Highly modular PDMS microwave-microfluidic chip reactor for MAOS applications

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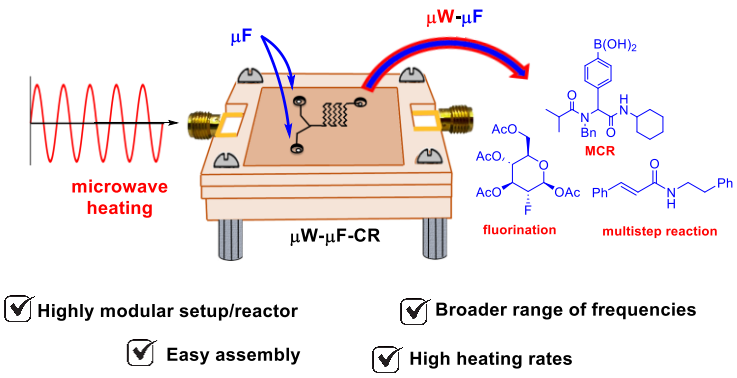
In this work, we introduce a microfluidic chip reactor based on a Complementary Split Ring Resonator (CSRR) for conducting microscale microwave-assisted organic synthesis (MAOS). This microwave-microfluidic chip reactor (µw-µf-CR) is easy to assemble and highly customizable, featuring interchangeable flow cells fabricated on inexpensive PDMS, providing high levels of versatility in terms of manufacturing and design. Various flow cells were designed and explored, offering internal volumes ranging from 2.82 to 6.48 µL and accommodating flow rates between 5 to 8 µL/min. This allows the reaction to be irradiated within a timeframe spanning from seconds to minutes. Remarkably, our setup design bears the potential to operate across a broad range of frequencies (around 2 or 6-12 GHz). Moreover, it provides controllable and efficient heating, reaching temperatures up to 120°C within seconds with a maximum low input power of 4.4 W. Simulations showed an excellent homogeneous heat distribution throughout the flow cell. The applicability of the µw-µf-CR was demonstrated in several organic reactions, where good yields and short reactions times were observed.



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1. Introduction

The application of microfluidic technology to chemical synthesis (µSyn) offers a new platform to enhance the performance of organic reactions. In contrast to conventional batch techniques, µSyn normally involves confined flowing liquids in miniature microreactors such as microtubes, microchannels, or microcapsules, which provides high rates of mixing, heat/mass transfer and a precise control down to nm and pL scales.[1] Additionally, the versatility of microreactor design and fabrication broadens its applicability by improving efficiency, controllability, and safety.[2] Microreactors are constantly regarded as a green technology as they promote the development of a sustainable synthetic chemistry with small quantities of reagents/solvents, short residence time and low energy consumption, which leads to minimal waste of resources.[2,3] In the continuous search for the ideal sustainable reactor, numerous enhancing technologies for process intensification in continuous flow have been adapted to microreactors including photochemistry, electrochemistry and MW-irradiation.[4,5] This latter has found interesting applications in organic synthesis, since the small diameter of microreactors is ideal for the use of MW heating, as it solves the problem of the limited penetration depth of microwave irradiation in batch, while addressing new scalability opportunities.[6,7] In this context, numerous benefits have been attributed to the combination of µSyn and MW-irradiation such as cleaner reactions characterized by shorter reaction times and enhanced yields when compared to conventional batch approaches.[8,9] To date, microwave heating devices commonly employed in µSyn predominantly rely on high-power magnetrons operating at 2.45 GHz (ISM frequency band). However, for many organic solvents, 2.45 GHz does not correspond to the frequency with the maximum dielectric loss, resulting in a non-optimal dielectric heating.[10] In this context, microwave reactors with access to a broader frequency range that would allow for more efficient coupling of microwave energy and therefore optimum heating are desirable.

Additionally, in recent years an emerging subdomain known as microwave-microfluidics has gained prominence. This field involves the integration of microwave circuits with miniaturized channels, resulting in microfluidic devices operating within the nL to µL scale, and capable of continuous-microwave irradiation. Such devices are typically characterized by the use of a broader frequency range spanning from 2.45 GHz to 25 GHz and by fast and efficient microwave heating using low-power inputs.[11] Although this rapidly advancing field has gained widespread use in chemical sensing and biomedicine,[12,13] examples of its applications in chemical synthesis remain isolated. The latter, despite the fact that the synergistic use of microwave heating and microfluidics could ultimately lead to high reactions rates and yields.[14,15]

In order to unlock the potential of microwave-microfluidics in microwave-assisted organic synthesis (MAOS), we became interested in developing a μw-μf-CR based on a Complementary Split Ring Resonator (CSRR) with controllable microwave heating. Notably, the high modularity of our reactor and setup enables easy assembly and interchangeability of various elements, including flow cells and microwave heaters working at varying frequencies. Our developed technology constitutes a substantial advancement towards tailored and more efficient microwave heating methodologies.

