Supplementary Material (ESI) for Lab on a Chip

Highly Efficient Chemoselective N-Acylation with Water Microreaction System in the Absence of Catalyst.

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1. Additional information of N-acylation of pirperidine (1a) 2,6-dimethyl piperidine (1e) and acetic anhydride

The exothermisity and endothermicity of the reaction itself may be shown by ΔT_{max}, which is temperature difference from ambient to maximal temperature of reaction mixture. Thus, as shown in Fig. S1 and Table S1, each ΔT_{max} for acylation of piperidine (**1a**) with bachwise neat, batwise onH_2O and μ-onH_2O method are 136°C, 13°C and 2°C, respectively. Indeed, this ΔT_{max} is prominent in batchwise neat method rather than μ-onH_2O and μ-subH_2O method.
Similarly, each ΔT_{max} for acylation of 2,6-dimethylpiperidine (**1e**) with bachwise neat, batwise onH_2O and μ-onH_2O method are -5°C, -2.4°C and -0.5°C, respectively as shown in Table S2.
Consequently in bachwise neat reaction, ΔT_{max} for the N-acylation of piperidine (**1a**) and 2,6-dimethyl piperidine (**1e**) was 136°C representing exothermicity and –5°C corresponding to the endothermicity, respectively.

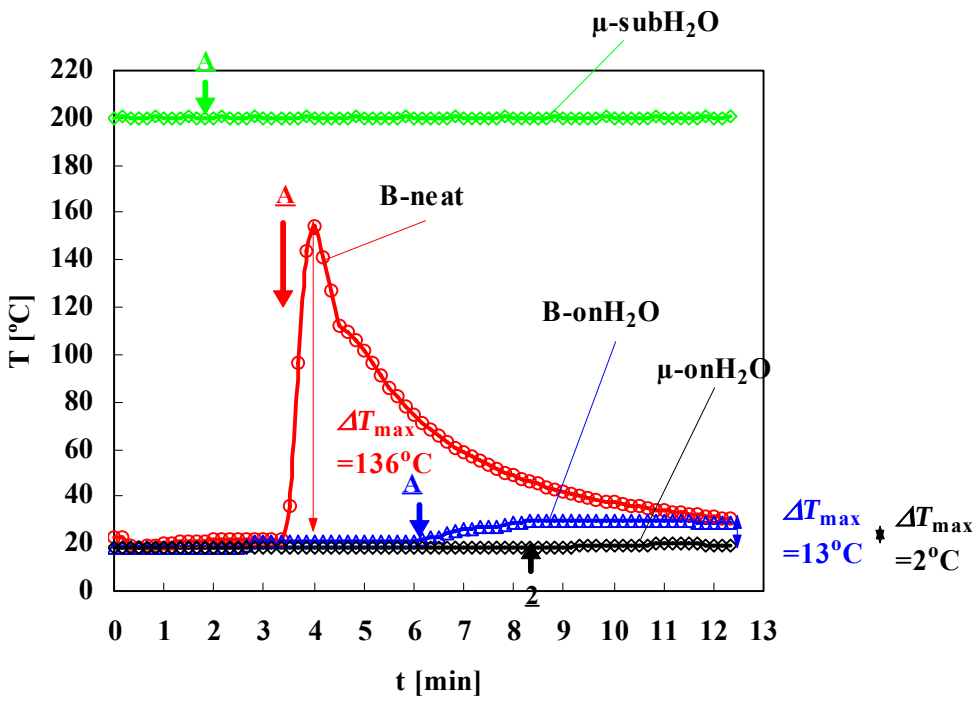
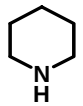
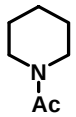


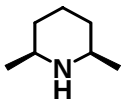
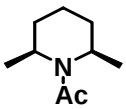
Fig. S1 Temperature vs. reaction time for various method of acylation of piperidine(1a) and acetic anhydride(A). The time to add or inject A is shown by downard arrow.

