Supporting Information

Room-temperature and ambient-pressure conversion of renewable carbohydrates to value-added aromatic *N*-heterocycles under ultrasonic irradiation conditions

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General Information

Chemicals

D-Glucose (99%), D-fructose (99%), D-mannose (99%), D-(+)-cellobiose (98%), lactose (98%), α-cellulose, dihydroxyacetone (97%), pyruvaldehyde solution (32 wt% in H_2O), cellulase (Cellic CTec3, ≥1000 uint/g), *ortho*-phenylenediamine (*o*-PDA, 98%), 4,5-difluoro-*o*-phenylenediamine (97%), 4-methyl-*o*-phenylenediamine (97%), 4-methoxy-*o*-phenylenediamine (97%), 4-chloro-*o*-phenylenediamine (97%), 4-fluoro-*o*-phenylenediamine (98%), barium hydroxide octahydrate ($Ba(OH)_2·8H_2O$, 98%), and cesium hydroxide monohydrate ($CsOH·H_2O$, 99.9%) were purchased from Aladdin Chemical Reagent Co. Maltose (95%) and maltotriose (96%) were purchased from Macklin. Glyceraldehyde (93%) was purchased from Alfa Aesar. Acetate buffer solution (pH 5.5) and 2,3-Diaminopyridine (97%) were purchased from J&K Scientific Ltd. Sodium carbonate (Na_2CO_3, ≥99.8%), potassium carbonate (K_2CO_3, ≥99.0%), lithium hydroxide (LiOH, ≥99%), sodium hydroxide (NaOH, 99%), potassium hydroxide (KOH, 95%), and calcium hydroxide ($Ca(OH)_2$, ≥95%) were purchased from Sinopharm Chemical Reagent Co. Glucose-2-D (98%) was purchased from Cambridge Isotope Laboratories, Inc. All chemicals were used without further purification as received.

Ultrasonic Apparatus

A transonic digital ultrasound bath with ultrasound waves frequency of 40 KHz produced by a 300 W generator through a transducer（KQ 300DE, Kunshan Corporation）was used as the source of ultrasonic irradiation to perform the reactions. Tubular glass reactors sealed with a rubber stopper were immersed in a deep-drawn tank containing water. The reaction was kept at the same temperature as the ambient temperature *via* exchanging the water in the ultrasonic bath with fresh water powered by a peristaltic pump.

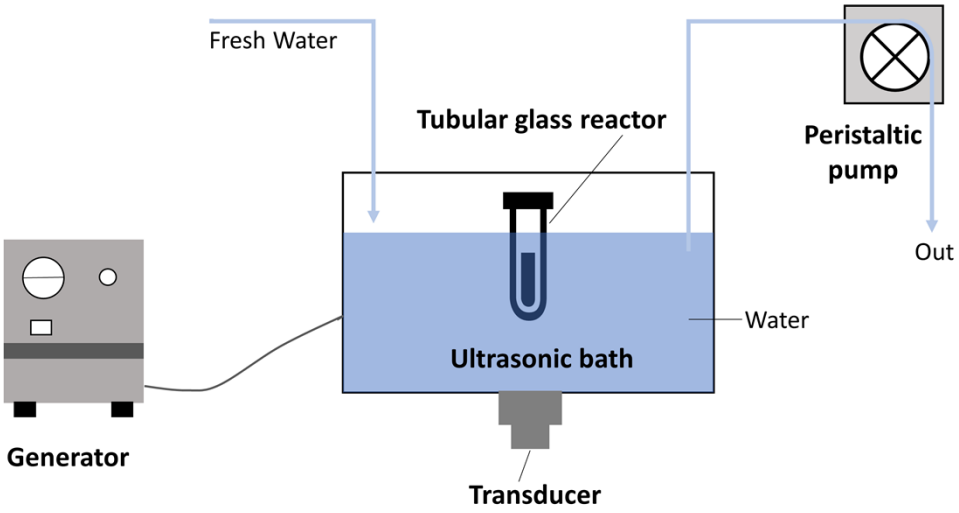


Figure S1. Schematic of the ultrasonic apparatus for ultrasound-enabled reactions.

Reaction for the ultrasound-enabled transformation of sugar to 2-MQs

Reaction experiments were performed in a tubular glass reactor (glass thickness 0.7 mm, 10 mL volume), equipped with a rubber septum. For typical runs, 22.5 mg of glucose (0.125 mmol), 54 mg (0.5 mmol) of *o*-PDA, sodium hydroxide (100 mg, 2.5 mmol), and 2.5 mL of H_2O were loaded into the reactor. The reactor was then sealed by a rubber septum with the assistance of adhesive tape. The reactor was degassed by using a needle through the rubber septum under vacuum and then charged with N_2. This degasification-recharge operation was repeated for three times to remove the air in the reactor. Then, the tubular reactor was immersed into the deep-drawn tank of the ultrasound apparatus, as shown in Figure S1. The reaction timing began when the ultrasonic radiation was turned on. The reaction was kept at the ambient temperature by circulating the bath water. The reactor was sonicated for a specific time. After the reaction, the reactor was removed from the ultrasonic bath and then the reaction mixture was sampled and analyzed.

Sodium hydroxide (NaOH) used in the reaction could be recycled. After the reaction, the resulted aqueous reaction mixture was subjected to an ethyl acetate extraction. After three times of extraction with proper amount of ethyl acetate, product 2-MQ (>99%) and most *o*-PDA (~70%) can be transferred into the organic layer. After removing water in the resulted aqueous solution via evaporation at reduced pressure, a solid residue was obtained. The obtained solid residue

further underwent a washing with ethyl acetate to dissolve the remaining *o*-PDA, finally giving rise to the solid residue, which mainly contains NaOH.

Product analysis

Reaction samples were analyzed by GC-FID, HPLC, and NMR. Upon the completion of the reaction, the reaction mixture was extracted by ethyl acetate. The resulted organic extract containing products was analyzed by GC-FID. An aliquot of the remaining aqueous solution was taken and neutralized by diluted HCl solution and then analyzed by HPLC for determining and quantifying sugars, sorbitol and water-soluble sugar fragments. GC-MS analyses were performed with a Shimadzu GC-2010 plus system equipped with a GC-MS-QP2010S detector and DB-5MS column (30 m × 0.25 mm × 0.25 μm). GC-MS system uses helium as the carrier. FID-GC analyses were performed with GC-9790 (FuLi) equipped with a FFAP column (30 m × 0.32 mm × 0.25 μm) and FID detector and quantitatively estimated by the combination of using naphthalene as an internal standard. The aqueous solution after syringe filtration with a 0.45 μm PTFE membrane was analyzed by a Shimadzu HPLC (10AT) equipped with isocratic pump and refractive index (RI) detector on a Bio-Rad Aminex HPX-87H (300 × 6.5 mm), using an aqueous solution of sulfuric acid (5 mM) at a flow rate of 0.5 mL min^{-1} and a column temperature of 60 °C. Quantification of each compound was based on calibration curves obtained by analyzed standard solutions with known concentration.