1. Materials and methods

MW Heater and flow cell design

The two CSRRs were designed to work at 2 and 8 GHz when loaded with a polydimethylsiloxane (PDMS) flow cell. Both CSRRs include a large central patch that accommodates the flow cell and ensures a consistent temperature distribution.[16] The final dimensions are A=6 mm and B=C=D=E=F=0.2 mm for a MW heater working at around 2 GHz and A=6 mm, B=D=0.5 mm, C=0.8 mm, and E=F=1.4 mm for a MW heater working at around 8 GHz (Fig. 1A-B). To assess the temperature distribution during MW heating, a COMSOL MW heating simulation with the microfluidic channel filled with MeCN was conducted. The resulting profile shows an excellent temperature uniformity inside the microfluidic channel, with similar results obtained using other commonly used organic solvents. (Fig. 1C-D). For accurate temperature measurements during the reactions, a thermocouple (RS PRO Type K, 0.076 mm) was inserted into the flow cell between the channels, with a thin layer of PDMS separating the reaction mixture and the sensor. As shown in Figures 1C-D, the thin layer of PDMS between the temperature sensor and the channel does not affect the temperature readout.

Due to the laminar regime as a consequence of the low volume of the flow cells, zig-zag-shaped channels were incorporated to induce turbulent flow and promote efficient mixing.[17] Three different flow cells were designed. In flow cell A, zig-zag channels were only incorporated in the reactor zone (2.82 μL or 6.48 μL), while flow cell B features an additional mixing zone right before the reactor area. Dimensions of the designed flow cells are shown in Fig. 1E-F (for more details see SI).

Flow cell manufacturing

PDMS flow cells were manufactured using soft lithography, for which, a 3D-printed mold was used. A temperature sensor was precisely placed in the middle, followed by pouring PDMS into the mold. This way, the temperature sensor is embedded into the flow cell and remains in place. PDMS was mixed with the curing agent in a 10:1 ratio, as recommended in the datasheet. For the curing process, the PDMS flow cell was allowed to cool down at room temperature for 12 h to ensure that all bubbles disappear, and then heated at 120 °C for 6 h until fully solidified. Finally, the flow cell was removed from the mold, inlets and outlets were punched with a 1.5 mm diameter puncher for PFA tubing to fit. A glass cover with 0.1 mm thickness was used to close the channels. For assembly, a non-permanent bonding method was used, in which the PDMS flow cell with glass cover sits on top of the MW-heater, the two pieces are sandwiched together with applied pressure using a laser-cut polymethyl methacrylate (PMMA) cover, positioner and support. The setup is tightly secured with 4 bolts and nuts (Fig. 2A-B). Chemicals and solvents are pumped through the system using syringe pumps and PFA tubing connected to the μw-μf-CR (for more details see SI).

