Supplementary Information (SI) for Reaction Chemistry & Engineering.

Supplementary Information

A Waste-free Packed-bed Continuous-flow Synthesis of Disulfiram with a Composite Catalyst

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General Information

Reagents

Carbon disulfide (CAS 75-15-0) was purchased from Energy Chemical (99%). Diethylamine (CAS 109-89-7) was purchased from Aladdin (99%). Dimethylamine solution (CAS 124-40-3) was purchased from Sinopharm Chemical Reagent Co., Ltd (33% in H_2O). Tetraethylthiuram disulfide (CAS 97-77-8) was purchased from Aladdin (97%). Tetramethylthiuram disulfide (CAS 137-26-8) was purchased from Aladdin (97%). MoS_2 (CAS 1317-33-5) was purchased from Macklin (99.9%). $Ca(OH)_2$ (CAS 1305-62-0) was purchased from General-Reagent (AR, ≥95%). NaOH (1310-73-2) was purchased from General-Reagent (AR, ≥96.0%). Na_2WO_4 (13472-45-2) was purchased from Adamas-beta (98%). Na_2HPO_4 (7558-79-4) was purchased from General-Reagent (AR, ≥99%). Hydroxyapatite (HAP, CAS 1306-06-5) was purchased from Bide Pharmatech Co., Ltd. Styrene (CAS 100-42-5) was purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd. Ethanol (CAS 64-17-5) was purchased from Sinopharm Chemical Reagent Co., Ltd (AR, >99.7%). Acetonitrile (CAS 75-05-8) was purchased from Honeywell (HPLC grade, >99.9%). Silica gel (CAS 112926-00-8) was purchased from Sinopharm Chemical Reagent Co., Ltd. Chloroform-*d* (CAS 865-49-6) was purchased from Adamas-beta (D, 99.8%+TMS 0.03%). 1,3-Diphenylisobenzofuran (CAS 5471-63-6) was purchased from Bidepharm (98.48%).

Instruments

Magnetic stirrer (C-MAG HS 7) was manufactured by IKA®. Centrifuge (TGL-16G) was manufactured by Shanghai Anting Scientific Instrument Factory. Microchannel (material# PTFE, 1/16”) was manufactured by Zhejiang Jiari Fluoroplastic Co., Ltd. T-micromixer was manufactured by IDEX (model# CT-108, 1/16”). Packed-bed microreactor (4.6 mm I.D. × 150 mm) was purchased from Taobao. Back pressure regulator (model# P-786, 40 psi) was manufactured by IDEX. Syringe pump (model# TBP-5010) was manufactured by Baoding Longer Precision Pump Co., Ltd. Mass-flow controller (model# CS200-A) was manufactured by Beijing Sevenstar Electronics Co., Ltd. Rotary Evaporator (model# RE-207B) was manufactured by Nanjing Keer Instrument Equipment Co., Ltd.

Chromatography Conditions

HPLC analyses of batch reactions were performed on Wufeng LC 100 system and SHIMADZU LC-2050 system with SHISEIDO CAPCELL PAK ADME S5 column (S-5 μm, 100 Å, 4.6 mm I.D. × 150 mm), at a detection wavelength of 254 nm and a flow rate of 1 mL/min, with water (pH = 3, adjusted with formic acid, as phase A) and acetonitrile (as phase B) as the eluents. The isocratic eluents conditions were A: B = 1:9. Styrene was used as the internal standard since it has a similar molar extinction coefficient to TETD, and it is separable from TETD on a regular reverse-phase HPLC column.

HPLC analyses of flow reactions were performed on a SHIMADZU LC-2050 system with SHISEIDO CAPCELL PAK ADME S5 column (S-5 µm, 100 Å, 4.6 mm I.D. × 150 mm), at a detection wavelength of 254 nm and a flow rate of 1 mL/min, with water (pH = 3, adjusted with formic acid, as phase A) and acetonitrile (as phase B) as the eluents. The isocratic eluents conditions were A: B = 1:9. A set of five calibration standard solutions containing 0.001 equiv., 0.005 equiv., 0.01 equiv., 0.015 equiv. and 0.02 equiv. of TETD were prepared. The yields of TETD were determined by the external standard (calibration curve) method (Fig. S1).

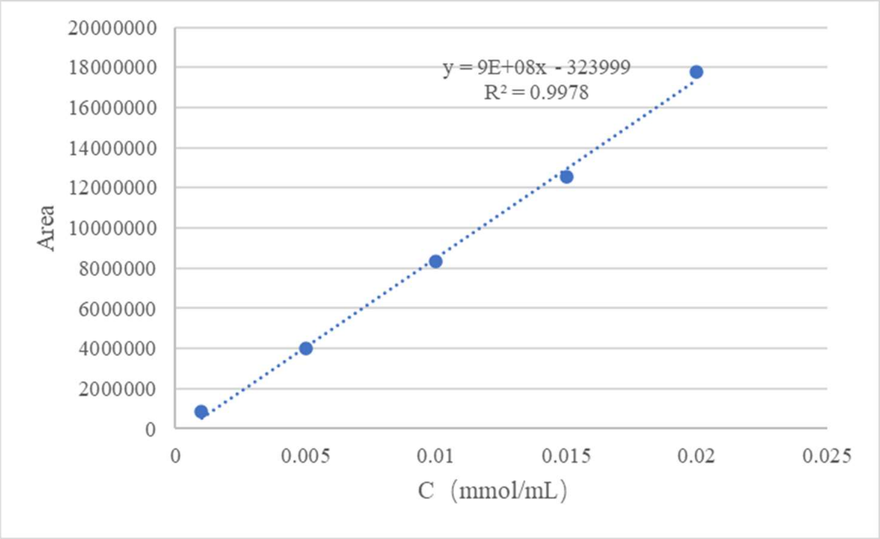


Fig. S1. Calibration curve for the quantification of TETD by UV-integrals.

XRD Analysis

The crystal structures of pristine and post-reaction samples were examined using X-ray diffraction (XRD) on a SHIMADZU XRD-6000 system (Cu Kα radiation, λ = 1.5406 Å), with data collected over a 2θ range of 5-90° at a scanning rate of 2°/min.

ICP-OES Analysis

The actual metal contents in the isolated product were measured by inductively coupled plasma optical emission spectrometry (ICP-OES), on a Thermo ICAP PRO system.

NMR Analysis

^{1}H NMR spectra were collected on 400 MHz NMR spectrometers (Bruker AVANCE III).^{13}C NMR spectra were collected on 101 MHz NMR spectrometers (Bruker AVANCE III). Chemical shifts for protons are reported in parts per million (ppm) downfield and are referenced to residual protium in the NMR solvent (δ $CDCl_3$ = 7.26). Data are presented as follows: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), coupling constants in Hertz (Hz), integration.

High-Resolution Mass-Spectroscopy (HRMS)

HRMS spectra were collected with the electrospray ionization (ESI) MS detection mode, on a SHIMADZU LCMS2020 system.

UV-Vis Analysis

UV-Vis spectroscopy was recorded on UV-Vis spectrometer (PerkinElmer LAMBDA750S) in 10 mm quartz cuvettes. Scan wavelength range was 300 to 700 nm.

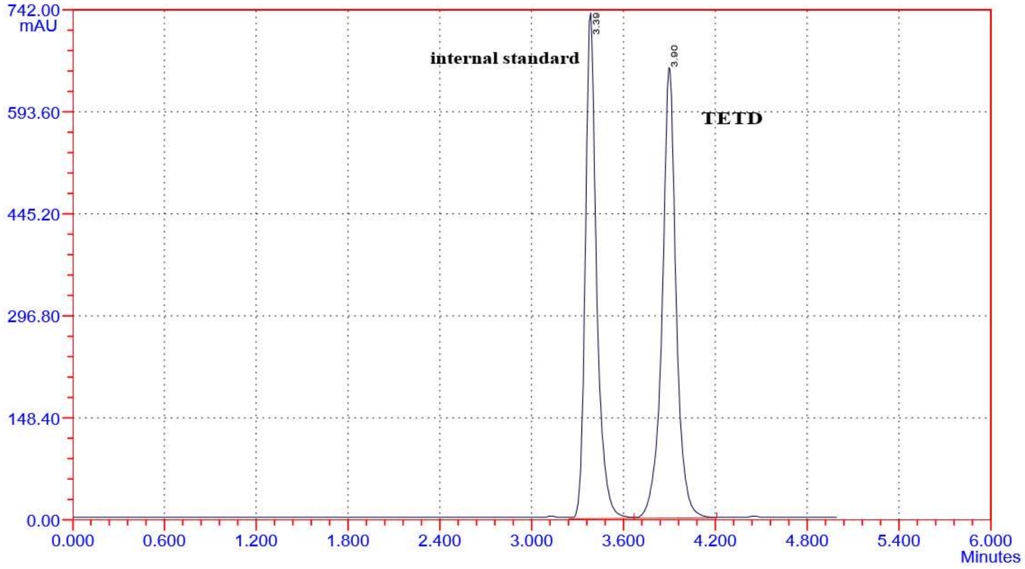
Batch Reaction Procedures

Procedure for the reaction with NaOH as the co-catalyst

Carbon disulfide (720 µL, 12 mmol), diethylamine (1040 µL, 10 mmol), MoS_2 (200 mg, 1.25 mmol) and NaOH (4 mg, 0.1 mmol) were added with ethanol (4 mL) in a round-bottom flask. An oxygen balloon was attached to the flask and the mixture was continuously stirred on a magnetic stirrer at room temperature for 14 h. The resulting mixture was centrifuged at 10000 rpm, and the supernatant (100 µL) was diluted with ethanol (1.50 mL) for HPLC analysis to determine the yield using external standard method.

