Electronic Supplementary Information

On-chip monitoring of chemical syntheses in microdroplets via surface-enhanced Raman spectroscopy

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1. Chemicals

The table below contains all used chemicals, chip materials

Table H-1: chemicals and chip materials

Chemicals and materials	**distributor**
SU-8 2050	*MicroChem,* USA
Developer mr-Dev 600	*micro resist technology ,* Berlin, Ger
PDMS Sylgard 184 Two components kit	*Ebalta,* Rothenburg, Ger.
Glass slides, 76 x 26 x 1 mm	*Roth*, Karlsruhe, Ger.
Elastosil E43	*Wacker Chemie*, Stuttgart, Ger
Silikontube 60°Shore - 1,30 x 1,25mm	*ESSKA.de, Hamburg, Ger*
Rain-X	*Kraco Car Care International Ltd, Altrincham,* UK
Isopropanol	*Roth*, Karlsruhe, Ger.
Thiourea p.a.	*Sigma-Aldrich,* Steinheim, Ger
N-Methylthiourea	*Sigma-Aldrich,* Steinheim, Ger
N,N'-Dimethylthiourea	*Sigma-Aldrich,* Steinheim, Ger
2-Bromoacetophenone	*Sigma-Aldrich,* Steinheim, Ger
2-Bromo-4'-fluoroacetophenone	*Sigma-Aldrich,* Steinheim, Ger
2-Bromopropiophenone	*Sigma-Aldrich,* Steinheim, Ger
Ethanol	*Roth*, Karlsruhe, Ger.
Silvernitrate	*Sigma-Aldrich,* Steinheim, Ger
Sodiumcitrate-2-hydrate	*Isocommerz,* Bt Herzberg/E., Ger
Fluorinert FC-40	*Sigma-Aldrich,* Steinheim, Ger

2. Devices

The table below contains all used devices and manufacturers

Table H-2: devices

devices	**distributor**
Femto plasma oven	*Diener electronic*, Ebhausen, Ger
SPIN 150 spincoater	*SPS-europe*, Putten, Ned.
RSM-10HS, magnet stirrer	*Phoenix Instrument*, Garbsen, Ger
FE5 Flood exposure illuminator	*SÜSS MicroTec*, Oberschleißheim, Ger
Swip KS 10 Digi shaking plate	*Edmund Bühler*, Hechingen, Ger
Elcometer 4340 automatic film applicator	*Elcometer Instruments*, Aalen, Ger
neMESYS syringe pumps	*Cetoni*, Korbußen, Ger
473 nm CW DPSS Laser	*Cobolt*, Stockholm, Sve.
IX71 - inverted Microscope	*Olympus*, Tokyo, Jpn.
Acton SP2750 Ramanspectrometer	*Princeton Instruments*, Acton, USA
ProEM 1600 CCD Camera	*Princeton Instruments*, Acton, USA

3. Chip fabrication

3.1. Master fabrication

A 100 µm layer of SU-8 photoresist was spin coated onto an 8 cm wide silica slide and heated according to the distributor information[1]. Afterwards it was illuminated through a photomask foil, heated up again and finally washed three minutes with developer, rinsed with isopropanol and dried with nitrogen.

3.2. Chip fabrication

Polydimethylsiloxane (PDMS) was poured into the mould, containing the master structure, and degased in vacuum. Afterwards it was placed on a hotplate and heated up to 90 °C for 60 minutes.

A glass slide was plasma cleaned for 10 minutes. The hardened PDMS was pealed from the mold and holes for the fluidic connections were punched out. Subsequently the structured surface was activated with air plasma and slightly pressed onto the glass slide. Silicon tubes, as fluidic connectors, were glued onto the previously stamped out holes and the whole structure was placed again on a heatable surface for 12 hours at 40 °C

