Supplementary Information

Rapid production of benzazole derivatives by a high-pressure and high-temperature water microflow chemical process

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Contents:

1. General Information on Benzazoles Production by High-Pressure High-Temperature Water Microflow Chemical Process

Schematic representation of the microflow reacting system used in the experiments is shown in **Figure S1**. The system was cosisted of the following instruments; 1) syringe pumps for compressed water (Pump 1; ISCO 260D) and substrates solution (Pump 2; ISCO 260D), 2) heater for generating high-temperature high-pressure water (Pre-Heater), 3) reactor heater (Heater), where SUS316 tube (inner diameter = 0.5 mm) was placed as microflow reactor, 4) heat exchanger for cooling eluents (Heat Exchanger), 5) back pressure regulator (Back Pressure Regulator; TESCOM 26-1761), 6) K-type thermocouples (TI), 7) tanks for providing distilled water (Tank 1) and substrates solution (Tank 2), 8) glass bottle for collecting samples (Collecting Bottle).

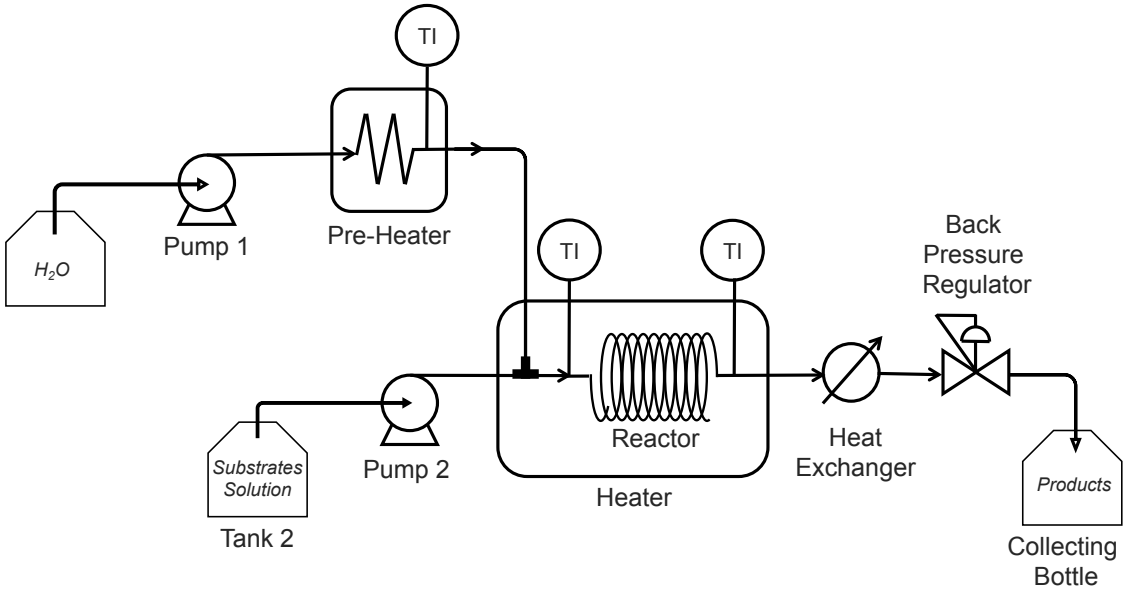


Figure S1. Microflow Reaction System for Benzazoles Production.

Optimization of reaction conditions for benzazoles synthesis was performed by controlling the following parameters; 1) temperatures at the start/end positions of microreactor, which were set at the same values to each other, 2) pressure through the back pressure regulator, 3) reactor volume by changing length of SUS316 tube with fixed inner diameter of 0.5 mm. The fluctuation of temperature and pressure was controlled within ±0.8 ºC and ±0.2 MPa, respectively, which were to be considered as experimental errors.

For all the experiments, flow rates of water and substrates solution were kept constant at 4.5 and 0.5 mL/min, respectively. Under the working conditions, Reynolds number and residence time of the fluid in the microreactor at various temperature and pressure were estimated as described below. Density and viscosity data from "NIST Chemistry Webbook" were utilized for these calculations.

Reynolds number (*Re*) was calculated based on equation (1).

$$Re = Du\rho_w/\mu_w \qquad (1)$$

where D: inner diameter (5.0×10^{-4} m), u: velocity of the object relative to the fluid (m/s), ρ_w: density of water (kg•m^{-3}), μ_w: dynamic viscosity of water (kg/(m•s)).
Graphical representation of Reynolds number at various temperatures/pressures is shown in **Figure S2 (b)**. Applied conditions in this investigation (pressure = 30~45 MPa; temperature = 350~445 ºC) correspond to the estimated Reynolds number of approximately $>3.0 \times 10^3$.