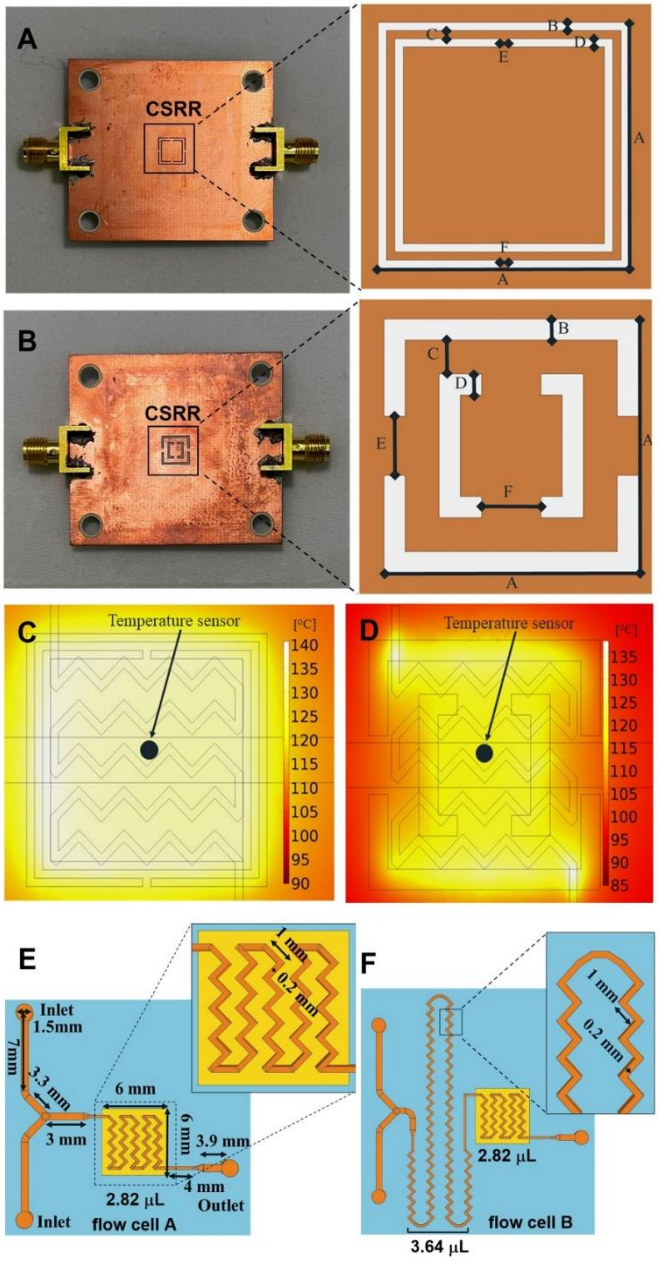


Fig. 1 A) 2 GHz CSRR. B) 8 GHz CSRR. C) COMSOL MW heating simulation at 2 GHz. D) COMSOL MW heating simulation at 8 GHz. E) Flow cell A. F) Flow cell B.

Complete setup

The complete setup is depicted in Fig. 3A-B. Before conducting reactions, the working frequency of the reactor loaded with reactants inside the flow cell is measured. The frequency is then entered into the signal generator to produce a MW signal for heating. Two setups are shown, with the first one working up to 2.5 GHz used in combination with the MW heater working at around 2 GHz and the second working between 6-12 GHz for experiments with the MW heater working at around 8 GHz. The setups are made to be similar with the possibility to change certain components to work at

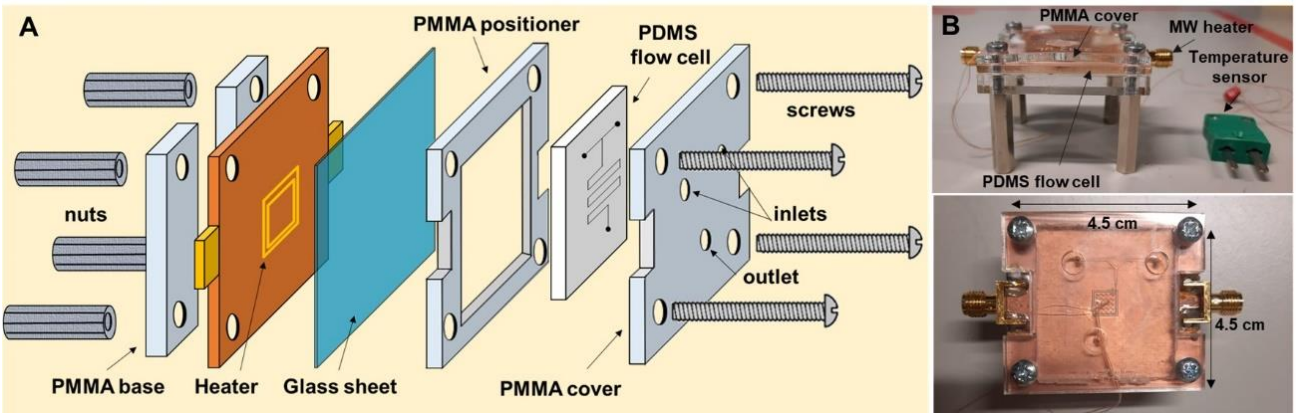


Fig. 2 A) Schematic representation of the μw-μf-CR. B) Picture of the assembled μw-μf-CR seen from the side (top image) and the top (bottom image).

different frequencies. Both setups consist of a signal generator (ADF4355 or ADF4372, Analog Devices) connected to a step attenuator (HMC941ALP4E, Analog Devices) that is controlled with Arduino Nano to limit MW heating power and, with that, keeps the reaction temperature constant. A power amplifier (KU PA BB 233 BBA, Kuhne electronics or ZVA-183WA-S+, Minicircuits in combination with CMPA601C025F, Wolfspeed) is needed to increase the MW power to achieve the set temperature. Finally, the isolator (COI02040618G, Cernex or PE83CR1006, Pasternack) is connected to the reactor to prevent damaging the power amplifier. The whole setup is controlled using a PC with a proprietary application developed in MATLAB for easy temperature and frequency control. The temperature was read using a temperature reader (TC01, National Instruments) connected to the temperature sensor. To supply the setup with electrical energy, two or four power supplies were used depending on the heating frequency (Fig. 3A-C, SI).

