Multicomponent Reactions to Form Heterocycles by Microwave-Assisted Continuous Flow Organic Synthesis

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The drive toward the ideal synthesis embracing step count, ideally just one, and yield, ideally one hundred percent, has been pursued aggressively since scientists began to construct molecules. Of course, there are many other factors that affect these two aspects of synthesis, including cost; starting material availability; safety; environmental concerns; and overall ease of the process, including work up and purification.[1] The nature of the synthesis project also plays a role. Complex molecule total synthesis is often driven by step count while showcasing innovative chemistry. Traditional structure−activity relationship evaluations in medicinal chemistry typically involve the preparation of an advanced intermediate that can be analogued readily to introduce the molecular diversity necessary to prepare a collection, or library, of structurally related compounds. One strategy that potentially meets the goals of total synthesis and library production is multicomponent reaction (MCR) chemistry, in which three or more starting materials are brought together in a highly convergent approach to rapidly build up molecular structure and complexity.[2] Usually, MCR transformations do not involve the simultaneous reaction of all reaction components; rather, they react in a sequence of steps that are programmed by the synthetic design. Often, this involves an equilibrium-driven step(s), followed by a nonequilibrium process that pulls the process to product, which means that, overall, MCR processes can be kinetically quite slow.

Microwave-assisted organic synthesis (MAOS)[3] has been demonstrated to be effective at increasing the rate of MCR procedures.[4] The vast majority of reports here deal with batch synthesis; i.e., the reaction components are all premixed and irradiated statically. Although the actual transformations themselves are kinetically much quicker, handling issues (e.g., capping and uncapping) associated with the one-at-a-time irradiation of pressurized vessels does much to offset this advantage. A significant improvement in output of MCR transformations could be achieved by performing them in a flowed format under microwave irradiation. We[5] and others[6] have been developing the area of microwave-assisted continuous flow organic synthesis (MACOS) that combines the sample-handling advantages of flow with the rate-enhancing features of MAOS. In this report, we detail the use of MACOS to prepare medicinally relevant, heterocyclic compounds in a MCR format.

For the purpose of MCR chemistry that can be conducted in a MACOS format, we have designed our own reactor system.[7] The capillaries used for this process are generally 1200 μm in diameter, although they can be of any size, and they are fed by integrated syringe pumps. We have demonstrated that two-component reactions, such as nucleophilic aromatic substitution and various metal-catalyzed coupling procedures, can be achieved with surprisingly fast kinetics.[5] This, of course, is necessary because of the short residence time that any one plug of reactants spends in the magnetron region of the microwave under continuous flow conditions. When reagents flow into the reactor from two starting material streams, such as would be the case to prepare arrays of compounds (e.g., libraries), there is concern over laminar flow that can lead to poor conversion. Laminar flow refers to the situation that arises when two streams of liquid enter a microchannel and do not mix, but rather flow along beside each other, with the consequence that reactions must take place at the interface of the two streams. The fast kinetics that we see indicate that there is adequate mixing, and this may well be the result of the microwave's heating that helps to promote turbulent flow. This becomes more complex when a third reagent stream is added, which is necessary for the 3-component-coupling reactions that we are conducting. Additionally, the stoichiometry in these processes is 1:1:1 where each stream carries one reaction component. Thus, a completely mixed solution is necessary as it enters the magnetron region of the microwave to give sufficient time for complete reaction.

The preparation of tetrahydropyrazolo[3,4-*b*]quinolin-5(6*H*)-ones (**4**) was accomplished by reacting equimolar amounts of dimedone (**1**), 5-amino-3-methyl-1*H*-pyrazole (**2**) and various substituted benzaldehydes (**3a**−**f**) in an efficient, microwave-assisted method (Table 1). This three-component reaction was attempted recently by prolonged refluxing in absolute ethanol, giving rise to moderate yields.[8] When the transformation was performed under MACOS conditions, excellent conversions were obtained in a matter of seconds. The three components were each introduced into the microwave through three separate leads, in equal concentrations, at the same rate. Introducing the components separately, instead of as a mixture, greatly expands the combinatorial efficiency of the system for library generation when much larger numbers of compounds are being prepared.[5b]

Reaction optimization consisted of varying the capillary diameter, microwave power, flow-rate, reaction concentration, and solvent. Solvent choice proved to be critical. Under these MACOS conditions, the flow system is open; there is no backpressure in the capillaries. As a result, it is not possible to achieve a temperature above the boiling point of the solvent, which is one of the primary reasons for the tremendous kinetics observed in a batch set up using MAOS that employs vessels capable of withstanding high pressures.[3] In our system,[5,7] a higher-boiling solvent is necessary to achieve suitable temperatures to drive reactions to completion in a very brief time period, that is, seconds. In this respect, DMSO and DMF are ideal because of their high boiling

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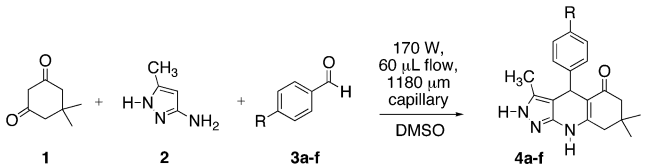
Table 1. MCR MACOS Reaction of a Variety of Aldehydes with Dimedone (**1**) and Pyrazole (**2**) to Form Quinolinones