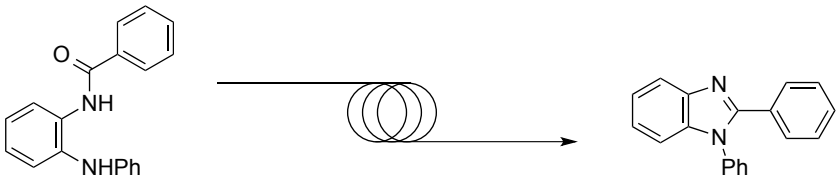
On the other hand, residence time (t) in the reaction tube was calculated using equation (2).

$$t = \pi\left(\frac{r}{20}\right)^2 \times L \times \rho_w \times \left(\frac{60}{F_{total}}\right) \qquad (2)$$

where t: residence time (s), r: inner diameter of microreactor SUS316 tube (= 0.5 mm), L: length of microreactor SUS316 tube (cm), ρ_w: density of water at certain temperature/pressure (g/cm^3), F_{total}: total flow rate of pumps (g/min).
Graphical representation of residence time using reactor of 450 cm length (0.88 cm^3) at various temperatures/pressures is shown in **Figure S2 (c)**.

Analysis of product mixtures was performed by GC-MS/MS (Varian 1200L), GC-FID (Agilent Technologies 5973 GC). For the quantitative analysis, the multipoint calibration curves were produced using the authentic samples with *n*-alkanes (carbon number is 12～16) as internal standard.

1-1. Typical Procedure for Benzazoles Production by Dehydration



1a **2a**

For production of 1,2-diphenyl-1*H*-benzo[*d*]imidazole **2a** by dehydration, N-methylpyrrolidone (NMP) solution of N-[2-(phenylamino)phenyl]benzamide **1a** of required molar concentration was placed in Tank 2 (substrate solution tank). Then, the solution in the tank was introduced into the syringe pump and applied to high pressure/-temperature water on the course of operation. The collected materials were dissolved in EtOAc with addition of internal standard, then followed by GC analysis. The results of screening process conditions were summarized in **Table S1**.

Table S1. Screening of Process Conditions for Production of 1,2-diphenyl-1*H*-benzo[*d*]imidazole (**2a**) from N-[2-(phenylamino)phenyl]benzamide (**1a**) via Dehydration.

Entry	Solvent; Conc. (M)	Reactor Vol. (cm^3)	Temperature (ºC)	Pressure (MPa)	Yield (%)[a]		Residence Time (s)[b]
					1a	**2a**	
1	NMP; 0.05	0.88	445	30	34	>65	1.63
2	NMP; 0.05	0.88	445	35	25	>74	2.26
3	NMP; 0.05	0.88	445	40	3	>96	3.07
4	NMP; 0.05	0.88	445	45	–	>99	3.87
5	NMP; 0.05	0.88	400	30	41	>58	3.79
6	NMP; 0.05	0.88	400	35	24	>75	5.04
7	NMP; 0.05	0.88	400	40	13	>86	5.55
8	NMP; 0.05	0.88	400	45	5	>94	5.88
9	NMP; 0.05	0.88	375	30	17	>82	5.92
10	NMP; 0.05	0.88	375	35	8	>91	6.23
11	NMP; 0.05	0.88	375	40	4	>95	6.46
12	NMP; 0.05	0.88	375	45	2	>97	6.64
13	NMP; 0.05	0.88	340	30	21	>78	7.10

14	NMP; 0.05	0.88	340	35	15	>84	7.23
15	NMP; 0.05	0.88	340	40	12	>87	7.35
16	NMP; 0.05	0.88	340	45	8	>91	7.45
17	NMP; 0.05	0.88	325	45	29	>70	7.74
18	NMP; 0.05	0.88	300	45	56	>43	8.17
19	NMP; 0.05	0.88	275	45	71	>28	8.55
20	NMP; 0.05	0.88	250	45	86	>23	8.89
21	NMP; 0.05	4.9	400	40	–	>99	30.8
22	NMP; 0.05	4.9	400	35	–	>99	28.0
23	NMP; 0.05	4.9	400	30	–	>99	21.1
25	NMP; 0.10	0.88	445	40	4	>95	3.07
26	NMP; 0.10	0.88	400	40	10	>89	5.55
27	NMP; 0.10	4.9	400	40	–	>99	30.8
28	NMP/AcOH; 0.05	0.039	400	40	_	86	0.27

[a] Yields were determined by GC-FID analysis using *n*-hexadecane as an internal standard.