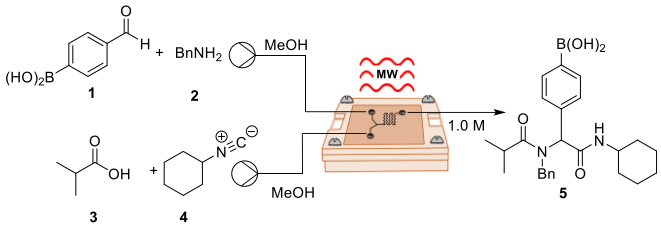
2. Results and discussion

With the developed technology in hand, the first step towards its validation involved testing its efficiency in heating organic solvents and eventually reaction mixtures. To do so, ethanol was injected into the flow cell and irradiated at a maximum heating power of 4.4 W. Pleasantly, we found that the temperature increased up to 120 °C in less than 10 s with a heating rate of 68 °C s^{-1} (Table 1, entry 5). The latter confirms that the solvent in the chip reactor can efficiently absorb microwave irradiation and reach high temperatures within seconds using minimal microwave power inputs. Similar measurements and excellent heating rates were obtained for other common organic solvents (Table 1).

Table 1. Heating rates of common organic solvents at around 2 GHz.

entry	solvent	heating rate (°C s^{-1})
1	DMF	80
2	DMA	68
3	Acetonitrile	68
4	Methanol	50
5	Ethanol	68
6	Acetone	62
7	THF	56
8	Ethyl acetate	54
9	Toluene	52

Table 2: Optimization of Ugi reaction conditions.[a]



entry	temperature, °C	flow rate, μL/min	t_R, s	5 (%)[b]
1	45	10	39	24
2	60	10	39	38
3	60	5	78	70
4	70	5	78	77(75)

[a]All reactions were carried out using **1** (0.5 mmol), $BnNH_2$ **2** (0.5 mmol, 1.1 equiv), **3** (0.55 mmol, 1.1 equiv), **4** (0.55 mmol, 1.1 equiv), 1.0 M, 2.01 GHz, maximum available power 4.4 W, μw-μf-CR, flow cell A (6.48 μL). [b]GC-MS yields using 3,5,6-trimethoxybenzaldehyde as an internal standard. Isolated yields in brackets.

Encouraged by these results, the next phase in the validation process involved assessing the efficacy of our μw-μf-CR in facilitating a reaction based on a literature MW procedure, serving as a benchmark for the comparison. To begin with, the four-component Ugi reaction for the synthesis of arylboronic acid analogs was chosen.[18] The reaction mixture, as described, underwent heating at 45 °C with a power input of 150 W for 30 min, resulting in the corresponding Ugi products in good to high yields. Owing to the intrinsic correlation between energy consumption and MW power generation, the production of high-power inputs invariably leads to increased energy usage (Energy = Power x Time). The latter results in a significant waste of energy, particularly when the reaction is carried out at moderate temperature using large power inputs. In this context, our μw-μf-CR emerges as a more sustainable alternative. The narrow channels of the device facilitate reaching high temperatures with minimal microwave input power.

