Supplementary Information (SI) for Green Chemistry.

Supporting Information

Catalyst-free *N*-dealkylation of aniline derivatives in water induced by high frequency ultrasound

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Materials and Methods

Experimental

1-Description of ultrasonic reactor

N-demethylation of *N*,*N*-dimethylaniline was carried out in an ultrasonic reactor purchased to Sinaptec Ultrasonic Technology (Fig.S1) (ultrasonic generator NexTgen LAB1000, $P_{electric}$= 75 W). This reactor was equipped with three piezoelectric materials (3 cm diameter) which generate the ultrasonic waves at a frequency of 550 kHz. During ultrasonic irradiation, piezoelectric materials were continuously cooled down thanks to a flow of air. The temperature of the solution was monitored with a thermocouple and maintained at 35°C thanks to a cooling jacket.

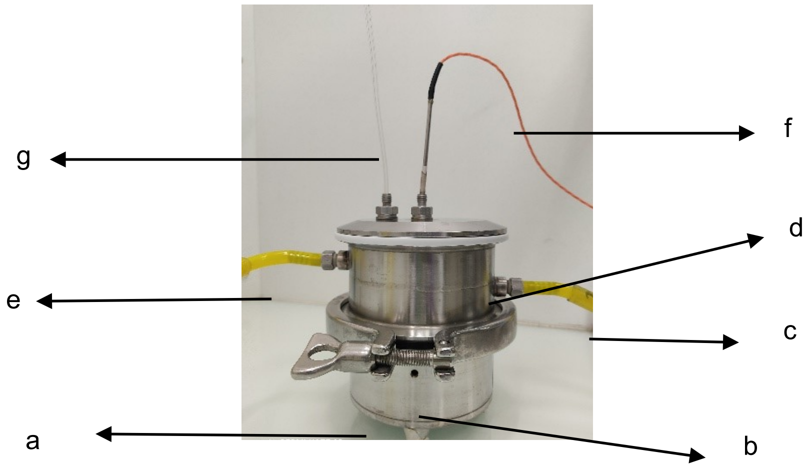

Fig.S1. *Experimental setup for the N-demethylation of N,N-dimethylaniline in water under high frequency ultrasound. (a) Transducer (location of piezoelectric materials), (b) compressed air inlet for piezoelectric materials cooling, (c) Inlet cooling solution, (d) Cooling jacket, (e) Outlet cooling solution, (f) Thermocouple, (g) Gas inlet.*

2-Dimethylaniline demethylation in water

In a typical procedure, argon was first bubbled at 20 mL/min into a 60 mL aqueous solution of DMA (5 mM in ultrapure water) for 30 minutes in order to remove oxygen from the solution (important step to avoid hydroxylation of the aromatic ring of DMA during the reaction). Then, the solution was subjected to a continuous ultrasonic irradiation (550 kHz) with an acoustic power density of 0.25 W/mL During ultrasonic irradiation, the bubbling of Ar was continued and the temperature of the solution was maintained to 35°C by connecting the cooling jacket of the reactor to a chiller (temperature of cooling liquid = 30°C). During the reaction, aliquots were taken for analysis by HPLC *(i.e.* determination of conversion, yield, selectivity). A similar procedure was employed for aniline derivatives described in the Figure 3 of the main manuscript.

To characterize the aniline derivatives, the crude reaction media was extracted twice with CH_2Cl_2 (note that ethyl acetate can be also used) at the end of the reaction. The organic phases were then combined, dried over $MgSO_4$ and then concentrated under vacuum. The as-obtained yellowish oily product was then purified on a preparative silica gel plate using an ethylacetate/cyclohexane (20/80) mixture as eluent. The product was then revealed by UV onto the plate and the corresponding mark on the silica plate scraped off and recovered with a spatula. The aniline derivatives were then desorbed from the silica by washing with CH_2Cl_2 (note that ethyl acetate or methanol can be also used). Aniline derivatives were analyzed by HPLC and ^{1}H NMR and compared to commercially available standards, also widely described in the literature.

Aniline: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (m, 2H), 6.78 (m, 1H), 6.73 (m, 2H). Rf = 0.4. Retention time on HPLC = 4.734 min (see conditions below in section 3)

3-chloroaniline: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (dd, 1H, *J* = 8.2 Hz), 6.70 (t, 1H, *J* = 2.1 Hz), 6.86 (dd, 1H, *J* = 8.0 Hz), 7.19 (t, 1H, *J* = 8.1 Hz). Rf = 0.33. Retention time on HPLC = 7.220 min (see conditions below in section 3)

3-nitroaniline: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dd, 1H, *J* = 7.8 Hz), 7.29 (t, 1H, *J* = 8.1 Hz), 7.51 (t, 1H, *J* = 1.7 Hz), 7.60 (dd, 1H, *J* = 8.1 Hz). Rf = 0.3. Retention time on HPLC = 5.520 min (see conditions below in section 3)

3-methoxyaniline: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (t, 1H, *J* = 2.25 Hz), 6.77 (m, 1H), 6.82 (m, 1H), 7.31 (t, 1H, *J* = 8.1 Hz), 3.83 (s, 3H). Rf = 0.3. Retention time on HPLC = 4.492 min (see conditions below in section 3)

3-HPLC Analysis

Calibration curves of N,N-dimethylaniline, N-methylaniline and aniline on HPLC

Standard solutions of *N*,*N*-dimethylaniline, *N*-methylaniline and aniline were prepared in water, at concentrations ranging from 0.001 to 6 mM. Samples were analyzed using high-performance liquid chromatography (HPLC) from SHIMADZU LC-40D equipped with a UV-Visible detector (wave length at 225 nm) and a C18 Agilent column (4.6 mm × 250 mm). The eluent was composed of a mixture of acetonitrile/water (50:50) flowing through the column at a flow rate of 0.8 mL min^{-1}. The injection volume was 20 µL, and the temperature of the column was set at 25 °C.