NMR spectra were recorded on a commercial instrument (Bruker Avance 400 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to the internal (NMR) solvent signal. For quantitative ^{1}H-NMR analysis, $CDCl_3$ or DMSO-d_6 was added as the deuterated NMR solvent and 1,4-dioxane (Aladdin, ≥99.9%) was added as the internal standard.

Conversion and yield calculations

The conversion of sugars and other feedstocks were calculated based on carbon atoms by using the equation in the following:

$$\text{Conversion} = \frac{mol_{initial\ carbohydrate} - mol_{remaining\ carbohydrate\ after\ reaction}}{mol_{initial\ carbohydrate}} \times 100\%$$

The product yield, given in C%, represents the fraction of carbon originating from the sugar or its derived feedstocks that is found in the product. The yields of all products were calculated based on carbon atoms by using the following equation:

$$\text{Yield} = \frac{mol_{carbon\ atoms\ from\ carbohydrate\ in\ product}}{mol_{carbon\ atoms\ in\ carbohydrate}} \times 100\%$$

Integrating enzymatic and chemical processes for low-temperature conversion of crystalline cellulose to 2-methylquinoxaline

Enzymatic hydrolysis of crystalline cellulose to glucose

To a round-bottom flask (25 mL) equipped with a magnetic stir bar, α-Cellulose (40.5 mg, 0.25 mmol based on glucose monomer units), cellulase blend (Cellic CTec3, 20 mg), and acetate buffer solution (pH 5.5, 5 mL) were loaded. The flask was then capped and immersed into a preheated oil bath (40 °C). After stirring for 72 h, the resulted solution was ultrafiltrated by a centrifugal filter unit with a membrane of 3 kDa cut-off (Pall). The filtrate was collected and sampled for analysis. The obtained enzymatic catalysis results are comparable to the previously reported results.[1]

Conversion of enzymatically hydrolyzed glucose to 2-methylquinoxaline at room temperature

To a flask tube (10 mL), the filtrate (5 mL) from cellulase hydrolysis, NaOH (200 mg, 5 mmol), and *o*-PDA (108 mg, 1 mmol) were loaded. The reactor was then sealed by a rubber septum with the assistance of adhesive tape. The reactor was then degassed by using a needle through the rubber septum under vacuum and then charged with N_2. This degasification-recharge operation was repeated for three times to remove the air in the reactor. Then, the tubular reactor was immersed into the deep-drawn tank of the ultrasound apparatus filled with water. The reaction was carried out under ultrasound irradiation for 20 h. After the reaction, the reactor was removed from the ultrasonic bath and then the reaction mixture was sampled and analyzed.

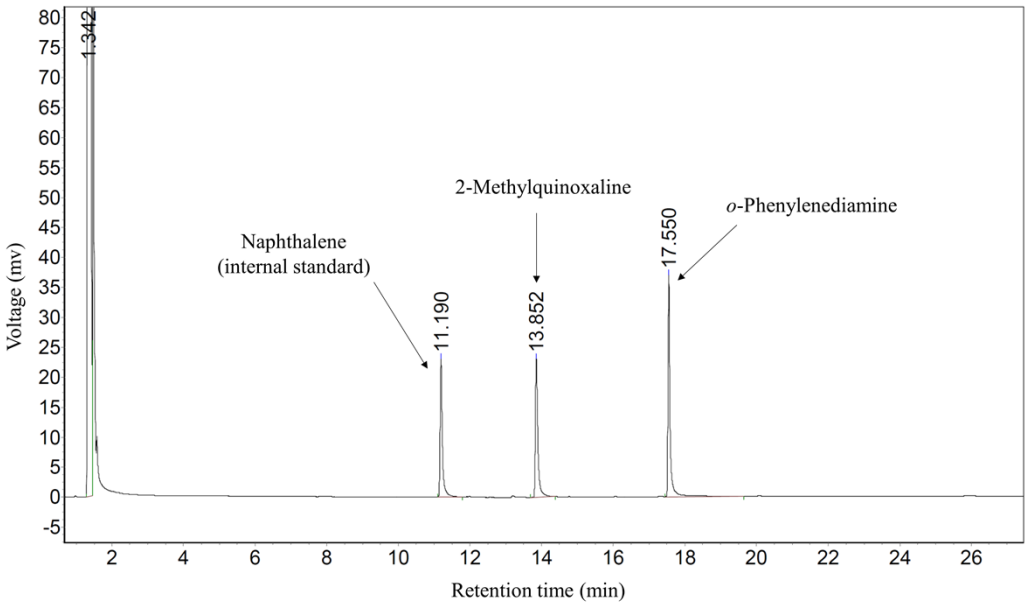


Figure S2. Representative GC-FID spectrum of the reaction mixture (organic layer) from conversion of glucose with *o*-PDA under ultrasonic irradiation. Reaction conditions: Glucose (22.5 mg), *o*-PDA (54 mg), NaOH (1.0 M), H_2O (2.5 mL), 20 °C (temperature variation within 3 °C), N_2 (1 bar), 20 h.

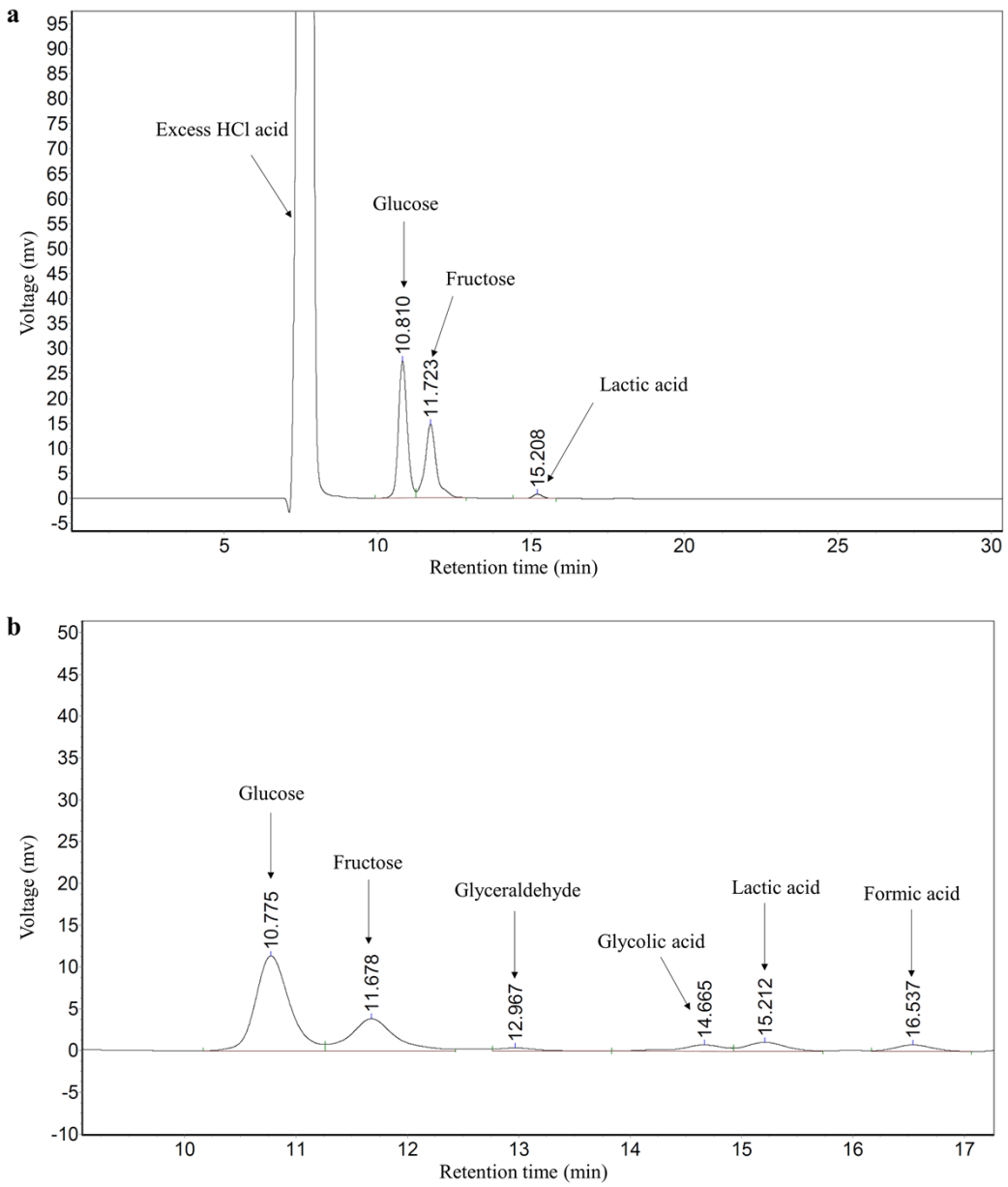
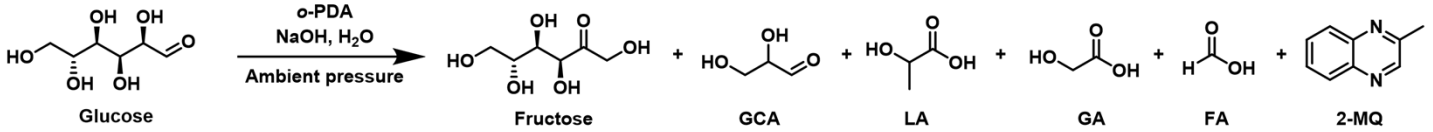