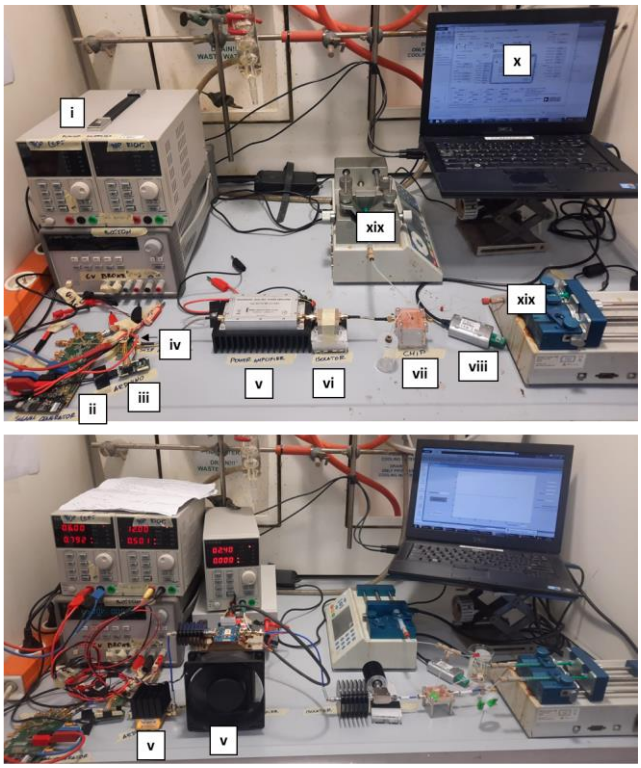


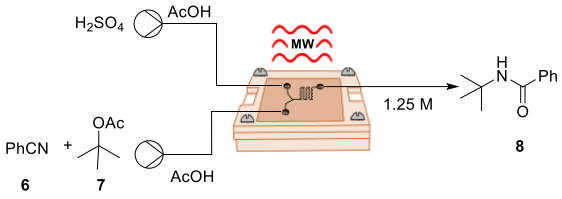
Fig. 3 A) Complete setup working up to 2.5 GHz. B) Complete setup working between 6-12 GHz.

We started our investigation by using a two-inlet-one-outlet 6.48 µL flow cell. The premixed mixture of benzaldehyde **1** and benzylamine **2** was injected through one inlet, while a mixture of carboxylic acid **3** and isocyanide **4** was injected through a second inlet. The reaction mixture was continuously flowed at a combined flow rate of 10 µL/min (t_R = 39 s), heated at 45 °C (2.01 GHz), and quenched upon exit. Interestingly, these conditions provided the desired product **5** in 24% yield (Table 2, Entry 1). The latter illustrates that, despite the narrow channels of our device, which can be an issue with MW-microreactors,[8] the reaction mixture was able to pick up enough microwave irradiation under flow conditions to undergo partial conversion. Increasing the temperature of the reaction afforded a slightly higher yield of 38% (Table 2, Entry 2). Notably, the desired product was obtained in 70% yield simply by reducing the combined flow rate to 5 µL/min (t_R = 78 s), most likely as a result of the reaction being exposed to irradiation for a longer period of time (Table 2, Entry 3). Finally, increasing the temperature to 70°C yielded an optimized 75% yield with a throughput of 0.23 mmolh^{-1} (Table 2, Entry 4). Remarkably, the use of our µw-µf-CR allowed us to successfully obtain the desired compound with high yields and short reaction times by using a low microwave power input of 1 W. Furthermore, in contrast to the original report, we were able to work at higher temperatures, which likely also contributed to the acceleration of the reaction. The latter, due to the high levels of control when working at µL scale, even when handling pungent compounds. This contribution represents a step forward towards odourless isocyanide chemistry.[19]

Following our successful validation experiments, we sought to explore and broaden the applicability of our µw-µf-CR in organic synthesis, therefore we chose a series of transformations. Since microreactors are particularly well suited for hazardous chemistry involving toxic or explosive reagents,[20] we chose to explore an exothermic Ritter reaction, a potent method for synthesizing valuable *N*-alkyl amide products by combining alcohols and nitriles. Nonetheless, this reaction involves the use of harsh and strongly acidic reaction conditions, which on a large scale could lead to safety concerns. Our investigation was based on the procedure outlined by Wirth *et al.*, who introduced the reaction in continuous flow using *tert*-butyl acetate as a cation source in a mixture of AcOH and H_2SO_4.[21] The described reaction took place in a 200 µL PTFE microreactor equipped with a micromixer, heated to 45°C, and maintained for a residence time of 6 min to afford the corresponding products in moderate to good yields.

In accordance with the original report, we opted for the two-inlet-one-outlet flow cell B (Fig. S1), incorporating extra mixing elements for this transformation. It is worth noting that we were able to observe the formation of the desired product **8** even at a flow rate of 20 µL/min, corresponding to a small residence time of 8.5 s (Table 3, Entry 1). To ensure full conversion and to secure a high yield of 80%, it was essential to elevate the temperature to 60 °C and reduce the flow rate to 8 µL/min (Table 3, Entry 4). It is noteworthy that, despite the seemingly minimal microliter volume of our reactor, the space-time yield (STY) for this transformation was slightly higher (0.170 mol h^{-1} mL) compared to the STY reported in the original study (0.104 mol h^{-1} mL).