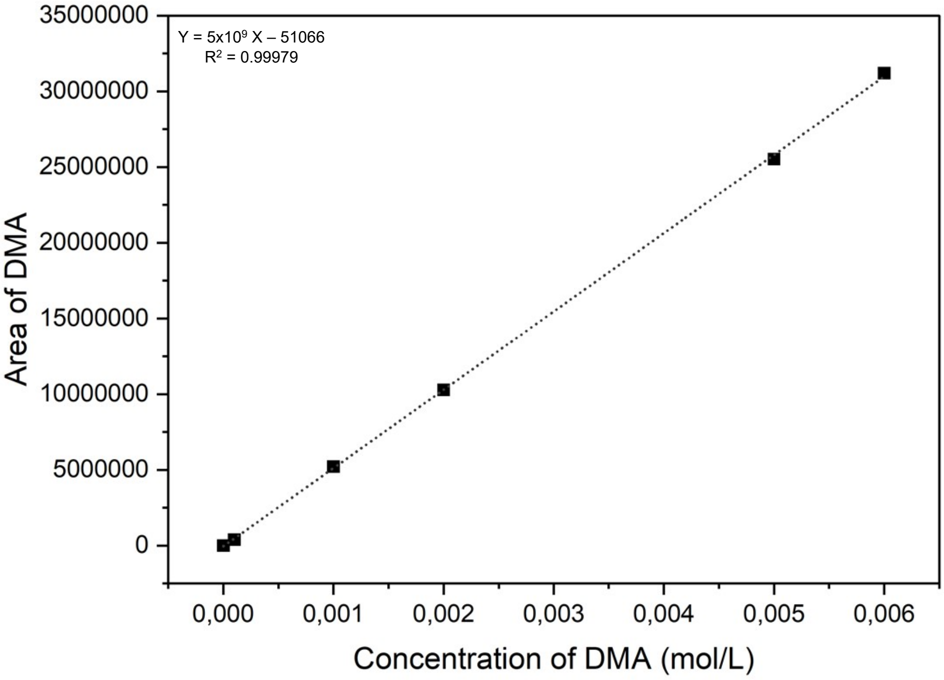

Fig.S2. *Calibration curve of N,N-dimethylaniline*

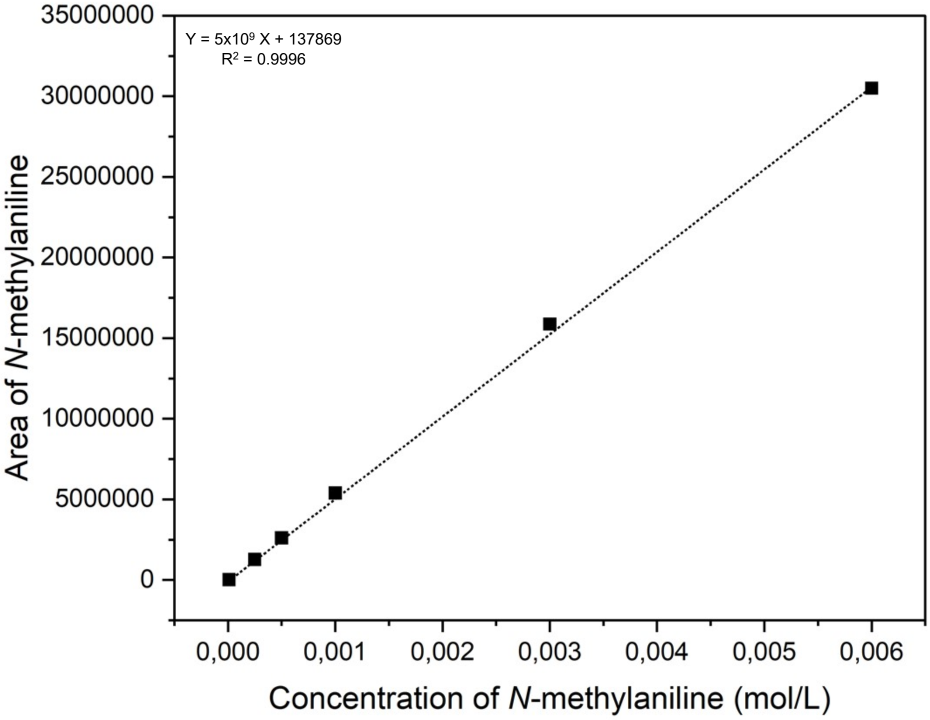

Fig.S3. *Calibration curve of N-methylaniline*

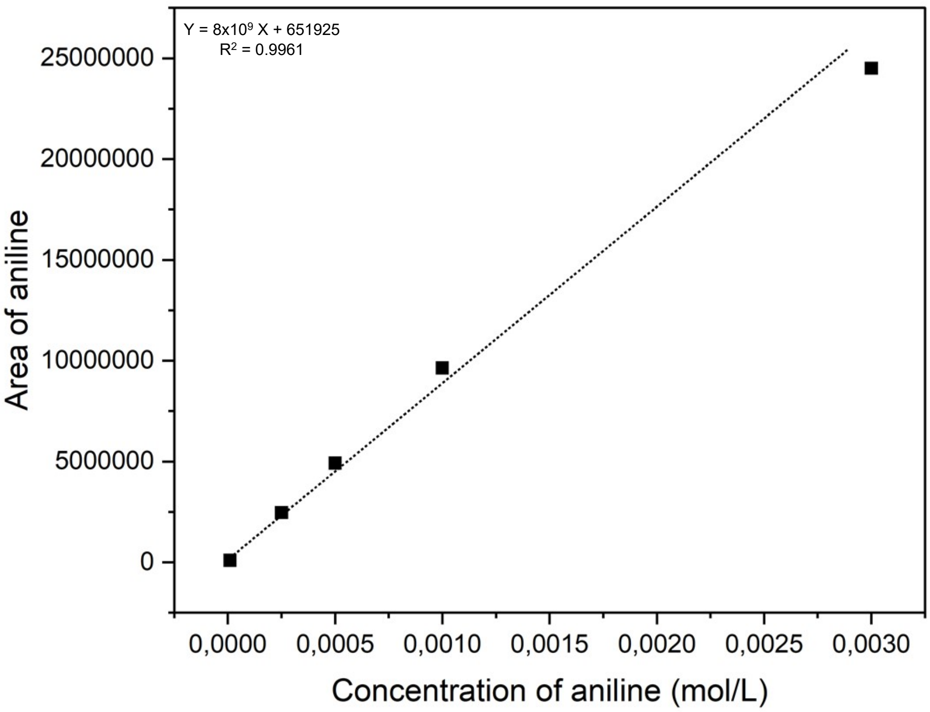

Fig.S4. *Calibration curve of aniline*

4-Additional figures

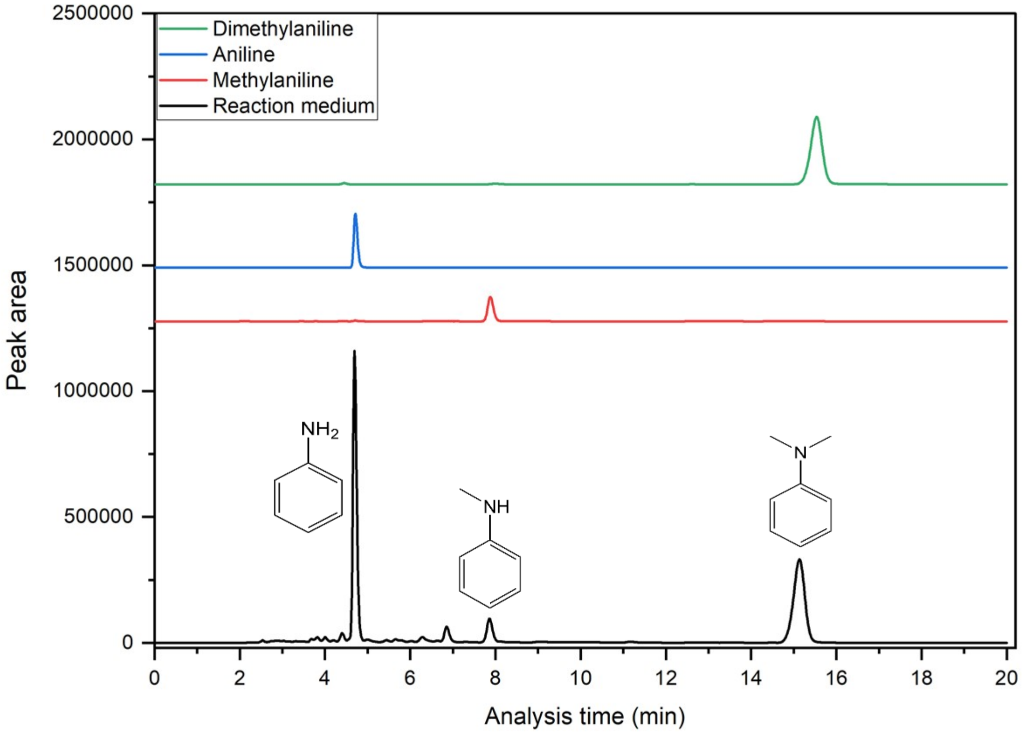

Fig.S5. *Example of a typical chromatogram collected during the ultrasonic irradiation of DMA. Reaction condition: 5 Mm DMA, 60 mL H_2O, 550 kHz, 35 °C, 0.25 W/mL.*

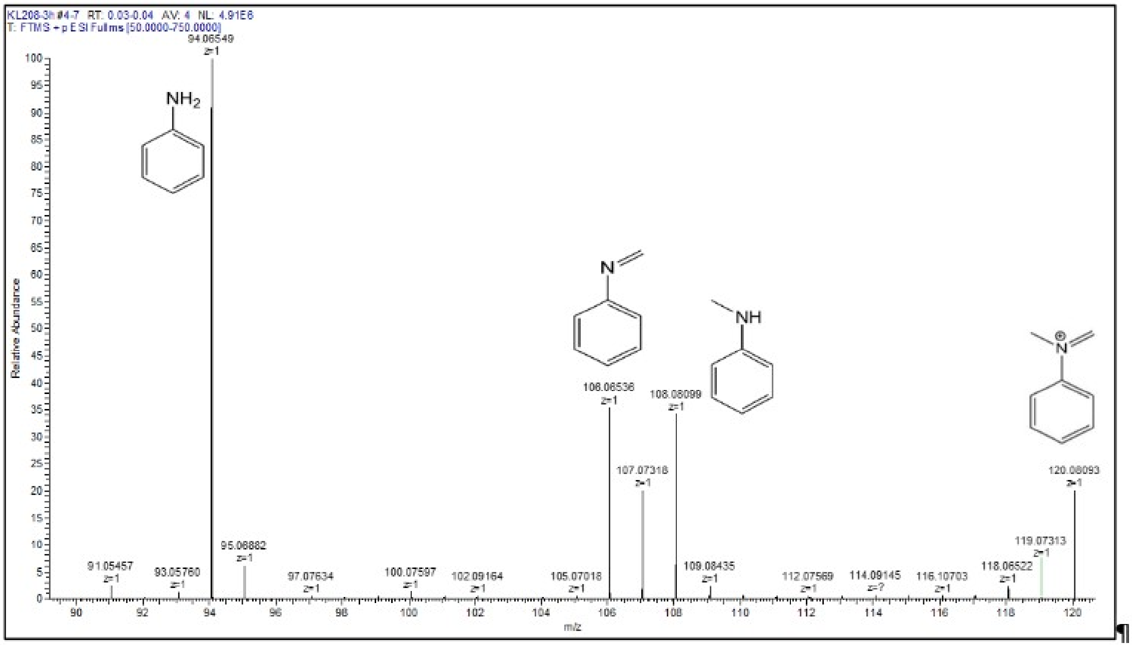

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Fig.S6. *Mass spectrum collected after 3h of ultrasonic irradiation of N,N-dimethylaniline. Reaction condition: 5 mM DMA, 250 mL, 20 mL/min Ar, 0.13 W/mL, 550 kHz, Temperature of the solution 35 °C.*

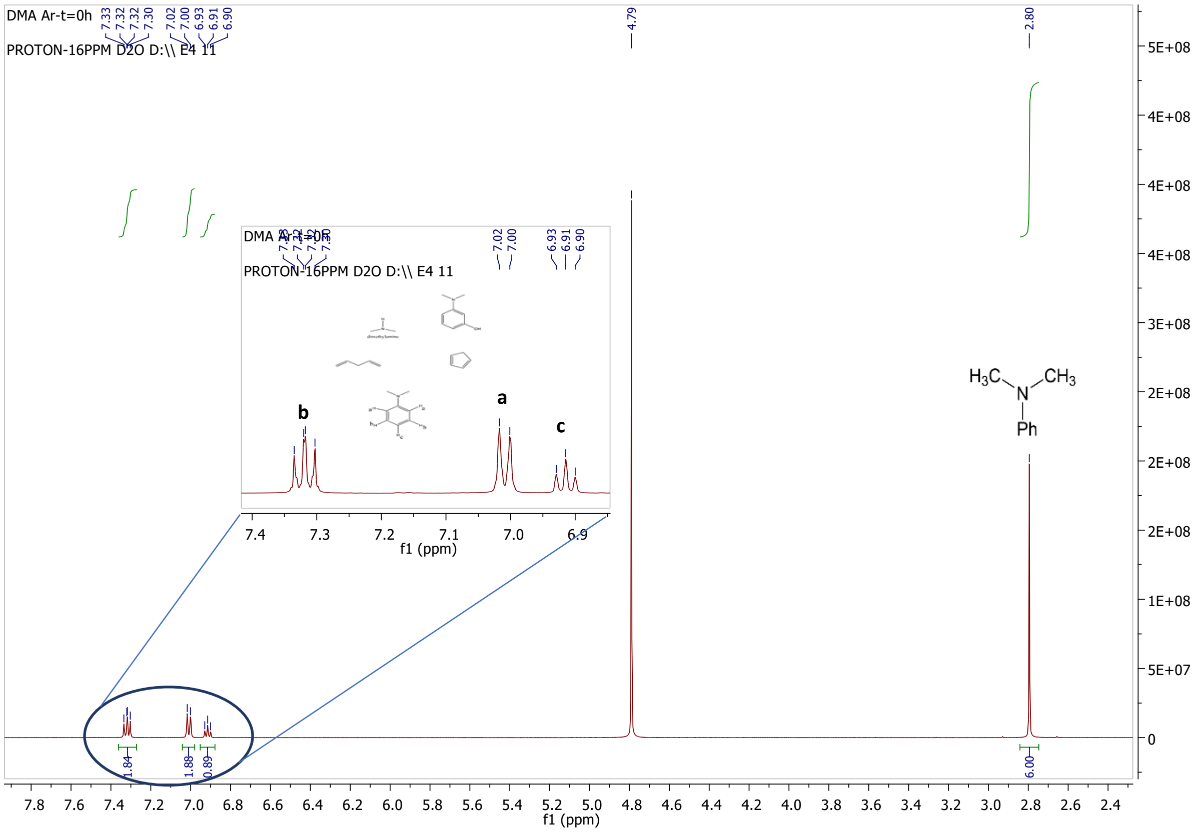


Fig.S7. *^1H NMR (500 MHz) of DMA before ultrasonic irradiation. Reaction conditions: 5 mM DMA in D_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL.*