[b] Residence time was estimated based on the equation (2).

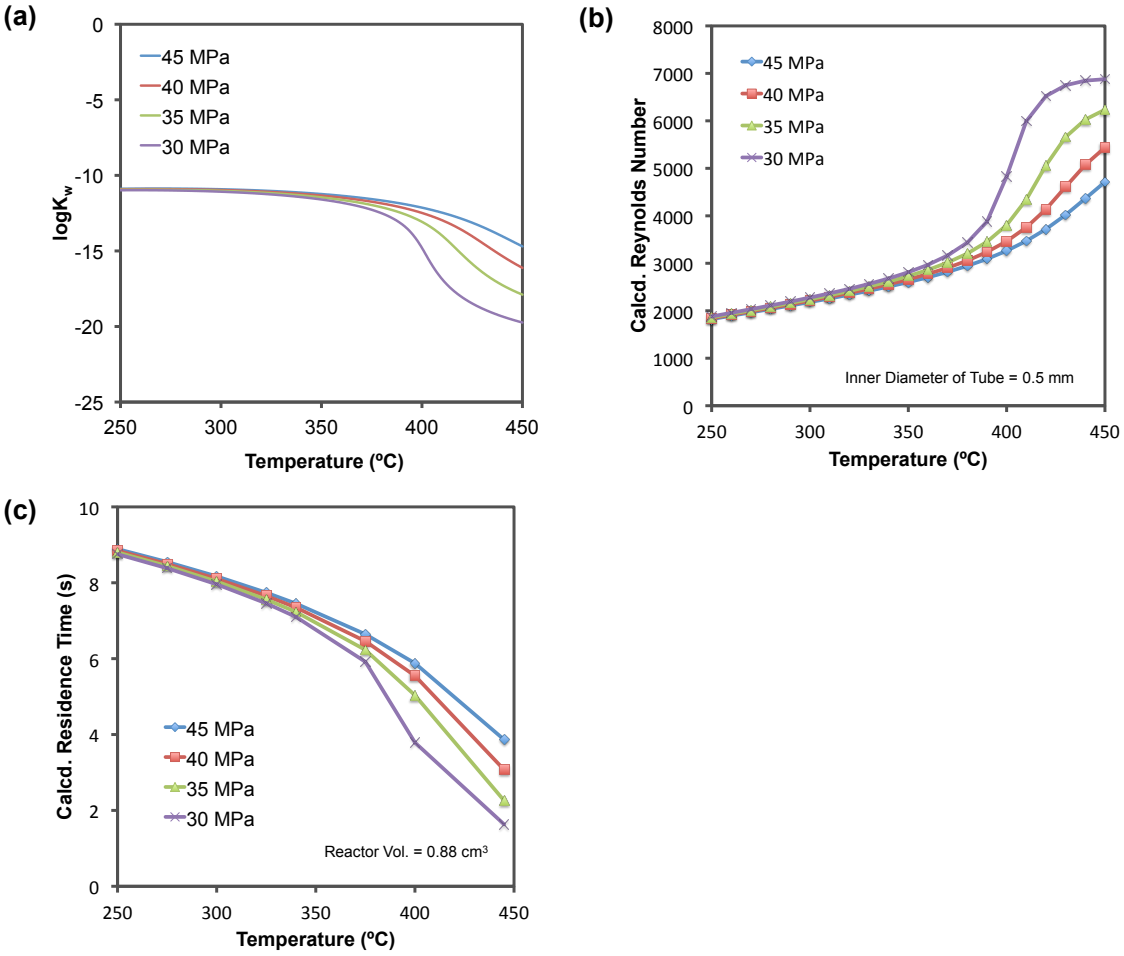


Figure S2. Some Calculated Parameters at Various Temperature and Pressure: **(a)** values of ionic products based on Marshall and Franck equation[S1]; **(b)** Reynolds number estimated by the equation (1); **(c)** residence time in reactor of 0.88 cm^3 volume, estimated by the equation (2).