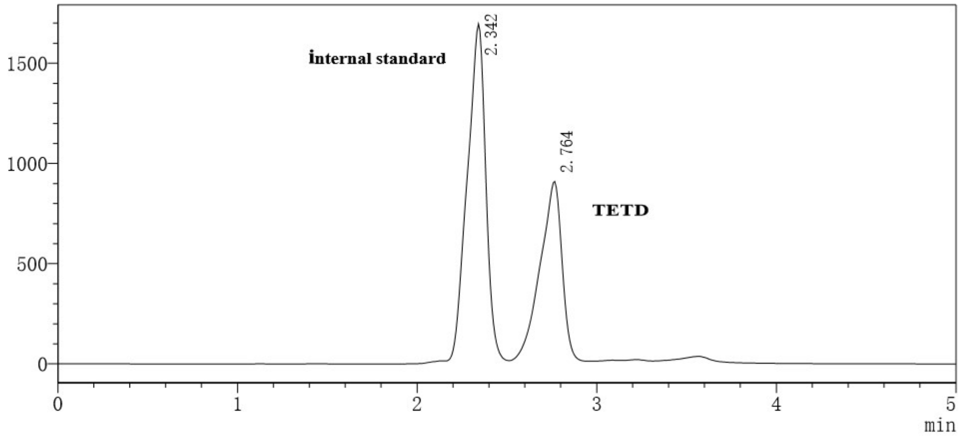
Procedure for screening solid base

Carbon disulfide (144 µL, 2.4 mmol), diethylamine (208 µL, 2.0 mmol), MoS_2 (40 mg, 0.25 mmol) and solid base were added with ethanol (4 mL) in a round-bottom flask. The investigated solid bases included $Ca(OH)_2$ (1.5 mg, 0.02 mmol), Na_2WO_4 (5.88 mg, 0.02 mmol), Na_2HPO_4 (2.84 mg, 0.02 mmol) and $Ca_{10}(PO4)_6(OH)_2$ (hydroxyapatite, 10.1 mg, 0.02 mmol). An oxygen balloon was attached to the flask and the mixture was continuously stirred on a magnetic stirrer at room temperature for 14 h. The resulting mixture was added styrene (internal standard, 1.0 mmol) and centrifuged at 10000 rpm. The supernatant (100 µL) was diluted with ethanol (1.50 mL) for HPLC analysis.



ID	Name	Retain.T	Height	Area	Conc	Tail.Factor	Theo.Plate
1		3.386	73620	378336.1	47.502	1.54	9790
2		3.896	65603	418127.5	52.498	1.12	8428
	Sum:		139223	796463.6	100.0000		

Fig. S2. HPLC trace of the experiment with $Ca(OH)_2$ as solid base.



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peak list
检测器A 254nm
peak number  retention time       area          height
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     2           2.764           8013203         910717
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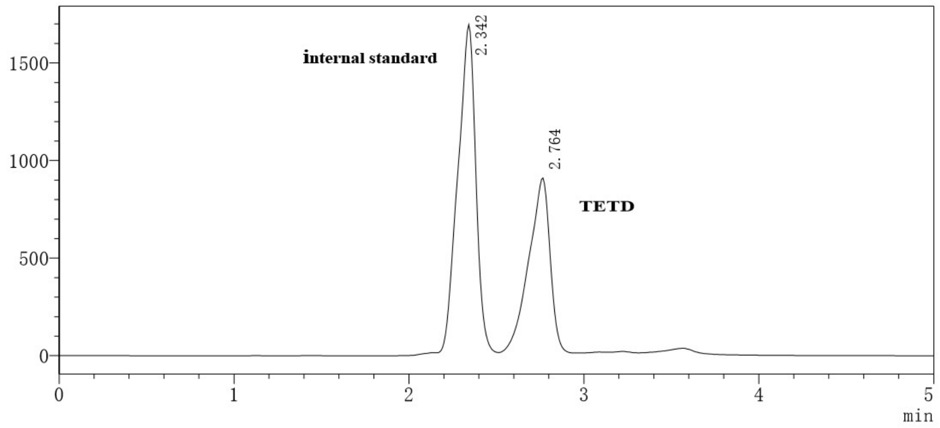
Fig. S3. HPLC trace of the experiment with Na_2WO_4 as solid base.



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peak list
检测器A 254nm
peak number  retention time        area            height
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      2             2.764          8013203          910717
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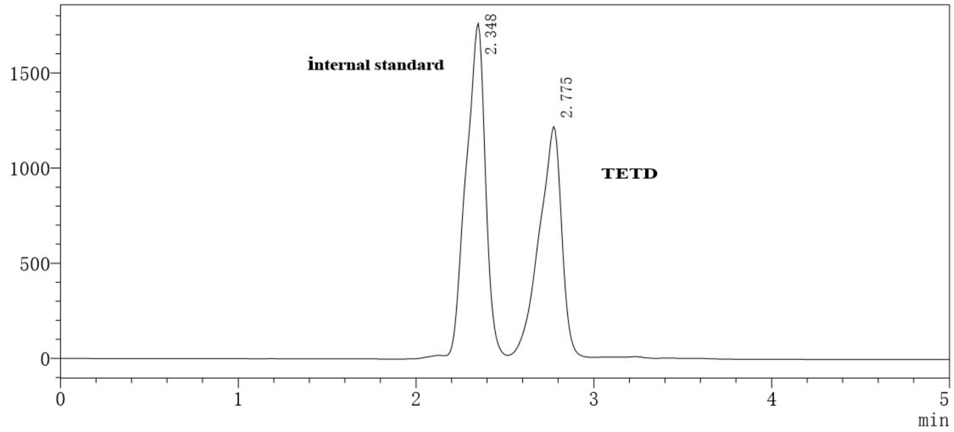
Fig. S4. HPLC trace of the experiment with Na_2HPO_4 as solid base.



