

Supporting information

Nitration Under Continuous Flow Conditions: Convenient Synthesis of 2-isopropoxy-5-nitrobenzaldehyde, an Important Building Block in the Preparation of Nitro-substituted Hoveyda-Grubbs Metathesis Catalyst

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In the preliminary experiments with the aforementioned microreactor we investigated the nitration of 2-hydroxybenzaldehyde (**2**) using acetic acid and 65 % HNO₃. A set of screening experiments, all run on a small scale, was performed using 3.40 M substrate in acetic acid and a second inlet stream of 65 % HNO₃. The outlet stream was quenched by dripping directly into water followed by extraction by ethyl acetate and analysis by Gas Chromatography (GC) (Table 1, Figure 1).

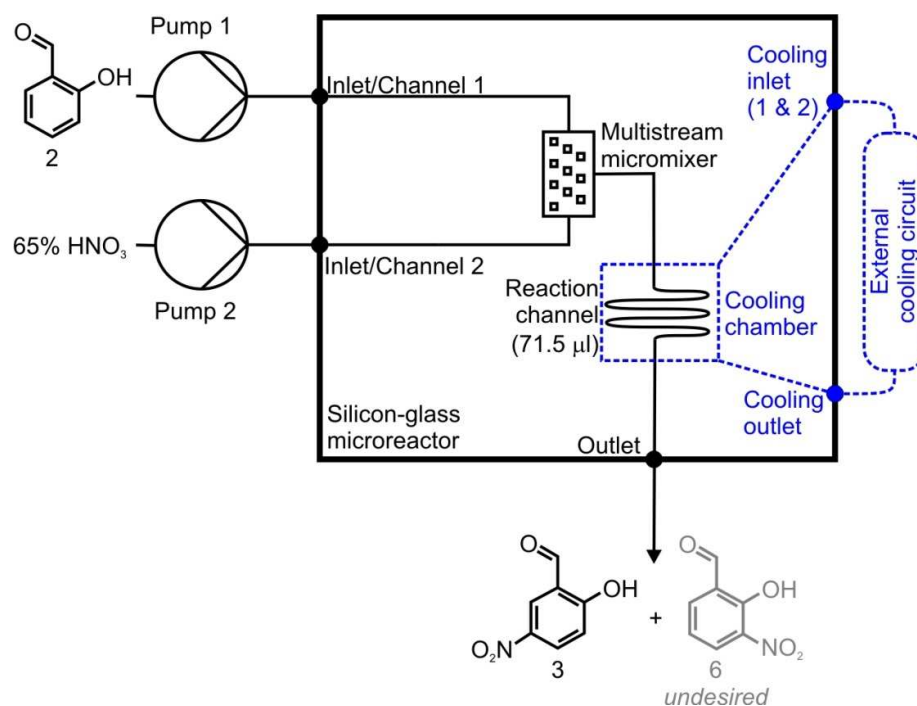


Figure 1. Set-up and optimal parameters for nitration reaction of 2-hydroxybenzaldehyde (**2**) in continuous flow.

The screening quickly revealed that the temperature is crucial for the correct outcome of the process. The optimal temperature of the nitration reaction was found to be 60 °C (Table 1, entries 3-5). Experiments run with lower temperatures led to incomplete conversion (Table 1,

entries 1 and 2). In turn, the optimal stoichiometric ratio of substrate **2** to 65 % HNO₃ was found to be equal to 1 : 4.36 (Table 1, entries 4 and 5) and with the 103 s residency time (Rt) the conversion was near complete (Table 1, entry 5). Unfortunately, despite several experiments we were unable to obtain an acceptable reaction selectivity. Variations of Rt, stoichio-metric ratio of reagents and process temperature led to the mixture where the ratio of isomers **3** to **6** was equal to 57 : 42 (Table 1, entry 5) in the best case.

Table 1. Screening experiments for the nitration of 2-hydroxybenzaldehyde **2** in acetic acid and 65 % HNO₃ in the microreactor

entry	Rt (s)	temp. (°C)	stoichiometric ratio (2 : 65 % HNO ₃)	2 (%) ^a	3 (%) ^a	6 (%) ^a
1	64	38	1 : 2.18	88	7	5
2	64	42	1 : 2.18	54	26	20
3	64	60	1 : 2.18	18	45	37
4	51	60	1 : 4.36	15	49	36
5	103	60	1 : 4.36	1	57	42

^a Determined by GC analysis.

Subsequently, the nitration of 2-hydroxybenzaldehyde (**2**) was performed with the use of fuming HNO₃ (Table 2) with the hope that the results in terms of selectivity will be better. A set of screening experiments, all run on a small scale, was performed using a 3.40 M solution of **2** in CH₂Cl₂ and neat fuming HNO₃. Unfortunately the selectivity was not improved (Table 2).