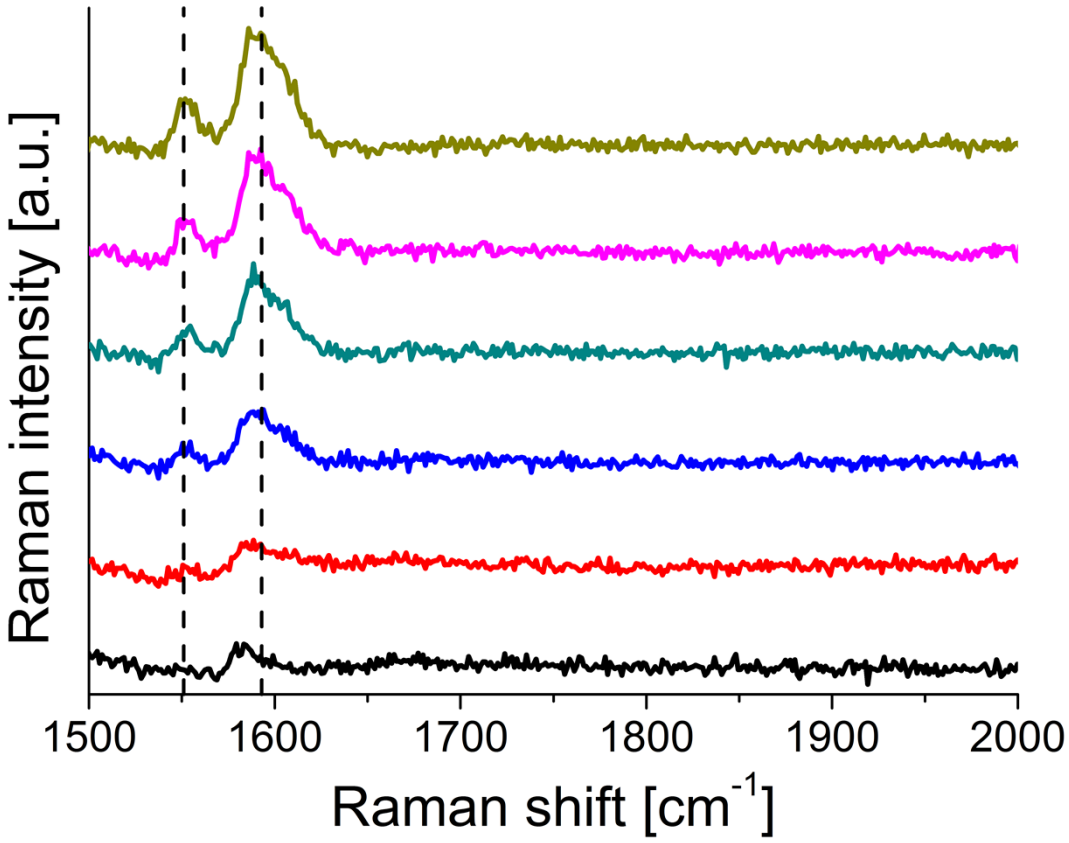
4. Reactant solutions

Silver nanoparticles were synthesises according to the procedure, described by Leopold and Lendl[2]. It was modified in a way that instead of pure water a 7:2 v/v ethanol/water mixture was used. For the reactant solutions of each 2-Bromoacetophenone, 2-Bromo-4'-fluoroacetophenone and 2-Bromopropiophenone 1 mmol were dissolved in 2 mL 9:1 v/v ethanol/water. 1.1 mmol of each compoud: Thiourea, N-Methylthiourea and N,N'-Dimethylthiourea were dissolved in 2 mL 8.5:1.5 v/v ethanol/water. These solutions were used for both, on- and off-chip reactions.
Microfluidic flows were generated using precision syringe pumps (neMESYS, Cetoni GmbH, Korbußen, Germany), equipped with 100 µL gastight syringes, which were connected to the chip via Teflon tubing.

5. Raman/SERS Measurements

Raman measurement were performed using a confocal dispersive Raman microscope (MonoVista CRS 750HR/IX71, S&I - Spectroscopy & Imaging GmbH, Warstein, Germany), based on an inverted microscope (Olympus IX 71, Tokyo, Japan), a spectrometer (Acton SP2750, Princeton Instruments, Acton, MA, USA) and a peltier-cooled EMCCD (electron multiplied charge coupled device)-Camera (ProEM 1600x200 eXcelon /UV, Princeton Instruments, Acton, MA, USA). A 473 nm, 50 mW continuous wave diode pumped solid state laser (Cobolt blues, Cobolt AB, Stockholm, Sweden) was used as excitation light source. The spectra acquisition time was 500 ms. All spectra ware baseline corrected and shifted along the Y-axis (fig. 2) or the X-axis (fig. 3) for clarity.

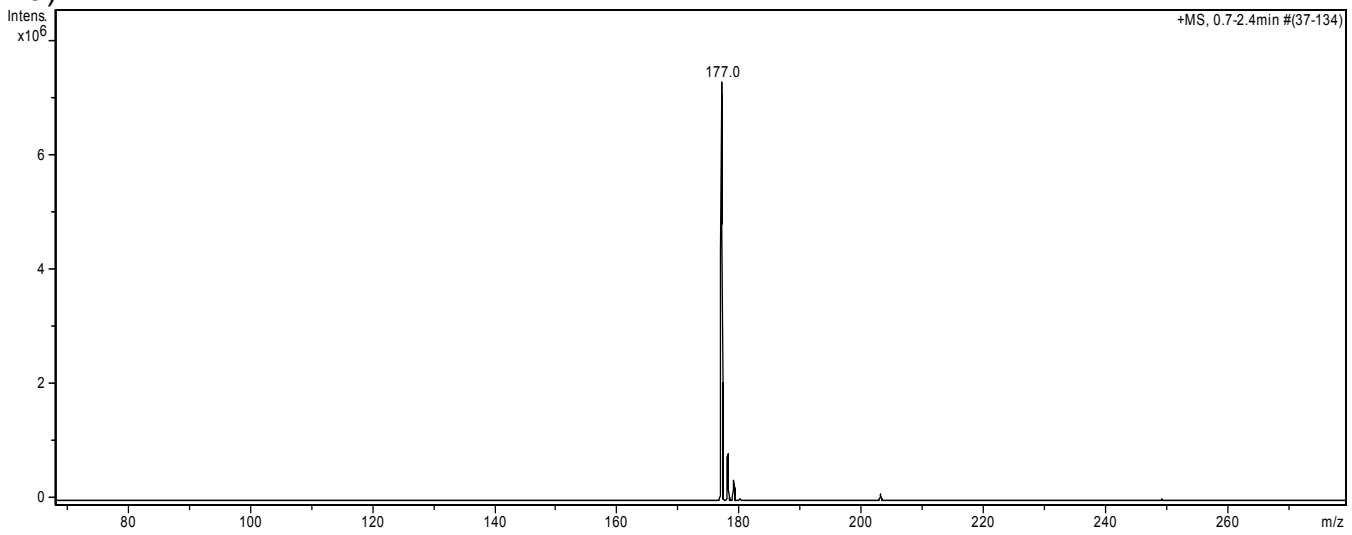
6. Raman spectra from off-line reaction



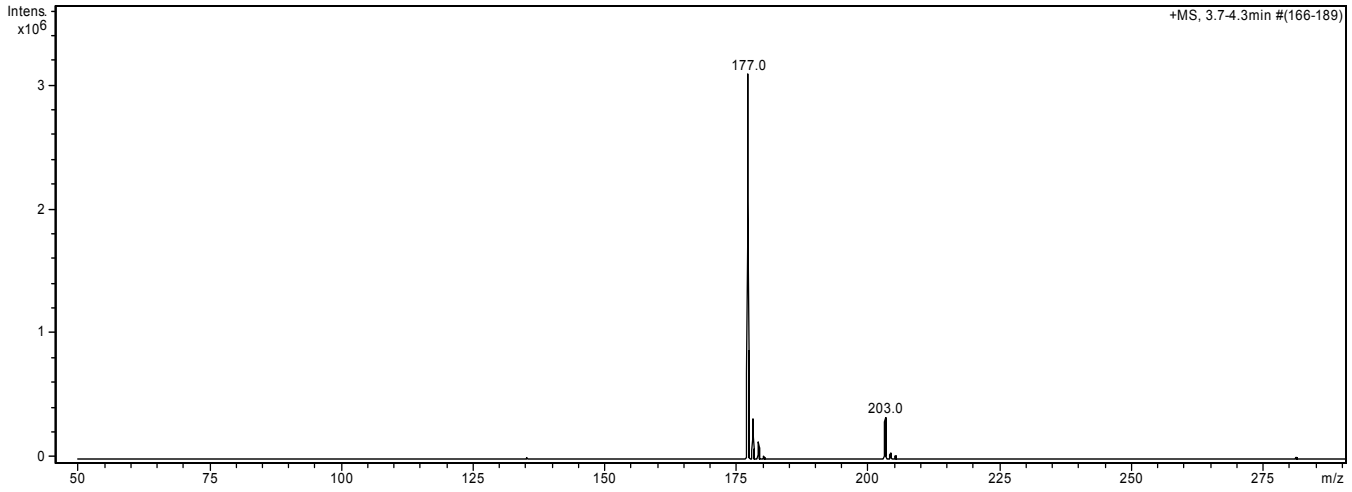
S 1. Synthesis in a batch reactor, spectra of reaction solution at 0 s (black line), 20 s (red line), 40 s (blue line), 60 s (dark green line), 80 s (pink line) and 100 s (grass green line); a strong increase of the Raman bands at 1551 cm^{-1} and 1593 cm^{-1} can be observed