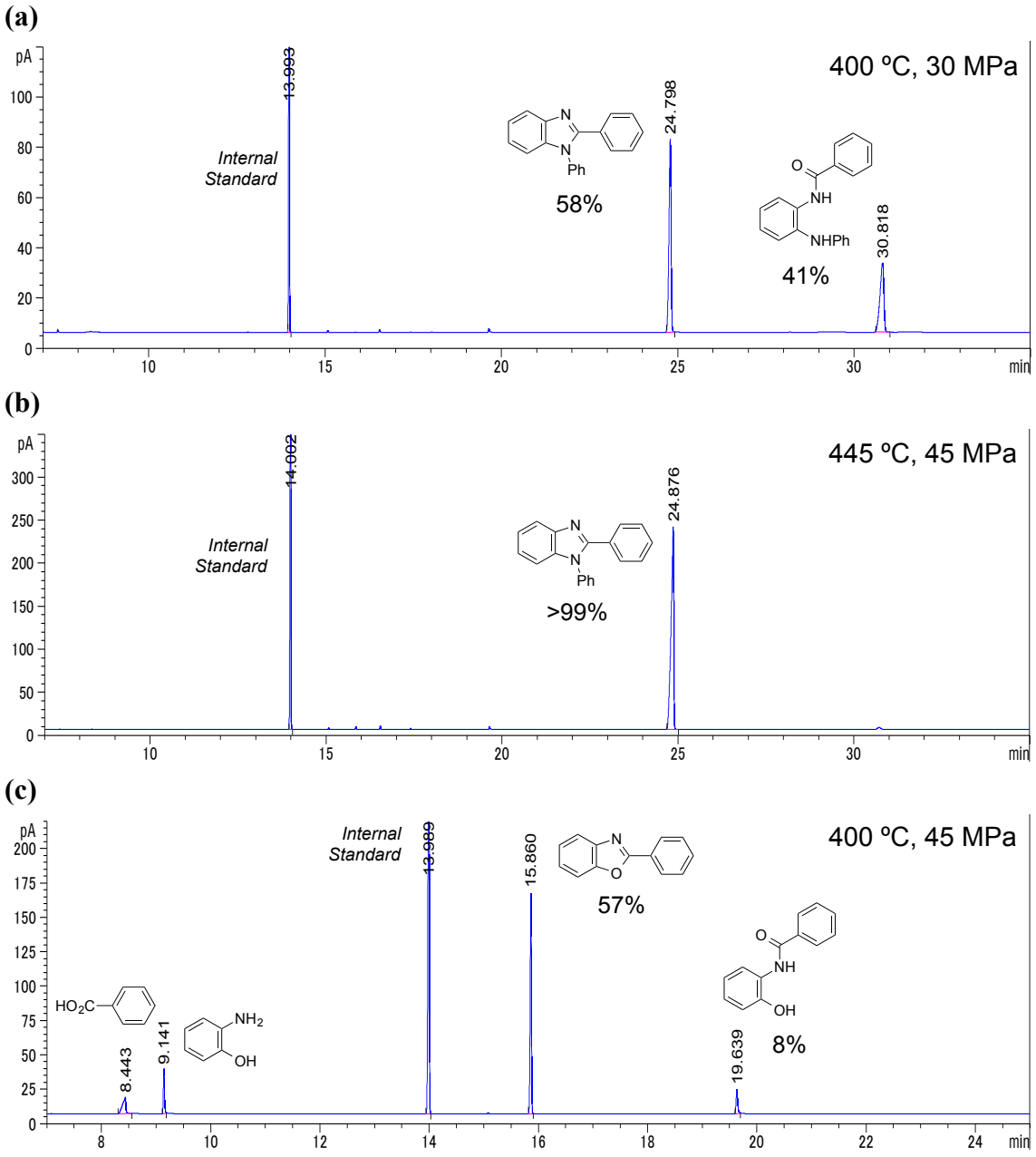
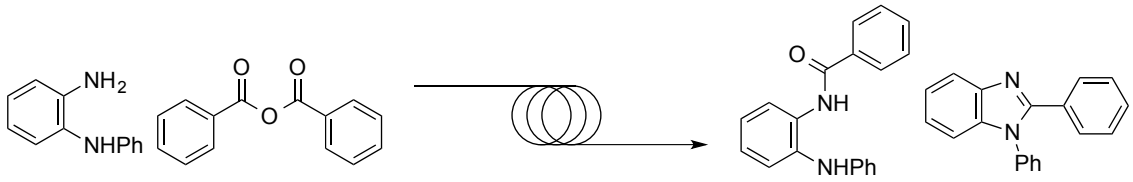


Figure S3. GC Charts of Obtained Materials by Dehydration Process (reactor volume = 0.88 cm^3): **(a)** and **(b)** Production of 1,2-diphenyl-1*H*-benzo[*d*]imidazole (**2a**) at 400 ºC, 30 MPa and 445 ºC, 45 MPa, respectively; **(c)** production of 2-Phenylbenzoxazole (**2b**) at 445 ºC, 45 MPa.