Figure S3. Representative HPLC spectra of the reaction mixture from conversion of glucose with *o*-PDA at room temperature. Reaction conditions: Glucose (22.5 mg), *o*-PDA (54 mg), NaOH (1.0 M), H_2O (2.5 mL), 20 °C (temperature variation within 3 °C), N_2 (1 bar). (a) ultrasonic irradiation for 6 h. (b) conventional stir for 33 h.

Table S1. Ultrasound-enabled conversion of glucose with *o*-PDA at room temperature and ambient pressure.



Entry	*o*-PDA (mmol)	NaOH (mol/L)	Reaction condition	Time (h)	Conv. (%)	Yield (%)						Mass balance (%)
						Fructose	GCA	LA	2-MQ	GA	FA	
1	0.5	1.0	Ultrasound / Air / 20°C	20	95.4	2.8	0.8	7.8	72.1	3.1	2.6	93.5
2	0.5	1.0	Stir / Air / 20°C	33	43.0	21.9	1.3	4.6	3.2	3.7	4.5	91.2
3	0.5	1.0	Stir / N_2 / 70°C	20	95.3	0.2	0.4	22.3	51.2	0.2	0.2	78.2
4	0.5	0.25	Ultrasound / N_2 / 20°C	20	80.2	25.6	0.6	0.6	48.7	0.5	0.5	95.4
5	0.5	0.5	Ultrasound / N_2 / 20°C	20	91.4	13.7	0.4	1.5	73.6	0.5	0.6	98.8
6	0.5	1.0	Ultrasound / N_2 / 20°C	6	69.8	24.6	0.8	4.6	39.2	0.1	0.1	99.4
7	0.5	1.0	Ultrasound / N_2 / 20°C	20	96.5	2.4	0.5	8.3	81.2	0.7	0.8	97.3
8	0.5	1.5	Ultrasound / N_2 / 20°C	20	97.3	2.1	0.6	13.8	78.1	0.6	0.6	98.5
9	0.25	1.0	Ultrasound / N_2 / 20°C	20	96.1	5.0	0.6	17.3	69.8	0.6	0.5	97.6
10	1.0	1.0	Ultrasound / N_2 / 20°C	20	97.0	4.0	0.4	5.9	82.0	0.4	0.4	96.0
11[a]	0.5	1.0	Ultrasound / N_2 / 20°C	20	86.8	13.9	0.8	4.2	63.1	0.9	0.8	96.4
12	0.5	1.0	Stir / N_2 / 20°C	60	70.7	24.3	0.9	4.3	39.6	0.1	0.2	98.2
13	0.5	1.0	Ultrasound / N_2 / 70°C	8	95.1	0.4	0.5	21.4	57.1	0.3	0.3	84.1
14	0.5	1.0	Ultrasound (50% intensity) / N_2 / 20°C	20	90.2	7.1	0.8	5.2	73.7	0.5	0.4	97.2

Reaction conditions: Glucose (22.5 mg), H_2O (2.5 mL), temperature deviation within 3 °C. For the reactions in a conventional stir manner, stirring speed was set at 500 rmp.

[a]Glucose (45 mg) was used.