7. MS spectra from off-line reaction

a)



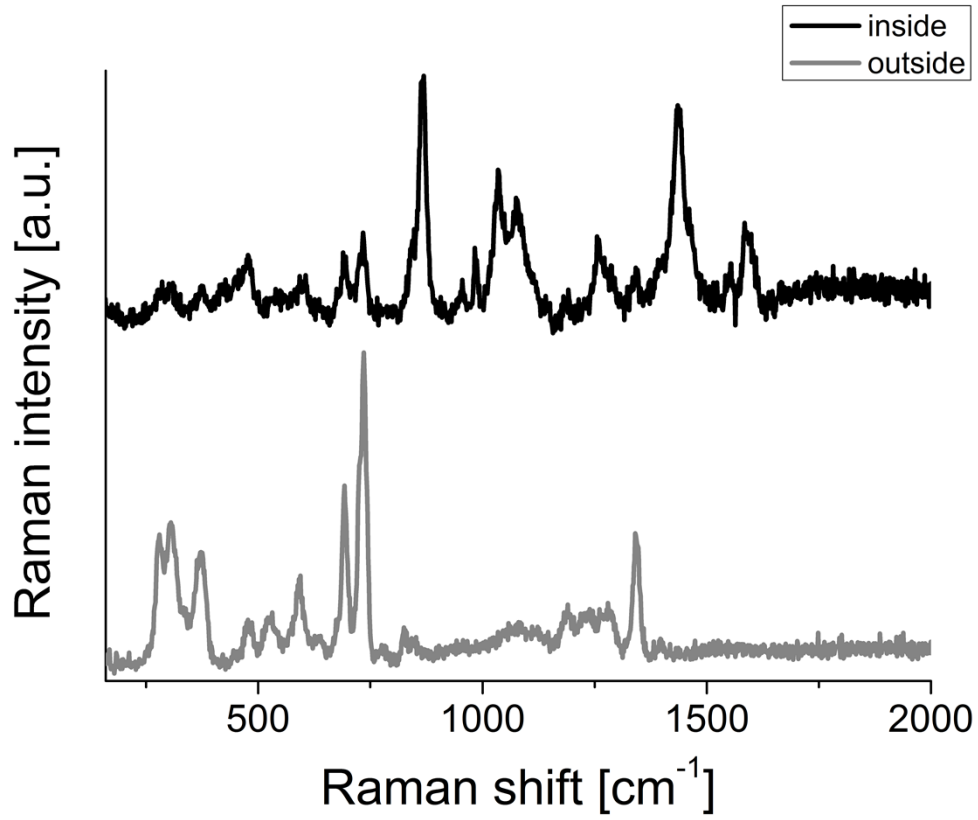
b)



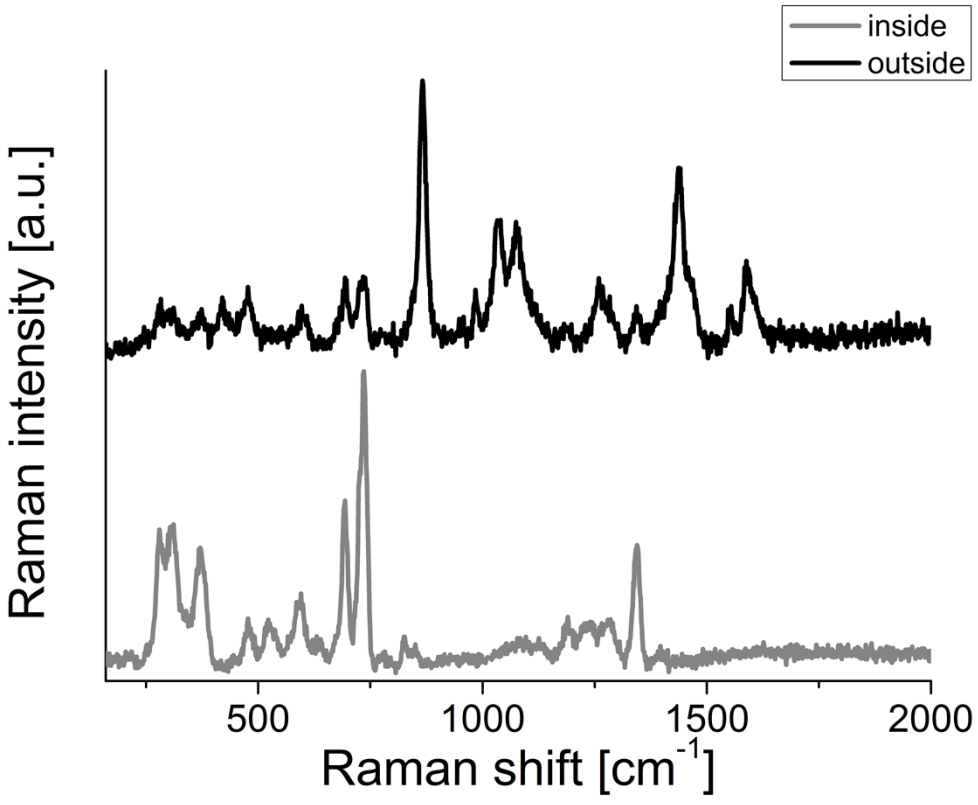
S 2. Mass spectra of a) the reaction product after 1 h reaction time and b) commercial available 2-Amino-4-phenylthiazols as comparison