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peak list
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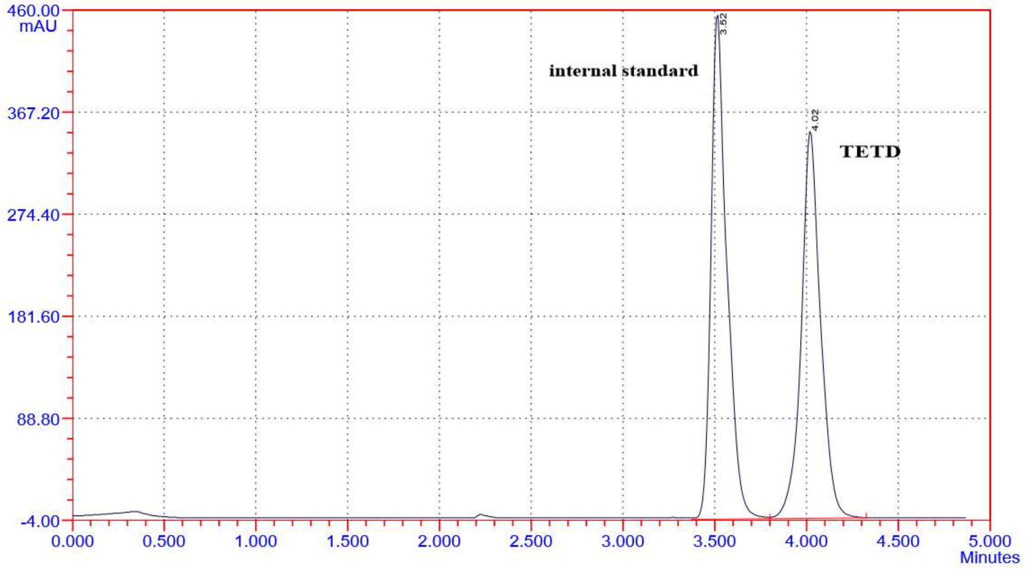
peak number  retention time        area            height
      1             2.348          13440985         1762527
      2             2.775          10972967         1221641
```

Fig. S5. HPLC trace of the experiment with hydroxyapatite as solid base.

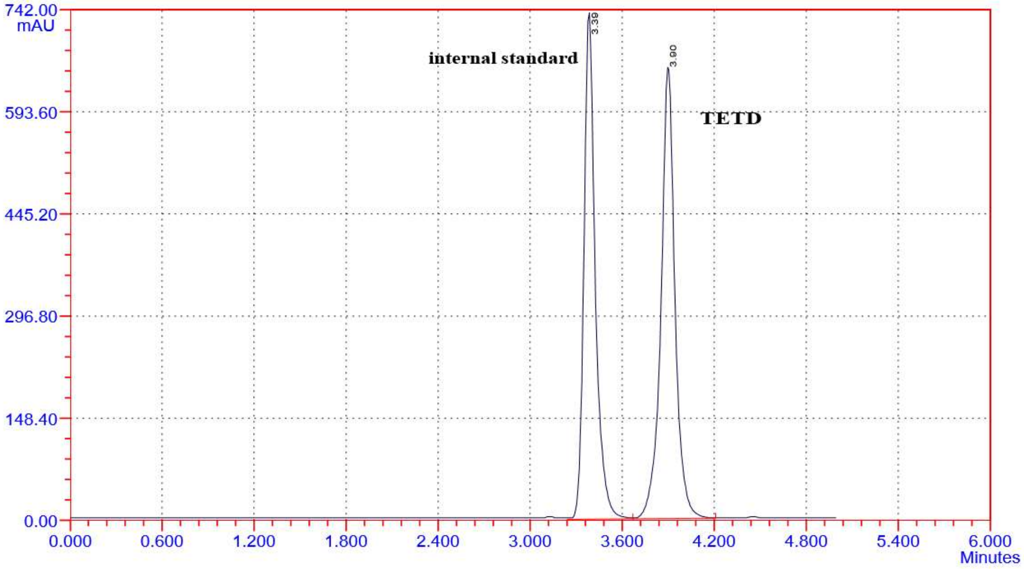
Procedure for exploring the loading amount of $Ca(OH)_2$

Carbon disulfide (144 μL, 2.4 mmol), diethylamine (208 μL, 2.0 mmol), MoS_2 (40 mg, 0.25 mmol) and a certain amount of $Ca(OH)_2$ were added with ethanol (4 mL) in a round-bottom flask. The following amounts of $Ca(OH)_2$ were tested: 0.005 equiv. (0.7 mg, 0.01 mmol), 0.01 equiv. (1.5 mg, 0.02 mmol), 0.02 equiv. (3.0 mg, 0.04 mmol) and 0.05 equiv. (7.4 mg, 0.1 mmol). An oxygen balloon was attached to each reaction flask and the mixture was continuously stirred on a magnetic stirrer at room temperature for 14 h. The resulting mixture was added styrene (internal standard, 1.0 mmol) and centrifuged at 10000 rpm. The supernatant (100 μL) was diluted with ethanol (1.50 mL) for HPLC analysis.



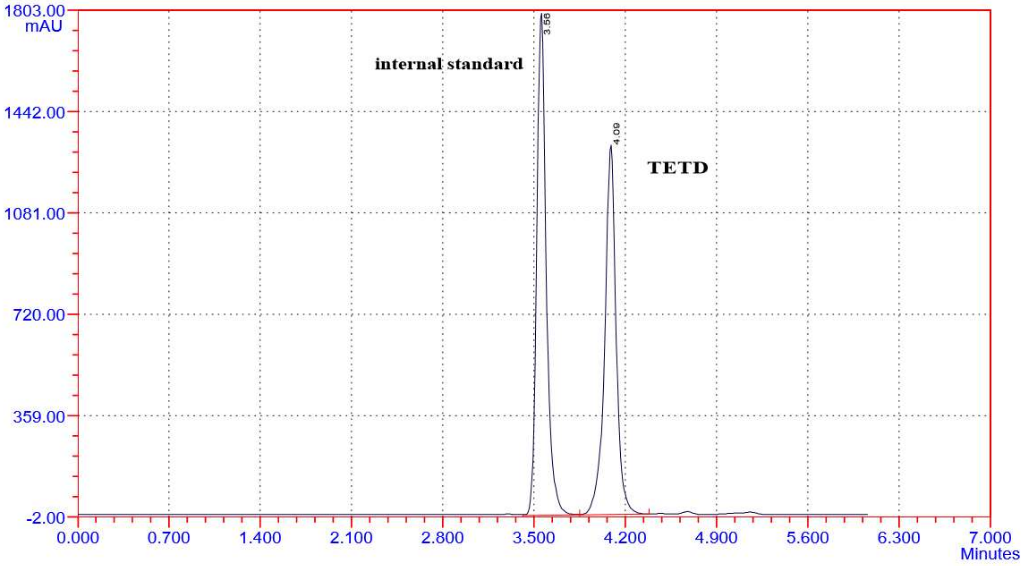
ID	Name	Retain.T	Height	Area	Conc	Tail.Factor	Theo.Plate
1		3.517	45819	275953.3	51.736	1.61	7694
2		4.018	35168	257432.0	48.264	1.13	6795
	Sum:		80987	533385.3	100.0000		

Fig. S6. HPLC trace of the experiment with 0.005 equiv. of $Ca(OH)_2$.



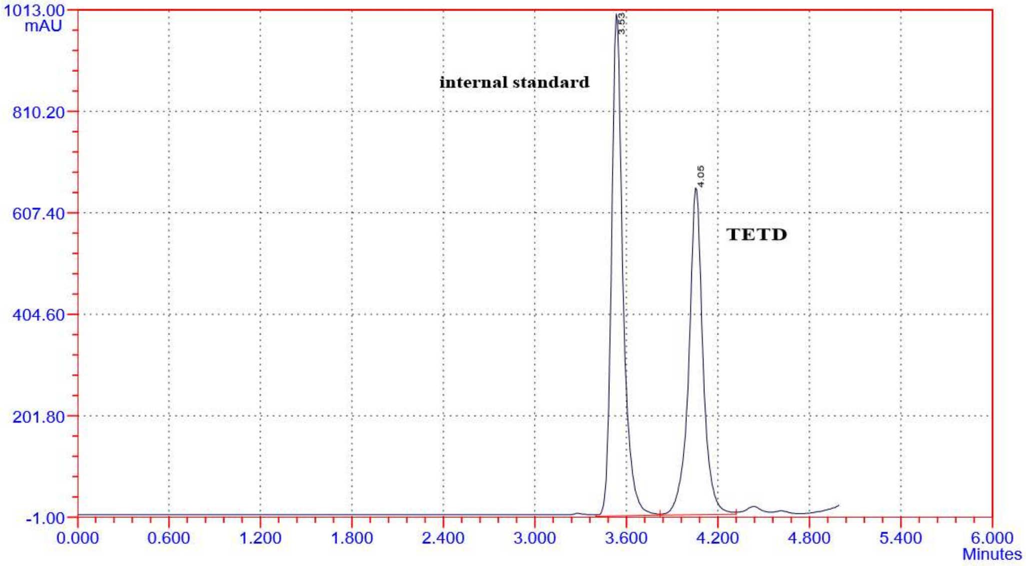
ID	Name	Retain.T	Height	Area	Conc	Tail.Factor	Theo.Plate
1		3.386	73620	378336.1	47.502	1.54	9790
2		3.896	65603	418127.5	52.498	1.12	8428
	Sum:		139223	796463.6	100.0000		

Fig. S7. HPLC trace of the experiment with 0.01 equiv. of $Ca(OH)_2$.



ID	Name	Retain.T	Height	Area	Conc	Tail.Factor	Theo.Plate
1		3.558	178815	916047.2	53.156	1.43	10878
2		4.091	131702	807284.8	46.844	1.04	10046
	Sum:		310517	1723331.9	100.0000		

Fig. S8. HPLC trace of the experiment with 0.02 equiv. of $Ca(OH)_2$.



ID	Name	Retain.T	Height	Area	Conc	Tail.Factor	Theo.Plate
1		3.533	100339	525373.4	55.268	1.72	9072
2		4.052	65361	425220.7	44.732	1.18	7733
	Sum:		165700	950594.1	100.0000		

Fig. S9. HPLC trace of the experiment with 0.05 equiv. of $Ca(OH)_2$.

Procedure for the experiment without a base

Carbon disulfide (144 μL, 2.4 mmol), diethylamine (208 μL, 2.0 mmol) and MoS_2 (40 mg, 0.25 mmol) were added with ethanol (4 mL) in a round-bottom flask. An oxygen balloon was attached to the flask and the mixture was continuously stirred on a magnetic stirrer at room temperature for 14 h. The resulting mixture was added styrene (internal standard, 1.0 mmol) and centrifuged at 10000 rpm. The supernatant (100 μL) was diluted with ethanol (1.50 mL) for HPLC analysis.

Procedure for the synthesis of tetramethylthiuram disulfide (TMTD)

Carbon disulfide (144 μL, 2.4 mmol), dimethylamine (307 μL, 2.0 mmol), MoS_2 (40 mg, 0.25 mmol) and $Ca(OH)_2$ (1.48 mg, 0.02 mmol) were added with ethanol (4 mL) in a round-bottom flask. An oxygen balloon was attached to the flask and the mixture was continuously stirred on a magnetic stirrer at room temperature for 14 h. The styrene (1.0 mmol) was added to supernatant as internal standard for HPLC analysis after the resulting mixture was diluted with acetonitrile and centrifuged at 10000 rpm.