Table S1

entry	substrate	product	method (solv.)	Ac_2O (AcOH) eq.	*T* (ΔT_{max}[e]) °C	*P* MPa	τ	conv. %	sel. %	yield %
1			B[a] (neat)	1.1	18[f](136)	0.1	12 min	93	91	85
2			B-on[b] (H_2O)	1.1	19[f] (13)	0.1	12 min	100	98	98
3	**1a**	**2a**	μ-on[c] (H_2O)	1.1	11(2)	0.1	1.1s	99.8	100	99.8
4			μ-sub[d] (H_2O)	1.1	200	5	9.9s	18	94	17

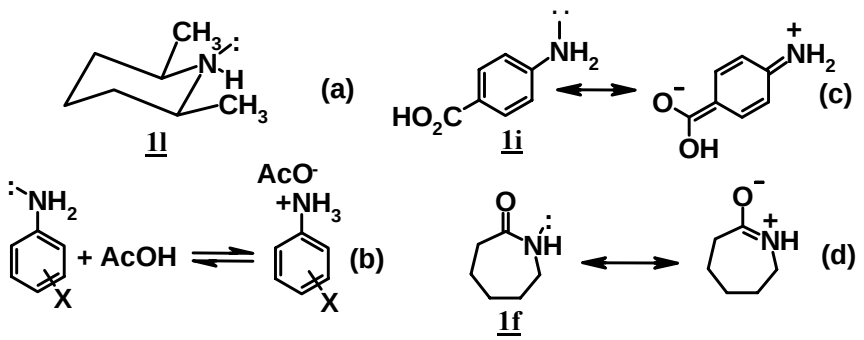
a) Neat(solvent-free) batchwise reaction ; b) Batchwise onH_2O system;
c) onH2O micro reaction system; d) subH_2O microreaction system;
e) Temperature difference of reaction mixture from abmient to maximal temperature;
f) Temperature of a reactant before exothermic reaction

Table S2

entry	substrate	product	method (solv.)	Ac_2O (AcOH) eq.	*T* (ΔT_{max}[f]) °C	*P* MPa	τ	conv. %	sel. %	yield %
1			B[a] (neat)	1.1	28[e](-5.0)	0.1	12 min	50	100	50
2			B-on[b] (H_2O)	1.1	28[e](-2.4)	0.1	12 min	8	100	8
3	**1e**	**2e**	μ-on[c] (H_2O)	1.1	23(-0.5)	0.1	1.1s	3	100	3
4			μ-sub[d] (H_2O)	1.1	100	5	9.9s	95	100	95

a) Neat(solvent-free) batchwise reaction ; b) Batchwise onH_2O system;
c) onH_2O micro reaction system; d) subH_2O microreaction system
e) Temperature difference of reaction mixture from abmient to maximal temperature;
f) Temperature of a reactant before endothermic reaction

2. Additional scheme for N-acylation mechanism



Scheme S1

3. Experimental procedure

In a typical procedure, a stream of amines or anilines is placed across one of acid anhydride, and then the mixtures are placed across a high-speed flow of ambient H_2O (or subH_2O), and finally introduced into the μ-reactor (Fig S2). The endothermic acylation proceeds rapidly as a result of the vigorous mixing caused by a turbulent flow with a Reynolds number of around 1.7 x 10^3 using subH_2O microreaction system (Fig S5-7). While the exothermic acylation seems to proceed rapidly as a result of internal exothermic heating of reactants in spite of the slow mixing caused by a laminar flow with a Reynolds number of around 2.6 x 10^2 using onH_2O microreaction system (Fig S3-4). Acylation may occur exclusively in the O/W microemulsion manner which is characteristic of the onH_2O (or subH_2O) microreaction system.[8a-c]

3-1. Acylation of piperidine (1a) by acetic anhydride with onH_2O microfluidic reaction system

The onH_2O acylation was carried out by a flow-type of microreaction system as shown in Fig. S3 and S4. The mixture of piperidine 45.0 g (0.53mol) and toluene 2.435 g (0.0264 mol, 0.05 equiv.), and separated acetic anhydride 59.3 g (0.58mol, 1.1 equiv) were charged into pump (JASCO PU-2086) A and B, respectively. As shown in Fig. S3, a 98.2 μL tube-microreactor (i.d. 0.50mm, length 500mm) made of SUS316 was connected with pump A, B and C. A mixed stream in tee A, where piperidine flow was placed across acid anhydride flow, was pumped at a linear velocity of 4.2 cm s^{-1} at ambient temperature and pressure was struck against ambient H_2O at a linear velocity of 42 cm s^{-1} at 11~50°C and 0.1MPa in a tee B, followed by the introduction to the microreactor. We can set up this microreactor in a water bath for cooling and heating operation. The reaction times (=residence time) were adjusted to be shorter than 5 s to suppress the consecutive hydrolysis of anhydride substrate (or amide product). Pressure was controlled by a back-pressure regulator (JASCO back-pressure regulator 880-81). The fluctuations of temperature and pressure were controlled within ±0.5 °C and 0.1 MPa, respectively, which was within experimental error.