8. Experiments proving the absence of analyte adsorption and dispersion

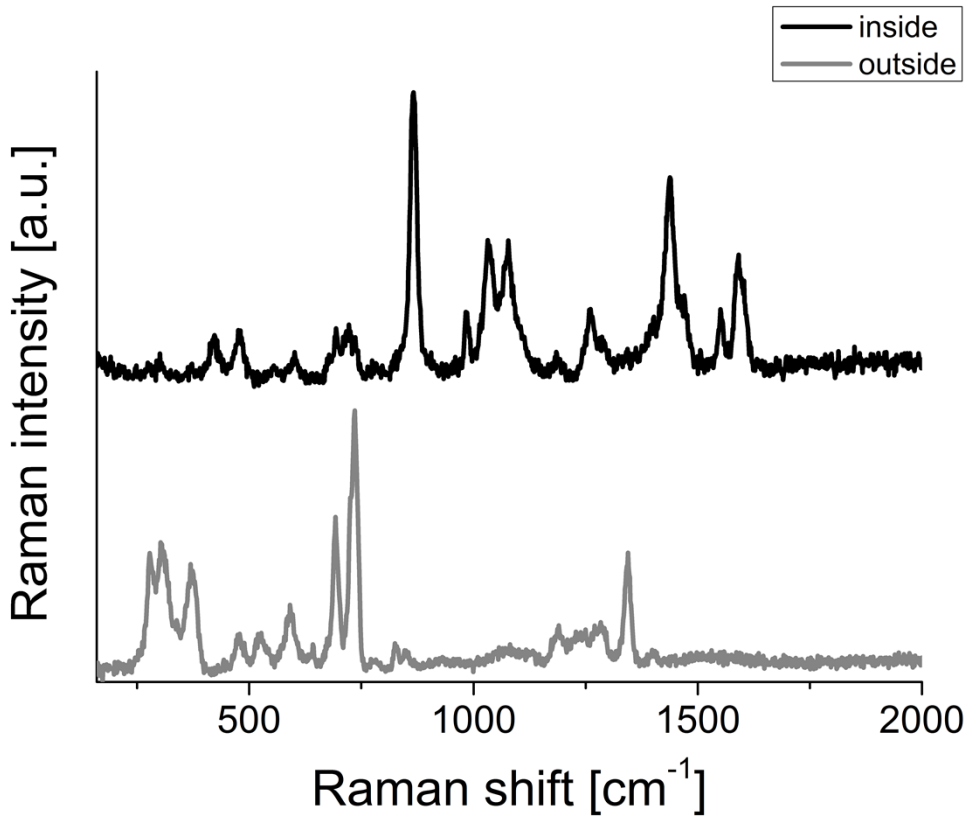
a)



b)



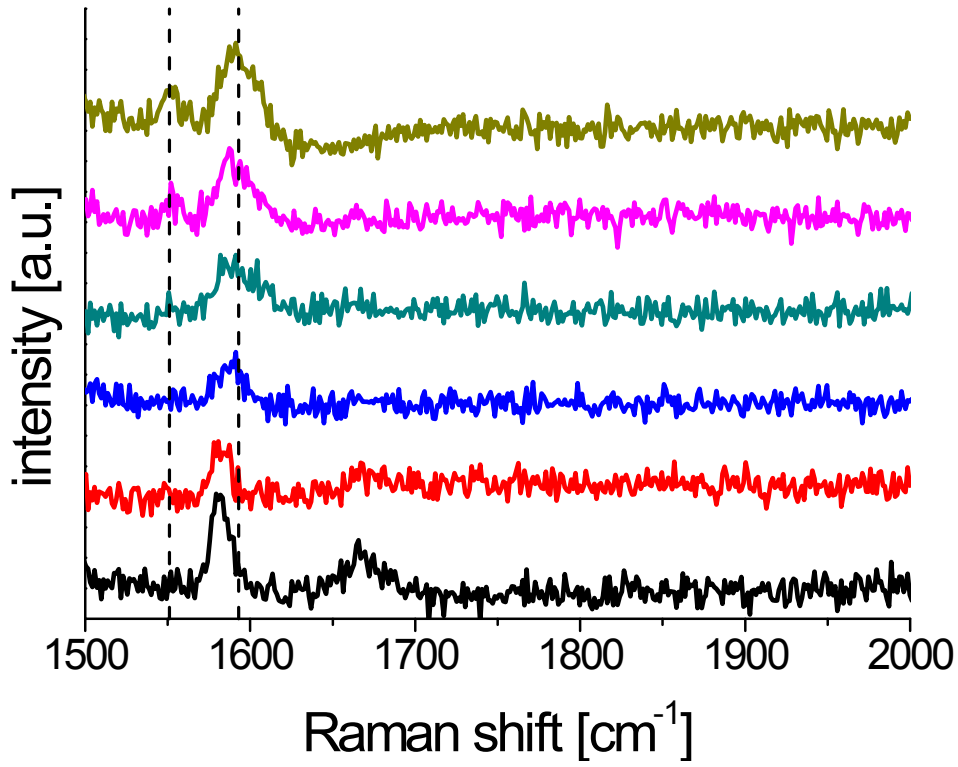
c)