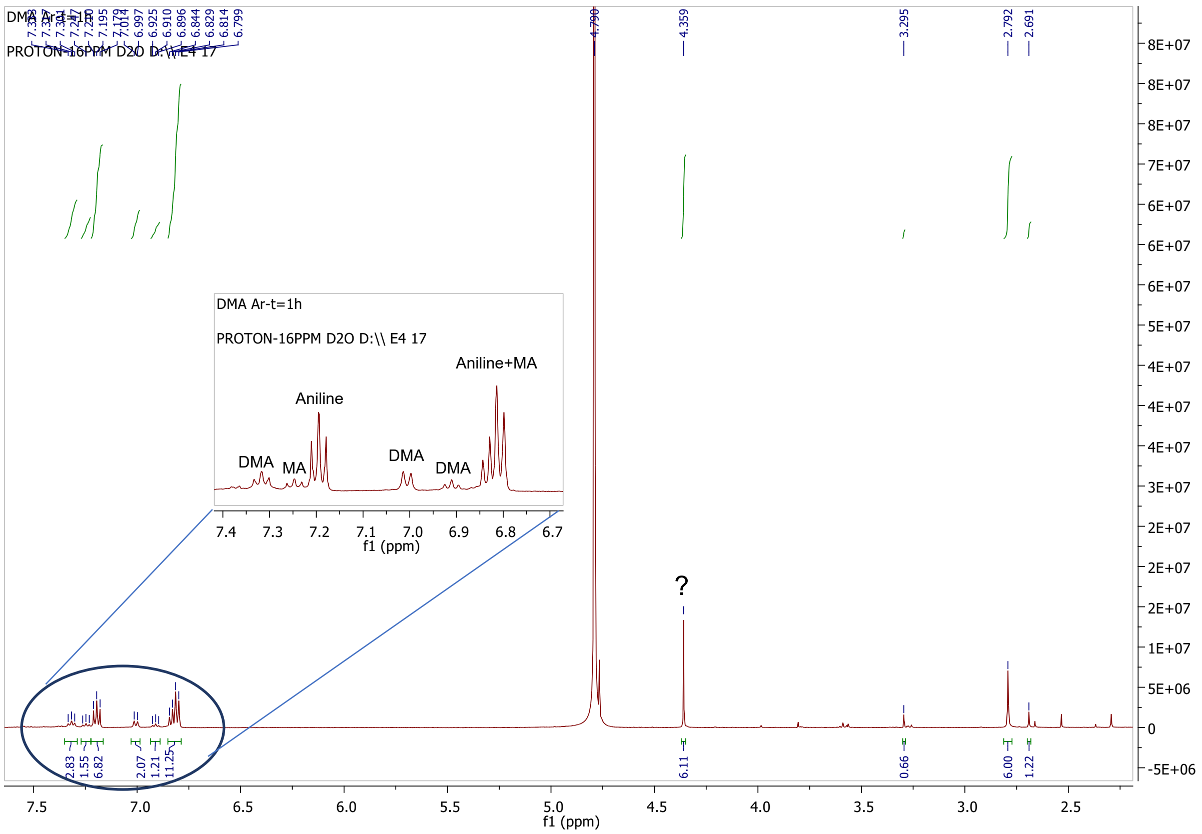


Fig.S8A. *^1H NMR (500 MHz) analysis. Reaction conditions: 5 mM DMA in 60mL D_2O, 550 kHz, 20 mL/mi n Ar, analysis after 1h of irradiation.*

Note: we carried out extensive MS analysis (in gas and liquid phase), in particular using sophisticated methodologies dedicated to the analysis of trace, to identify the unknow peak observed at 4.36 ppm. This single peak could correspond, based on the current literature,[2] to structures close to glycolamide which could be formed by recombination of HCN and CO, two products previously observed during pyrolysis of DMA.[3] Further additional analysis by high resolution mass spectrometry revealed the presence of a product at a m/z = 76.0393 which perfectly fits with the formula of protonated glycolamide ($C_2H_6O_2N$; m/z = 76.0398). See below Figure S8B. However, at this stage, we prefer remaining safe regarding the nature of this impurity. This product was formed only when the reaction time was extended over 3 h (at 0.13 W/mL), which further supports the formation of an oxygenated product, as discussed in the main manuscript,

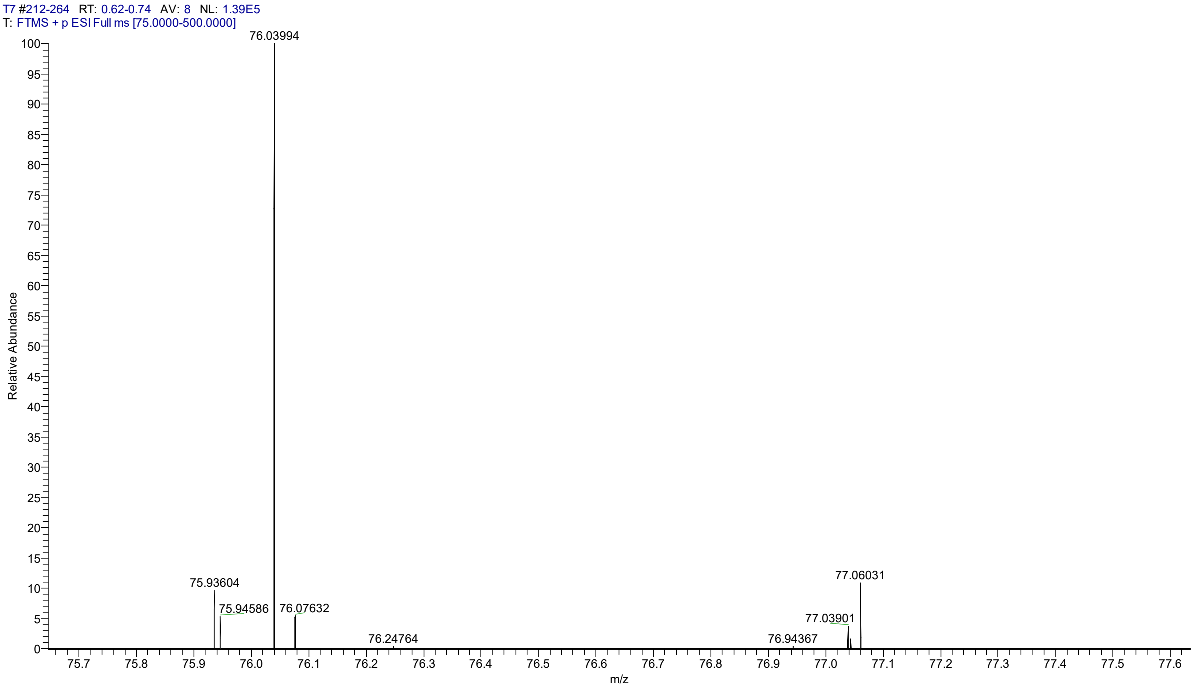


Fig.S8B. *HRMS corresponding to the unknown substance observed at 4.36 ppm*

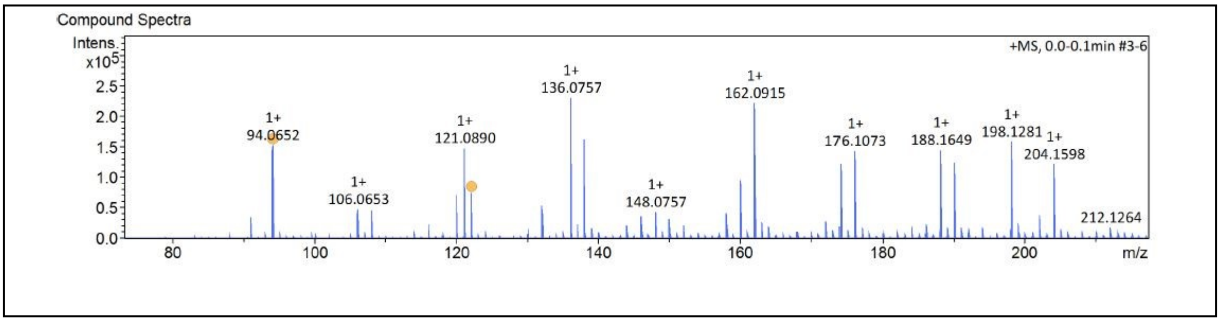


Fig.S9. *HRMS spectrum of the liquid phase after 1h of ultrasonic irradiation. Reaction conditions: 5 mM DMA in 60mL H_2O, 550 kHz, 20 mL/min Ar, 100 % amplitude, 0.25 W/mL, Solution temperature was maintained at 35°C.*

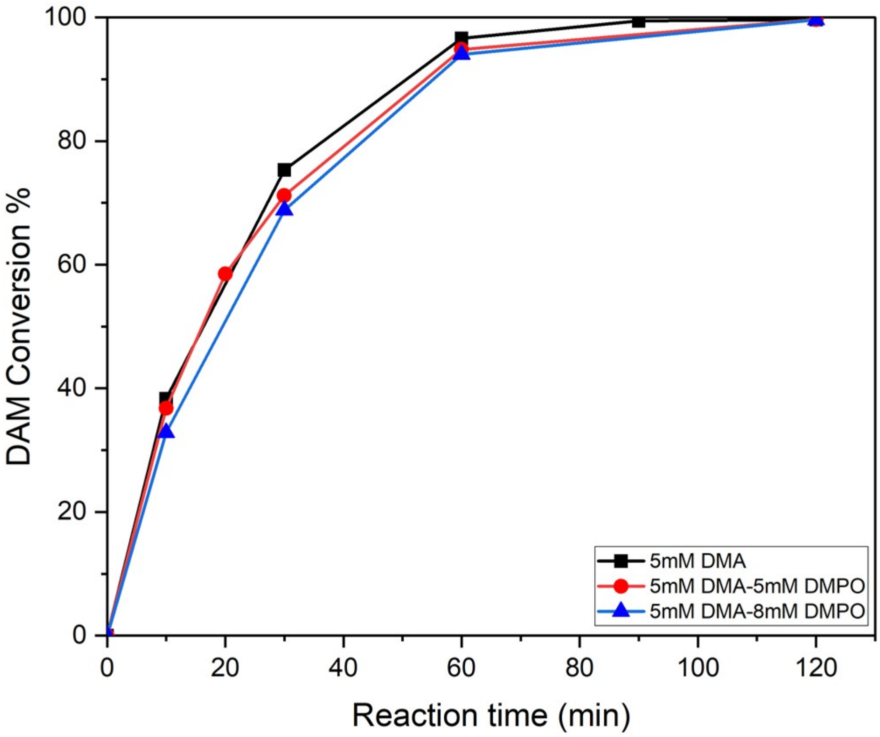


Fig.S10. *DMA conversion as a function of the reaction time without and with DMPO (5 and 8 mM). Reaction conditions: 5 mM DMA and DMPO (5 or 8 mM) in 60mL H_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL, 35°C.*

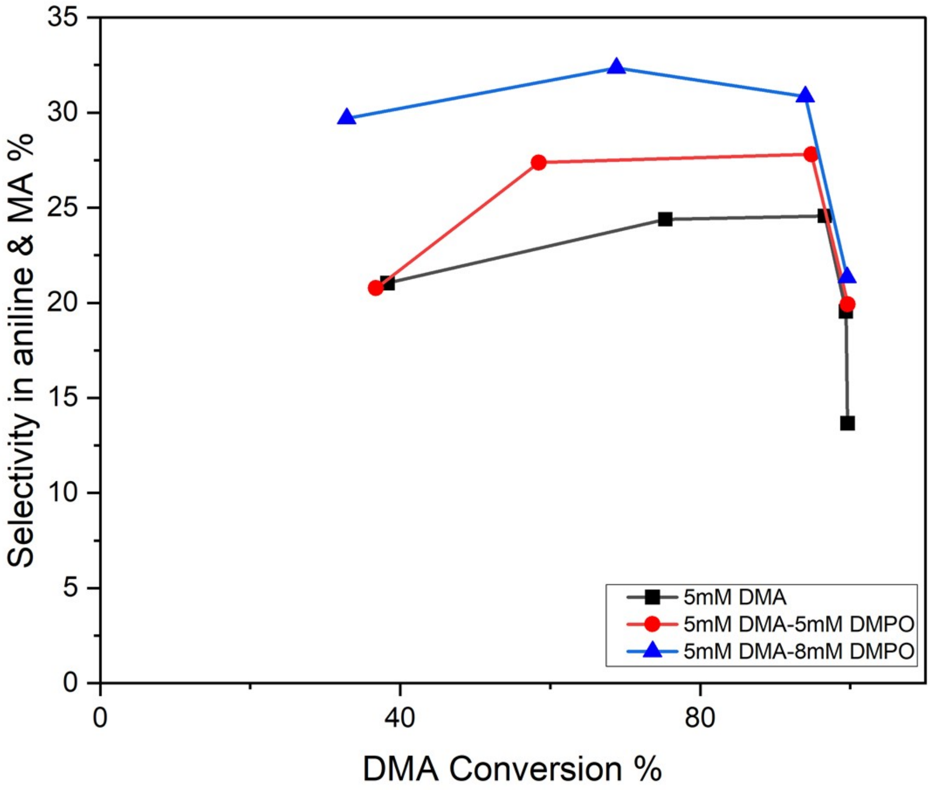


Fig.S11. *Influence of DMPO on the overall selectivity to aniline and methylaniline. Reaction conditions: 5 mM DMA and DMPO (5 or 8 mM) in 60mL H_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL, 35°C.*

10- Hydrogen peroxide (H_2O_2) quantification

Hydrogen peroxide was quantified as described in our previous work.[1] Evolution of the H_2O_2 concentration was monitored over a UV visible spectrophotometer (ThermoFisher Evolution 60S).