Detailed analysis of the reaction mixture was performed by GC-MS/MS (Varian CP-3800-1200L) or by GC-FID (Agilent Technologies Inc., GC 6890N) of an authentic sample for qualitative analysis. Quantification of the product was obtained by a multipoint calibration curve for each products based on the internal standard of toluene by GC-FID (Agilent Technologies Inc., GC 6890N). Reaction time (residence time) was calculated using the following equation (1-1) as shown below,

$$t = \pi\left(\frac{r}{20}\right)^2 \times \left(\frac{L_1\rho_{25}}{F_A + F_B}\right) \tag{1-1}$$

where τ : reaction time[sec], F_A: flow rate of pump A(=4.996g/min), F_B: flow rate of pump B (=0.498g/min), r :inner diameter of SUS316 tube (=0.50mm), L_1: the length of microreactor tube (=50.0cm), ρ_{25} :density of water at 25ºC, 0.1MPa (=0.994g/cm^3). Density and volume were determined with the software of the NIST/ASME Steam properties.[8a-c] Reaction time t=1.1 s was obtained in this example.

After 30 min, 1ml of GC sample solution was collected and diluted with 1ml of acetone to prevent from producing biphasic solution. Thus initial molality of 0.47 mol/kg was decreased to 0.26mol/kg. Molality of **1a** and acetyl piperidine (**2a**) in the sample solution were estimated from the ratio of GC peak area based on toluene with calibration. Then conversion, selectivity and yield were determined by the equation as bellow,

$$\text{conv.}[\%] = 100 - \text{reactant}\ [\%] \tag{1-2}$$

$$\text{sel.}[\%] = \frac{\text{product(s)}\ [\%]}{\text{conv.}} \times 100 \tag{1-3}$$

$$\text{yield}[\%] = \frac{\text{conv.} \times \text{sel.}}{100} \tag{1-4}$$

The results of conv.=99.8%, sel.=100% and yield=99.8% of **2a** were derived from the GC analysis (Table S1 entry3). Therefore, no significant side reactions such as hydrolysis, hydration and pyrolysis are occurred. Indeed the tube and connecter made by PTFE or glass may be available instead of the onH_2O microreaction system because of low pressure.

3-2. Acylation of 2,6-dimethylpiperidine (1e) by acetic anhydride with subH_2O microreaction system

The subH_2O acylation was carried out by a flow-type of microreaction system equipped with a high-pressure and high-temperature infrared spectroscopy (JASCO FTIR/620) as shown in Fig. S5-S7. The mixture of 2,6-dimethylpiperidine (**1e**) 22.042g (0.1947mol) and toluene 0.897g (0.0097mol, 0.05 equiv.), and also acetic anhydride 21.867g (0.21mol, 1.1 equiv) was charged into a pump (JASCO PU-2086) A and B.

As shown in Fig. S6, a 48.5 μL tube-microreactor 316 (i.d. 0.50mm, length 247mm) made of SUS316 was installed into a furnace (Fig. S5) in place of high-pressure and high-temperature IR flow cell. The subH_2O microreaction system can heat up momentarily at high temperatures of 50°C to above 250°C with ambient substrate solution and then can quench

to sufficiently low temperatures within 10 s after the reaction, by passing through a cooling flange and cooling coil (i.d. 0.50mm, length 460cm). That is, a stream of the **1e** and anhydride mixture at a linear velocity of 4.2 cm s^{-1} at ambient temperature and a pressure of 5 MPa was struck against subH_2O at a linear velocity of 42 cm s^{-1} at 100°C and 5MPa in a tee, followed by the introduction to the microreactor (placed in a furnace; Maximum 0.5kW), in which the temperature was realized to raise up to subcritical temperatures around 250°C within 0.05 s. In order to effect the rapid heating and to prevent temperature changes upon the addition of substrate, the interior space of this furnace was vacuumed at the pressure of 400-600 Pa, leading to the radiation heating without the convection. The reaction times (=residence time) were adjusted to be shorter than 30 s to devoid of the consecutive hydrolysis of anhydride substrate and ester product. Pressure was controlled by a back-pressure regulator (JASCO back-pressure regulator 880-81). The fluctuations in temperature and pressure were controlled within ±0.2 °C and 0.1 MPa, respectively, being allowed within experimental error.