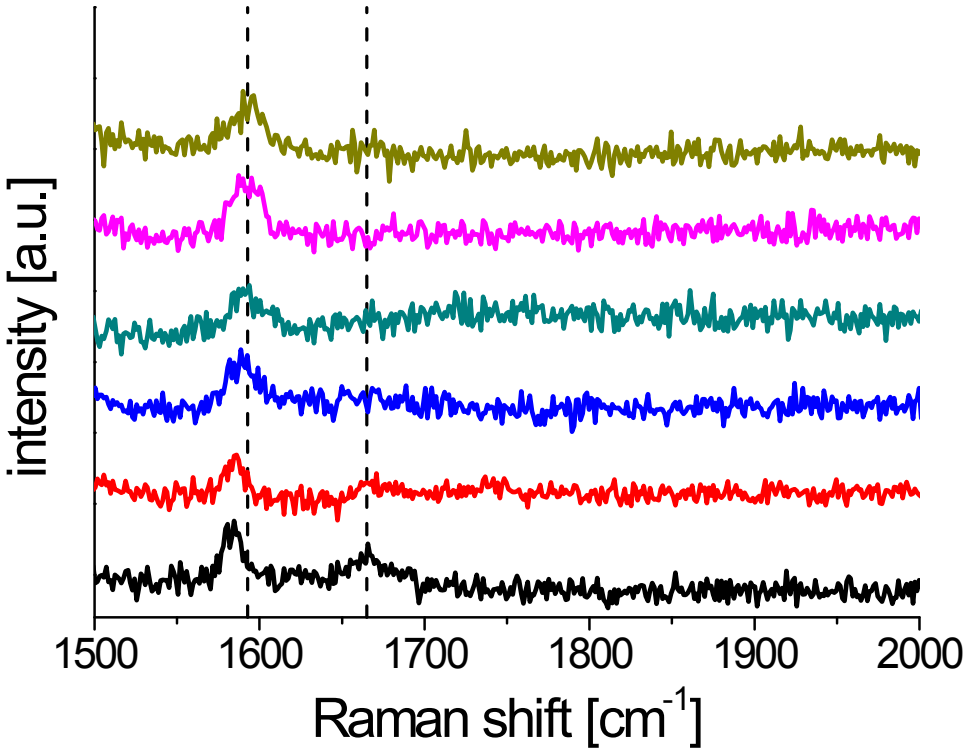
S 3. Spectra of reaction solution (black lines) and droplet carrier oil (grey lines) at a) 0 minutes b) 60 minutes and c) 120 minutes; no memory effect or diffusion of the reactant into the carrier oil can be observed.

9. Raman spectra of thiazole syntheses

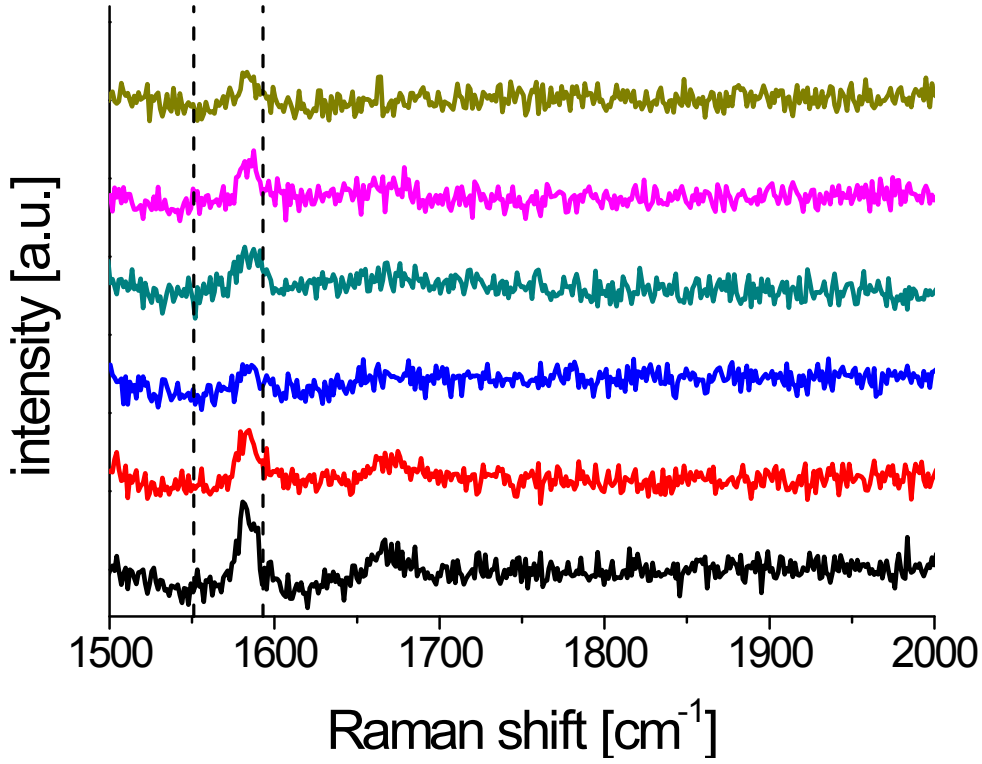
a)



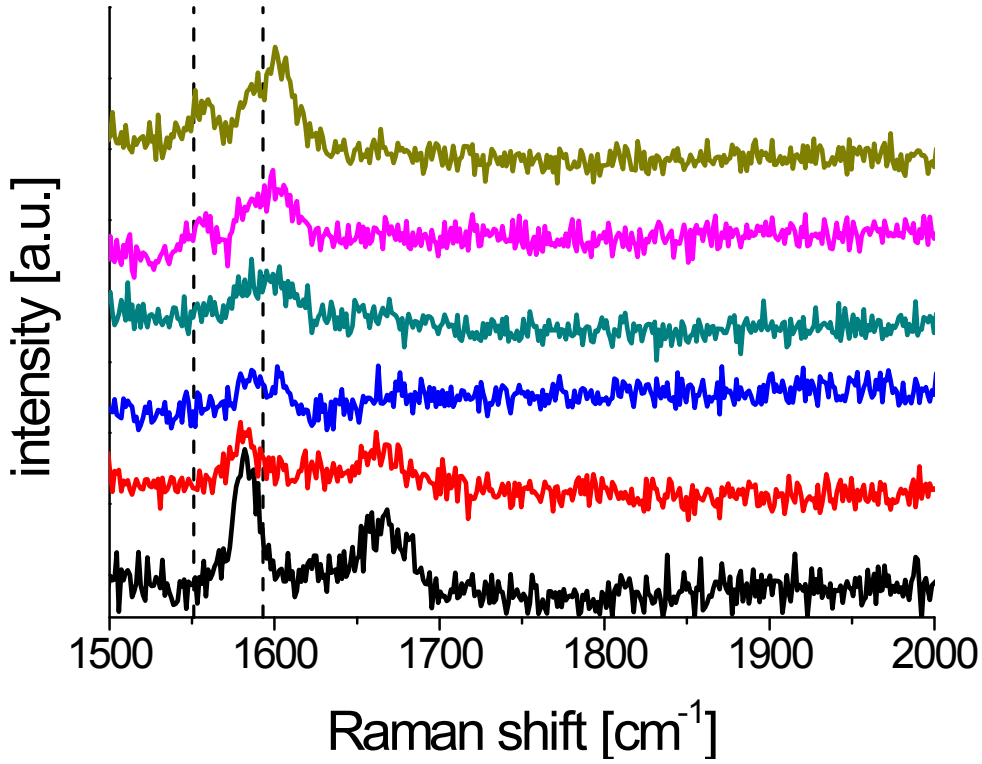
b)