Scale-up experiment for the synthesis of tetramethylthiuram disulfide (TMTD)

Carbon disulfide (1440 μL, 24 mmol), dimethylamine (3070 μL, 20 mmol), MoS_2 (400 mg, 2.5 mmol) and $Ca(OH)_2$ (14.8 mg, 0.2 mmol) were added with ethanol (40 mL) in a round-bottom flask. An oxygen balloon was attached to the flask and the mixture was continuously stirred on a magnetic stirrer at room temperature for 14 h. Upon completion of the reaction, the resulting mixture was diluted with acetonitrile and filtered to remove the solid catalyst MoS_2 and co-catalyst $Ca(OH)_2$. The filtrates were evaporated and cold crystallized using ethanol. TMTD was isolated with a yield of 57.5% (1.38 g). The product was confirmed by NMR and HRMS analyses. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): δ 3.62 (d, *J* = 11.1 Hz, 12H). **^{13}C NMR** (110 MHz, $CDCl_3$) δ (ppm): δ 193.73, 47.55, 42.08. **HRMS**: calculated for $C_6H_{12}N_2S_4^+$ ($[M+H]^+$) = 240.9956, found 240.9960. The actual metal contents in the isolated TMTD were determined by ICP analyses (see further to the below). The metal contents of Mo and Ca in TMTD were both higher than those of TETD because the latter was synthesized with a packed-bed reactor designed to prevent catalyst leaching (see the following section).

Flow Reaction Procedures

Preparation of the packed-bed reactor

A 4.6 mm × 150 mm stainless column filled with a mixture of MoS_2 and $Ca(OH)_2$ powder in a weight ratio of 27:1 was used as a packed-bed reactor. Importantly, this mixture must be thoroughly grinded in a ceramic mortar before filling up the reactor. In addition, a thin pad of silica gel (300 mg) was filled at the outlet end of the column to prevent catalyst leaching, with cotton wool sealing both column ends.

The porosity and liquid hold-up of the micro-packed bed were calculated as follows:

$$\varepsilon = 1 - \frac{V_{soild}}{V_{total}} \ldots\ldots(1)$$

$$V_{soild} = \frac{m_{soild}}{p_{soild}} \ldots\ldots(2)$$

Porosity: $$\varepsilon = 1 - \frac{\frac{2.4g}{4.8g \cdot cm^{-3}}}{\pi \cdot (2.3mm)^2 \cdot 150mm} = 0.80$$

Liquid hold-up: $$V_{liquid} = \varepsilon \cdot V_{total} = 0.8 \cdot 2.5cm^3 = 2cm^3$$

Procedure for the flow experiment at room temperature

Carbon disulfide (1.8 mL, 30 mmol), diethylamine (2.6 mL, 25 mmol) were mixed in ethanol (50 mL). The packed-bed (4.6 × 150 mm) was filled with 2.4 g MoS_2 and $Ca(OH)_2$. The solution-phase reactant was introduced into the T-mixer by a syringe pump at a flow rate of 0.1 mL/min, while molecular oxygen was introduced to the reactor via a mass flow controller (MFC). An intermittent flow with a gas-liquid volume ratio of 2:1 was formed, and flowed into the packed-bed microreactor at room temperature. The reaction mixture resided in the microflow reactor for about 20 minutes, and flowed to the collection tank through a 40 psi back-pressure regulator (BPR). The pressure of the entire reactor system was maintained at approximately 0.8 MPa. After 40 min of run (2 residence times) when the steady state was reached, the reaction mixture was collected every 10 min interval which corresponds to 1.0 mL of solution. A small fraction (200 μL) of each sample was withdrawn and diluted to 4 mL with ethanol for HPLC analysis using external standard method.