The reaction products were first obtained as a suspension in water, but were separated completely from the aqueous solution within the collection of 40 min. Detailed analysis of the reaction mixture was performed by GC-MS/MS (Varian CP-3800-1200L) for qualitative analysis and GC-FID (Agilent Technologies Inc., GC 6890N) for quantitative analysis using calibration curve of an authentic sample based on the internal standard of toluene. Reaction time (residence time) is calculated by the following equation (1-5) as below,

$$t = \pi\left(\frac{r}{20}\right)^2 \times \left(\frac{L_1\rho_{100} + L_2\rho_{50}}{F_A + F_B}\right) \qquad (1\text{-}5)$$

where τ : reaction time[sec], F_A: flow rate of pump A(=4.996g/min), F_B: flow rate of pump B (=0.487g/min), r: inner diameter of SUS316 tube (=0.50mm), L_1: the length of microreactor tube (=24.7cm), L_2: the tubular length of cooling coil (=440cm), ρ_{100} :density of water at 100ºC,5MPa (=0.961g/cm^3), ρ_{50} :density of water at 50ºC,5MPa (=0.990g/cm^3) . Density and volume were determined with the software of the NIST/ASME Steam properties. [10b] Reaction time t=9.9 s was obtained in this example.

After 30min, 1ml of GC sample solution was collected and diluted with 1ml of acetone to prevent from producing biphasic solution. Thus initial molality of 0.37 mol/kg was decreased to 0.19 mol/kg. Molality of **1e** and acetyl diemthylpiperidine (**2e**) in the sample solution was estimated from the ratio of GC peak area based on toluene with calibration. Then conversion, selectivity and yield were determined by the equation (1-2), (1-3) and (1-4). The results of conv.=95%, sel.=100% and yield=95% of **2e** were derived from the GC analysis.

3-3. Batchwise reaction of acylation of piperidine (1a) with acetic anhydride

The acylation was carried out by using a batch reactor consists of glass vials(internal volume of 30 cm^3), which was inserted a K type thermocouple and was placed above a balance.

In a solvent-free (neat) condition, 13.6 mmol of piperidine was loaded into the reactor, and then 15.0 mmol (1.1 equiv.) of acetic anhydride were added with shaking using spatel. After that, 0.7mmmol (0.05 eqiv.) toluene was poured into the reactor. All products were characterized and analysed by the same method as described for onH_2O microreaction system. The results of conv.=93%, sel.=91% and yield=85% of acetyl piperidine (**2a**) were derived from the GC analysis.

In onH_2O reaction, 25.064 g of pure water and then 13.6 mmol of piperidine were loaded into the reactor, some portions of 15.0 mmol (1.1 equiv.) of acetic anhydride was added with shaking by spatel. Finally, 0.7mmmol (0.05 equiv.) toluene was added. All products were characterized and analyzed by the same method as described for onH_2O microreaction system. The conversion (99.9%), the selectivity (98%) and yield (98%) of acetyl piperidine (**2a**) were calculated from the GC analysis.

