amount of quaternized product based on peak area by LC/MS. ^c Different byproducts were detected in the crude.

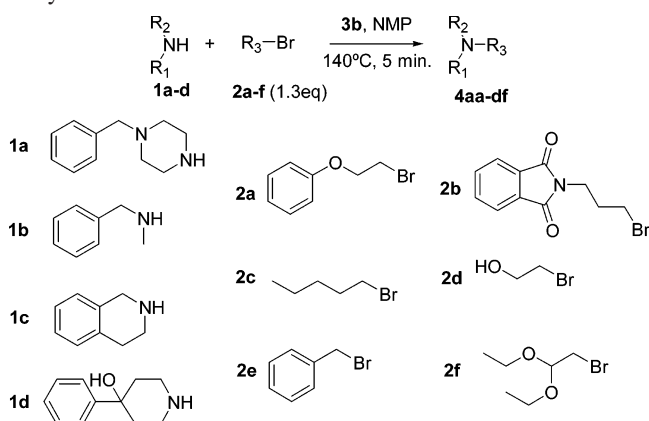
and solvent in a single-mode oven, as full control of individual reactions are maintained in this reactor.⁹ The results are given in Table 1.¹⁰ Note the yield of the desired product increased with temperature as expected, but at 150 °C (entry 4) no further progression of the reaction was detected, and the amount of quaternized product increased. The effect of changing the solvent from NMP to DMF or DMSO did not seem to have a dramatic impact on the reaction (entries 4–6);¹¹ however, the nature of the base influenced the outcome of the reaction (entries 7 and 8). To explore the effect of longer reaction times and larger amounts of alkylating agent, the temperature of the reaction was reduced 10 °C to avoid as much as possible the presence of quaternized products. When the time was doubled (entry 9), the yield decreased due to the presence of some traces of dialkylated product. Finally, the use of 1.3 equiv of **2a** provided the best balance between conversion, yield, and lack of dialkylated byproducts (entry 10).

Heating homogeneity of the multiwell plate was tested using 24 equal reactions at 100 °C for 5 min (Table 1, entry 1), similar to previously reported conditions.⁸ Under these nonoptimized conditions, reactions were not allowed to proceed to completion in order to examine and compare the progress of the reaction in each reaction vessel.¹²

The yields obtained in the multimode oven ranged from 80 to 87%. Comparing these results with the data obtained in the single-mode instrument (Table 1, entry 1), it is interesting to note that reaction yields are slightly higher in the multimode instrument than in the single-mode, and it can be concluded that the system offered enough reproducibility to develop further parallel chemistry. When yields were distributed according to their position in the plate (Figure 1) it could be observed that the highest yields were achieved in the center of the plate; meanwhile, the lowest were located at the corners. Nüchter and Ondruschka observed similar results.⁴



■ 80% ■ 87%

Figure 1. Yield distribution throughout the plate after irradiation with the multimode instrument.**Scheme 1.** N-Alkylation of Four Amines with Six Alkylbromides

Once the performance of the multiwell plate was evaluated, a set of 24 different compounds was prepared in parallel using the fully optimized conditions given in Table 1 entry 10, combining four amines with six alkylating agents (Scheme 1). To make an appropriate correlation across instruments, the same reactions were performed in the single-mode reactor. Results of the experiments are presented in Table 2.

According to these results, good reproducibility between both instruments was achieved. On average, the difference in yield between both instruments is ~2.3%. The maximum difference in yield is 6%, entry 15. Moreover, the alkylation of the amine **1a** with **2d** and **2f** was not completed under the general reactions conditions reported here. These results were achieved with both instruments (entries 4 and 6). One important feature that should be noticed is the time used to perform these 24 reactions. The single-mode instrument needed 2.5 h to complete the whole sequence of reactions; meanwhile, the multimode used only 40 min to get comparable results, and for this reason, this system blended the advantages of parallel approach and microwave heating.

In conclusion, using a simple N-alkylation reaction as a model, the performance of the multiwell plate was evaluated, and the system provided enough reproducibility of results

Table 2. Comparison of Results for the Preparation of 24 Individual Compounds Using Single-Mode and Multimode Instruments

entry	product	1a–d	2a–f	single-mode yield (%) ^a	multimode yield (%) ^a
1	4aa	1a	2a	89	88
2	4ab	1a	2b	84	87
3	4ac	1a	2c	90	86
4	4ad	1a	2d	61	63
5	4ae	1a	2e	91	96
6	4af	1a	2f	56	59
7	4ba	1b	2a	85	85
8	4bb	1b	2b	83	84
9	4bc	1b	2c	86	87
10	4bd	1b	2d	76	74
11	4be	1b	2e	92	95
12	4bf	1b	2f	70	72
13	4ca	1c	2a	91	92
14	4cb	1c	2b	78	81
15	4cc	1c	2c	87	81
16	4cd	1c	2d	84	79
17	4ce	1c	2e	86	88
18	4cf	1c	2f	85	87
19	4da	1d	2a	94	94
20	4db	1d	2b	89	92
21	4dc	1d	2c	96	94
22	4dd	1d	2d	94	95
23	4de	1d	2e	94	93
24	4df	1d	2f	90	91

^a Percentages are based on the product peak area by LC/MS.

to develop further parallel chemistry. Using fully optimized conditions, sets of 24 compounds were synthesized in the well plate and in the single-mode instrument at the same time. The comparison of the results obtained from both systems showed no major yield differences. For this reason, the preparation of compounds in multiwell plates under microwave irradiation effectively combines productivity and speed. Ongoing work devoted to extending this approach to other reactions in a parallel format will be the subject of future publications.

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Supporting Information Available. Full experimental details and characterization of the compounds are available as Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) As the single-mode instrument, we used Emrys Optimizer microwave reactor (Personal Chemistry A. B., currently Biotage). Temperature of the reaction is measured by an IR sensor outside the vial. A detailed description of the instrument can be found in www.biotage.com.
- (10) Yields are based on the product peak area as compared to total peak area of an LC/MS chromatogram (UV, DAD). The reported yields are calculated from analysis of the crude reaction mixtures and should be interpreted as an indication of the yields in which the products are formed. Results were confirmed in two independent experiments.
- (11) Due to the limitations of the CombiCHEM reactor, high boiling point solvents were used. To facilitate the work up of the reaction, polymer-supported bases were used because they are more suitable for parallel synthesis.
- (12) Detailed results of these experiments are included in the Supporting Information.

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