Procedure for exploring the temperature effect

Carbon disulfide (1.8 mL, 30 mmol), diethylamine (2.6 mL, 25 mmol) were mixed in ethanol (50 mL). The packed-bed (4.6 × 150 mm) was filled with 2.4 g MoS_2 and $Ca(OH)_2$. The solution-phase reactant was introduced into the T-mixer by a syringe pump at a flow rate of 0.1 mL/min, while molecular oxygen was introduced in the reactor via a mass-flow controller (MFC). An intermittent flow with a gas-liquid volume ratio of 2:1 was formed, and flowed into the packed-bed microreactor. The reaction mixture resided in the microflow reactor for about 20 minutes, and flowed to the collection tank through a 40 psi back-pressure regulator (BPR). The pressure of the entire reactor system was maintained at approximately 0.8 MPa. Besides, the thermostatic water bath containing the packed-bed microreactor, BPR and the collection tank was used to avoid clogging. The temperature of water bath was adjusted to 35, 45, 55 and 65 °C. After 40 min of run (2 residence times) when the steady state was reached, the reaction mixture was collected every half-hour interval, which corresponds to 3.0 mL of solution. A small fraction (200 μL) of each sample was withdrawn and diluted to 4 mL with ethanol for HPLC analysis using external standard method.

Procedure for exploring the retention time effect

Carbon disulfide (1.8 mL, 30 mmol), diethylamine (2.6 mL, 25 mmol) were mixed in ethanol (50 mL). The packed-bed (4.6 × 150 mm) was filled with 2.4 g MoS_2 and $Ca(OH)_2$. The solution-phase reactant was introduced into the T-mixer by a syringe pump at a fixed flow rate, while molecular oxygen was introduced in the reactor via a mass-flow controller (MFC). An intermittent flow with a gas-liquid volume ratio of 2:1 was formed, and flowed into the packed-bed microreactor. The reaction mixture resided in the microflow reactor for a period of time, and flowed to the collection tank through a 40 psi back-pressure regulator (BPR). The pressure of the entire reactor system was maintained at approximately 0.8 MPa. Besides, the packed-bed microreactor, BPR and the collection tank were immersed in a thermostatic water bath at 45 °C. Flow rates at 0.10, 0.15, 0.20, 0.25 and 0.30 mL/min were adjusted to test different residence times. After the steady state was reached (2 residence times), the reaction mixture was collected at a time interval that corresponds to 3.0 mL of solution. A small fraction (200 μL) of each sample was withdrawn and diluted to 4 mL with ethanol for HPLC analysis using external standard method.

Procedure for exploring the catalyst loading

Carbon disulfide (1.8 mL, 30 mmol), diethylamine (2.6 mL, 25 mmol) were mixed in ethanol (50 mL). The packed-bed (4.6 × 150 mm) was filled with varying loadings of MoS_2 and $Ca(OH)_2$ which was adjusted to 1.2 g, 1.8 g and 2.4 g. The solution-phase reactant was introduced into the T-mixer by a syringe pump at a flow rate of 0.1 mL/min, while molecular oxygen was introduced in the reactor via a mass-flow controller (MFC). An intermittent flow with a gas-liquid volume ratio of 2:1 was