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Microwave Heating Outperforms Conventional Heating for a Thermal Reaction that Produces a Thermally Labile Product: Observations Consistent with Selective Microwave Heating

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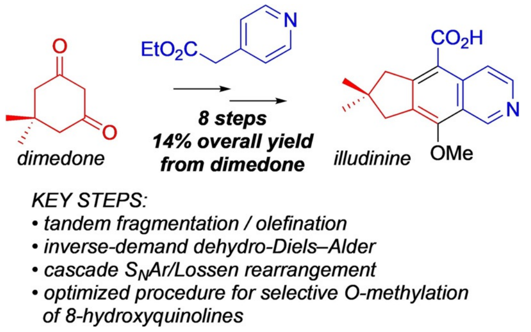
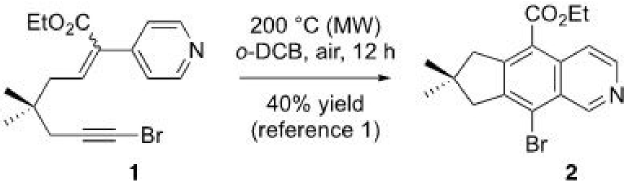
Abstract: Microwave (MW) heating is more effective than conventional (CONV) heating for promoting a high-temperature oxidative cycloisomerization reaction that was previously reported as a key step in a total synthesis of the natural product illudinine. The thermal reaction pathway as envisioned is an inverse electron-demand dehydro-Diels–Alder reaction with in situ oxidation to generate a substituted isoquinoline, which itself is unstable to the reaction conditions. Observed reaction yields were higher at a measured bulk temperature of 200 °C than at 180 °C or 220 °C; at 24 hours than at earlier or later time points; and when the reaction solution was heated using MW energy as opposed to CONV heating with a metal heat block. Selective MW heating of polar solute aggregates is postulated to explain these observations.

We recently reported a synthesis of illudinine[1] in conjunction with broader efforts to produce targets of interest bearing neopentylene ring fusions.[2] Previously reported syntheses of illudinine required 14[3] to 16[4] steps, many of which were dedicated to crafting the neopentylene ring fusion. Our reported synthesis of illudinine featured tandem fragmentation and olefination methodology from our lab,[5] and it was relatively efficient, providing synthetic illudinine in 8 steps and 14 % overall yield from commercially available dimedone (Scheme 1).



Scheme 1. Overview of illudinine synthesis from reference 1.

Our synthesis of illudinine featured a key oxidative cycloisomerization (Scheme 2). Related oxidative cycloisomerizations of styrenes have been reported recently,[6] along with evidence that they proceed by way of an intramolecular Diels–Alder (IMDA) cycloaddition followed by concerted extrusion of molecular hydrogen.[6b] We built from this work to examine inverse electron-demand vinylpyridine Diels–Alder substrates (e.g., **1**), finding that the bromoalkyne (as opposed to the terminal alkyne) was necessary for cycloisomerization to outcompete general decomposition in the reaction mixture. The 40 % yield of isoquinoline **2** that we observed was sufficient to advance material through to the final target, but it was the weakest link in our chain of synthetic reactions.



Scheme 2. Thermally promoted oxidative cycloisomerization reaction.

Here we report a re-examination of this reaction, paying particular attention to any differences between microwave (MW) and conventional (CONV) heating.[7] In contrast to the 40 % yield we reported using MW heating (Scheme 2), CONV heating produced isoquinoline **2** in only 15 % yield after 12 hours. The yield of **2** increased to 39 % after 24 hours of CONV heating, but it diminished to 23 % after 36 hours. These observations gave us cause for concern that the isoquinoline product was not stable to the high-temperature reaction conditions. We confirmed the thermal instability of isoquinoline **2** by heating it at 220 °C in 1,2-dichlorobenzene and monitoring its disappearance over time as it decomposed into a complex mixture of unidentified products (Table 1).

In total, we examined three reaction temperatures (180 °C, 200 °C, and 220 °C) at various time-points using both MW and CONV heating (Table 2). Two trends emerged. First, at each of the three temperatures, the yield of product increases within the first 24 hours, then decreases thereafter, presumably due to the competition between product formation and its thermal decomposition. Second, *MW heating is systematically superior to CONV heating* in all direct comparisons.

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Table 1. Thermal stability test for isoquinoline **2**.

t [h][a]	Mole fraction of **2**[b]
0	1.00
6	0.89
12	0.76
18	0.61
24	0.51
36	0.17
48	0.08

[a] Isoquinoline **2** in 1,2-dichlorobenzene heated at 220 °C in a sealed vial for different lengths of time. [b] The normalized mole fraction of **2** remaining relative to an internal standard after each time period, as estimated by ^{1}H NMR analysis. See SI for more details.