1-2. Typical Procedure for Benzazoles Production by N-Acylation/Dehydration Sequential Condensation Process



1a **2a**

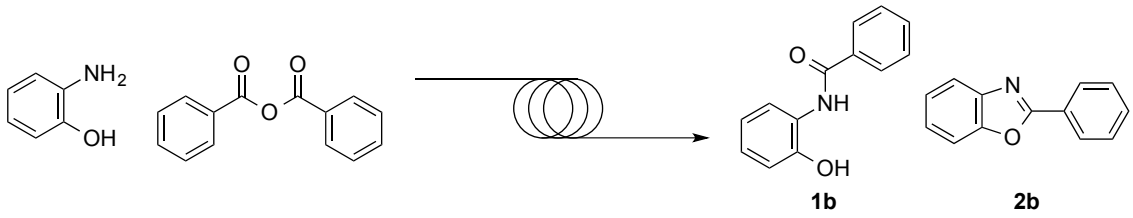
For production of 1,2-diphenyl-1*H*-benzo[*d*]imidazole (**2a**) by N-acylation/dehydration sequential condensation process, 0.05 M solution of N-phenyl-1,2-benzenediamine and benzoic anhydride (1.25 eq) in NMP was placed in Tank 2. The experiments were carried out following the procedure as described in the **Section 1-1**. The results of screening process conditions were summarized in **Table S2**.

Table S2. Screening of Process Conditions for Production of 1,2-diphenyl-1*H*-benzo[*d*]imidazole (**2a**) by N-Acylation/Dehydration Sequential Condensation Process.[a]

Entry	Temperature (ºC)	Pressure (MPa)	Yield (%)[b]		Residence Time (s)[c]
			1a	**2a**	
1	400	30	40	>59	3.79
2	400	35	26	>73	5.04
3	400	40	17	>82	5.54
4	400	45	10	>89	5.88
5	445	30	13	>86	1.63
6	445	35	11	>88	2.26
7	445	40	7	>92	3.07
8	445	45	0	98	3.87

[a] Reactor volume = 0.88 cm^3; concentration of substrate solution = 0.05 M. [b] Yields were determined by GC-FID analysis using *n*-hexadecane as an internal standard. [c] Residence time was estimated based on the equation (2).

Table S3. Screening of Process Conditions for Production of 2-Phenylbenzoxazole (**2b**) by N-Acylation/Dehydration Sequential Condensation Process.[a]

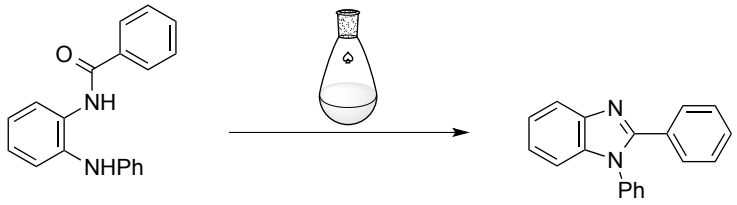


1b **2b**

Entry	Sovent; Conc. (M)	Temperature (ºC)	Pressure (MPa)	Yield (%)[b]		Residence Time (s)[c]
				1b	**2b**	
1	NMP; 1.0	400	40	14	65	5.55
2	NMP; 1.0	400	45	14	65	3.87
3	NMP; 1.0	445	40	8	81	3.07
4	NMP; 1.0	445	45	10	76	3.87
5	2-Propanol; 0.05	400	40	–	59	5.55
6	EtOH; 0.1	400	40	15	55	5.55

[a] Reactor volume = 0.88 cm^3. [b] Yields were determined by GC-FID analysis using *n*-hexadecane as an internal standard. [c] Residence time was estimated based on the equation (2).

2. Typical Procedure of Control Experiments



1a **2a**

1.25 mmol of N-[2-(phenylamino)phenyl]benzamide (**1a**) was placed in 100 mL flask, and H_2O/NMP (22.5 mL/2.5 mL) was added. Then the solution was stirred at 120 ºC in hot bath. After stirred for 24 h, the solution was cooled to room temperature. The solution was diluted by EtOAc with addition of *n*-hexadecane as an internal standard, followed by GC analysis.

For the other conditions in control experiments, solvent sets of H_2O (25 mL; Table 2,

entry 1) and H_2O/AcOH (22.5 mL/2.5 mL; entry 3) were used, instead of H_2O/NMP (22.5 mL/2.5 mL) solvent set in the above procedure.

References

[S1] W. L. Marshall, E. U. Frank, *J. Phys. Chem. Ref. Data*, 1981, *10*, 295–303.