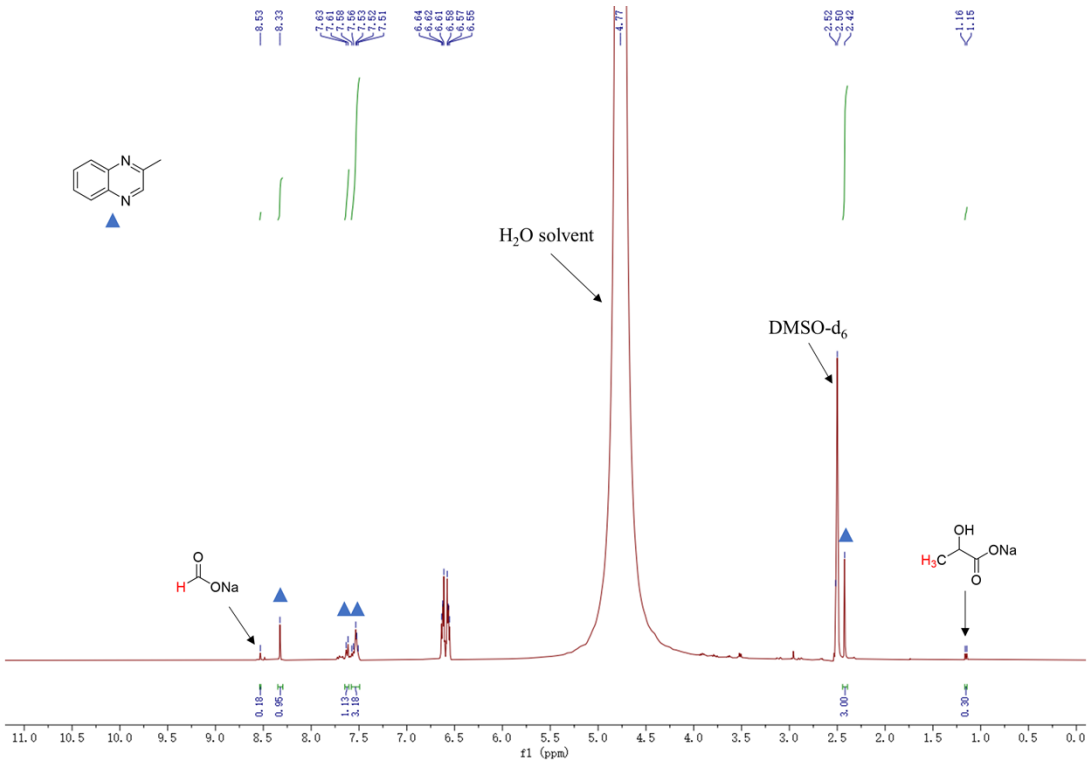


Figure S4. ^{1}H NMR spectrum of the resulted reaction mixture from transformation of glucose and *o*-PDA under ultrasound irradiation at room temperature and ambient pressure. Reaction conditions: Glucose (22.5 mg), *o*-PDA (54 mg), NaOH (1.0 M), H_2O (2.5 mL), 20 °C (temperature variation within 3 °C), N_2 (1 bar), 20 h. The reaction refers to Table 1, entry 1 (Table S1, entry 7).

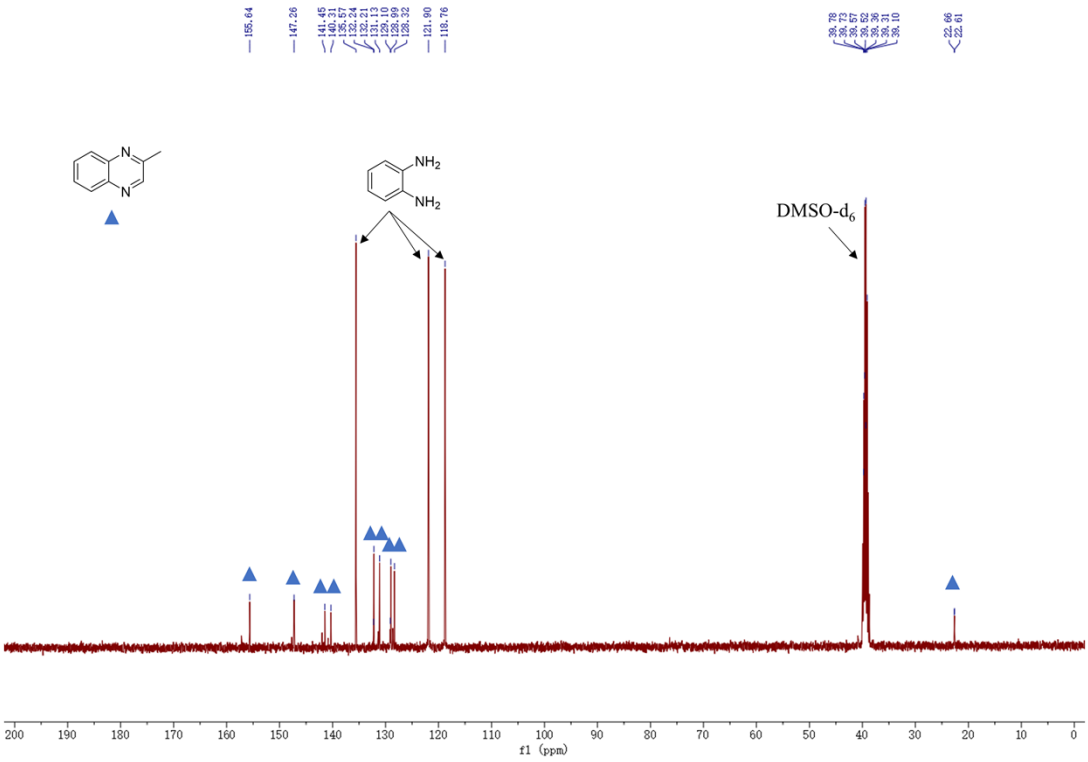


Figure S5. ^{13}C NMR spectrum of the resulted reaction mixture from transformation of glucose and *o*-PDA under ultrasound irradiation at room temperature and ambient pressure. Reaction conditions: Glucose (22.5 mg), *o*-PDA (54 mg), NaOH (1.0 M), H_2O (2.5 mL), 20 °C (temperature variation within 3 °C), N_2 (1 bar), 20 h. The reaction refers to Table 1, entry 1 (Table S1, entry 7).

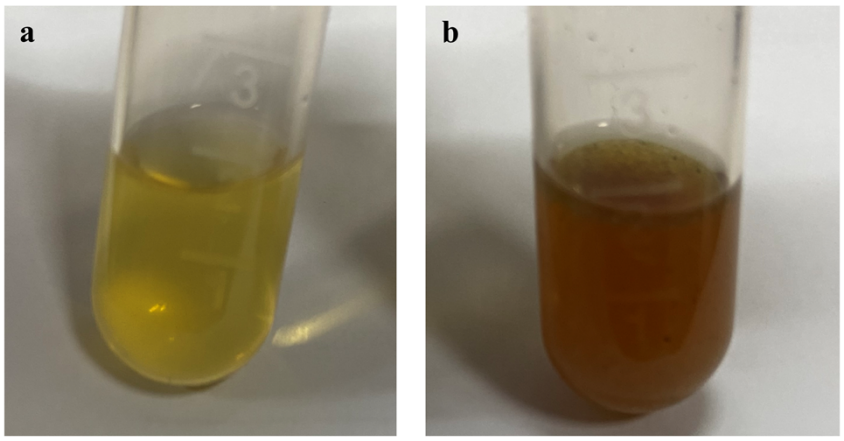


Figure S6. Photos of the glucose reaction mixture after 20 h reaction *via* using different energy source. **a**, glucose reaction in 1 M NaOH aqueous solution in the presence of *o*-PDA at 20 °C under ultrasound irradiation. **b**, glucose reaction in 1 M NaOH aqueous solution in the presence of *o*-PDA at 70 °C by conventional stirring. (The reaction mixture changing from light yellow transparent solution to dark brown suspension implied the reaction was subjected to undesired Maillard-type reactions[2] and/or caramelisation.[3])

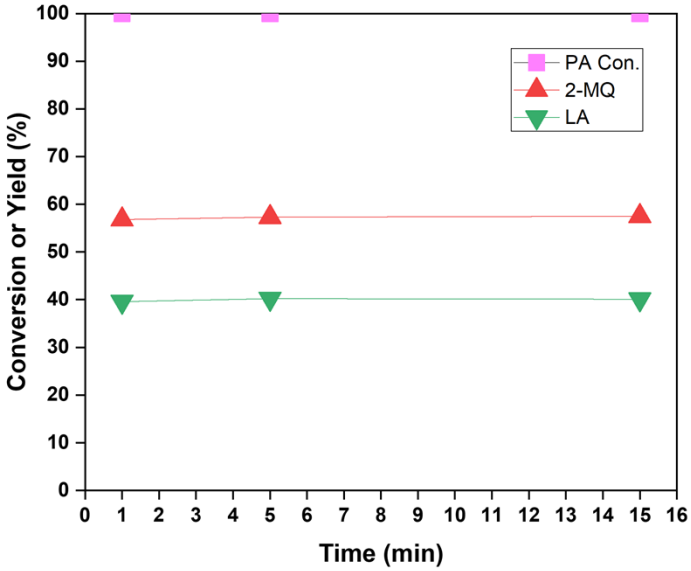


Figure S7. Time course of the reaction of PA at 20 °C under 1 bar N_2. Reaction conditions: PA (0.25 mmol), *o*-PDA (54 mg), NaOH (1.0 M), H_2O (2.5 mL).