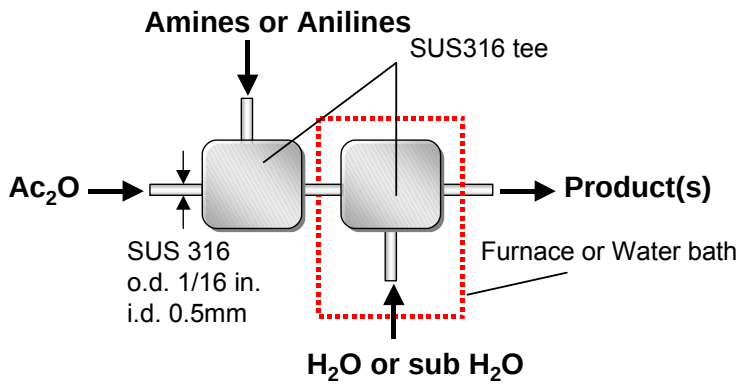


Fig. S2 Illustrative diagram of **μ**-onH_2O and **μ**-subH_2O

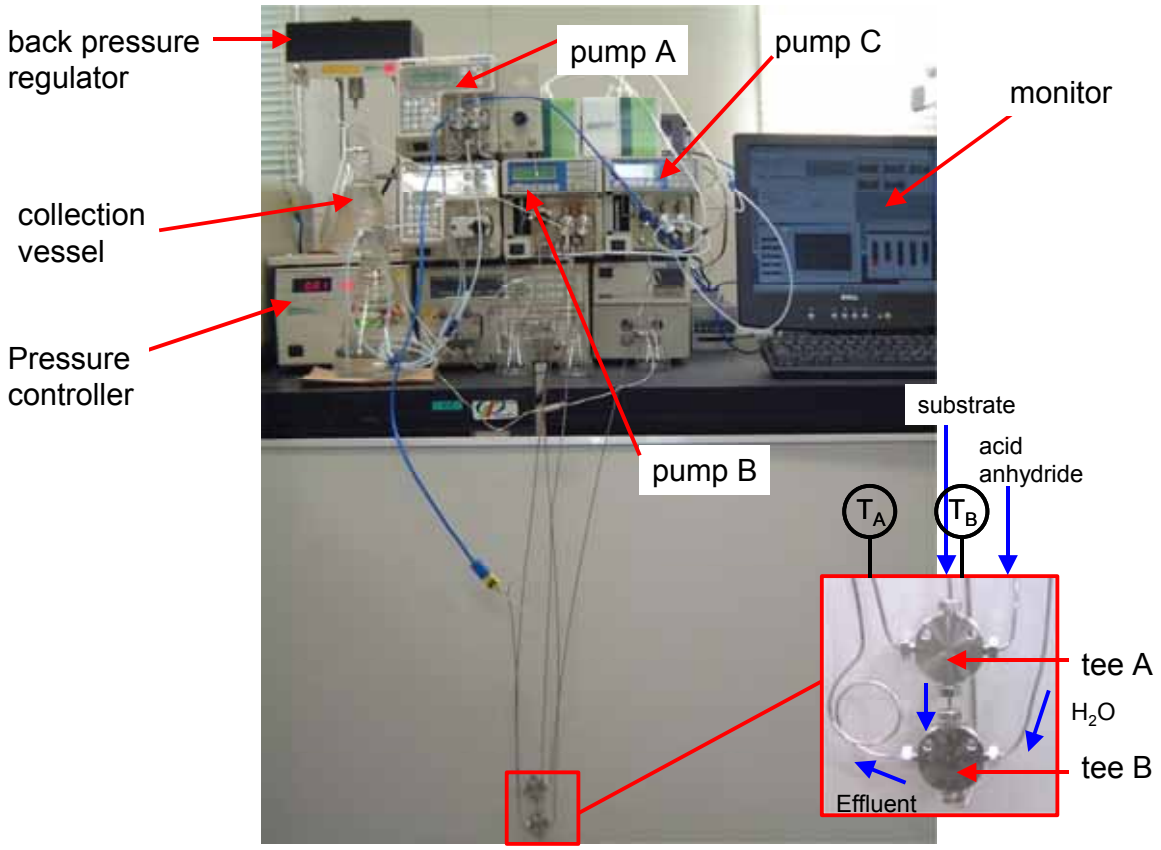


Fig. S3 Total-view of onH_2O microreaction system

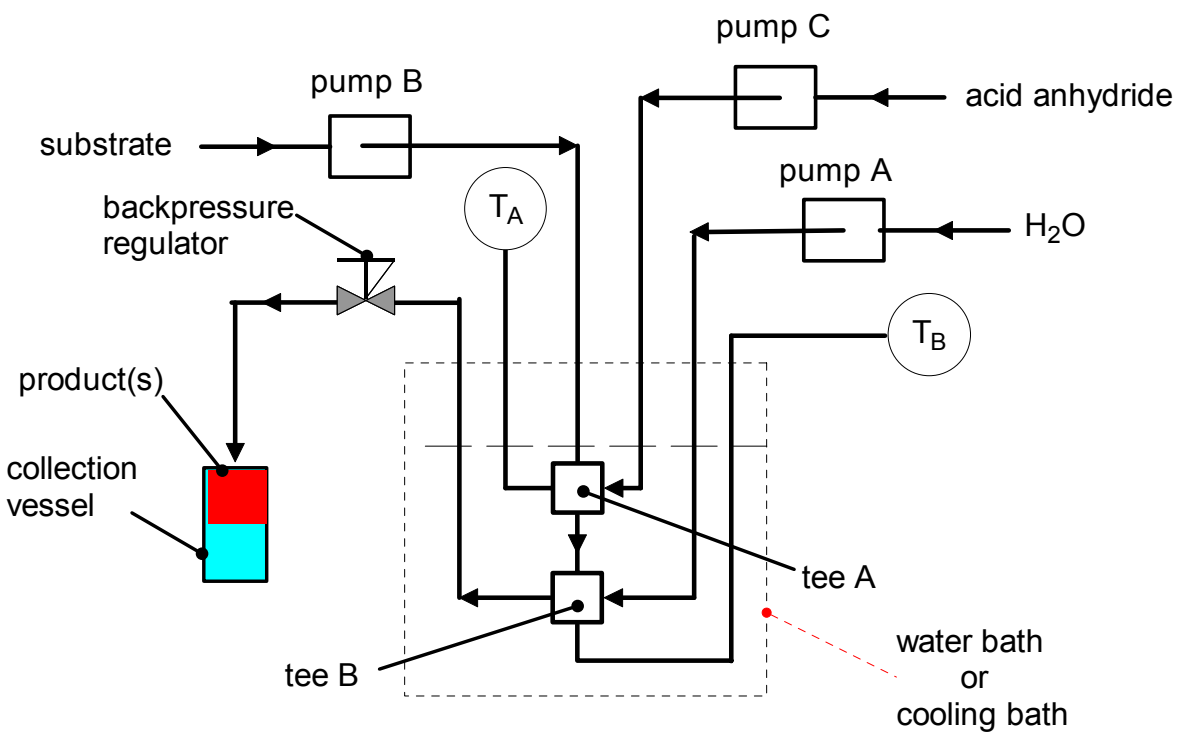


Fig. S4 Schematic diagram around furnace in onH_2O microreaction system

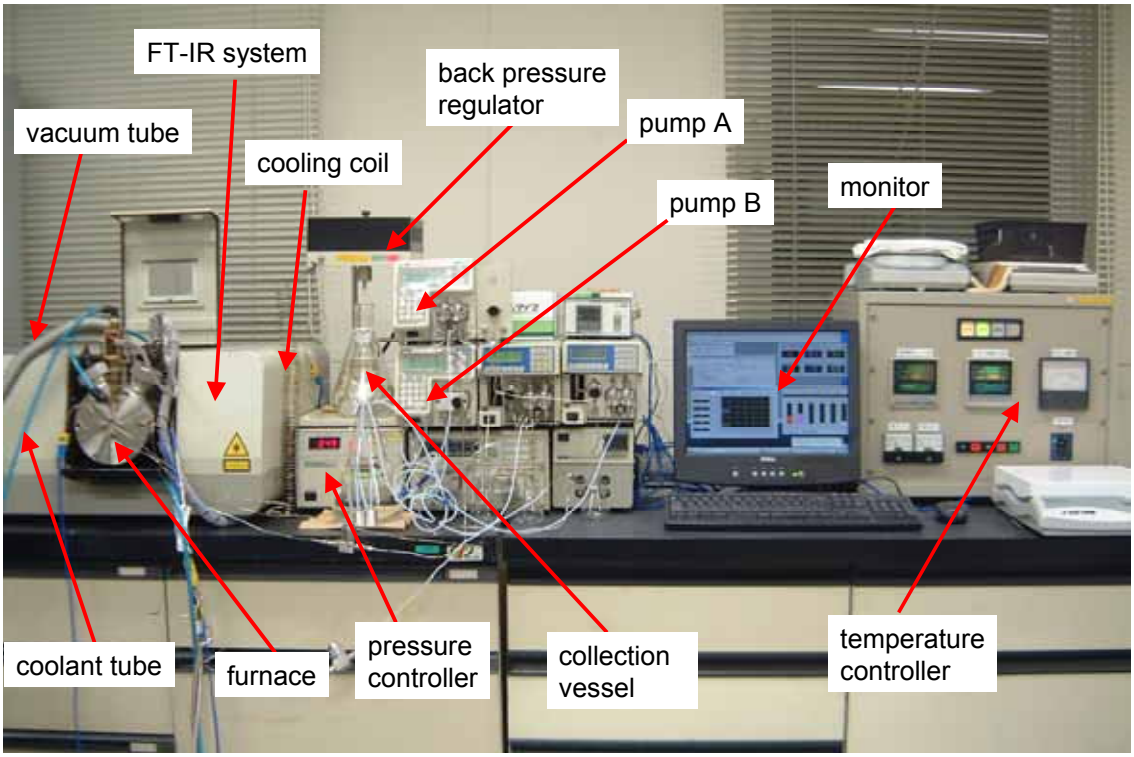


Fig. S5 Total-view of subH_2O microreaction system

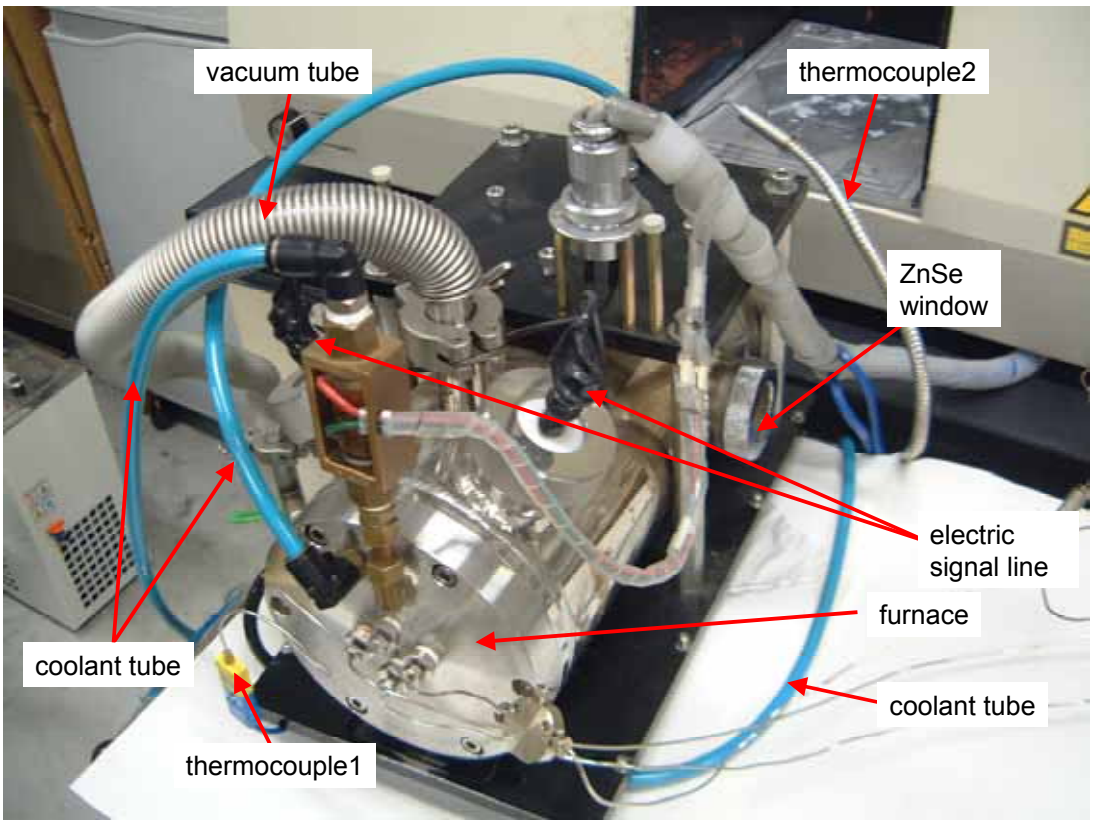


Fig. S6 Total-view of furnace in subH_2O microreaction system