Table 2. Comprehensive set of yields for the oxidative cycloisomerization of 1→2 at various times and temperatures using either MW heating[a] or CONV heating.

Entry	*T* [°C]	*t* [h]	% Yield [MW heating]	% Yield [CONV heating]
1	180	12	34	13
2	180	24	42	22
3	180	36	30	17
4	180	48	21	10
5	180	72	10	<5
6	200	12	39; 40[b]	15
7	200	17	56;[b] 58	26
8	200	24	62; 62[b]	39
9	200	30	51;[b] 53	29
10	200	36	49;[b] 50	23
11	220	12	40	15
12	220	17	49	26
13	220	24	55	28
14	220	30	38	20

[a] MW heating temperature was recorded using a calibrated external IR sensor except where noted. [b] MW heating temperature was recorded using an internal fiber optic probe.

Figure 1. Cartoon representation of selectively heated polar nanophases in nonpolar solution.

Microwave heating is well established and accepted as a useful *tactical* approach to organic reactions, in that dedicated MW reactors are known to provide rapid and uniform heating to high temperatures and pressures in a manner that is safe, convenient, and practical for routine use in chemical synthesis.[8,9] In contrast, the *strategic* application of MW heating—to achieve results in solution-phase organic reactions that cannot be obtained using CONV heating—remains a matter of ongoing interest[10–12] and debate.[7,12m] We have reported several examples of specific reactions that can be accelerated by MW heating above and beyond Arrhenius predictions for the measured bulk temperature,[13–15] and we have advanced a working hypothetical model involving selective MW heating of polar components of a reaction mixture—perhaps aggregated into soluble polar nanophases in otherwise non-polar solution (Figure 1)—to rationalize our observations.[16,17]

As applied here, our tentative explanation is that *selective MW heating of the starting material accelerates product formation relative to product decomposition.* Starting material **1** may aggregate in solution into polar nano/microscale domains that are more susceptible to MW heating than the less polar bulk solvent. Generation and transient storage of thermal energy therein creates chemically defined temperature domains that are hotter than the bulk solution.[17] Product (**2**) that forms in these high-temperature domains can subsequently partition into the lower temperature bulk solution, provided that the product is better solvated than the starting material. If the starting material is selectively heated at higher temperatures than the product, then thermal oxidative cycloisomerization of the starting material to form the product will be accelerated relative to thermal decomposition of the product.

Selective MW heating can be described as a MW-specific thermal effect. So-called "non-thermal" effects that relate to quantum mechanical resonant-energy transfer process have been discussed in detail elsewhere;[7,16,17] they are not invoked here and are dubious in any case of MW heating. In the selective heating model, thermal reactivity deviates from temperature-based expectations because the measured system temperature does not fully reflect the thermal energy of the selectively heated components.[19] Selective heating can provide strategic advantages in chemical synthesis.

This reaction system is our first example that (1) demonstrates a strategic advantage of MW heating, and that (2) we consider to be of practical synthetic utility[18] (e.g., because of its central role in our illudinine synthesis[1]). Our previous reports[13,14] feature highly specialized reaction designs of limited synthetic utility in order to observe significant MW-specific rate accelerations: open quartz glassware, unusual hydrocarbon solvents (e.g., *p*-xylene and naphthalene), dilute reaction conditions, and dynamic temperature and/or power profiles that can be sensitive to equipment parameters and variables like flask size and shape, wall thickness, etc. Here, we used sealed Pyrex tubes, including those that come standard with the commercial CEM microwave reactor, a high-boiling solvent originally selected for synthetic convenience,[1] and easily reproducible constant temperature profiles. Whereas our previously reported experiments were designed to maximize MW-specific rate enhancements at the expense of synthetic utility, this system reveals the strategic value of MW heating in a routine lab-scale organic synthesis endeavor.