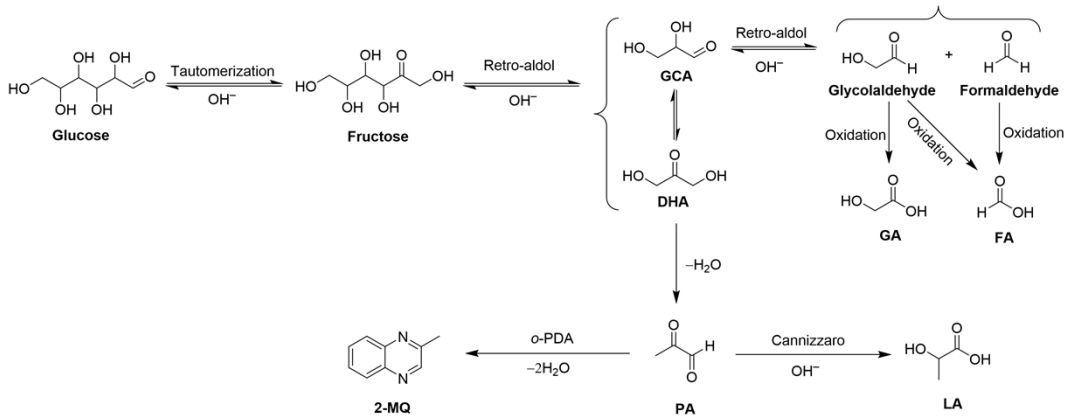


Figure S8. Plausible ultrasound-enabled reaction pathways for the conversion of glucose in 1M NaOH aqueous solution at 20 °C in air.

Kinetic isotope effect (KIE) studies

A 10 mL glass tube reactor was charged with glucose (45 mg, 0.25 mmol), *o*-PDA (108 mg, 1 mmol), sodium hydroxide (200 mg, 5 mmol) and H_2O (5 mL). The reactor was then sealed by a rubber septum with the assistance of adhesive tape. The reactor was then degassed by using a needle through the rubber septum under vacuum and then charged with N_2. This degasification-recharge operation was repeated for three times to remove the air in the reactor. Then the tubular reactor was immersed into the deep-drawn tank of the ultrasound apparatus to start the reaction. Aliquots of the reaction mixture were taken through the septum with a long needle at set time intervals for products analysis. An identical study with glucose-2-D (45.3 mg, 0.25 mmol) was performed under same reaction conditions, and the initial rates of these reactions were used to calculate the isotope effect. The data from these studies are shown in Figure S9.

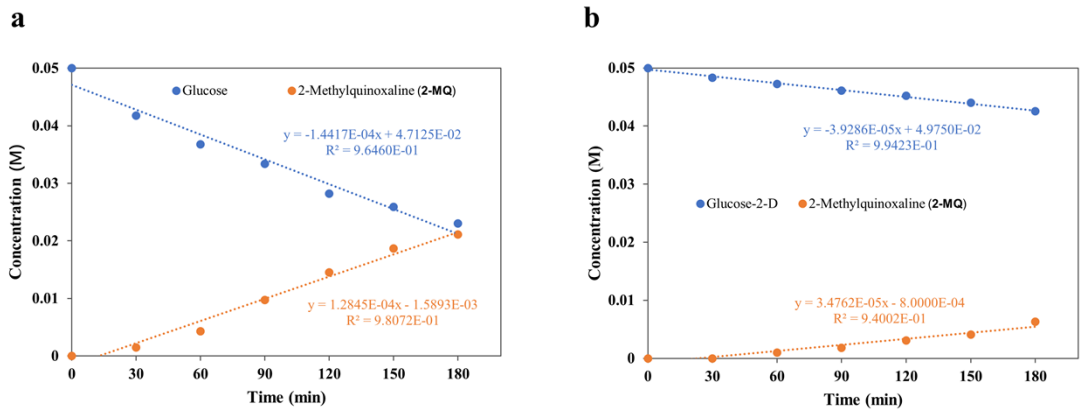


Figure S9. Kinetic isotope effect (KIE) studies for the ultrasound-enabled conversion of glucose to 2-MQ in the presence of o-PDA at 20 °C and ambient pressure of N_2. **a**, initial rates of glucose reaction. **b**, initial rates of glucose-2-D.

^{1}H NMR spectra for the quantification of synthesized 2-MQs

For quantifying the yield of 2-MQs products in the reaction, 1,4-dioxane is used as the internal standard. The NMR assignments for the synthesized 2-MQs products are based on the data of pure compounds.[4–7]

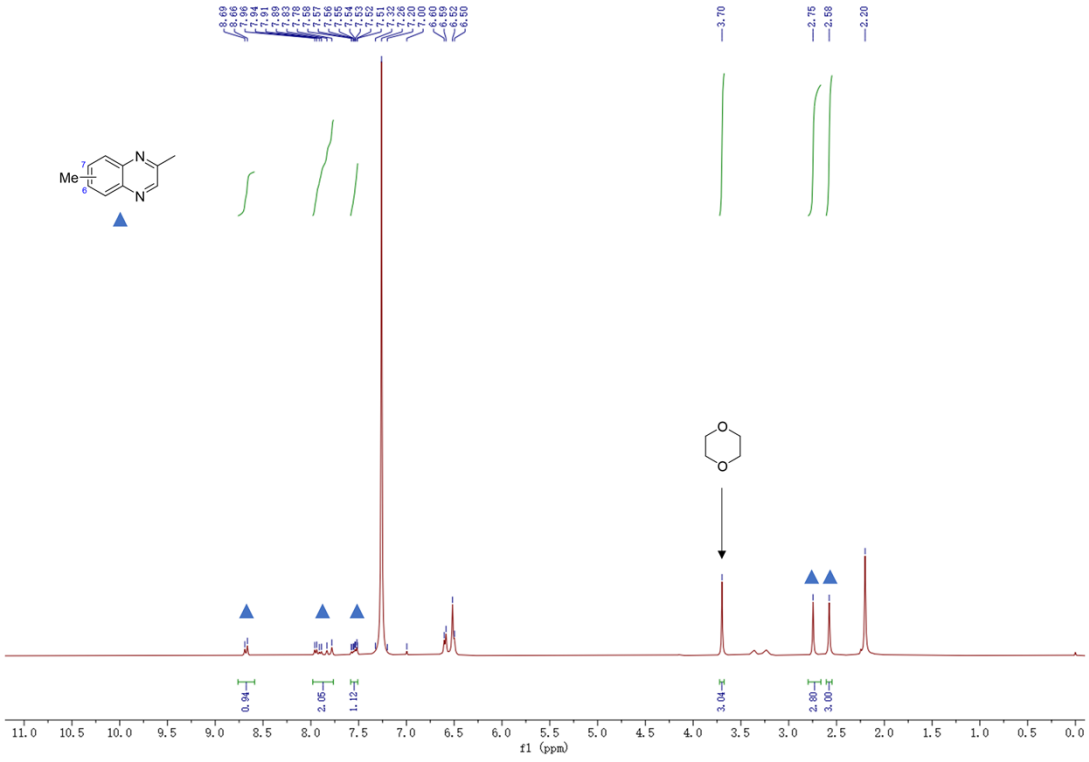


Figure S10. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **5**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 0.39H), 8.66 (s, 0.52H), 7.78–7.96 (m, 2H), 7.51–7.58 (m, H), 2.75 (s, 3H), 2.58 (s, 3H).