Principle

H_2O_2 reacts with TiO^{2+} to form a yellow-orange complex Ti (IV)-H_2O_2. The absorption spectrum of this complex shows a maximum absorption wavelength at 412 nm.

Calibration curve

$TiOSO_4$ solution 0.02 M in H_2SO_4 0.5 M

0.552 g of titanium oxysulfate ($TiOSO_4$) were mixed with 2.8 mL of H_2SO_4 (18 M). The solution was then diluted with water to reach a final volume of 100 mL.

Standards solutions of H_2O_2

The H_2O_2 solutions were prepared from a commercial H_2O_2 solution (35 wt%), with concentrations ranging from 0-0.005 mol/L. For calibration, 0.5 mL volume of H_2O_2 solution was mixed with 0.5 mL volume of the $TiOSO_4$ solution. The absorbance was measured at 412 nm. The calibration curve is provided in Figure S13.

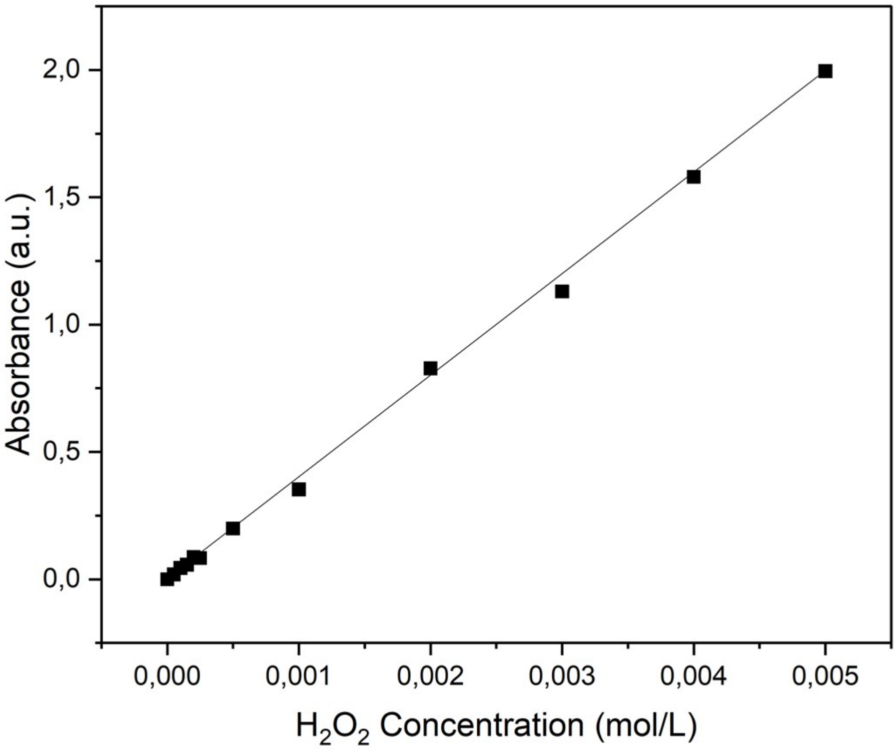


Figure S12. *Hydrogen peroxide calibration curve collected at 412 nm*

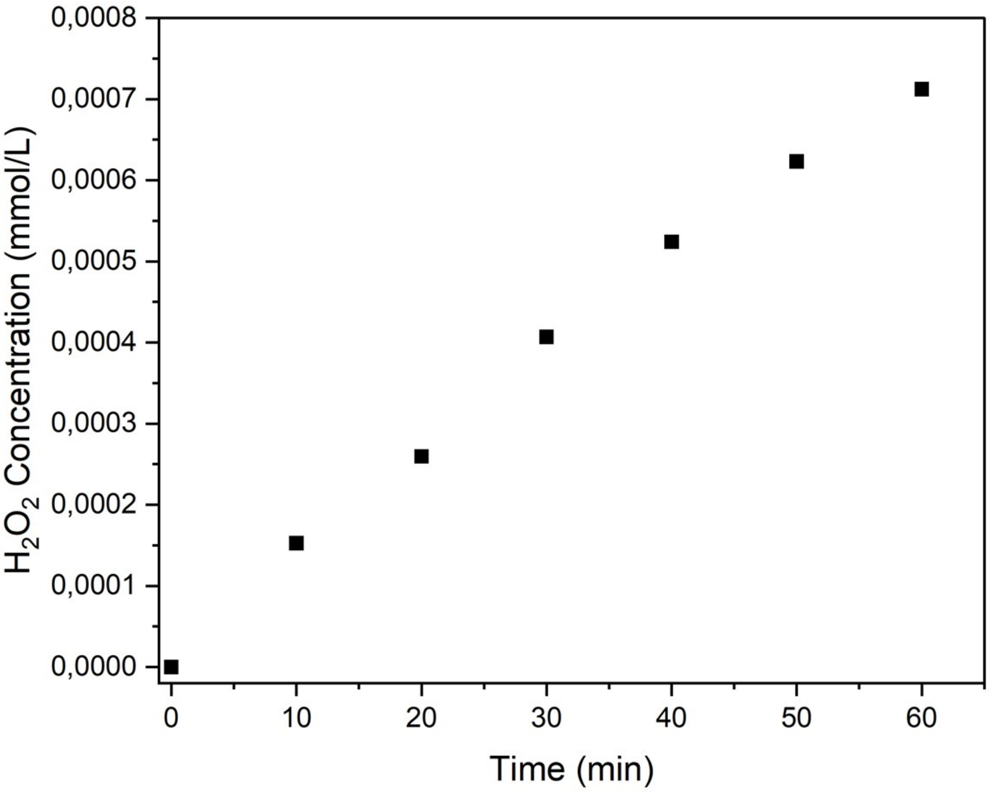
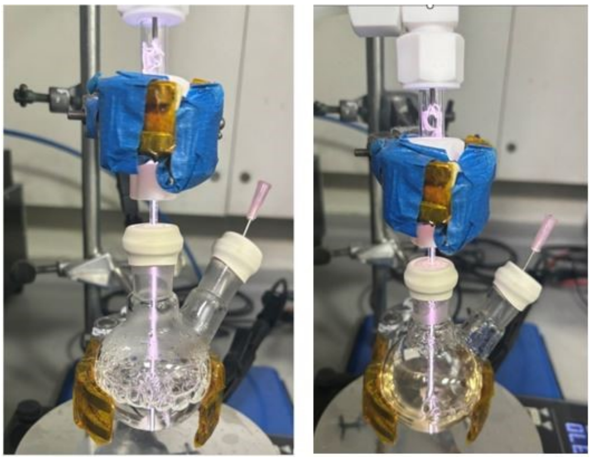


Figure S13. *In-situ H_2O_2 production under ultrasonic conditions* (550 kHz, 60 mL H_2O, 20 mL/min Ar, 0.25 W/mL).

Non-thermal plasma experiments

The non-thermal plasma reactor was set up as previously described.[4] Briefly, the plasma reactor consisted of a tungsten pin (1.8 mm diameter) acting as the HV electrode in the centre of a quartz tube (8 mm internal diameter and 10 mm outside diameter). In both cases, the plasma forming electrode sections were connected to reactors via narrower quartz tubing (1 mm internal diameter and 3 mm outside diameter) to carry the plasma/plasma generated species to the liquid interfaces. Argon was used as a feeding gas. The reaction set up used for the non-thermal plasma (NTP) assisted reactions (Figure S14) consisted of a 50 ml two-necked round bottom flask (RBF) and plasma generating probe. Both necks of the RBF were sealed with septa; one neck had a pierced hole to accommodate a quartz tube carrying plasma/plasma generated species to the liquid interface; the other was pierced with a needle for pressure control and to ensure the reactions could be carried out under the inert argon atmosphere. A magnetic stir bar was added to enable stirring.

A solution of *N*,*N*-dimethylaniline (20 mL) was placed under argon flow (450 mL/min) and treated with plasma (12-14.0 kV/ 9 W/ 20 kHz) for up to 60 minutes. The temperature of the solution was recorded with an IR thermometer: at the start (25°C), 5 minutes (27°C), 15 minutes (32.5°C), 30 minutes (38.1 °C), 45 minutes (39.6°C) and at the end of 60 minutes treatment (40.2 °C). The plasma plume was consistent through the reaction. The aliquot 0.2mL was taken at the end of reaction and analyzed via LCMS (Figure S15).



Start of irradiation **After irradiation**

Figure S14. *Picture of reaction setup, reaction condition: 20 kHz, Argon flow: 450 mL/min, Voltage: 12-14 kV, Power: 8.5-9W.*

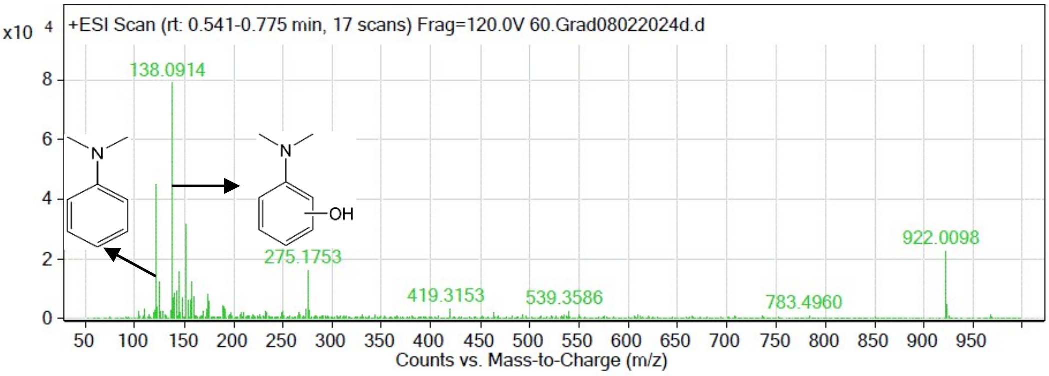


Fig.S15. LC-MS analysis of the DMA solution treated by plasma: mass spectrum of main peak (retention time: 0.541-0.775 min). Analysis was performed on a LC-MS +ESI-LC-qTOF equipped with a C18 Agilent poroshell column (1.9µm 2.1x50mm). The mobile phase was composed of acetonitrile and water containing 0.1 % formic acid (required for ESI) (50:50) at flow rate 0.4 mL/min. The injection volume was 0.5 µL.