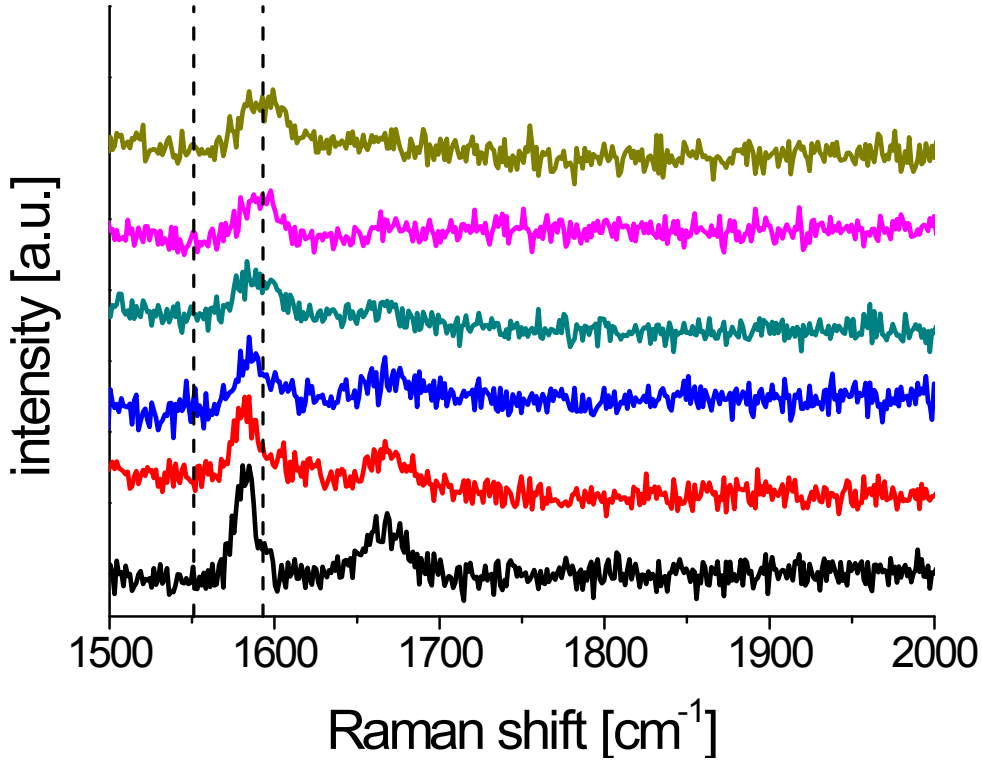
c)


intensity [a.u.]
1500
1600
1700
1800
1900
2000
Raman shift [cm-1]

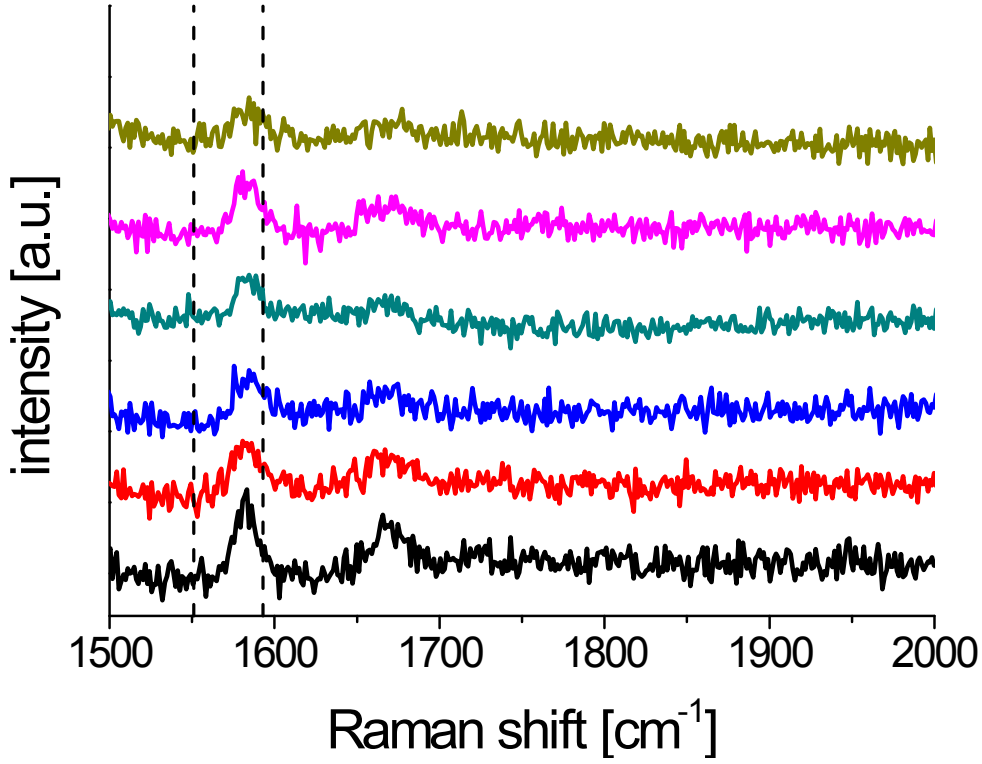
d)


intensity [a.u.]
1500
1600
1700
1800
1900
2000
Raman shift [cm-1]