For now, the strategic advantage of MW heating in this oxidative cycloisomerization reaction system remains observatio-

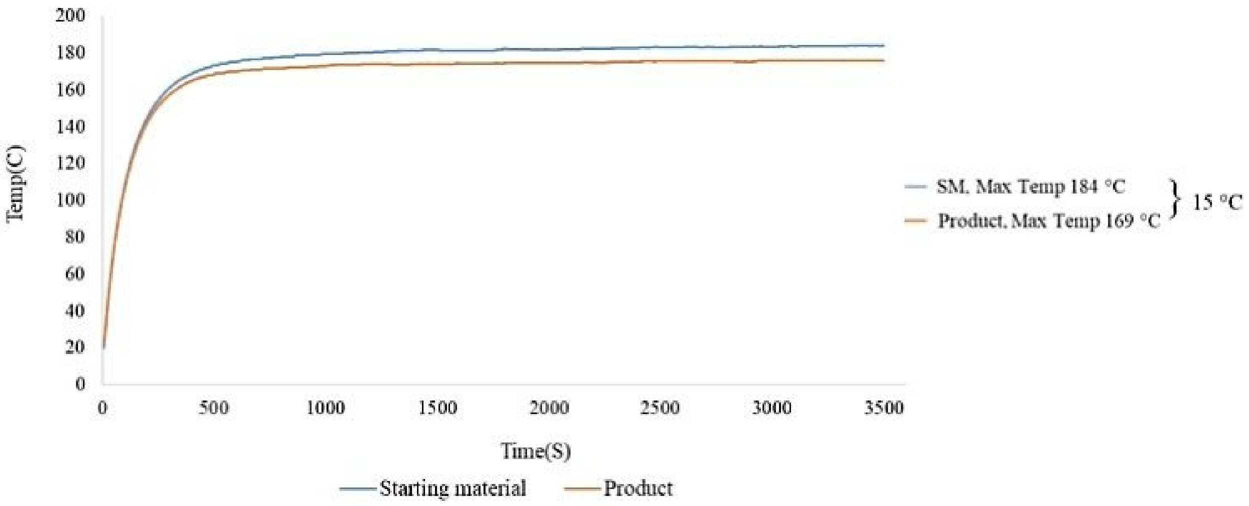

Figure 2. Plot of temperature vs. time for solutions of the starting material (**1**, blue line) and product (**2**, orange line) heated using 25 W of power at a concentration 0.12 M in 1,2-dichlorobenzene (*o*-DCB). Temperature recorded using an internal fiber optic probe.

nal, and selective MW heating remains a postulated rationale. However, some preliminary support for this rationale comes from the observation that the starting material generates heat in solution more efficiently than the product upon interaction with incident MW radiation (Figure 2), creating opportunities for selective MW heating. If selective heating of nano/micro-scale aggregates of **1** creates local temperature domains[17,19] that are hotter than the bulk, then thermal reactivity of **1** will be accelerated relative to bulk thermal processes such as decomposition of **2**.

In summary, we report the application of MW heating to produce a thermally unstable product at higher yield than is produced using CONV heating: i.e., going beyond the theoretical limits of the Bunsen burner.[20] This work improves a key step in our previously reported synthesis of illudinine from 40% to 62% yield, thereby increasing the overall yield of the 8-step synthesis from ca. 14% to ca. 22%. This work exemplifies a potential strategic advantage of MW heating and perhaps will lead to broader understanding and application of selective heating based on solution-phase aggregation phenomena. Finally, we emphasize that these experiments were conducted in sealed Pyrex vials at constant temperature, which is a standard protocol for using MW reactors for preparative chemistry.[18] Ongoing efforts in our MW chemistry research program focus on providing experimental validation and support for the working hypothesis of selective MW heating of polar components in solution, and on identifying other organic reaction systems and experimental design criteria in which significant strategic advantages for chemical synthesis can be anticipated, realized, and leveraged to advance the state of the art in organic synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Illudinine · Isoquinolines · Microwave chemistry · Microwave effects · Selective heating

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[15] Bulk temperature measurements in organic reaction solutions can be problematic, both under MW and CONV heating. We measured and/or controlled bulk solution temperatures using internal thermo-coupled fiber optic probes and external infrared pyrometers alternatively, explaining why each is appropriate for our reaction conditions. We also used the physical property of solvent reflux to define and control bulk solution temperature, while documenting, accounting for, and mitigating the possible impact of microwave-specific superheated boiling. Ultimately, all temperature measurements are based on measuring physical responses to thermal energy, and as such are limited by our ability to measure and translate physical responses of temperature probes into readable temperature data.

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[18] Our previous efforts generally required the use of open-vessel heating at variable temperature and in quartz vials in order to observe significant rate accelerations under MW heating, thereby limiting practical utility, as has been pointed out previously.

[19] Strictly speaking, temperature is undefined for systems that are not at thermal equilibrium. The "bulk solution temperature" that we measure using internal and/or external thermometric instruments is presumably a weighted average of thermal energies of all solution components. See reference 16 for further discussion.

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