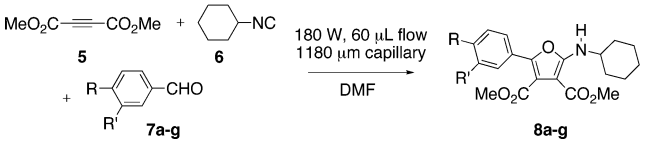


1 2 3a-f 4a-f

entry	3	R	product	conversion (%)[a], (isolated yield)[b]
1	**a**	$N(CH_3)_2$	**4a**	95 (94)
2	**a**	$N(CH_3)_2$	**4a**	trace[c]
3	**b**	CN	**4b**	100 (55)
4	**c**	CO_2Me	**4c**	100 (88)
5	**d**	Br	**4d**	100 (80)
6	**e**	OH	**4e**	94 (94)
7	**f**	OMe	**4f**	91 (71)

[a] Conversion determined by ^1H NMR spectroscopy of crude product on the basis of aldehyde consumption. [b] Percent yield following chromatography on silica gel. [c] Reaction was performed in a manner identical to that for entry 1, but without MW irradiation.

Table 2. MCR MACOS Reaction of a Variety of Aldehydes with Isocyanide **6** and DMAD (**5**) to Produce Tetrasubstituted Furans



5 6 7a-g 8a-g

entry	R	R′	product	conversion (%)[a], (isolated yield)[b]
1	NO_2	H	**8a**	83 (79)
2	H	NO_2	**8b**	70
3	CF_3	H	**8c**	76 (76)
4	CO_2Me	H	**8d**	71
5	F	H	**8e**	57
6	Cl	H	**8f**	55
7	OMe	H	**8g**	30

[a] Percent conversion determined by ^1H NMR spectroscopy of crude product on the basis of aldehyde consumption. [b] Percent yield following chromatography on silica gel.

points and good microwave-absorbing ability owing to their large dipole.[3] Additionally, their excellent solvating capacity allows for high reagent concentrations (e.g., 2−4 M), which also assists in enhancing the reaction rate. We have recently developed the methodology to implement backpressure into our flow system, and this will be published in due course.

To probe microchannel[9] vs microwave effects, the first experiment was repeated in the absence of microwave irradiation, and only a trace amount of product was detected (Table 1, entry 2). This confirmed that the increase in reaction rate is primarily due to the effects of microwave irradiation, and that there is no appreciable "microchannel effect" leading to enhanced kinetics. We have not checked to be certain, but this could be the result of laminar flow in the absence of microwave irradiation that promotes turbulent flow leading to fully mixed reactant streams and better kinetics.

It is a commonly held belief that microchannel devices produce only small amounts of product (e.g., milligrams). To address this concern, the reaction in entry 1 was flowed for 29 min resulting in the collection of 319 mg of product; thus, a single capillary can quickly provide grams of material. A significant advantage of MACOS is that reactions need to be optimized only once, for the production of larger amounts of material is simply a matter of flowing an already optimized reaction longer. This concept has been referred to in the literature as "scaling out" rather than "scaling up".[6] Splitting reactant streams and sending reactions through our bundled (multi)capillary reactor system[5c] into a common collection device will multiply output again by the number of capillaries through which any one reaction is sent.

The application of MCR MACOS to the preparation of a small library of aminofurans from DMAD (**5**), cyclohexyl isocyanide (**6**), and a number of substituted benzaldehydes (**7a**−**g**) was also investigated (Table 2). When others performed similar transformations under conventional conditions, the reaction required refluxing in benzene for 2−9 h, yielding only modest results.[10] Under our MACOS conditions, conversions either equaled or surpassed previous reports; most importantly, though, the MACOS procedure requires seconds in a flowed format to obtain similar yields that were obtained in hours using conventional methods under batch conditions.

As can be seen from Table 2, electronic properties of the substituted benzaldehyde significantly impact on conversion. The electron-withdrawing nitro group in **7a** (entry 1) gave the highest conversion, whereas the electron-donating methoxy group in **7g** (entry 6) gave the lowest. Diversity in this collection can be enhanced further by also varying the isocyanide or by converting the esters to amides in a libraries-from-libraries[11] approach to enhanced molecular diversity.

In conclusion, a unique approach to multicomponent reactions by microwave-assisted, continuous flow organic synthesis has been developed. Although MCR approaches are known in batch microwave conditions, they are without precedent in a flow mode. Flowed synthesis, in general, holds multiple advantages over batch reactions. One of the principal features is that when a reaction exits the reaction chamber, it is complete—or at least as complete as it is going to be. As a result, with the implementation of real-time, in-line reaction monitoring (e.g., LC, GC, etc.), optimization can be performed rapidly with instantaneous changes of feedstock into the capillary reactor. Optimization of conventional batch reactions is a slow, iterative process that includes reaction setup, quench, workup, analysis, and setting up the next set of conditions. Thus, MCR MACOS methodology holds great promise for both total synthesis and medicinal chemistry applications.

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Supporting Information Available. General procedures for the preparation of the quinolinones and furans and their spectral characterization. A schematic diagram and photo of

the reactor system are also available. This material is available free of charge via the Internet at http://pubs.acs.org.

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