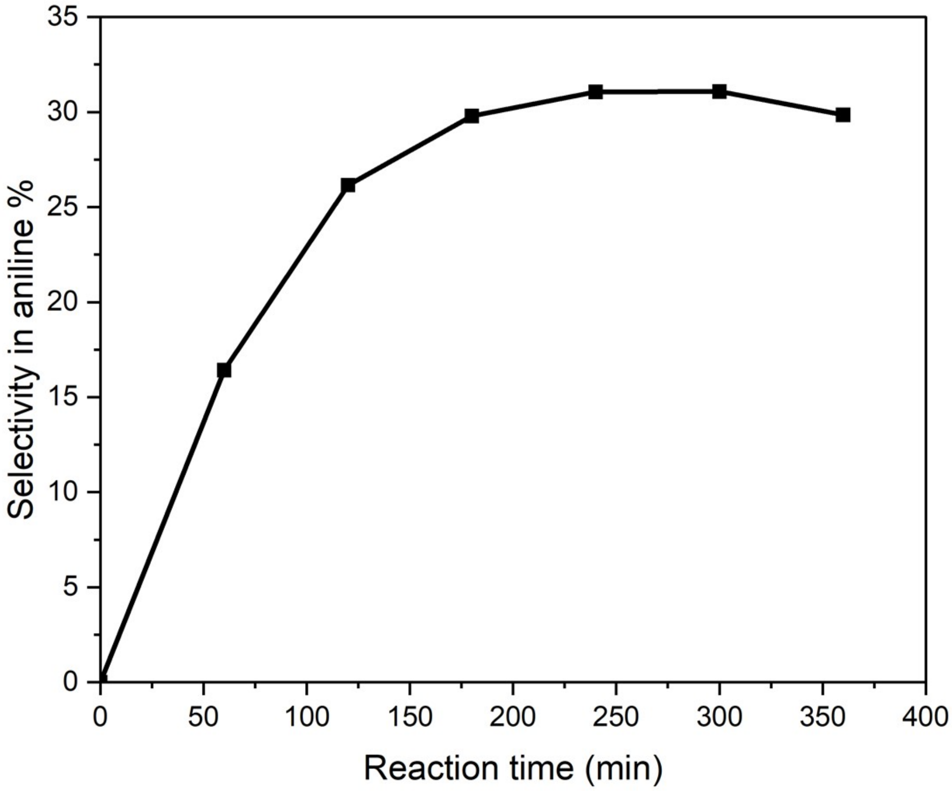


Fig.S16. *Yield to aniline as a function of reaction time. Reaction conditions: 5 mM DMA in* H_2O*, 550 kHz, 20 mL/min Ar, 0.13 W/mL, 35°C.*

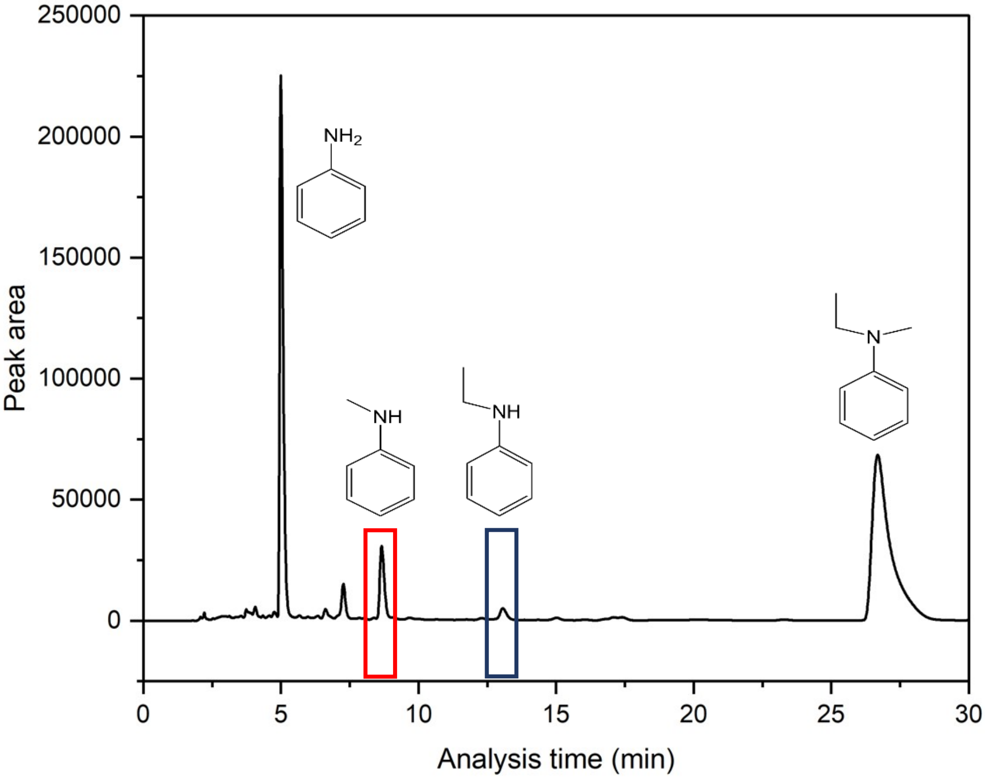


Fig. S17. *Typical HPLC chromatogram collected from N-ethyl,N-methylaniline. Reaction conditions: 1 Mm N-ethyl,N-methylaniline in* H_2O*, 550 kHz, 35 °C, 0.13 W/mL*

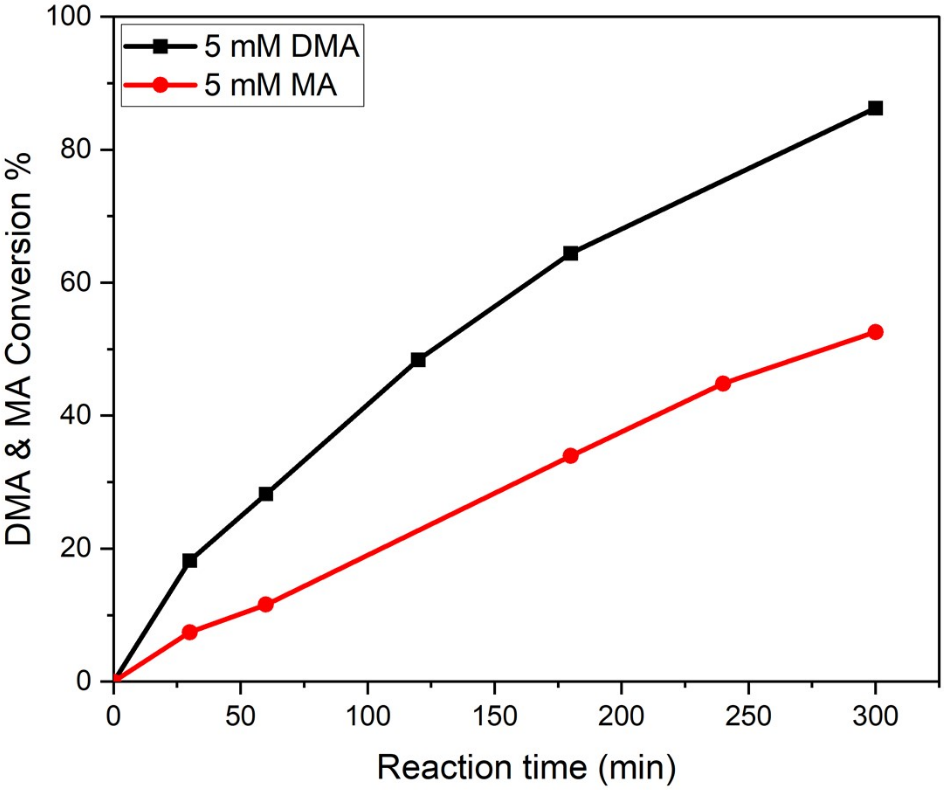


Fig. S18. *Conversion of DMA and MA as a function of the reaction time. Reaction conditions: 5 mM DMA or MA (in H_2O), 550 kHz, 20 mL/min Ar, 0.13 W/mL and 35°C.*

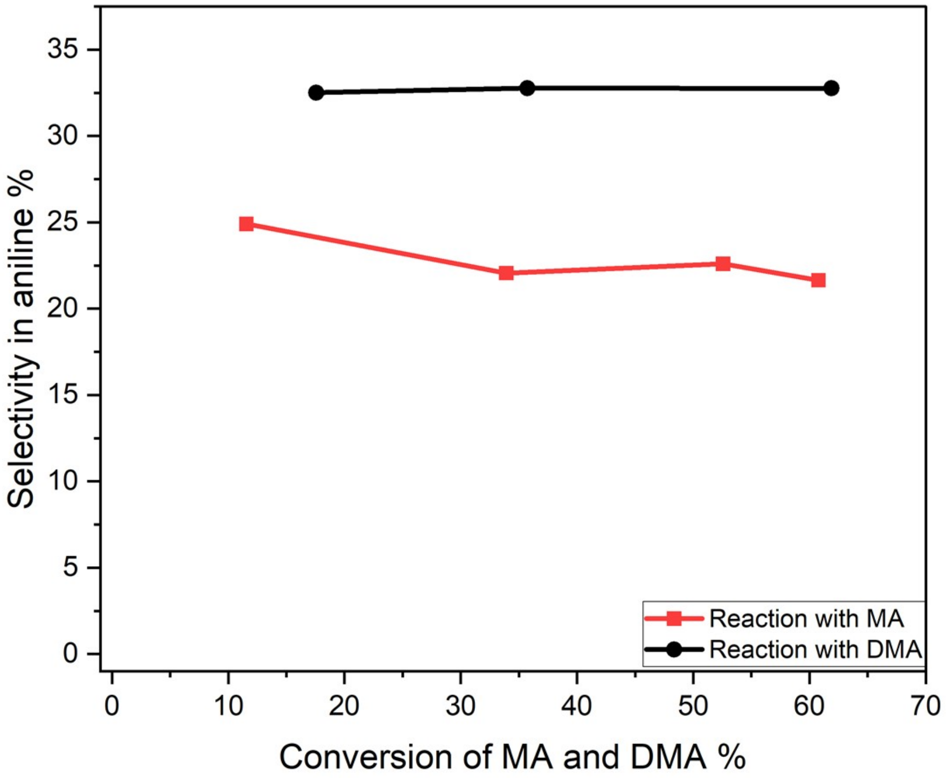


Fig. S19 *S*electivity to aniline (from DMA and MA) as a function of the DMA and MA conversion. *Reaction conditions: 5 mM DMA, (or MA) in* H_2O*, 550 kHz, 20 mL/min Ar, 100 % amplitude, 0.25 W/mL and 35°C.*