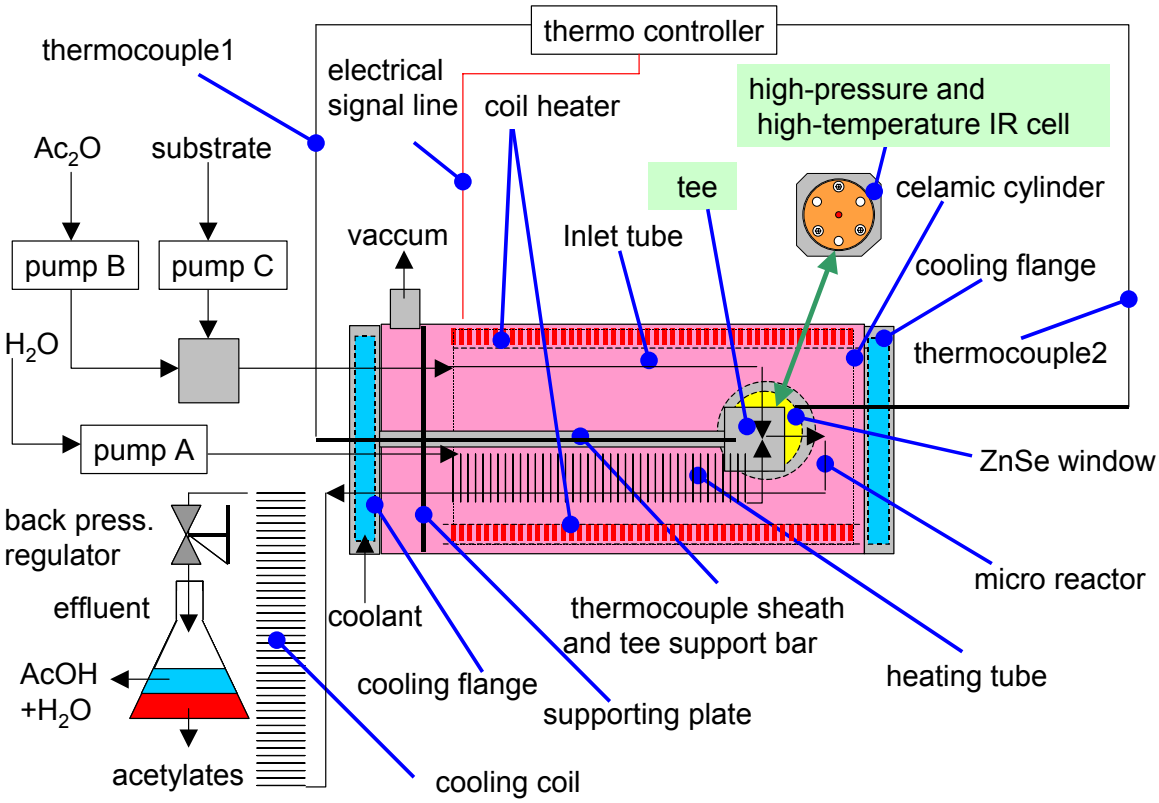


Fig. S7 Schematic diagram around furnace in subH_2O microreaction system

4. Calculation of dielectric constant of water

High-pressure and high-temperature water has an important feature to be able to continuously change physico-chemical properties such as dielectric constant along with temperature and pressure. Especially dielectric constant of pure water is correlated as a function of temperature and density (NIST/ASME Steam properties), which can estimate with the International Association for the