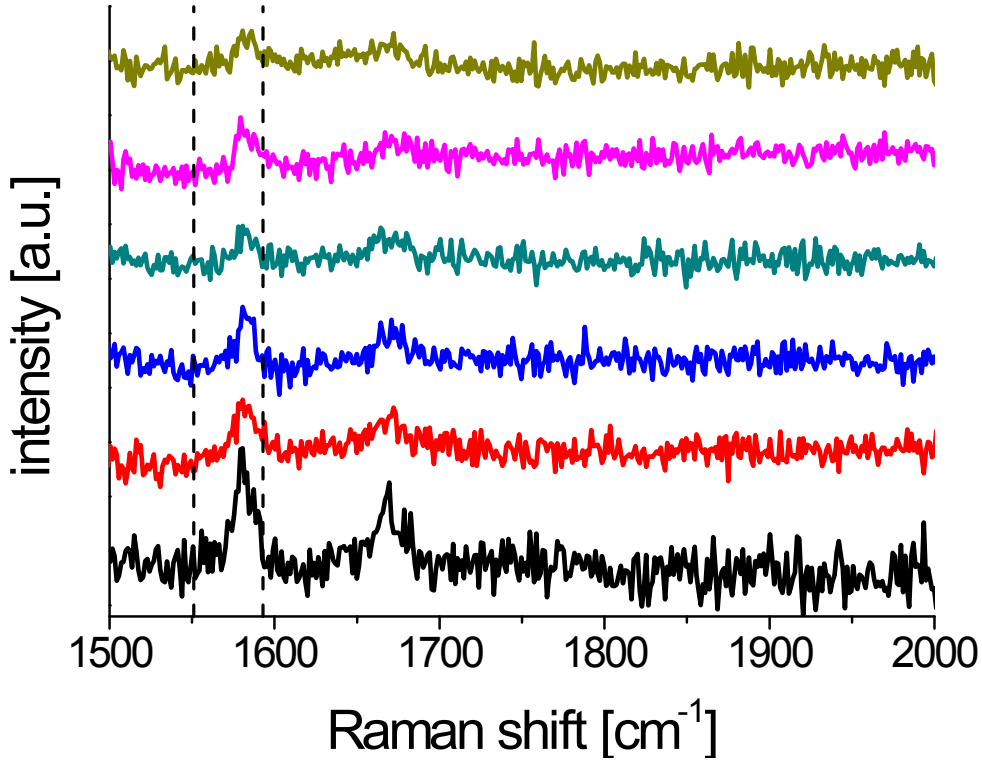
e)


intensity [a.u.]
1500
1600
1700
1800
1900
2000
Raman shift [cm-1]

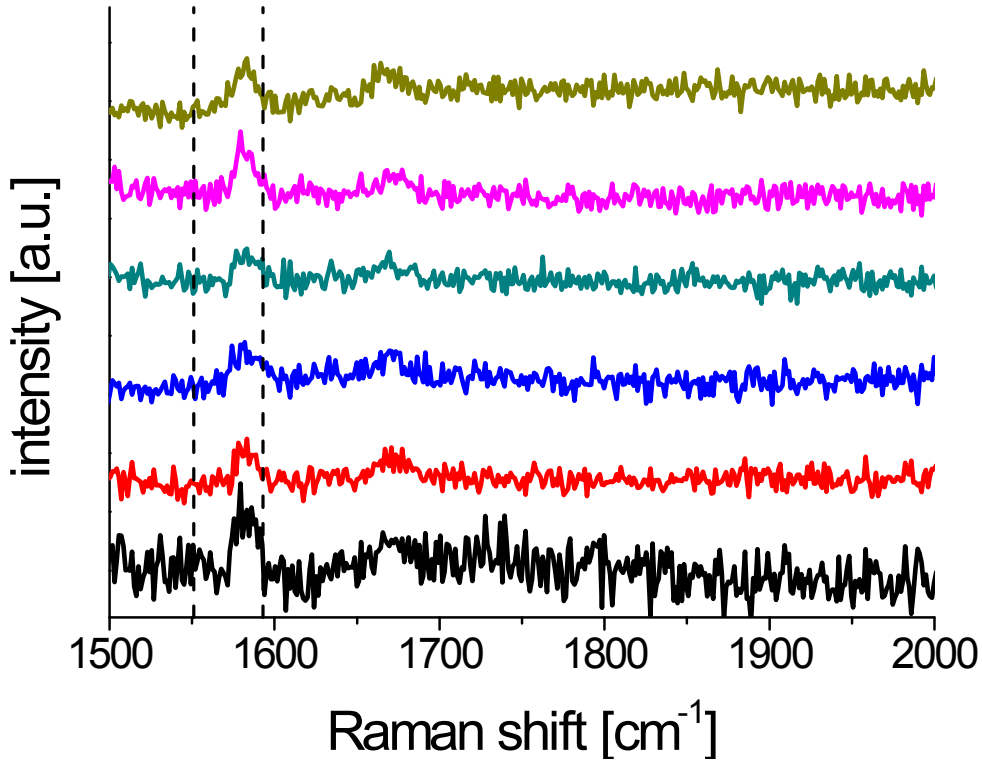
f)


intensity [a.u.]
1500
1600
1700
1800
1900
2000
Raman shift [cm-1]