formed, and flowed into the packed-bed microreactor. The reaction mixture resided in the microflow reactor for a period of time, and flowed to the collection tank through a 40 psi back-pressure regulator (BPR). The pressure of the entire reactor system was maintained at approximately 0.8 MPa. Besides, the packed-bed microreactor, BPR and the collection tank were immersed in a thermostatic water bath at 45 °C. Flow rates at 0.1 mL/min After the steady state was reached (2 residence times), the reaction mixture was collected at a time interval that corresponds to 3.0 mL of solution. A small fraction (200 μL) of each sample was withdrawn and diluted to 4 mL with ethanol for HPLC analysis using external standard method.

Procedure for exploring the molar ratios of CS_2/Et_2NH and reactant concentrations

A certain amount of carbon disulfide and diethylamine were mixed in ethanol (50 mL). The following amounts of CS_2/Et_2NH were tested: 1.8 mL (30 mmol)/ 2.6 mL (25 mmol), 1.5 mL (25 mmol)/ 3.125 mL (30 mmol), 1.5 mL (25 mmol) / 2.6 mL (25 mmol), 3.6 mL (60 mmol)/ 5.2 mL (50 mmol), 0.9 mL (15 mmol)/ 1.3 mL (12.5 mmol). The packed-bed (4.6 × 150 mm) was filled with 2.4 g MoS_2 and $Ca(OH)_2$ The solution-phase reactant was introduced into the T-mixer by a syringe pump at a flow rate of 0.1 mL/min, while molecular oxygen was introduced in the reactor via a mass-flow controller (MFC). An intermittent flow with a gas-liquid volume ratio of 2:1 was formed, and flowed into the packed-bed microreactor. The reaction mixture resided in the microflow reactor for a period of time, and flowed to the collection tank through a 40 psi back-pressure regulator (BPR). The pressure of the entire reactor system was maintained at approximately 0.8 MPa. Besides, the packed-bed microreactor, BPR and the collection tank were immersed in a thermostatic water bath at 45 °C. Flow rates at 0.1 mL/min After the steady state was reached (2 residence times), the reaction mixture was collected at a time interval that corresponds to 3.0 mL of solution. A small fraction (200 μL) of each sample was withdrawn and diluted to 4 mL with ethanol for HPLC analysis using external standard method.

Scale-up experiment for the synthesis of tetraethylthiuram disulfide (TETD) under the optimized conditions in flow

Carbon disulfide (1.8 mL, 30 mmol), diethylamine (2.6 mL, 25 mmol) were mixed in ethanol (50 mL). The packed-bed (4.6 × 150 mm) was filled with 2.4 g MoS_2 and $Ca(OH)_2$. The solution-phase reactant was introduced into the T-mixer by a syringe pump at a flow rate of 0.1 mL/min, while molecular oxygen was introduced in the reactor via a mass-flow controller (MFC). An intermittent flow with a gas-liquid volume ratio of 2:1 was formed, and flowed into the packed-bed microreactor. The reaction mixture resided in the microflow reactor for about 20 minutes, and flowed to the collection tank through a 40 psi back-pressure regulator (BPR). The pressure of the entire reactor system was maintained at approximately 0.8 MPa. Besides, a 45 °C thermostatic water bath containing the packed-bed microreactor, BPR and the collection tank was used to avoid clogging. The resulting mixture was collected at the downstream for a 7 hours period, with 60 minutes between samplings. Upon completion of the reaction, 36 mL of the resulting mixture was collected. A small fraction (200 μL) of resulting mixture was withdrawn and diluted to 4 mL with ethanol for HPLC analysis using external standard method. TETD was isolated by cold crystallization and filtration, followed by drying for 30 min at 50 °C, with an isolated yield of 86.4% (2.12 g). The product was analyzed by NMR and HRMS. