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Supporting Information

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On-line monitoring of a microwave-assisted chemical reaction by Nanoliter NMR-spectroscopy

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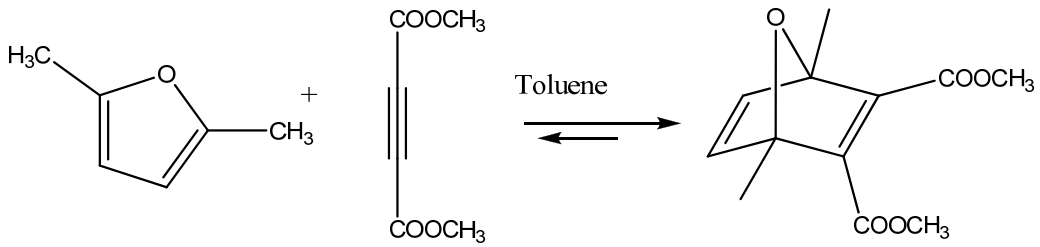
11 Pages

-Experimental section.

Description of the set-up for the on-line monitoring of a microwave-assisted chemical reaction. In figure 1, three different parts can be distinguished: the loading of the reagents (pump), the reaction zone (microwave reactor) and the detection (NMR-chip). The pump used was a high-force syringe pump, Harvard Apparatus PHD 2000 – 71-2000, which enables the low flow rates employed. Regarding the microwave reactor, the cavity and the magnetron are connected via a microwave output connector with a length of 2.1 m. It allows the proximity between the cavity and the NMR magnet without causing any problem in the electric circuit of the microwave generator. The temperature sensor is an external optic fiber introduced into the microwave cavity closed to the sample, obtaining the following reaction temperature values, 150ºC, 135ºC and 125ºC. The control of power, temperature and time is followed via a front panel keyboard in the microwave reactor. A capillary which defines the reaction volume is wound around a Weflon™ bar (combination of carbon and Teflon, in this case with a carbon percentage of 15%). Weflon™ is used for a more efficient absorption of the microwave irradiation to heat up such a small sample volume. The NMR-chip was fabricated by Micronit Microfluidics (http://www.micronit.com/).

For the interfacing to the detection system, the capillary which form the reaction cell (fused-silica capillary, length 55 cm; ID

100 µm) is connected to the capillary attached to the NMR-chip (fused-silica capillary, length 62 cm, ID 40 µm). The length and diameters of the capillaries used were chosen in order to define a very small reaction volume and interfacing volume between the microwave cell and the NMR-chip. Thus, the volume exposure to the microwave irradiation is 1.6 µL (length 21 cm, ID 100 µm) and the interfaced volume is 1.9 µL (length 14 cm, ID 100 µm connected to 62 cm, ID 40 µm) being the total set-up volume, from the pump to the NMR-chip 5.1 µL.



Scheme S1. Diels-Alder cycloaddition of 2,5-dimethylfuran and dimethyl acetilendicarboxilate in toluene-H to afford the corresponding cycloadduct. Chemical reaction studied to prove the performance of the set-up. Any reaction with certain requirements (high solubility in the reaction solvent and not overlapped peaks at the NMR spectrum) could in principle have been chosen, due to the possibility of altering the reaction time depending on the rate of the reaction, simply modifying the reaction volume (for a certain flow rate) for example, just changing the number of windings of the capillary that constitute the microwave flow cell. It shows the versatility of the system, making the set-up a more standard approach to monitor a microwave-assisted chemical reaction.

Dimethyl acetilendicarboxilate (99%) and 2,5-dimethylfuran (99%) were purchased from Sigma-Aldrich and used without further purification. Non-deuterated toluene (99,5%) from sigma Aldrich was used as a solvent.

Gomez, M.V. et al./ Scheme S1

Entry	Temperature	Conversion in the reaction product (%)
1	150	22
2	135	31
3	125	33

Table S1. Stopped-flow measurements. Reaction temperature and reaction conversion on the product for a reaction time of 8 minutes.

To perform the experiment on stopped-flow a heating time of 8 minutes and a cooling time of 2 minutes were applied when the pump was off. Consecutively, the pump was on and the product analyzed on the NMR-chip. The flow rate was 0.21 μL/min. The reaction temperature can not be higher than 150°C because of a bad control by the microwave reactor when using higher values.

Gomez, M.V. et al./ Table S1

Entry	Reaction time (min)	Conversion in the reaction product (%)
1	2.5	15
2	4	25
3	6	30
4	8	31

Table S2. Stopped-flow measurements. Reaction time and reaction conversion on the product at 135°C.