Table 2. Screening experiments for the nitration of 2-hydroxybenzaldehyde **2** with fuming HNO₃ in the microreactor

entry	Rt (s)	temp. (°C)	stoichiometric ratio (2 : fuming HNO ₃)	2 (%) ^a	3 (%) ^a	6 (%) ^a
1	42	25	1 : 2.2	0	68	32
2	45	25	1 : 4.4	0	69	31
3	150	10	1 : 4.4	0	60	40
4	120	10	1 : 4.4	0	64	36
5	120	10	1 : 6.0	0	65	35
6	51	10	1 : 4.4	0	63	37
7	51	0	1 : 6.0	5	59	36
8	60	0	1 : 4.4	7	63	30
9	51	-10	1 : 4.4	17	49	34
10	70	-10	1 : 6.0	15	47	38

^a Determined by GC analysis.

Fabrication of the microreactor used in this work

Microreactor consists of glass, silicon and glass. Firstly the silicon body is prepared (Fig. 2). Silicon wafer, double-side polished, 400 μm thick and (100)-oriented is used. Fabrication of microfluidical channels and cooling chamber (120 μm deep) started from silicon wafer oxidation (1.4 μm -thick silicon dioxide) (step I), next photolithography (step II) and both sides wet anisotropic etching (40% KOH solution at 80°C) (step III) are done. Fabrication of micromixer structure starts from second silicon wafer oxidation (1.4 μm -thick silicon dioxide) (step IV), next second photolithography (step V) and bottom side wet anisotropic etching (step VI). After micromachining 0.3 μm -thick silicon dioxide as chemically resistive layer (step VII) is formed.

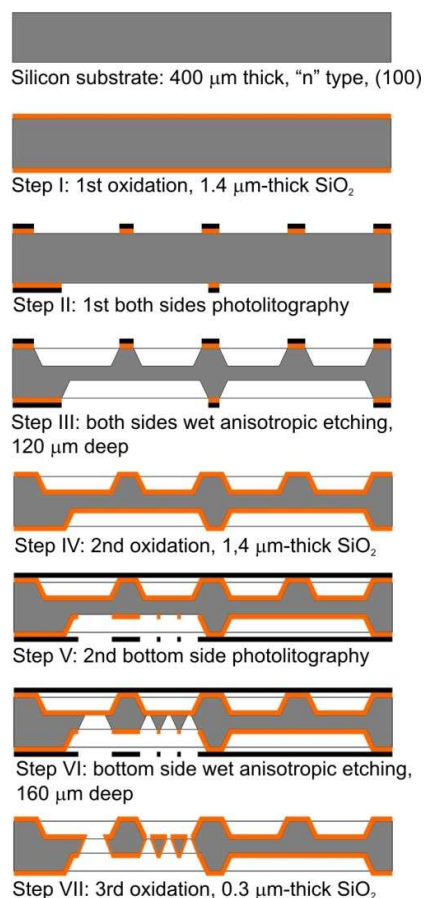


Figure 2. Fabrication steps of the silicon body

In parallel, top glass wafer (Borofloat 3.3, Schott) is prepared. Firstly, via holes ($\Phi=0,8$ mm) of fluidic inlets, outlets are mechanically drilled. Following, deep isotropic etching (40% HF at room temperature) to form cavities for temperature sensors are made.

Wafers assembling (Fig. 3) starts from anodic bonding (450°C, 1,5 kV) of silicon body and bottom glass wafer. Finally, the top glass is anodically bonded (450°C, 1.5 kV) to the silicon body.

The precise pill-like NTC temperature sensors (10 k Ω , Epcos) are fixed (thermally conductive glue) inside cavities etched in the top glass.

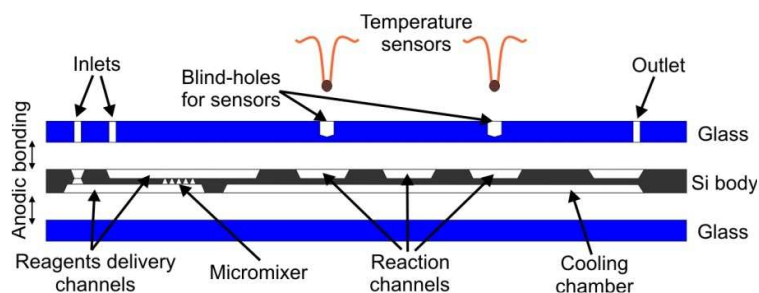


Figure 3. Assembling steps of microreactor chip