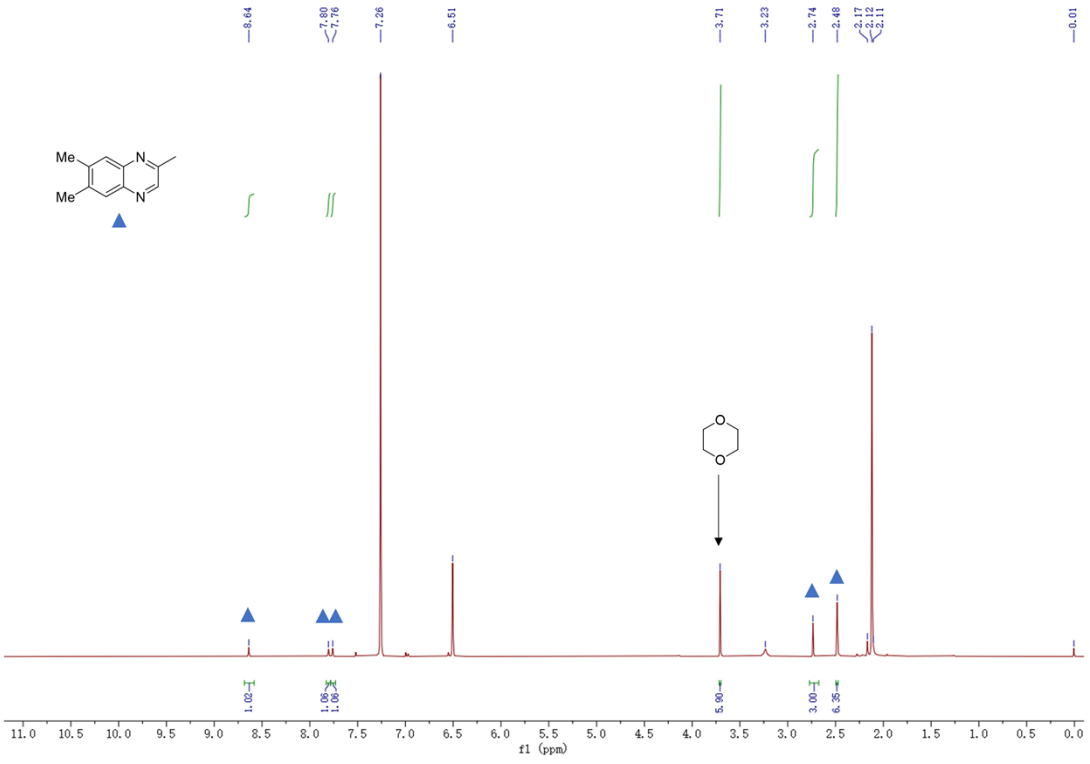


Figure S11. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **6**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.80 (s, 1H), 7.76 (s, 1H), 2.74 (s, 3H), 2.48 (s, 6H).

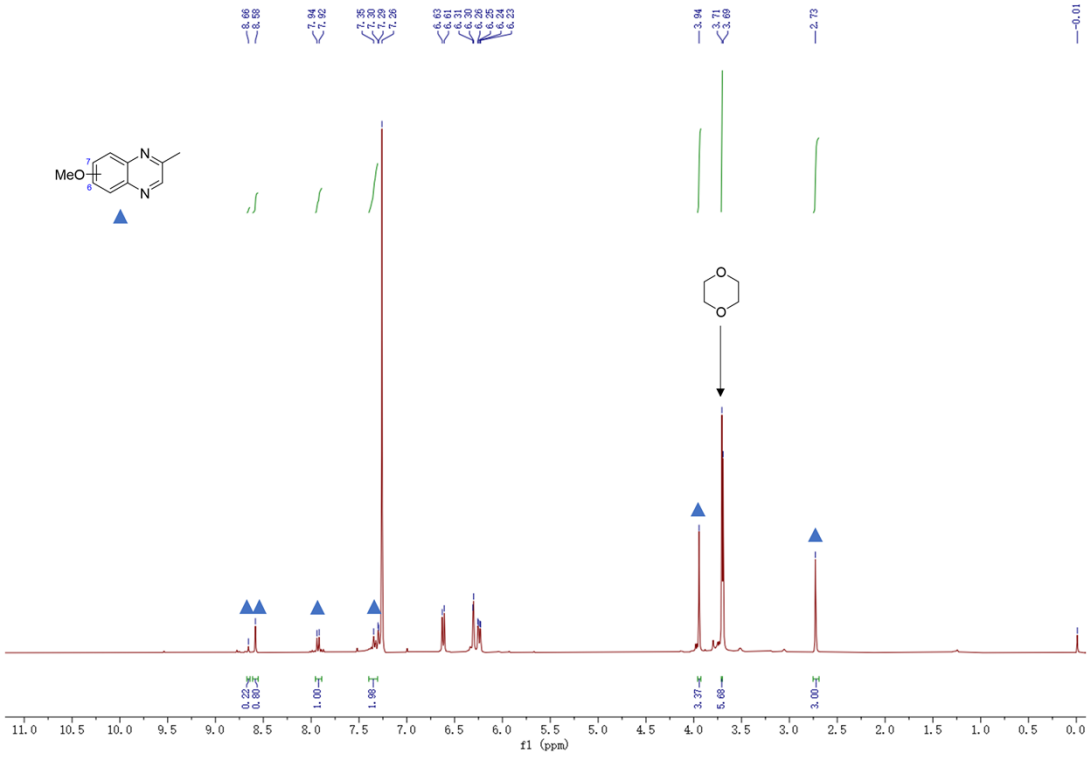


Figure S12. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **7**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 0.22H), 8.58 (s, 0.80H), 7.90–7.96 (m, 1H), 7.26–7.35 (m, 2H), 3.94 (s, 3H), 2.73 (s, 3H).