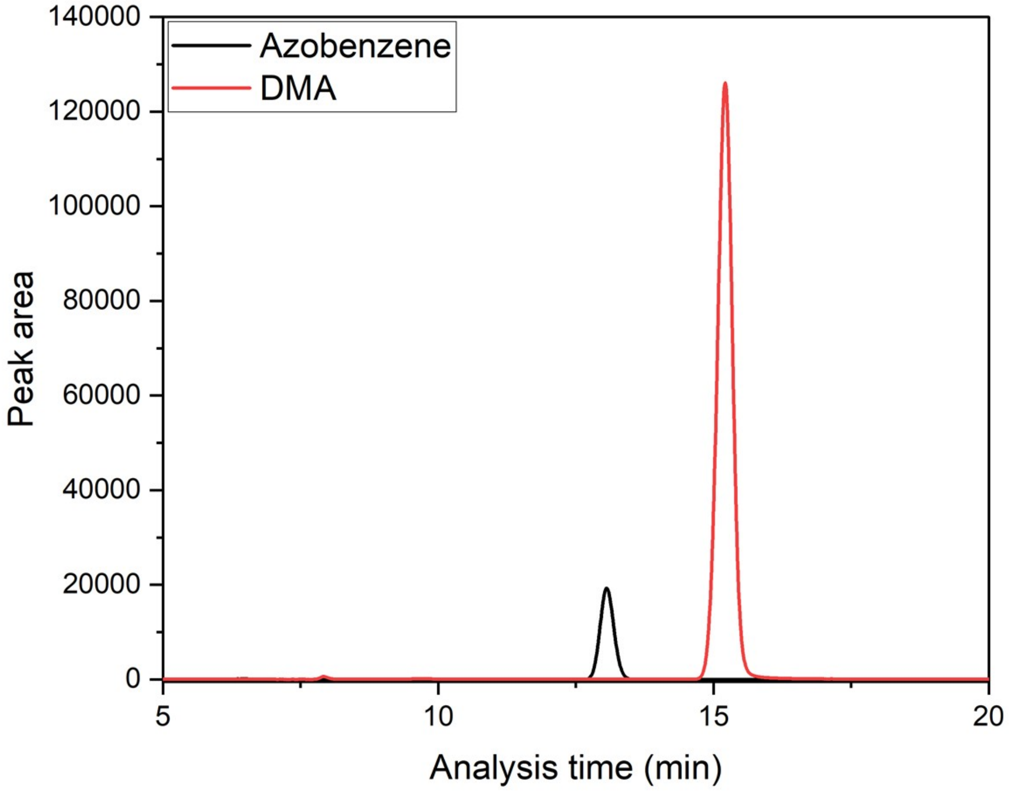


Fig. S20. *Retention time of DMA and azobenzene in HPLC chromatogram (C18 Agilent column (4.6 mm × 250 mm), eluent: acetonitrile/water (50:50) flowing through the column at a flow rate of 0.8 mL min*$^{-1}$*, injection volume: 20 μL at 25 °C.*

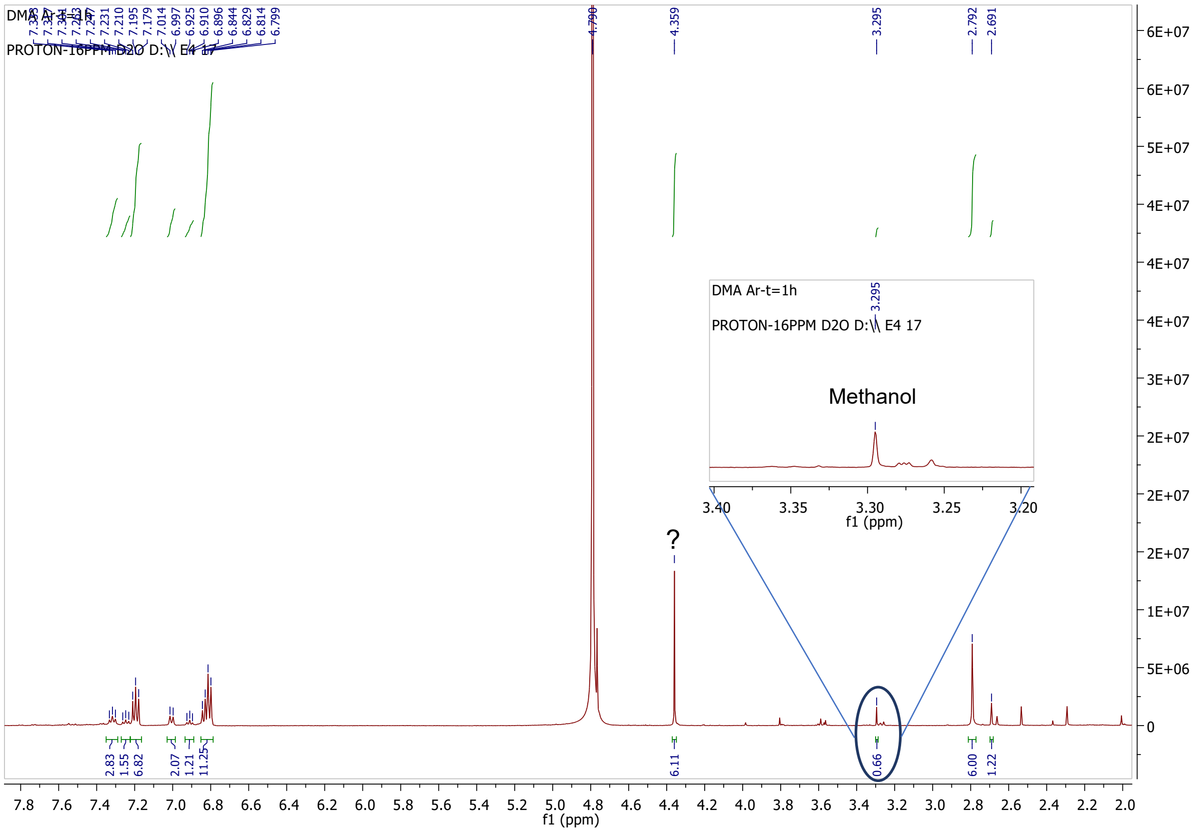


Fig.S21. *^{1}H NMR (500 MHz) analysis showing MeOH production during the DMA demethylation under HFUS. Reaction conditions: 5 mM DMA in D_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL, 35°C, spectra collected after 1 h of ultrasonic irradiation.*

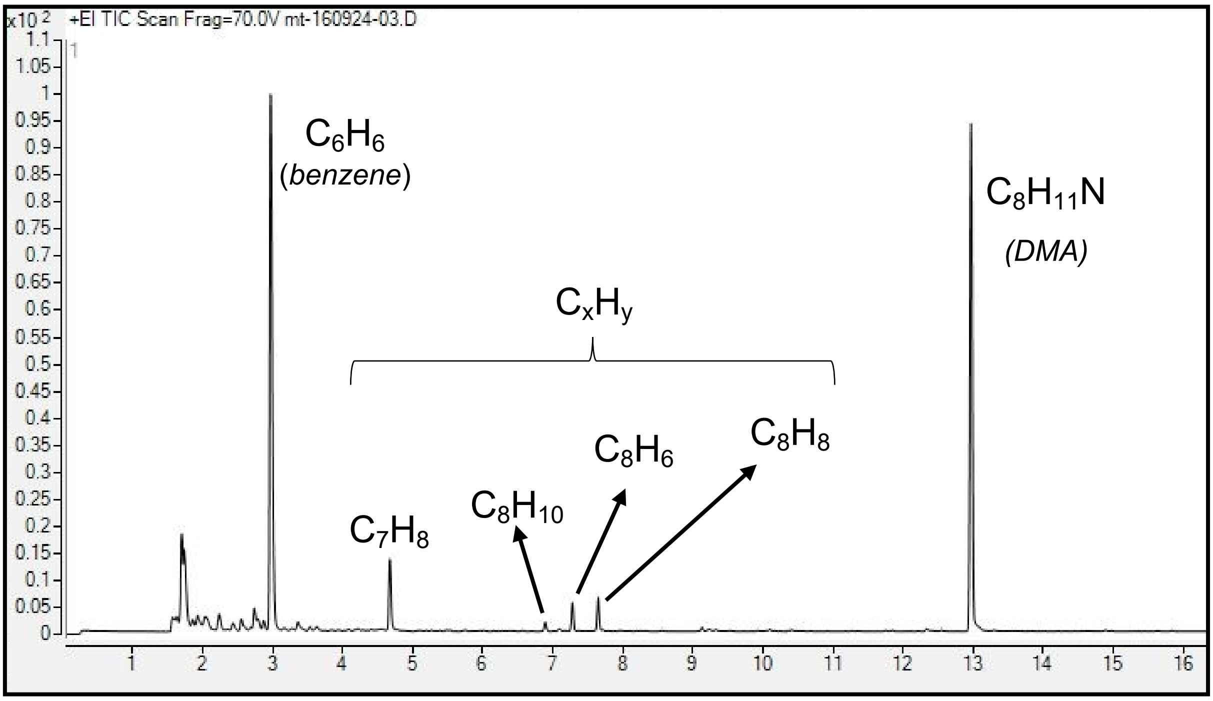


Fig. S22. *GC-MS analysis of gases trapped during the ultrasonic irradiation of DMA solution. Reaction conditions: 5 mM DMA in H_2O, 550 kHz, 20 mL/min Ar, 0.13 W/mL and 35°C.*

Note: The gas phase was analyzed by connected the gas exit of the ultrasonic reactor to a recovery bag. The gas trapped within the recovery bag was then manually injected in a GC-MS in Head Space heated at 200°C, in split mode (10:1). The GC-MS was composed of a gas phase chromatograph 8890 (Agilent), which was coupled to a mass spectrometer 7250, accurate-mass Q-TOF (Agilent). A HP-5MS column (30X0.25X0.25) was used for the separation. The initial temperature was set to 40°C for 2 min and the temperature was then increased at a rate of 6°C/min until the final temperature was reached (200°C). Finally, the temperature was maintained at 200°C for 10 additional minutes.

18- UHPLC-HRMS Analysis of the reaction medium

The LC-HRMS analysis was performed using an Acquity UPLC® BEH C18 1.7 µm, 2.1 x 100 mm column, with the aqueous phase being water containing 0.1% formic acid, and the organic phase being acetonitrile containing 0.1% formic acid. The gradient started with 10% B, remaining constant for 1 minute, then increased to 70% A over 5 minutes. Afterward, it increased to 100% B in 2 minutes, remaining constant for 2 minutes. The column was then reconditioned for 5 minutes with 10% B. This analysis was performed with a constant flow rate of 0.4 mL/min. HRMS analysis was conducted in positive mode with a mass range of 100 to 1500 m/z and a resolution of 70,000. The source gas parameters for sheath, auxiliary, and spare gas were 40, 30, and 0, respectively. The voltage and capillary temperature were set to 2.8 kV and 150°C, respectively.

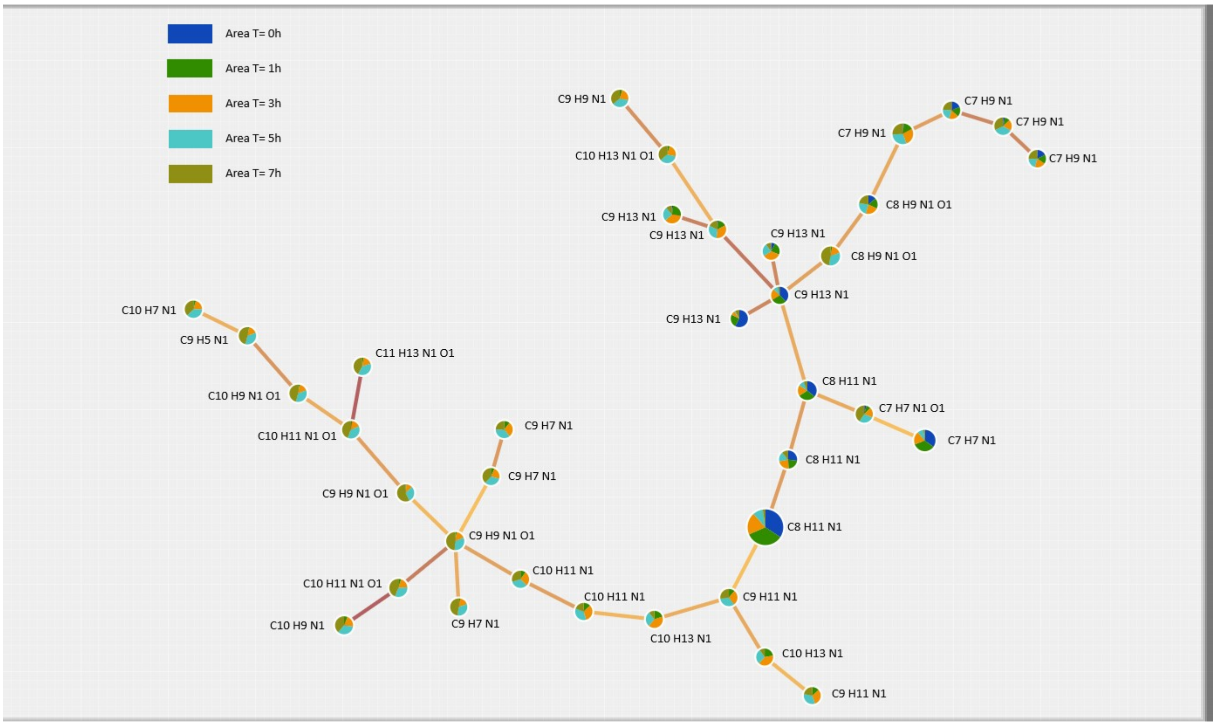


Fig.S23. *Ultra-High-Performance Liquid Chromatography (UHPLC) coupled to HRMS showing molecular network connecting all detected molecules according to mass differences (losses or additions of functional groups) and similarities in fragmentation mass spectra collected during the demethylation of DMA in water under HFUS. Reaction conditions: 5 mM DMA in 250mL H_2O, 550 kHz, 20 mL/min Ar, 100 % amplitude, 0.13 W/mL, Solution temperature was maintained at 35°C, Irradiation time: 7 h.*