Properties of Water and Steam (IAPWS) standard formula and available from NIST (U.S. Department of Commerce, National Institute of Standards and Technology)[8a, b] (*see remarks below). Thus at a given temperature and pressure it is easily possible to calculate some physicochemical properties such as dielectric constant. For the sake of convenience, temperature and pressure dependence of dielectric constant was shown in Fig. S8

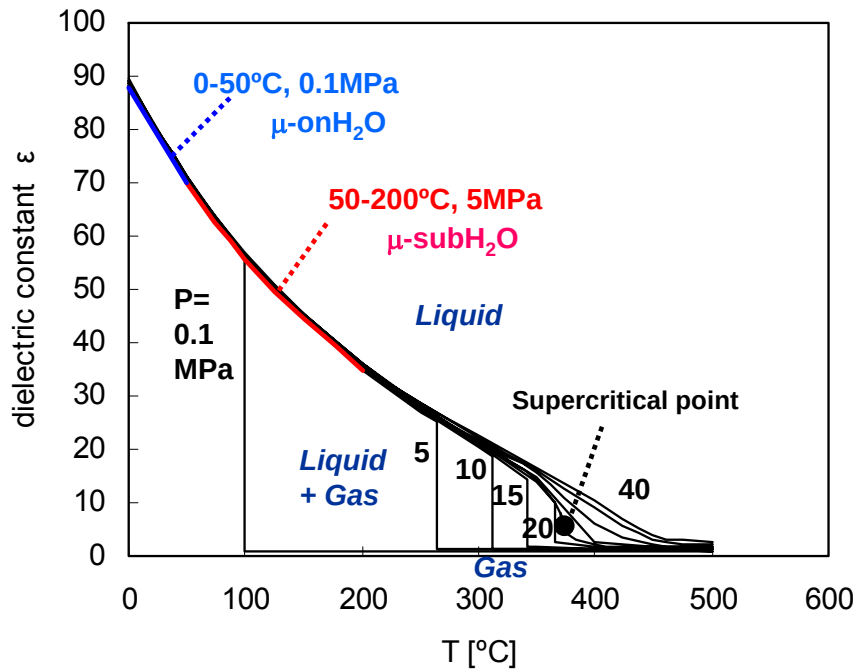


Fig. S8 Dielectric constant of water

in 0~50 ºC at 0.1MPa and 50~250 ºC at 5MPa of onH_2O and subH_2O microreaction system, respectively.

*In reference 8a,b, reference therein with regard to calculation of dielectric constant at high-pressure and high-temperature water as shown below.

D. P. Fernandez, A. R. H. Good win, E.W. Lemmon, J. M. H. L. Sengers and R. C. Williams, "A Formulation for the static Permittivity of Water and Steam at Temperature from 238 to 873K at Pressures up to 1200MPa, Including Derivatives And Debye-Hückel Coefficients'', *J.Phys.Chem Ref. Data*, **1997**, 26, 1125.