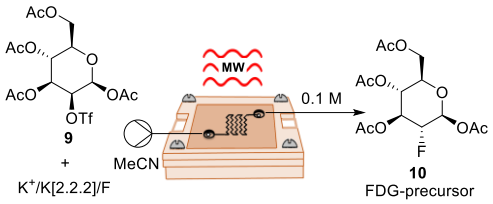
Table 3: Optimization of Ritter reaction conditions.[a]



entry	temperature, °C	flow rate, µL/min	t_R, s	8 (%)[b]
1	45	20	8.5	38
2	60	20	8.5	56
3	60	10	17	70
4	60	8	21	80
5	80	8	21	51

[a] All reactions were carried out using **6** (0.5 mmol), **7** (1.0 mmol, 2 equiv), 1.25 M, maximum available power 4.4 W, µw-µf-CR, flow cell B, 2.04 GHz. [b]Isolated yields.

Table 4: Optimization of fluorination reaction conditions.[a]



entry	reactor	T, °C	flow rate, µL/min	t_R, s	10 (%)[c]
1[b]	CEM	70	-	5 min	65
2	µw-µf-CR	70	5	34	44
3	µw-µf-CR	80	5	34	60
4	µw-µf-CR	90	5	34	63(61)
5	µw-µf-CR	90	8	21	45

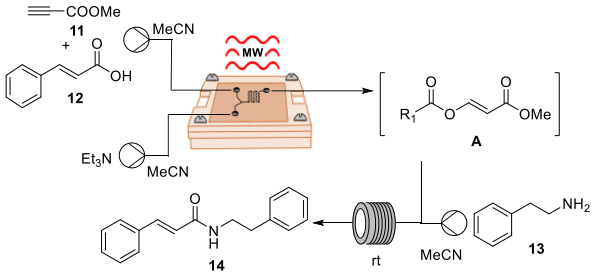
[a]Reactions were carried out using **9** (0.1 mmol), Kryptofix® 222 (0.1 mmol, 1 equiv), KF (0.07 mmol, 0.7 equiv), 0.1 M, 2.0 GHz, maximum available power 4.4 W, µw-µf-CR, flow cell A (2.82 µL). [b] Same equivalents as [a], reaction performed in CEM, 50 W, 2.45 GHz. [c]GC-MS yields using 3,5,6-trimethoxybenzaldehyde as an internal standard.

After confirming the ability of our reactor in handling exothermic reactions, we turned our attention to explore further applications. We directed our focus towards a fluorination reaction for the potential synthesis of radiotracers. These compounds find extensive application in positron emission tomography (PET), a robust molecular imaging technique applied in diagnosis and therapy control.[22] Despite the high demand, the synthesis of radiotracers poses several challenges, including the rapid decay of radioisotopes, the high cost of precursors, and the generation of highly toxic byproducts. Due to these challenges, radiotracers are commonly produced in small quantities, on-demand, and preferably through rapid processes.[23,24] In this scenario, the synthesis of radiotracers appeared to be an ideal challenge for our µw-µf-CR. As a proof-of-concept, we conducted the non-radioactive synthesis of the precursor of popular radiotracer 2-[^{19}F]-fluoro-2-deoxy-D-glucose (FDG). We commenced by assessing the compatibility of the reaction under microwave (MW) heating using a CEM discover reactor. To do so, a mixture of **9** and KF/K_{222}/K_2CO_3 in anhydrous acetonitrile was heated at 70 °C with an input power of 50 W for 5 min. Pleasantly, the desired fluorinated product **10** was achieved with an 65% yield (Table 4, Entry 1). Subsequently, we aimed to replicate this reaction in our µw-µf-CR. The premixed mixture of **9** and KF/K_{222}/K_2CO_3 was introduced into the 2.82 µL flow cell A (Fig. S1) and heated at 70 °C with a flow rate of 5 µL/min (t_R = 34 s), resulting in the formation of desired compound **10** with a yield of 44% (Table 4, Entry 2). By elevating the reaction temperature to 90°C, we achieved the desired product in 61% yield (Table 4, Entry 4). The obtained results, highlight the potential of our technology for the on-demand production of radiopharmaceuticals.[25]

Furthermore, the impact of microreactors in drug discovery cannot be denied. The pharmaceutical industry consistently seeks the advancement of new technologies that can expedite the drug discovery process by swiftly generating small quantities of drug candidates for initial testing.[26] Generally, these syntheses often entail multistep processes, and given that amide bonds are ubiquitously present in active pharmaceutical ingredients (API), we envisioned a two-step reaction for the synthesis of secondary amides as the next challenge for our µw-µf-CR.