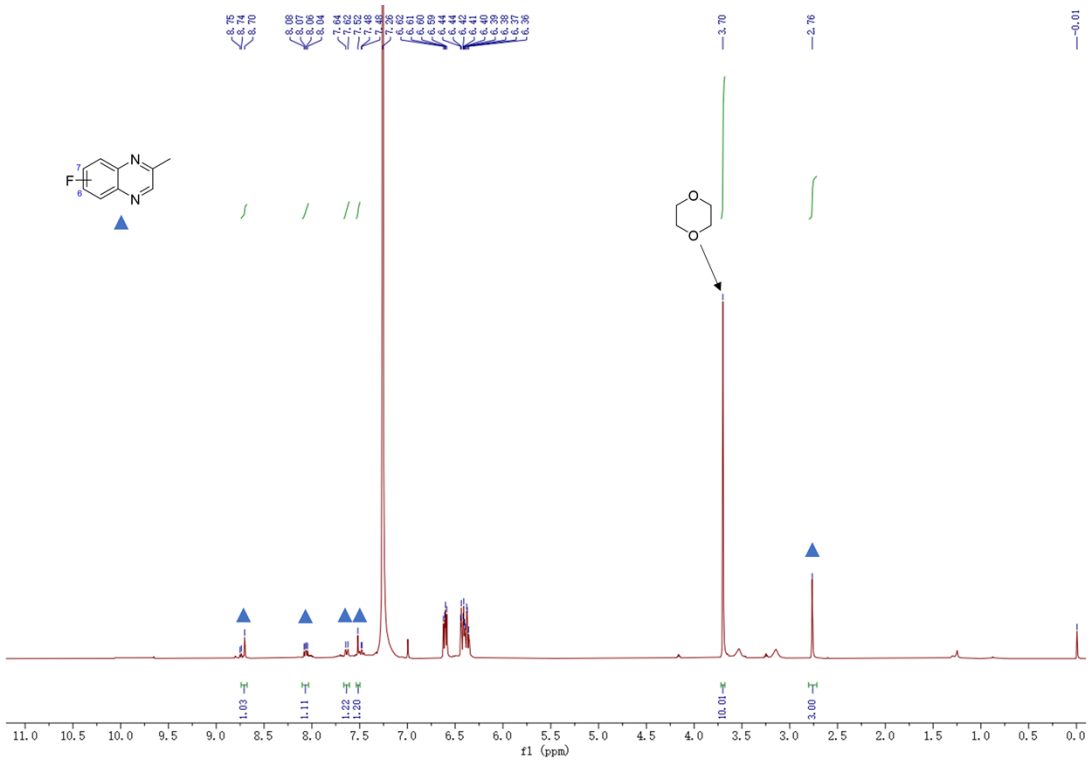


Figure S13. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **8**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70–8.75 (m, 1H), 8.04–8.08 (m, 1H), 7.48–7.64 (m, 2H), 2.76 (s, 3H).

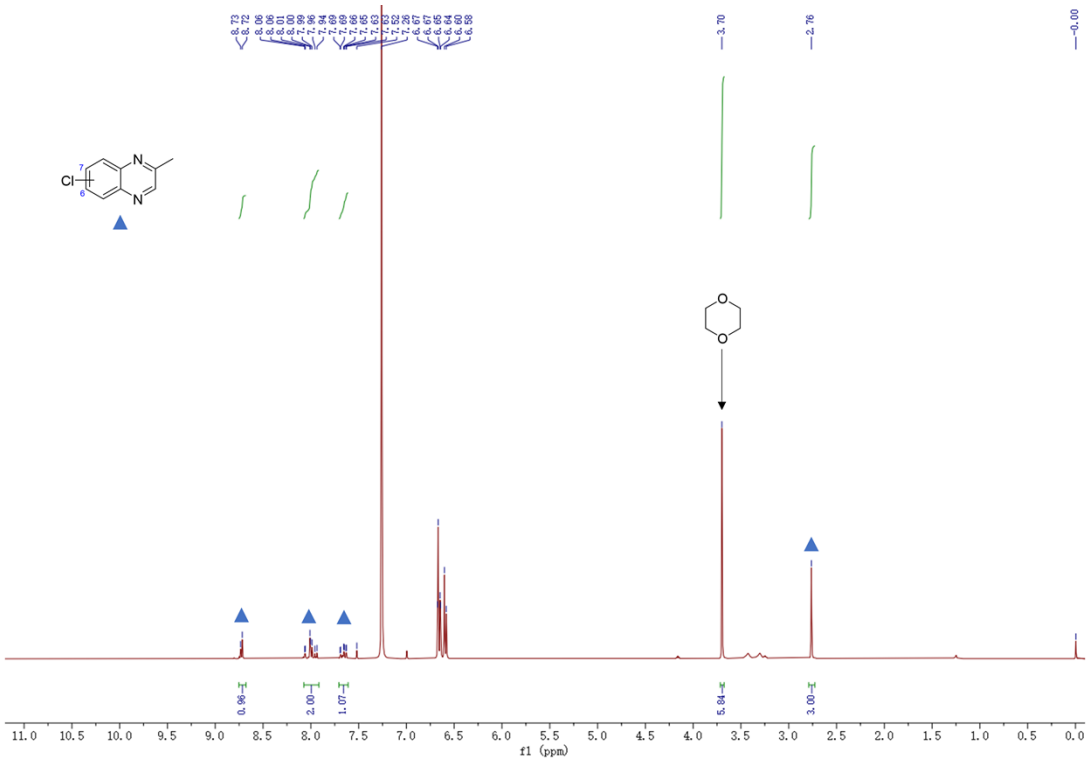


Figure S14. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **9**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 0.40H), 8.72 (s, 0.58), 7.94–8.06 (m, 2H), 7.63–7.69 (m, 1H), 2.76 (s, 3H).