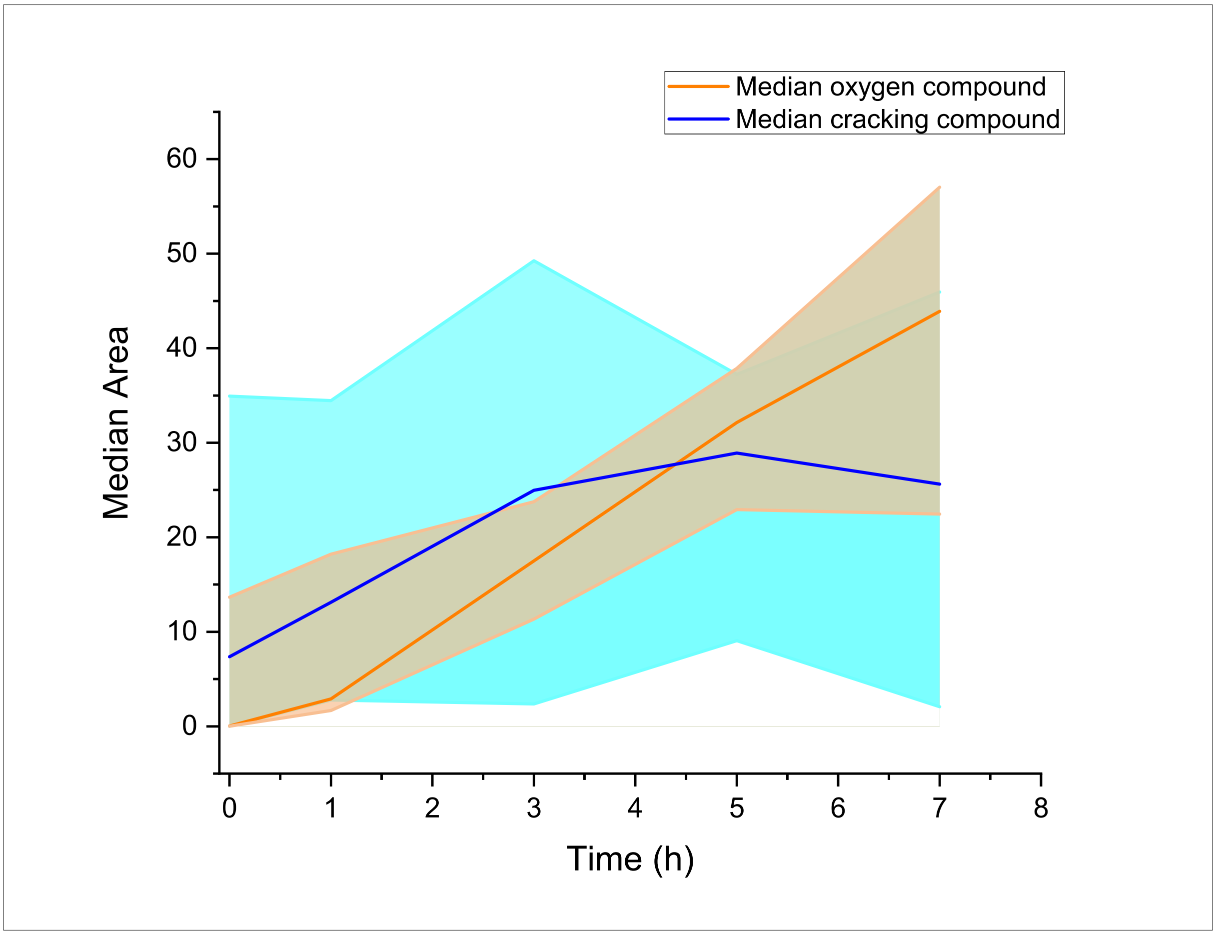


Fig.S24. *Molecular temporal network collected during the ultrasonic irradiation of DMA. Reaction condition: 5 mM DMA in H_2O, 550 kHz, 20 mL/min Ar, 0.13 W/mL and 35°C.*

Detail for the calculation of the energy efficiency.

Example: At 0.25 W/mL, the conversion rate of DMA is 0.69 mmol/h

- Energy required to break two N-CH_3 of DMA = 544 kJ/mol
- Energy required to convert 0.69 mmol of DMA to aniline = 0.375 kJ
- Acoustic energy provided in 60mL of ultrasonic irradiation at 0.25 W/mL = 0.25 x 60 = 15 W = 15 J/s, *i.e*. 54 kJ for one hour.

Energy efficiency = 0.375/54 x 100 = 0,7 %

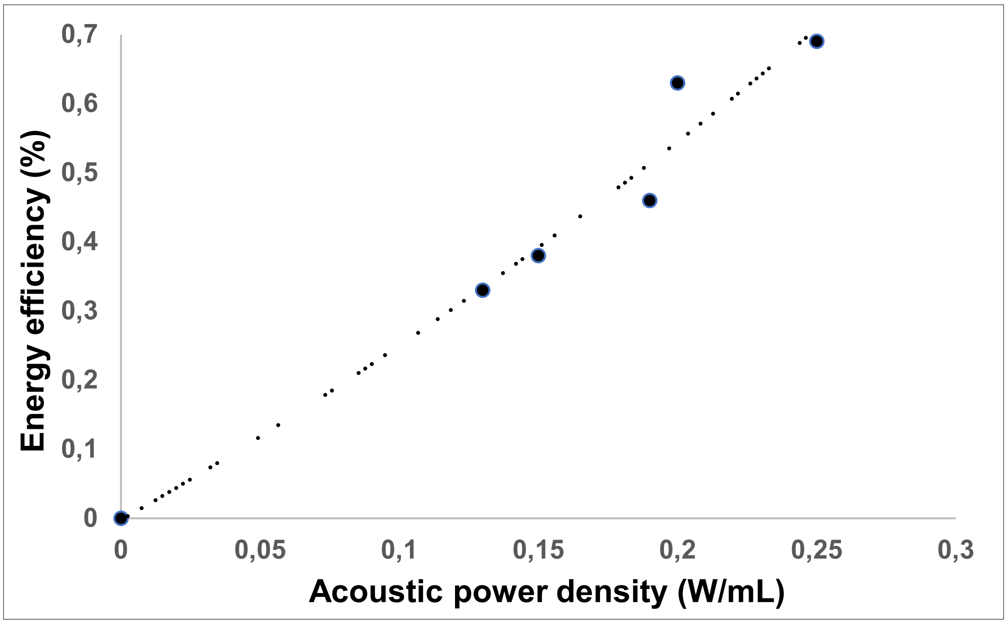


Fig. S25. Energy efficiency as a function of the acoustic power density

Additional figures (^{1}H NMR of aniline derivatives)

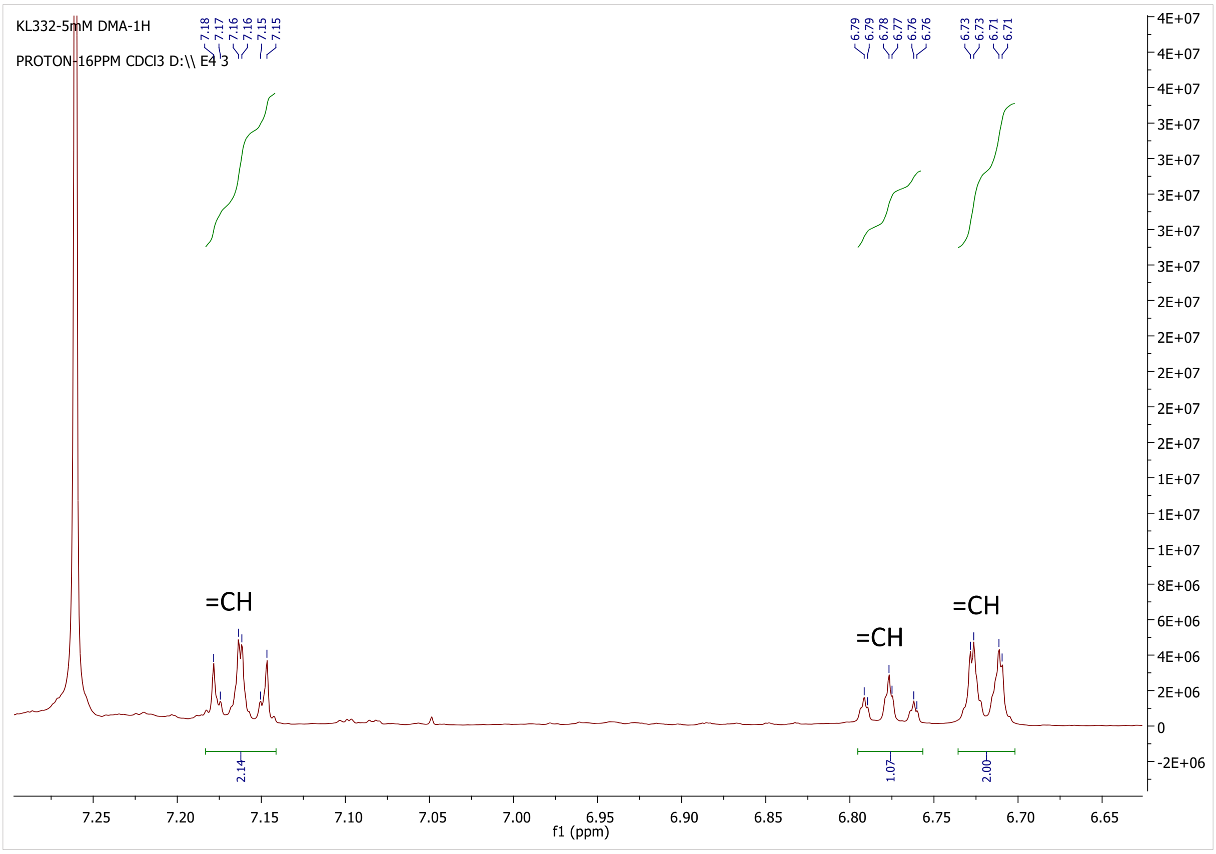


Fig.S26. *^{1}H NMR (500 MHz) of aniline from dealkylation of DMA under ultrasonic irradiation. Reaction conditions: 5 mM DMA in H_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL.*