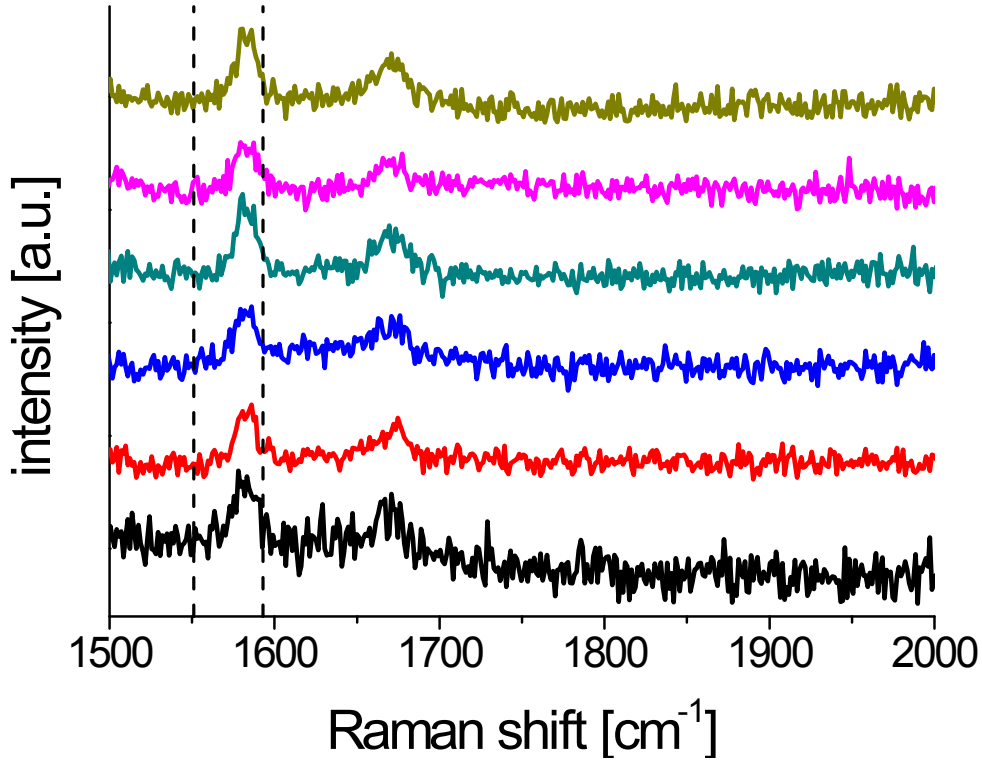
g)


intensity [a.u.]
1500
1600
1700
1800
1900
2000
Raman shift [cm-1]

h)

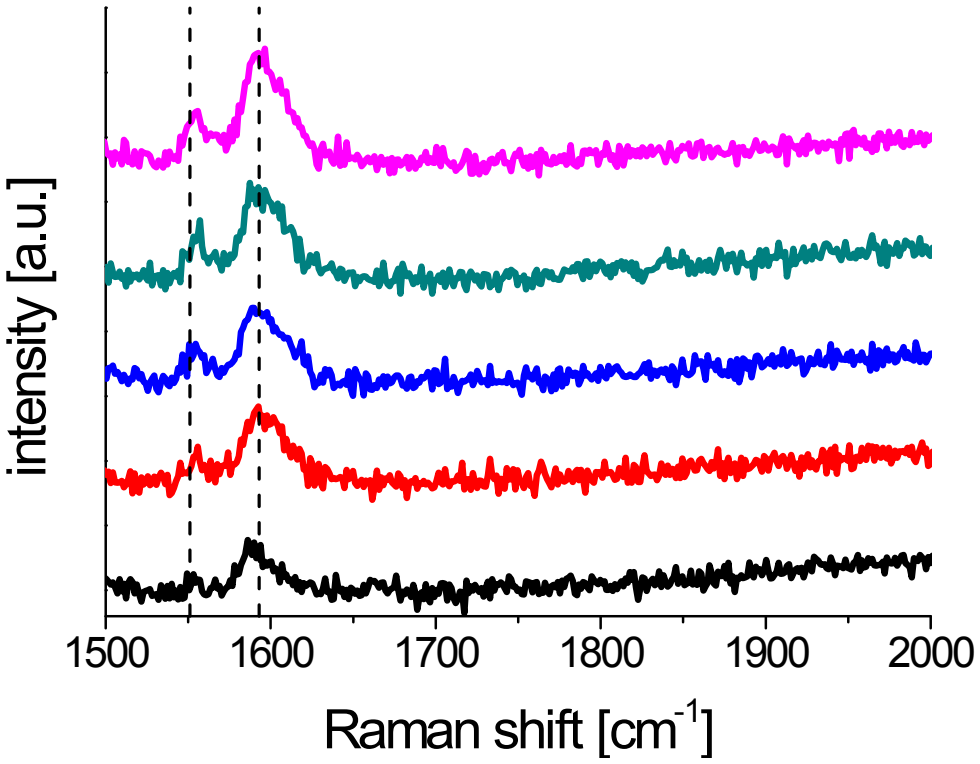

intensity [a.u.]
1500
1600
1700
1800
1900
2000
Raman shift [cm-1]

i)



S 4. Spectra of reaction solution at 0 s (black line), 20 s (red line), 40 s (blue line), 60 s (dark green line), 80 s (pink line) and 100 s (grass green line), dashed lines mark the indicator Raman bands of the original reaction product a) 2-Bromoacetophenone and Thiourea b) 2-Bromoacetophenone and N-Methylthiourea c) 2-Bromoacetophenone and N,N‘-Diemthylthiourea d) 2-Bromo-4‘-Fluoroacetophenone and Thiourea e) 2-Bromo-4‘-Fluoroacetophenone and N-Methylthiourea f) 2-Bromo-4‘-Fluoroacetophenone and N,N‘-Dimethylthiourea g) 2-Bromopropiophenone and Thiourea h) 2-Bromopropiophenone and N-Methylthiourea h) 2-Bromopropiophenone and N,N‘-Dimethylthiourea

10. Raman spectra of thiazole synthesis with downstream added nanoparticles



S 5. Synthesis in microfluidic chip, where nanoparticles are added ad the dispensing unit. Due to the missing SERS effect measurements start at t= 20s. Spectra of reaction solution at 20 s (black line), 40 s (red line), 60 s (blue line), 80 s (dark green line), 90 s (pink line); an increase of the Raman bands at 1551 cm^{-1} and 1593 cm^{-1} can be observed

1 MicroChem Corp., http://www.microchem.com/pdf/SU-82000DataSheet2025thru2075Ver4.pdf, (accessed October 2014).
2 N. Leopold and B. Lendl, *J. Phys. Chem. B*, 2003, **107**, 5723.