For this investigation, we took inspiration from the one-pot two-step direct amidation reaction of carboxylic acids as reported by Xu *et al.* [27]. Their protocol featured the *in situ* formation of an *α*-acyl enol ester **A** as an active intermediate, followed by nucleophilic acyl substitution by primary amines, resulting in the generation of various secondary amides in good to high yields. While the nucleophilic substitution was rapidly accomplished, the bottleneck in the reaction lies in the formation of intermediate **A**, which took up to 5 h in some cases. In this context, we became interested in advancing the two-step transformation in continuous flow and exploring the possibility of expediting the initial step of the reaction using our µw-µf-CR. If successful, this approach could potentially lead to the rapid synthesis of secondary amides within minutes. Given that the reaction was initially conducted in batch at room temperature, our initial goal involved evaluating its performance under MW irradiation using a CEM discover reactor. A mixture of cinnamic acid **12**, methyl propiolate **11** and triethylamine in MeCN was irradiated at 50 °C and 50 W for 25 min. Following irradiation, TLC analysis revealed the complete consumption of the starting material and the formation of intermediate **A**. Then amine **13** was added, and the reaction mixture was stirred for an additional 10 min at room temperature, resulting in the desired secondary amide **14** in 85% yield (Table 5, Entry 1).

Table 5: Optimization of a two-step amidation reaction conditions.[a]



entry	reactor	T, °C	flow rate, µL/min	t_R	14 (%)[c]
1[b]	CEM	50	-	s1: 25 min s2: 10 min	85
2	µw-µf-CR	50	s1: 10 S2:10	s1: 39 s s2: 10 min	30
3	µw-µf-CR	70	s1: 10 s2: 10	s1: 39 s s2: 10 min	57
4	µw-µf-CR	70	s1: 8 s2: 12	s1: 49 s s2: 10 min	69
5	µw-µf-CR	70	s1: 5 s2: 15	s1: 78 s s2: 10 min	83
6	µw-µf-CR	70	s1: 5 s2: 25	s1: 78 s s2: 7 min	91 (87)

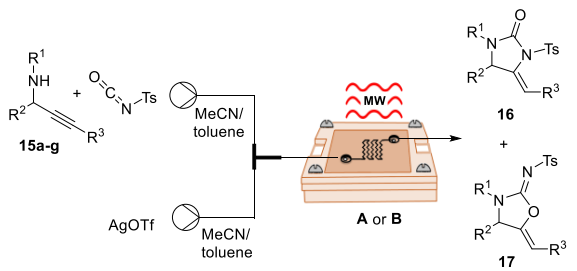
[a]Reactions were carried out using **12** (0.1 mmol), Et_3N (0.11 mmol, 1.1 equiv), **11** (0.2 mmol, 2 equiv), maximum available power 4.4 W, µw-µf-CR, flow cell A (6.48 µL), 2.04 GHz. [b] Same equivalents as [a], reaction performed in CEM, 50 W, 2.45 GHz. [c] ^{1}H NMR yields using 3,5,6-trimethoxybenzaldehyde as an internal standard. Isolated yields in brackets.

The adaptation of the reaction to our μw-μf-CR proved to be straightforward and effective. For the first step, we utilized the two-inlet-one-outlet 6.48 μL flow cell A (Fig. S1), while the second step was performed in a 200 μL PFA tubing reactor. Optimal conditions for the transformation were identified as a combined flow rate of 5 μL/min at 70 °C for the first step, paired with 30 μL/min for the second step, yielding the desired product **14** in an excellent 87% yield with a throughput of 0.043 mmol h^{-1} (Table 5, Entry 6).