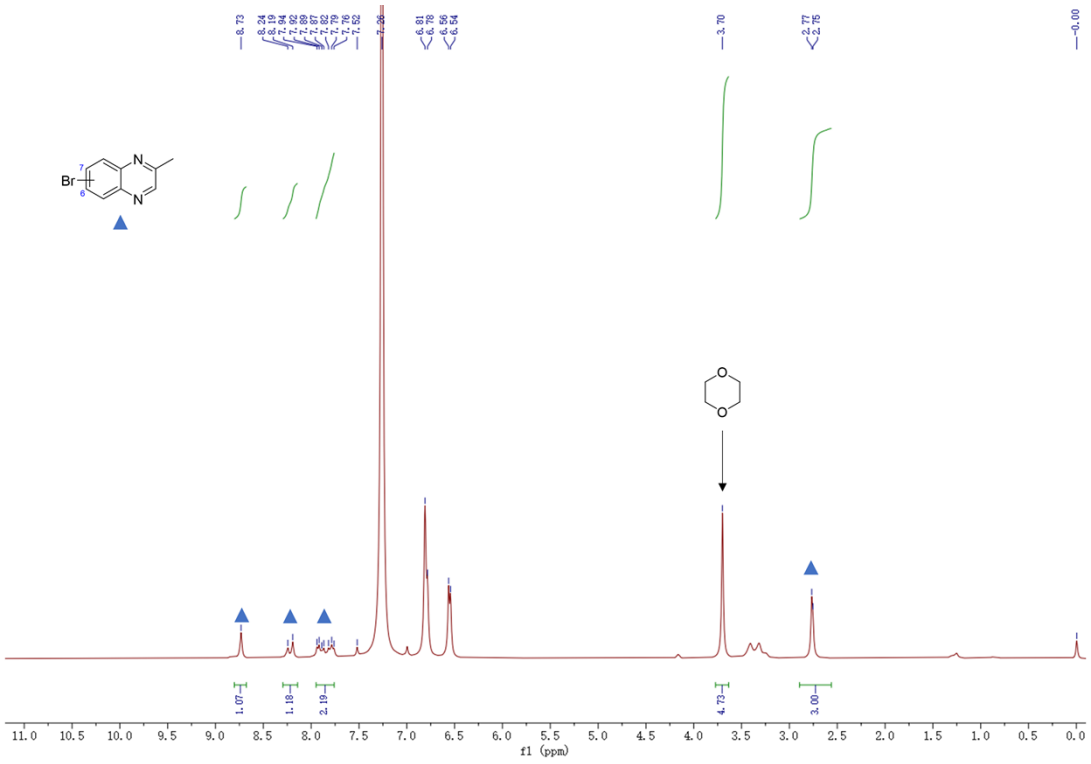


Figure S15. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **10**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.24 (s, 0.41H), 8.19 (s, 0.61H), 7.76–7.94 (m, 2H), 2.76 (s, 3H).

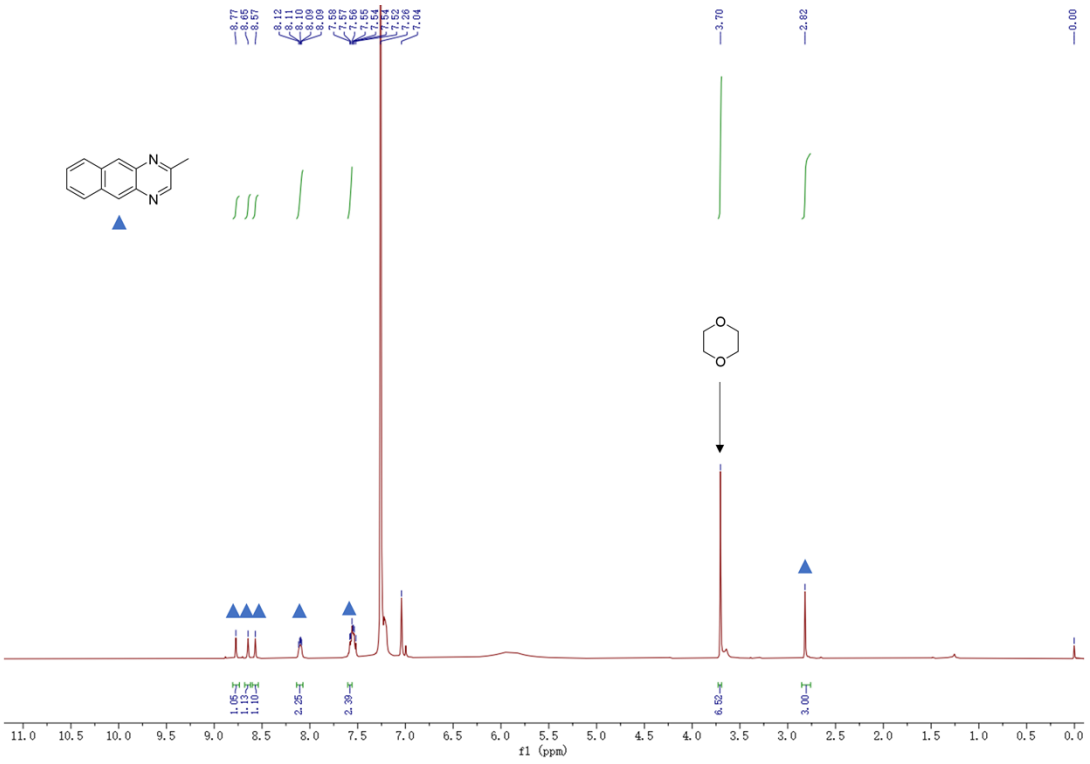


Figure S16. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **11**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 8.09–8.12 (m, 2H), 7.55–7.58 (m, 2H), 2.82 (s, 3H).

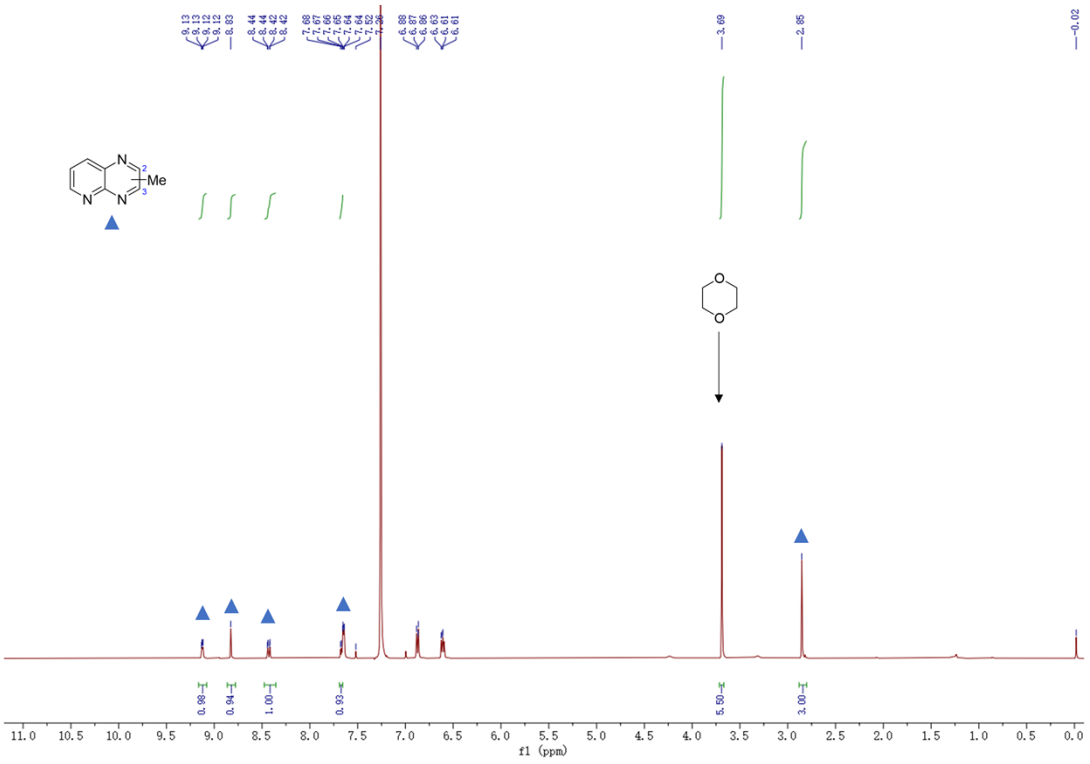


Figure S17. ^{1}H NMR spectrum of the resulted reaction mixture for synthesizing product **12**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12–9.13 (s, 1H), 8.83 (s, 1H), 8.42–8.44 (m, 1H), 7.65–7.68 (m, 1H), 2.85 (s, 3H).

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