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): δ 4.03 (s, 8H), 1.48 (m, 6H), 1.38–1.19 (m, 6H). **^{13}C NMR** (110 MHz, $CDCl_3$) δ (ppm): δ 192.71, 52.04, 47.62, 13.50, 11.47. **HRMS**: calculated for $C_{10}H_{21}N_2S_4^+$ ($[M+H]^+$) = 297.0583, found 297.0573. The metal contents in product were determined by ICP analyses (see below).

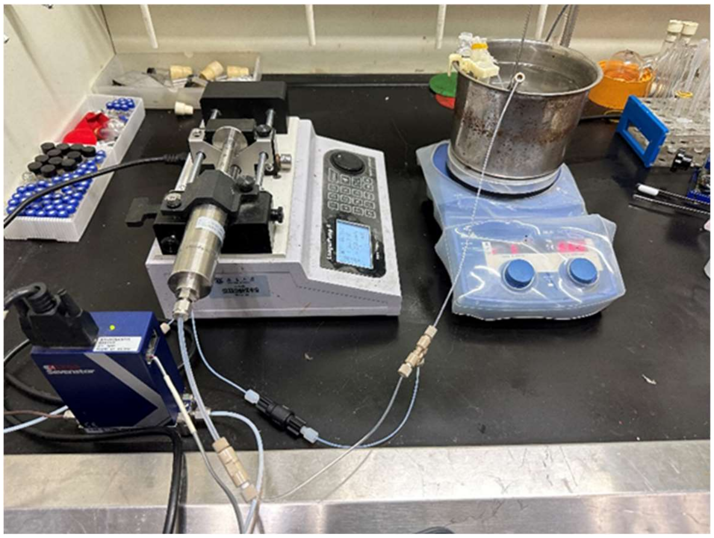


Fig. S10. Synthesis of TETD with a packed-bed microflow reactor

Procedure for the ROS (reactive oxygen species) trapping experiment

MoS_2 (40 mg, 0.25 mmol), 1,3-diphenylisobenzofuran (16.9 mg, 0.0625 mmol) and ethanol (4 mL) were stirred under O_2 atmosphere at room temperature for 14 h. A small solution (10 μL) before reaction was taken and analyzed for UV-Vis. The resulting mixture after reaction was centrifuged and the supernatant (10 μL) liquid was analyzed for UV-Vis. The UV-Vis absorbance of DFBF decreased sharply from 2.96 to 0.054 at 410 nm (DW=1.00 nm).

Economic evaluation of material costs

From an economic perspective, the market prices of all materials were evaluated (Table S1), confirming that the process remains economically viable within higher local catalyst/substrate ratio.

Table S1. Economic evaluation of material costs

Materials	Purity	Costs (\$/t)
CS_2	>99%	688.6
Et_2NH	>99%	1652.7
EtOH (anhydrous)	>99.7%	826.4
O_2	≥99.5%	59.2
MoS_2	>98.5%	7574.9
$Ca(OH)_2$	>90%	89.5
TETD	>98%	3167.7

XRD analysis of pristine and post-reaction samples

XRD analysis confirmed that the MoS_2 catalyst maintained its structural integrity after the prolonged reaction, as evidenced by the unchanged diffraction peak positions. This indicates robust stability of the catalyst, suggesting no phase transformation or significant degradation occurred under the reaction conditions (see Figure 4). Furthermore, the sharp diffraction peaks, particularly the characteristic (002) peak at 14.4° (Cu Kα, $\lambda = 1.5406$ Å), confirm the well-ordered crystalline structure and characteristic interlayer stacking along the c-axis in the hexagonal 2H phase.

ICP Analysis

To determine the degree of catalyst leaching, Fig. S11 present the dissolved the Ca and Mo in the solution in the absence of silica gel measured by inductively coupled plasma optical emission spectrometry (ICP-OES) during a 7-hours stability test. In the initial stage (0-1 h), a release of Ca and Mo was detected. Over the subsequent 2 to 7 hours, the dissolution rate of these elements gradually declined, aligning with the stabilization of performance observed throughout the 7-hours duration. It is worth noting the yield of TETD showed a moderate decrease (from 92% to 70%) in the absence of silica gel (Table S2), suggesting that silica gel plays a key role in preventing catalyst leaching and preserving reaction efficiency.