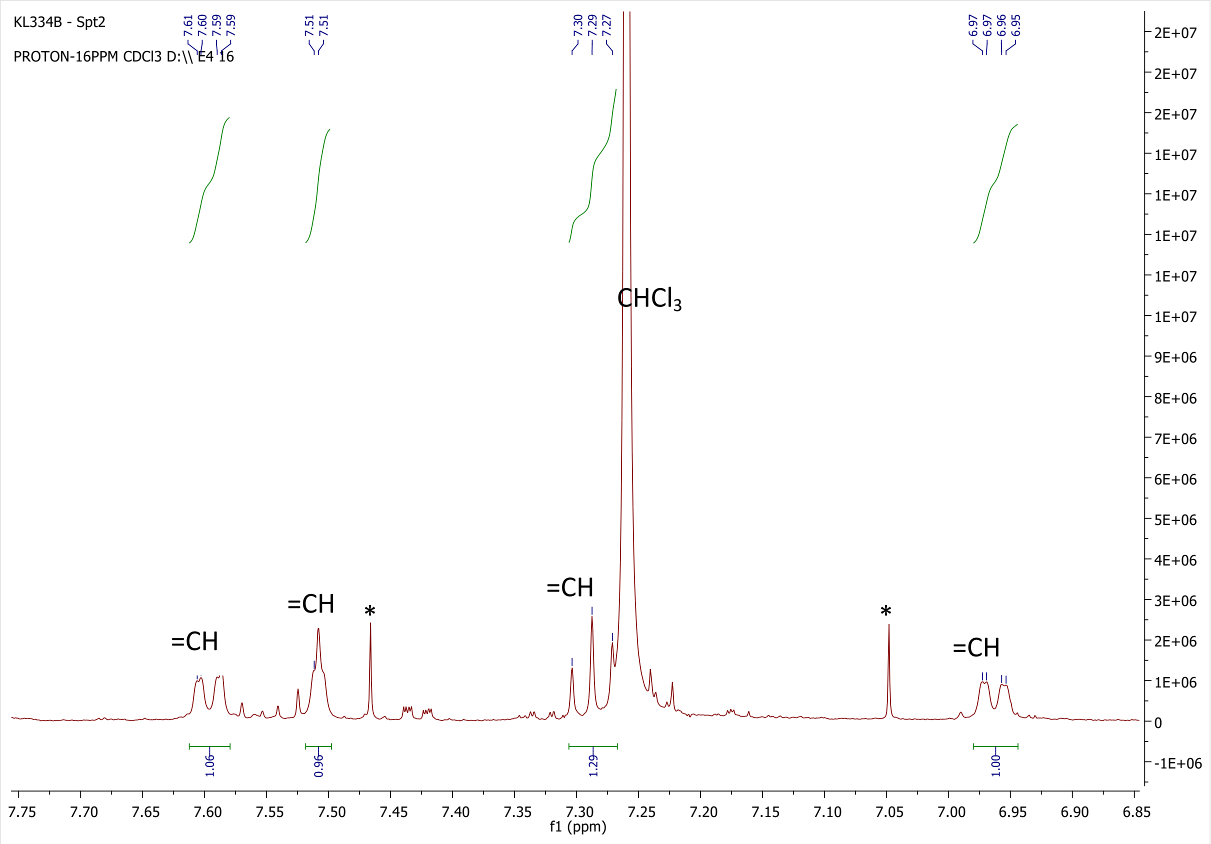


Fig.S27. *^{1}H NMR (500 MHz) of* 3-nitroaniline *from dealkylation of NO_2-DMA under ultrasonic irradiation. Reaction conditions: 5 mM DMA in H_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL. (* = satellite peaks of the $CHCl_3$ signal)*

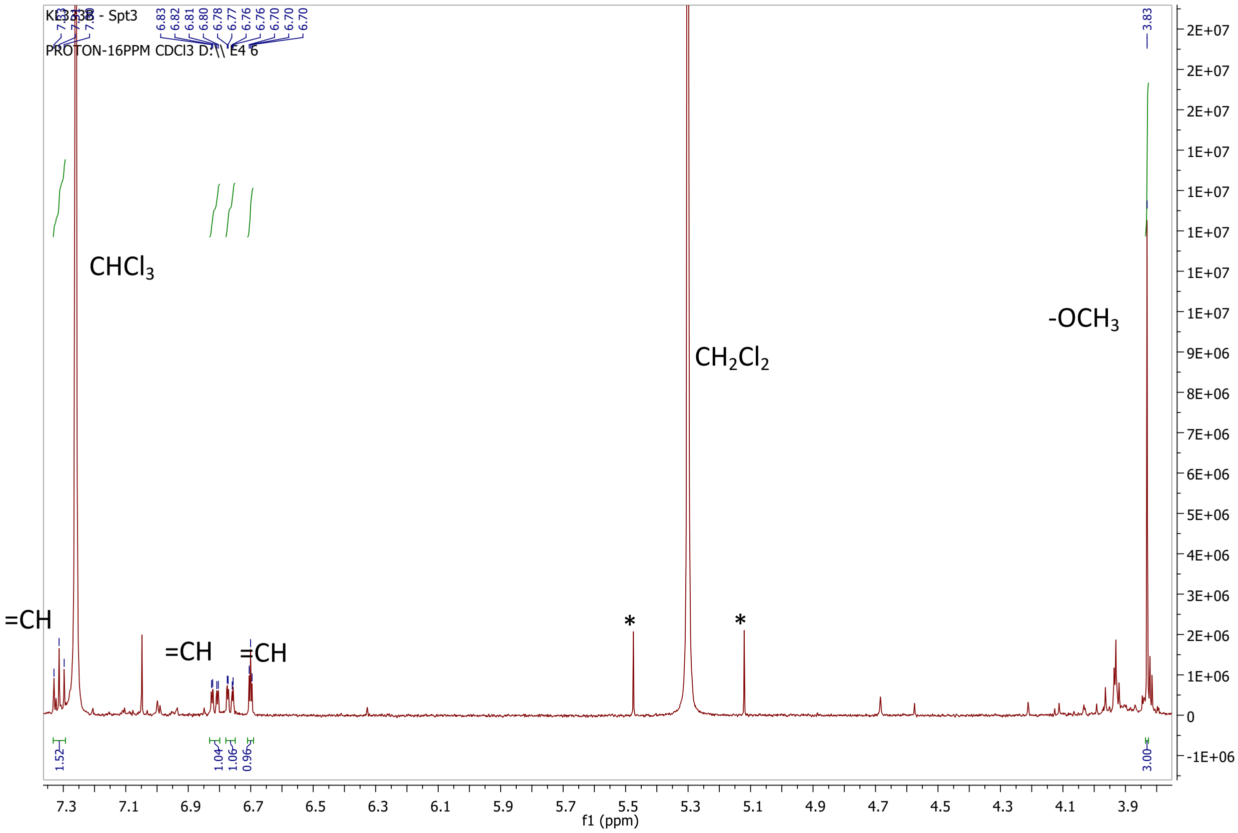


Fig.S28. *^{1}H NMR (500 MHz) of* 3-methoxyaniline *from dealkylation of MeO-DMA under ultrasonic irradiation. Reaction conditions: 5 mM DMA in H_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL. (* = satellite peaks)*

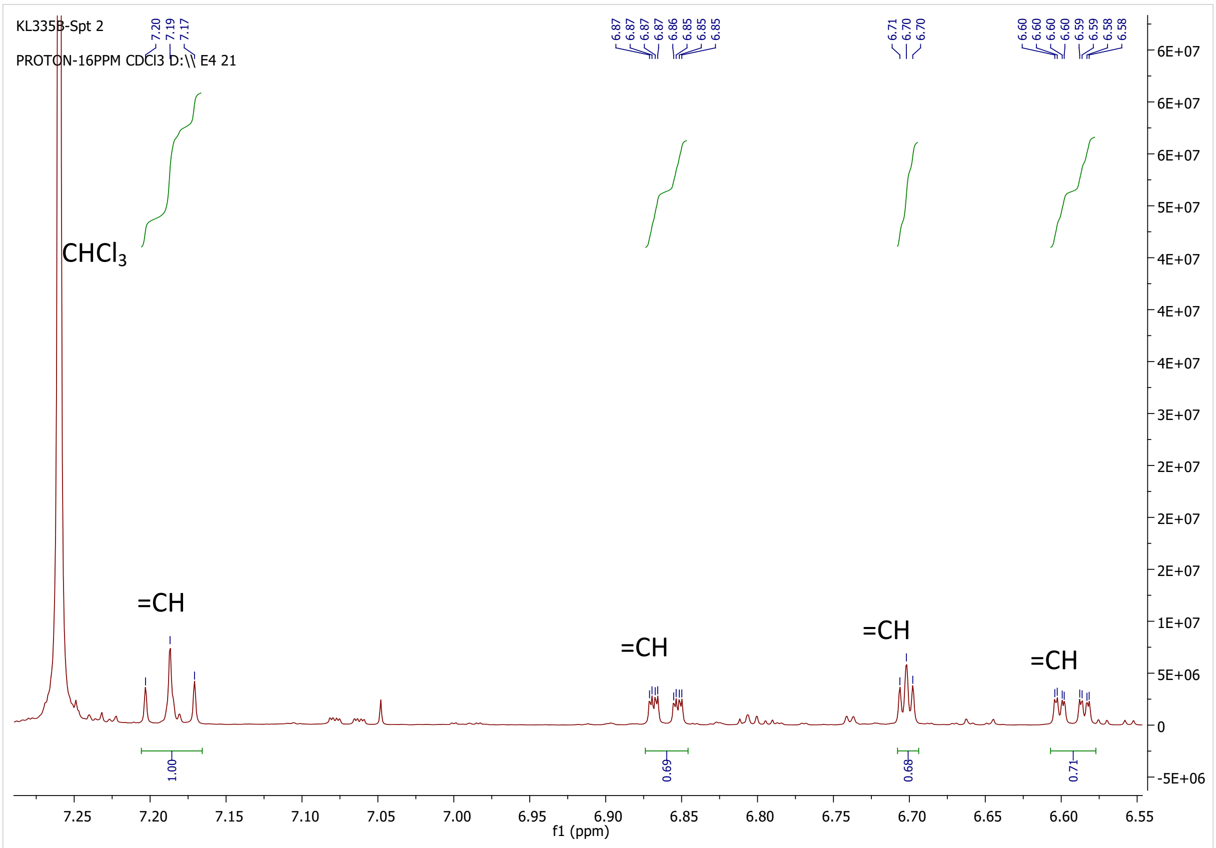


Fig.S29. *^{1}H NMR (500 MHz) of* 3-chloroaniline *from dealkylation of Cl-DMA under ultrasonic irradiation. Reaction conditions: 5 mM DMA in H_2O, 550 kHz, 20 mL/min Ar, 0.25 W/mL.*

Reference

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4. a) P. Roszkowska, A. Dickenson, J. E. Higham, T. L. Easun, J. L. Walsh, A. G. Slater, *Lab Chip*, 2023, **23**, 2720-2728; b) P. Roszkowska, A. M. Scholes, J. L. Walsh, T. L. Easun, A. G. Slater, *React. Chem. Eng*., 2024, **9**, 1896-1903.