In addition, given the importance of frequency in microwave dielectric heating, several studies have been focused on its possible impact on the reaction outcome, in terms of yields, reaction rates, and product distribution.[10,28,29] In the light of this, and since our μw-μf-CR have access to a broader range of frequencies, we decided to investigate this matter. For this, we selected a silver-catalysed cycloisomerization of propargylic ureas previously reported by our group.[30] Remarkably, during the course of this study, we discovered that the introduction of a base or an acid into the reaction medium allowed for the selective formation of imidazolidin-2-ones **16** or oxazolidin-2-imines **17** using a silver catalyst (for additional details see SI). Following a rapid optimization of reaction conditions using our μw-μf-CR at 2.04 GHz, we successfully selectively obtained the desired imidazolidin-2-one **16a** in 80% yield under protocol A, and oxazolidin-2-imines **17a** with a yield of 81% under protocol B (see SI). Once the reactions were fully optimized, the subsequent phase of our investigation involved conducting the reactions at a higher frequency. The Ag-catalyzed cycloisomerization reactions were carried out using our optimized conditions at 7.69 GHz. Nevertheless, there were no appreciable variations in yields or product ratios between the reactions carried out at 2.04 GHz and 7.69 GHz (Table 6, Entry 1-2). This outcome could be rationalized by the fact that the impact of higher frequencies on the heating rates of organic solvents has been found to be more pronounced in non-polar solvents than in polar solvents, suggesting that nonpolar solvents could be more advantageous in organic reactions at higher MW frequencies.[28]

Lastly, a series of imidazolidin-2-ones **16** and oxazolidin-2-imines **17** were synthesized in high yields and excellent selectivity, demonstrating the potential of our reactor in the manufacture of small libraries of compounds (Table 6).

Table 6: Ag-catalyzed cycloisomerizations.[a]



A = 25 mol% Et_3N, 5 mol% AgOTf, MeCN:toluene (1:1), 0.25 M, 5 μL/min, t_R = 34 s, 80 °C
B = 2 equiv AcOH, 20 mol% AgOTf, MeCN:toluene (1:1), 0.5 M, 7 μL/min, t_R = 24 s, 100 °C

Entry	15	R^1	R^2	R^3	Protocol	16 (%)[c]	17 (%)[c]
1	**15a**	Bn	*i*-pr	Ph	**A**	80	6[d]
					B	7[d]	81
2[b]	**15a**	Bn	*i*-pr	Ph	**A**	76	8[d]
					B	8[d]	77
2	**15b**	PMB	Pr	Ph	**A**	73	9[d]
					B	5[d]	78
4	**15c**	PMB	*p*-FC_6H_4	*p*-(tBu)C_6H_4	**A**	78	7[d]
					B	nd	78
5	**15d**	Bn	Ph	thiophen-3-yl	**A**	77	15[d]
					B	nd	85
6	**15e**	Bn	naphthyl	Ph	**A**	85	nd
					B	nd	88
7	**15f**	Bn	2-benzofuranyl	Ph	**A**	72	nd
					B	5[d]	65
9	**15g**	Bn	Ph	*p*-$(CH_3)C_6H_4$	**A**	70	5[d]
					B	12[d]	79

[a]All reactions were carried out on a 0.1 mmol scale, maximum available power 4.4 W, μw-μf-CR, flow cell A (2.82 μL), 2.04 GHz. [b] Reactions performed at 7.69 GHz. [c]Isolated yield. [d] ^1H NMR yields using 3,5,6-trimethoxybenzaldehyde as an internal standard.

3. Conclusions

In conclusion, we have successfully developed a microwave microfluidic chip reactor (μw-μf-CR) with controllable and efficient heating based on a Complementary Split Ring Resonator (CSRR). The developed technology features high levels of modularity enabling easy assembly and interchangeability of various elements, including PDMS flow cells and microwave heaters. Remarkably, our setup design bears the potential to operate in a broad range of frequencies and can reach temperatures up to 120°C within seconds using a maximum available input power of 4.4 W. In addition, excellent heating rates for a variety of solvents were obtained. The μw-μf-CR demonstrated applicability in several organic transformations, including an exothermic reaction, fluorination, and a two-step amidation. The desired products were obtained in high yields and short residence times, albeit optimal results required the application of low flow rates. Despite the seemingly minimal microliter volume of our reactor, modest throughputs of up to 0.48 mmolh^{-1} were achieved; strategies to increase the volume and thus the throughput of our microreactors are being investigated. Moreover, we briefly studied the influence of the microwave frequency on a Ag-catalyzed cycloisomerization reaction; nevertheless, no significant variations were observed between the reactions performed at 2.04 GHz and 7.69 GHz. Future studies in our laboratory aim to explore such effect further, particularly in reactions involving non-polar solvents. Finally, our μw-μf-CR represents a significant advancement towards fast, tailored and efficient microwave heating methodologies in the field of microfluidics, thus bringing new and exciting opportunities to μSyn.

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Conflicts of interest

In accordance with our policy on Conflicts of interest please ensure that a conflicts of interest statement is included in your manuscript here. Please note that this statement is required for all submitted manuscripts. If no conflicts exist, please state that "There are no conflicts to declare".

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