Gomez, M.V. et al./ Table S2

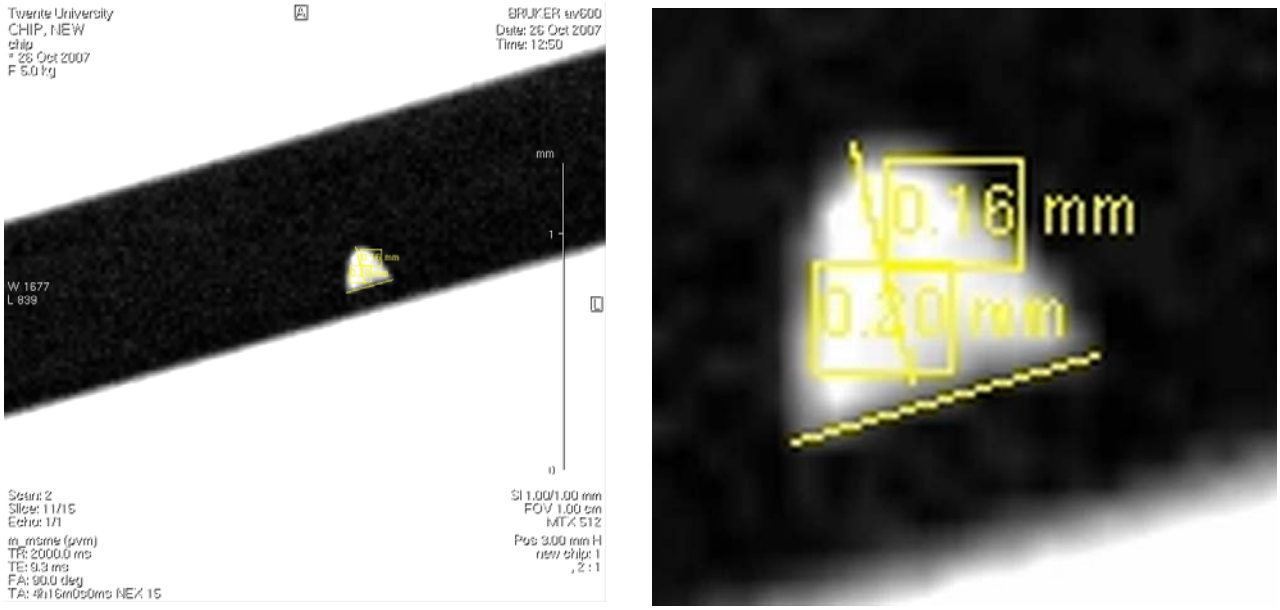


Figure S1. Magnetic Resonance Image picture of NMR-chip sample channel with its dimensions.

If we consider the shape of the sample channel a triangle, the area is 0.016 mm^2

Taking the detection length calculated by Finite Element Method Magnetics (FEMM) software (FEMM v4.2) (see below), the detection volume of the NMR chip is 0.006 mm^3 (6 nL).

FEMM is a software package used to estimate the detection length underneath the radiofrequency microcoil. With this package an axisymmetric coil can be simulated, while taking into account the separation of the wires, the dimensions of the wires and the Eddy currents.

A length value of z = 184 μm has been taken, where the B1 is the 50% of the maximum value. Considering a symmetrical microcoil, the total detection length is 368 μm.

Gomez, M.V. et al./ Figure S1

a)

Entry	t_{min}-t_{max} (sec)	$t_{average}$ (min)	Conversion in the reaction product (%)
1	0-50	0.42	7
2	58-108	1.4	10
3	116-166	2.35	13
4	174-224	3.3	16
5	232-282	4.3	17
6	290-340	5.3	18
7	348-398	6.2	13
8	406-456	7.2	17

b)

Entry	t_{min}-t_{max} (sec)	$t_{average}$ (min)	Conversion in the reaction product (%)
1	0-50	0.42	9
2	58-108	1.4	15
3	116-166	2.35	18
4	174-224	3.3	22
5	232-282	4.3	23
6	290-340	5.3	24
7	348-398	6.2	24
8	406-456	7.2	30

c)

Entry	t_{min}-t_{max}	$t_{average}$	Conversion in the reaction product

	(sec)	(min)	(%)
1	0-50	0.42	11
2	58-108	1.4	16
3	116-166	2.35	23
4	174-224	3.3	28
5	232-282	4.3	31
6	290-340	5.3	33
7	348-398	6.2	34
8	406-456	7.2	37

Table S3 On-flow measurements (a) reaction time and reaction conversion on the product at 125°C;(b) reaction time and reaction conversion on the product at 135°C; (c) reaction time and reaction conversion on the product at 150°C.

Considering a flow rate of 0.21 µL/min and a reaction volume of 1.6 µL, the maximum reaction time is 7.6 min. (456 sec.)
Regarding the detection, the acquisition parameters in the ^{1}H-NMR experiments were optimized to have a measurement time of 50 sec. (100 scans, 0.5 sec. acquisition time, and no delay times). All the measurements were launching on-queue. Considering that there is a dead time of 8 sec. from one measurement to the next one when launching them all on-queue, 8 different conversion values can be (see column 1 and 2 table S3) distinguished in the reaction volume, because of the use of the NMR chip.
The third column shows the average between the minimum and the maximum reaction time for each portion of the volume. The higher value from this time-range (second column, table S3), in minutes, is the one represented in figures 2 and 4.
Considering a flow rate of 0.21 µL/min and the total time to perform an experiment (time to fill the system, reaction time

and detection time) of approximately 40 min., the volume necessary to obtain a set of data for a certain temperature, is about 9 µL. This illustrates that optimization of the reaction conditions is in accordance to the principles of Green Chemistry [1].

Gomez, M.V. et al./ Table S3

References

1. P. T. Anastas, T. C. Williamson, Green Chemistry Frontiers in Benign Chemical Synthesis and Processes; Oxford University Press, New York, **1988.**