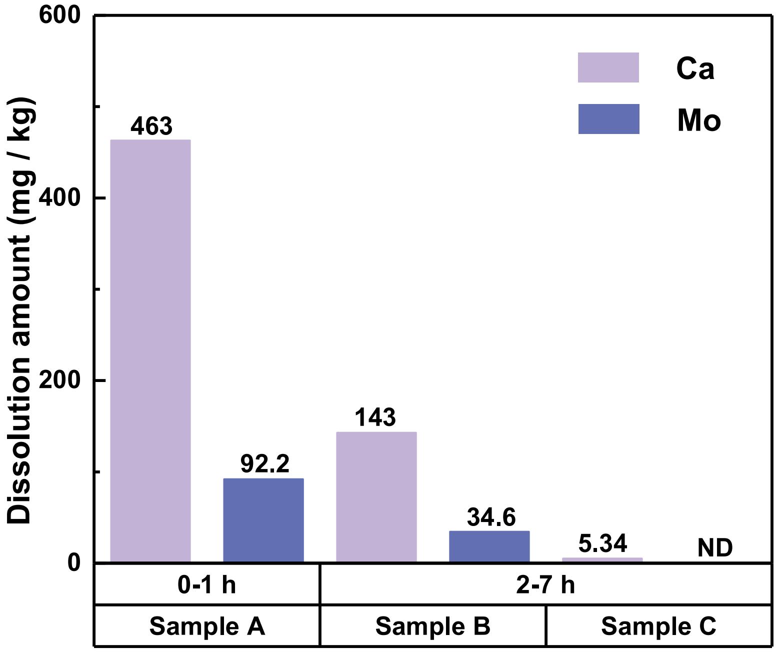
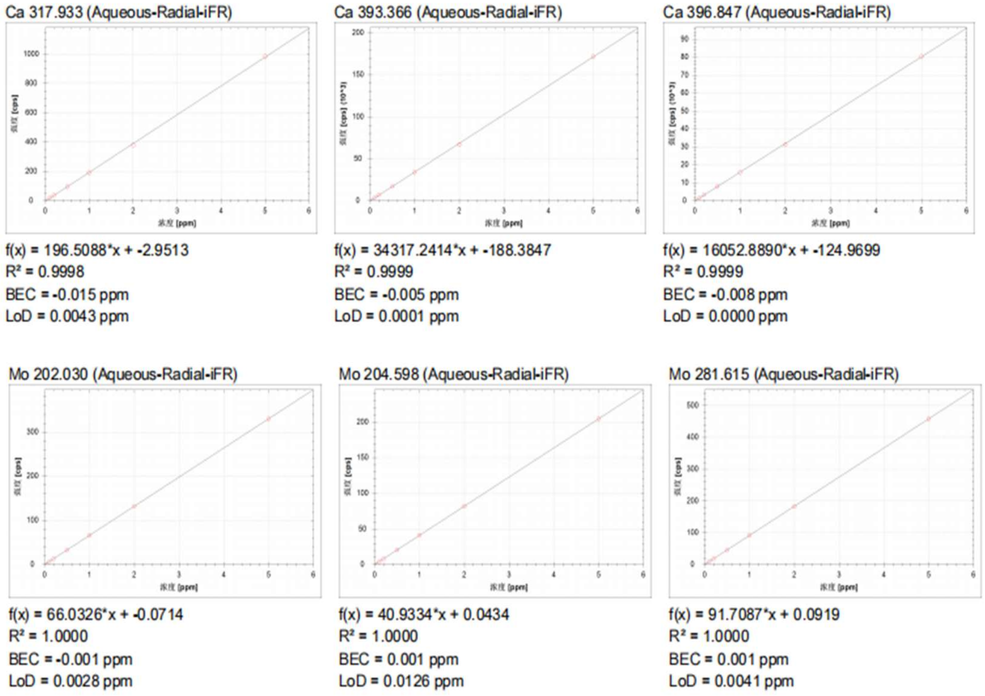


Fig. S11. ICP-OES results of dissolved Ca and Mo ions concentrations from scaled-up reaction over a 7 hours period. The denominator in the calculation is based on the mass of the total mass of the reaction mixture. Sample A: ICP Analysis of solution in the absence of silica gel from 0 to 1 h. Sample B: ICP Analysis of solution in the absence of silica gel from 2 to 7 h. Sample C: ICP Analysis of isolated product in the presence of silica gel from 2 to 7 h.

Table S2. HPLC yields of TETD under different conditions

	Sample A	Sample B	Sample C
Average yield by (%, by HPLC)	71.9	70.2	92.1

(a)



f(x) = 196.5088*x + -2.9513
R² = 0.9998
BEC = -0.015 ppm
LoD = 0.0043 ppm

f(x) = 34317.2414*x + -188.3847
R² = 0.9999
BEC = -0.005 ppm
LoD = 0.0001 ppm

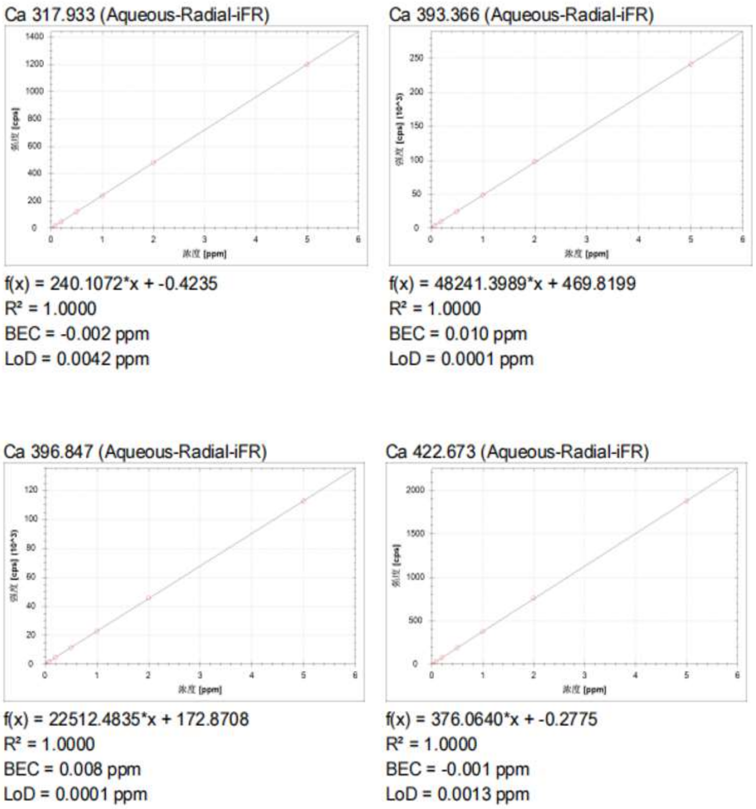
f(x) = 16052.8890*x + -124.9699
R² = 0.9999
BEC = -0.008 ppm
LoD = 0.0000 ppm

f(x) = 66.0326*x + -0.0714
R² = 1.0000
BEC = -0.001 ppm
LoD = 0.0028 ppm

f(x) = 40.9334*x + 0.0434
R² = 1.0000
BEC = 0.001 ppm
LoD = 0.0126 ppm

f(x) = 91.7087*x + 0.0919
R² = 1.0000
BEC = 0.001 ppm
LoD = 0.0041 ppm

(b)

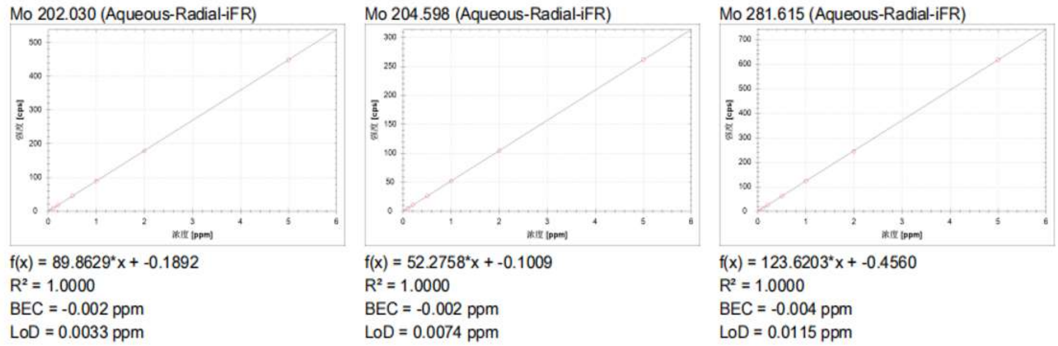


f(x) = 240.1072*x + -0.4235
R² = 1.0000
BEC = -0.002 ppm
LoD = 0.0042 ppm

f(x) = 48241.3989*x + 469.8199
R² = 1.0000
BEC = 0.010 ppm
LoD = 0.0001 ppm

f(x) = 22512.4835*x + 172.8708
R² = 1.0000
BEC = 0.008 ppm
LoD = 0.0001 ppm

f(x) = 376.0640*x + -0.2775
R² = 1.0000
BEC = -0.001 ppm
LoD = 0.0013 ppm



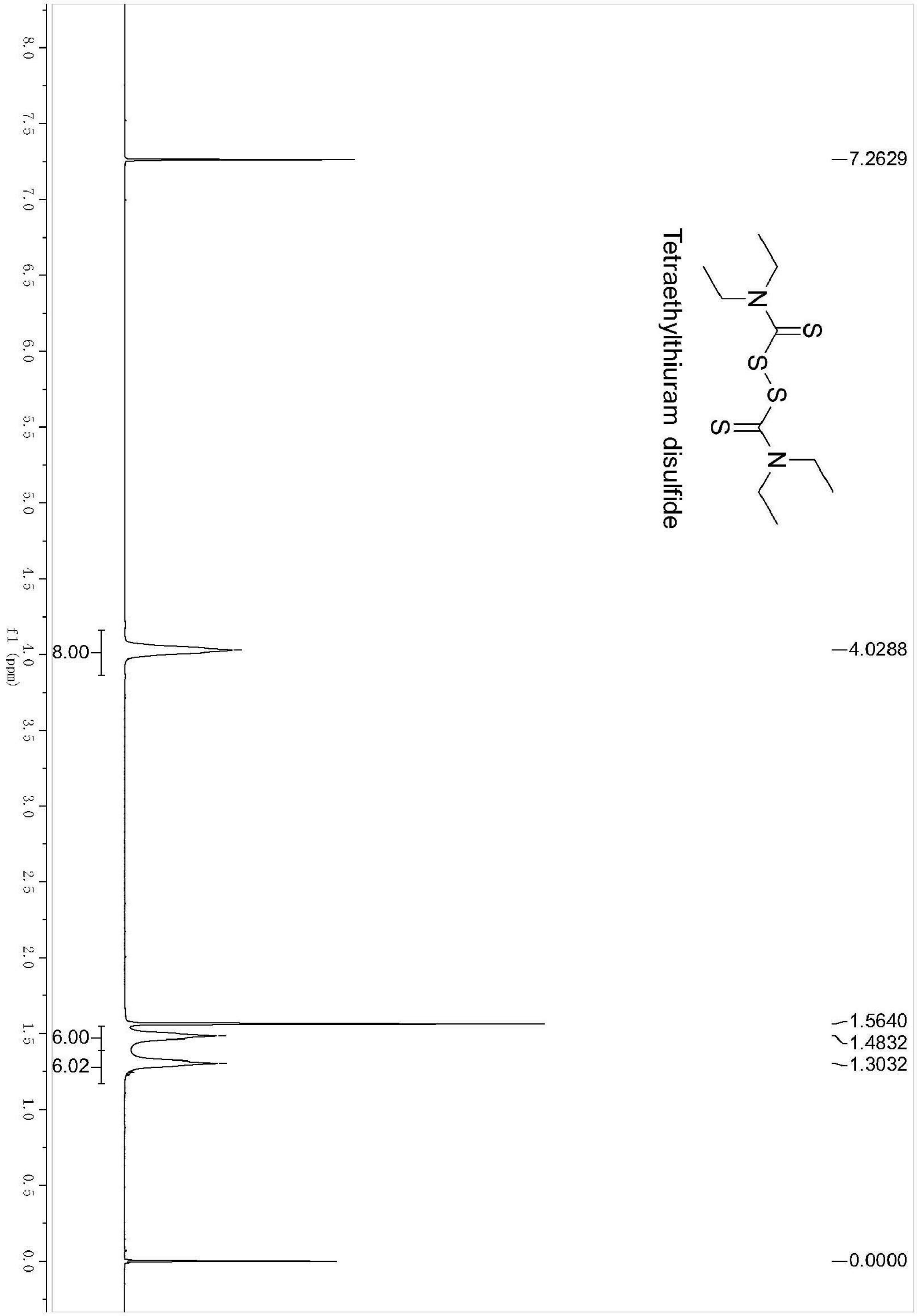
f(x) = 89.8629*x + -0.1892
R² = 1.0000
BEC = -0.002 ppm
LoD = 0.0033 ppm

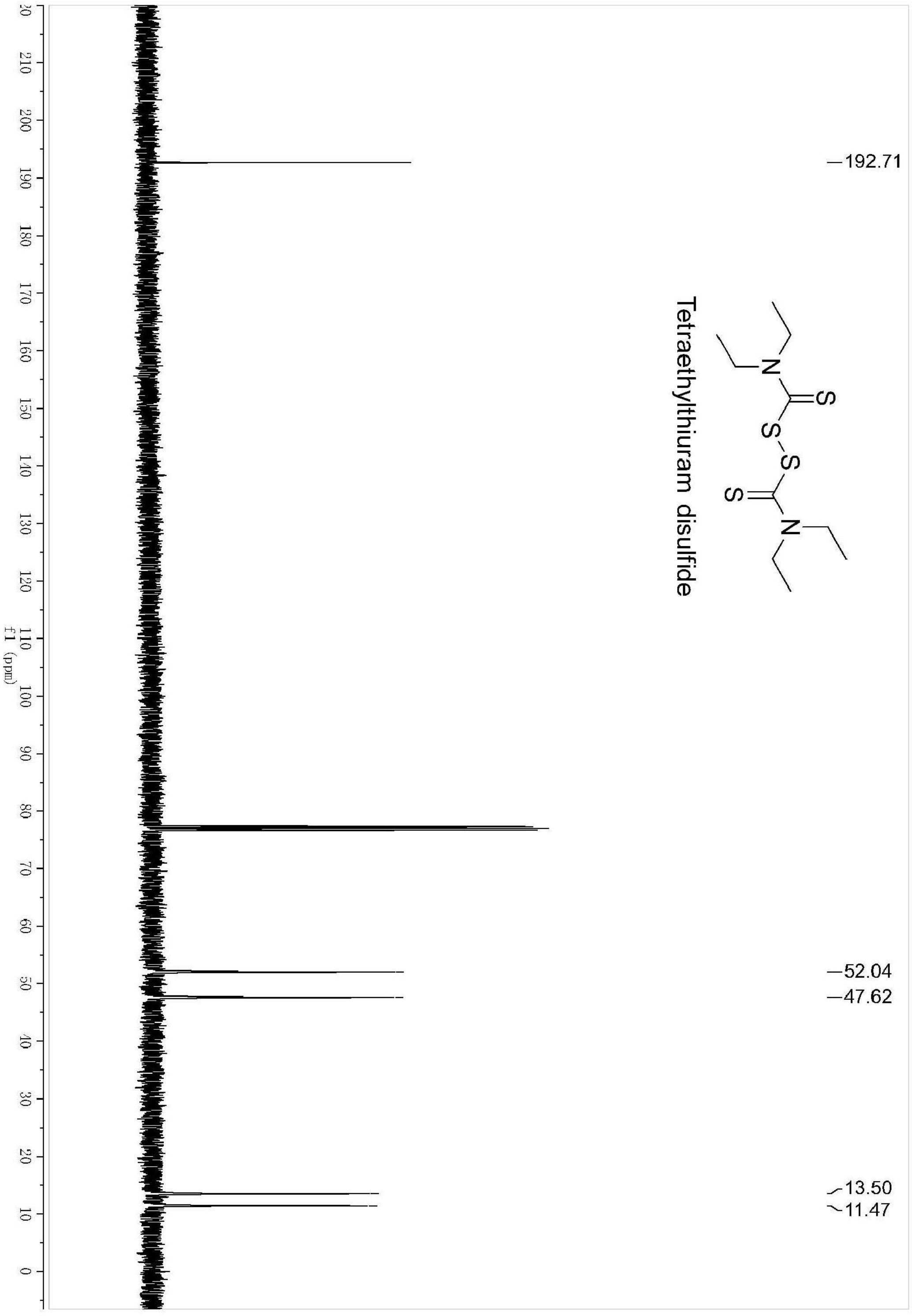
f(x) = 52.2758*x + -0.1009
R² = 1.0000
BEC = -0.002 ppm
LoD = 0.0074 ppm

f(x) = 123.6203*x + -0.4560
R² = 1.0000
BEC = -0.004 ppm
LoD = 0.0115 ppm

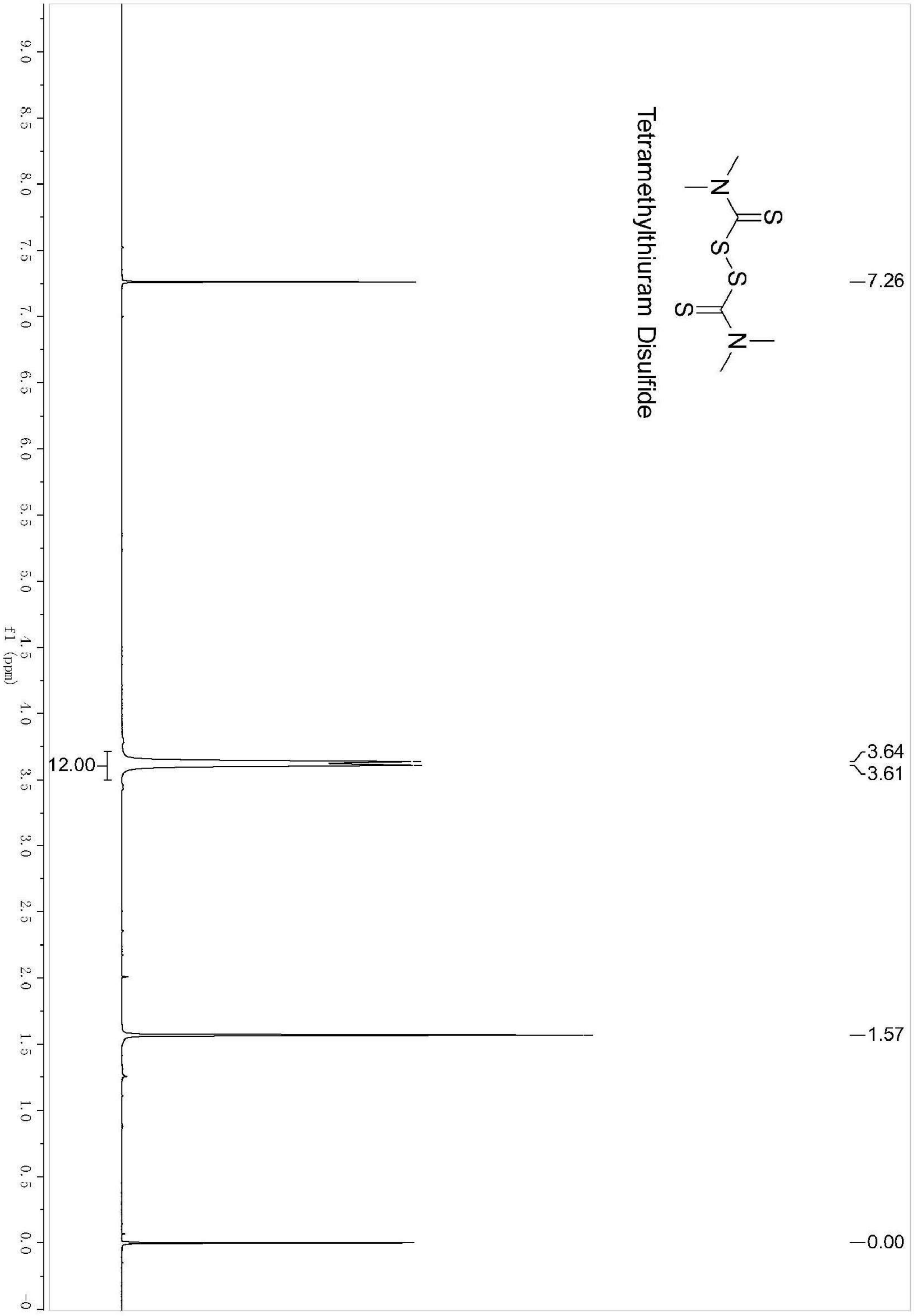
Fig.S12. ICP analyses of Mo and Ca with calibration curves. (a) Sample A and Sample B. (b) Sample C.

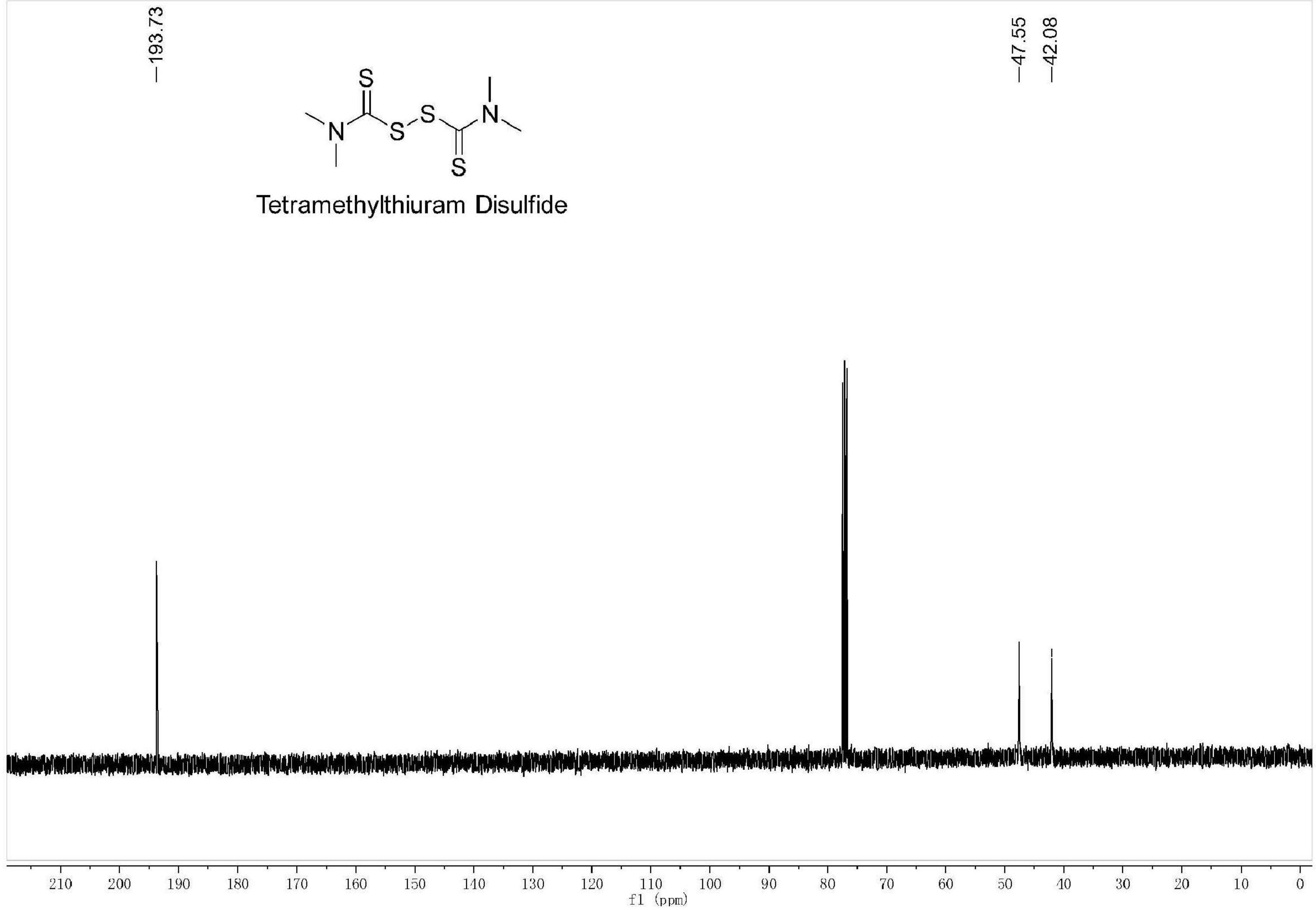
NMR Spectra


Tetraethylthiuram disulfide
S
N
S
S
S
N
—7.2629
—4.0288
—1.5640
—1.4832
—1.3032
—0.0000
8.00
6.00
6.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

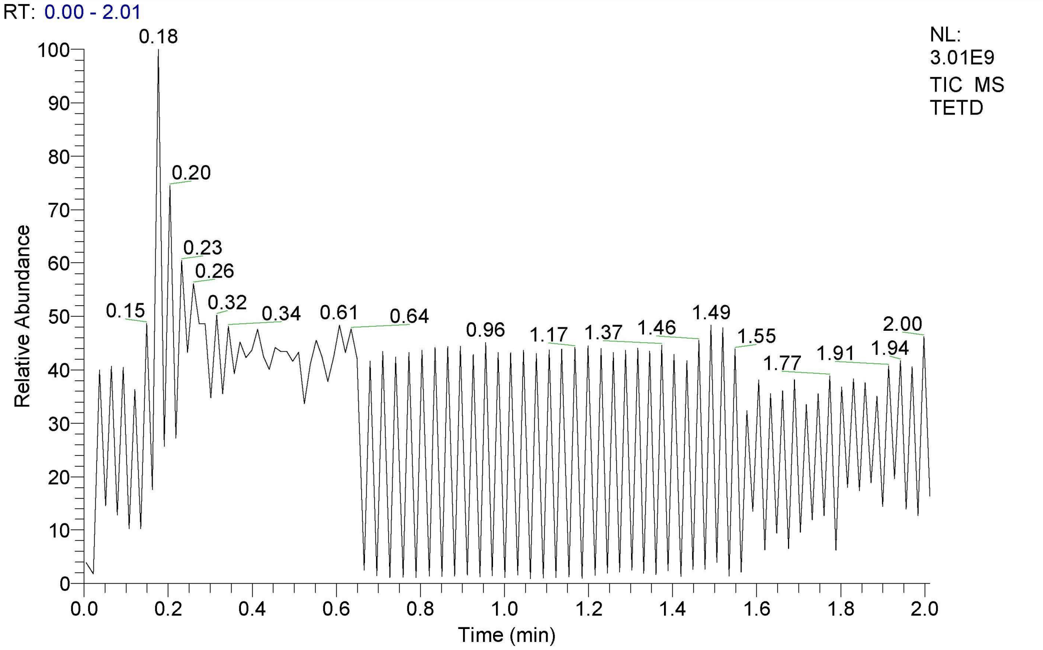


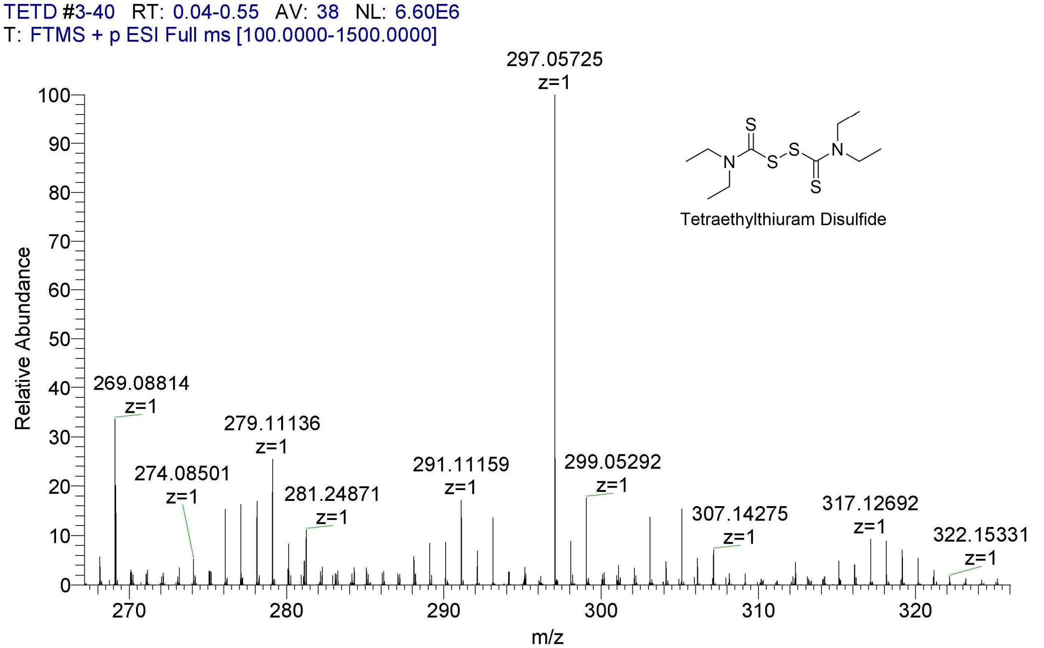
Tetraethylthiuram disulfide
S
S
S
S
N
N
192.71
52.04
47.62
13.50
11.47
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

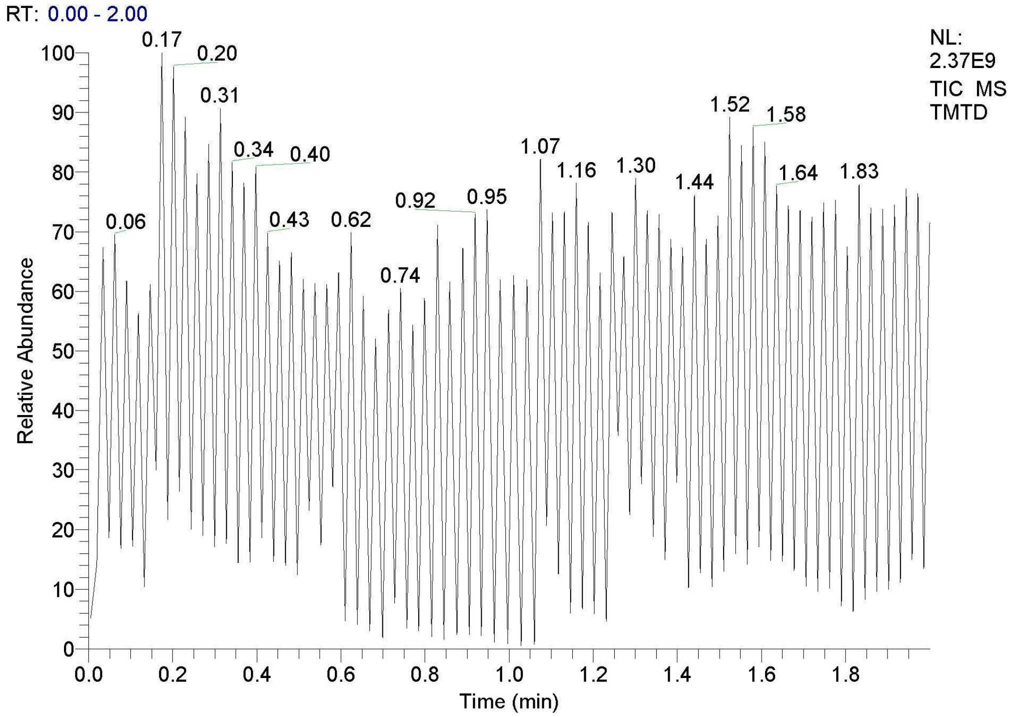

Tetramethylthiuram Disulfide
S
N
S
S
S
N
7.26
3.64
3.61
1.57
0.00
12.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

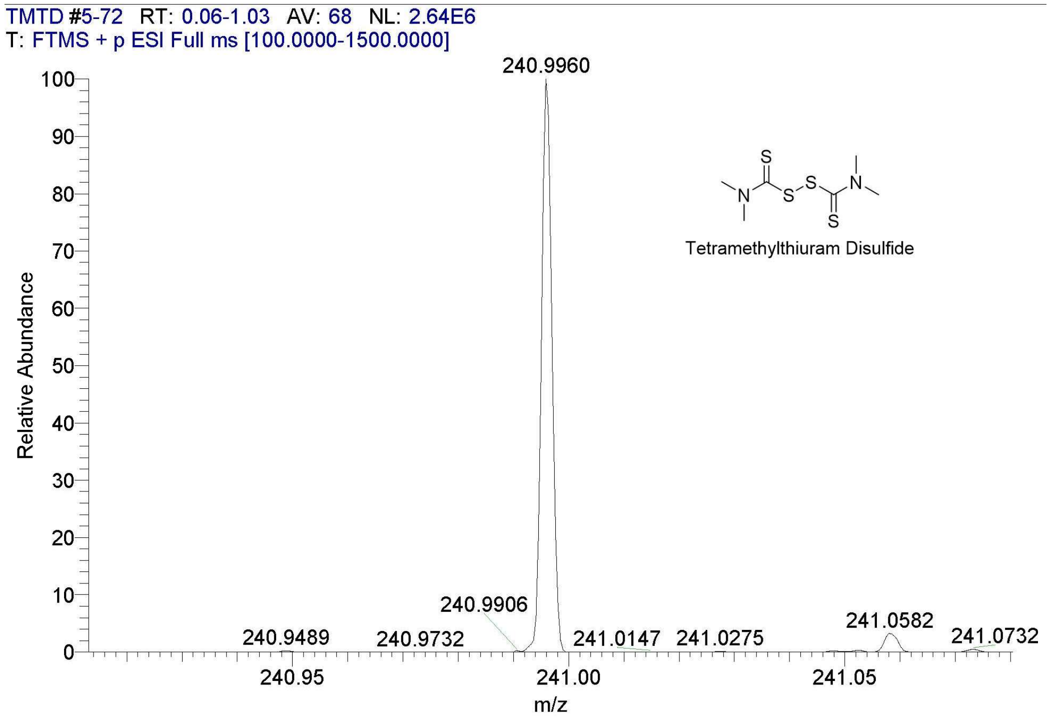

—193.73
—47.55
—42.08
Tetramethylthiuram Disulfide
S
N
S
S
N
S
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HRMS Spectra






RT: 0.00 - 2.00
NL:
2.37E9
TIC MS
TMTD
Relative Abundance
100
90
80
70
60
50
40
30
20
10
0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
Time (min)
0.06
0.17
0.20
0.31
0.34
0.40
0.43
0.62
0.74
0.92
0.95
1.07
1.16
1.30
1.44
1.52
1.58
1.64
1.83


TMTD #5-72 RT: 0.06-1.03 AV: 68 NL: 2.64E6
T: FTMS + p ESI Full ms [100.0000-1500.0000]
Relative Abundance
100
90
80
70
60
50
40
30
20
10
0
240.95
241.00
241.05
m/z
240.9960
240.9906
240.9489
240.9732
241.0147
241.0275
241.0582
241.0732
S
N
S
S
N
S
Tetramethylthiuram Disulfide