JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Accelerated Oxidation of Organic Sulfides by Microdroplet Chemistry

Jia Li,[⊥] Chengyuan Liu,[⊥] Hao Chen, and Richard N. Zare*

Cite This: J. Org. Chem. 2021, 86, 5011−5015 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We report the rapid oxidation of organic sulfides to sulfoxides by means of microdroplet chemistry at room temperature using a spray solution containing an organic sulfide dissolved in water/methanol, dilute (11%−14%) sodium hypochlorite (NaClO), and 5% chloroauric acid ($HAuCl_4$). Ultrasonic nebulization, easy ambient sonic-spray ionization, or electrosonic spray ionization serves as the microdroplet source. High-resolution mass spectrometry was used as an online detector, and nuclear magnetic resonance was used as an offline detector. We found that the sulfoxide yields vary between 66 and 95%, the highest rate of product formation is 195 mg/min for benzyl phenyl sulfoxide, and the time required is a few minutes, which is much less than that required for the conventional means of achieving this chemical transformation. We also applied this microdroplet method to protein fingerprinting. We found that protein sequences containing methionine can be quickly oxidized, providing useful information for protein structure determinations.

INTRODUCTION

Sulfoxides are important intermediates for the synthesis of many natural compounds[1−3] and can be prepared by oxidizing organic sulfides under various conditions.[4−10] In past work, the oxidation has generally been achieved using hydrogen peroxide (H_2O_2), molecular oxygen (O_2), photocatalysis, and catalytic metallic nanoparticles. This procedure is in contrast to special conditions such as promoter ionic liquids or inorganic salts.[11−22] Bulk reactions require a long reaction time, and oxidation does not necessarily stop at the first step of converting the sulfides to sulfoxides.[23] Thus, there is a need to produce sulfoxides more selectively. Sodium hypochlorite is a cheap and convenient oxidizing reagent and can react with a variety of functional groups. Commercial sodium hypochlorite (11%−14%) in water is a strong oxidant, which oxidizes sulfide compounds. When using sodium hypochlorite to oxidize sulfides or disulfides in a bulk solution, a mixture of sulfones and sulfoxides appears at the same time. We describe an alternative approach for transforming sulfides into sulfoxides using easy ambient sonic-spray ionization (EASI) of a solution containing a sulfide, sodium hypochlorite, and chloroauric acid.[24] As previously reported,[25,26] owing to the limit flow rate of EASI, ultrasonic nebulization (UN) was developed as a new method to scale up the synthesis of accelerated microdroplet reactions. The reactant solution in the ultrasonic nebulization cell can be immediately atomized to large amount of microdroplets with an average diameter of 6.9 μm to form a so-called "ultrasonic fountain". Therefore, we scaled up the accelerated synthesis of sulfoxides from sulfides in microdroplets using ultrasonic nebulization.

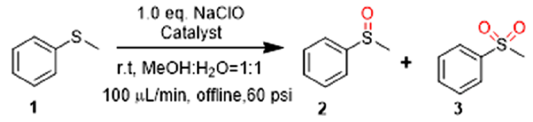
RESULTS AND DISCUSSION

We initially investigated how to optimize the oxidation of thioanisole, which was synthesized with an isolated yield of 90%.[27] The best conditions are using a spray solution of methanol/water (1:1 v:v) containing thioanisole (10 mM) and a commercial 11%−14% NaClO liquid (10 mM) with or without a chloroauric acid catalyst via the EASI offline setup (Figure S1a). The collection time was 2 min for each entry given in Table 1. In the absence of a catalyst, the thioanisole was completely converted to the corresponding sulfoxide and sulfone but with poor chemoselectivity (57:43) (Table 1, entry 3). When 1% $HAuCl_4{\cdot}3H_2O$ was added to the reaction system while all other quantities were kept the same, the selectivity increased slightly so that the sulfoxide to sulfone ratio became 66:34 (Table 1, entry 2). In the case of 5% $HAuCl_4{\cdot}3H_2O$, the chemoselectivity was found to be 91:9 (Table 1, entry 1), and the performance remained stable with increasing dosages of the catalyst. However, when the same equivalent of $Au(PPh_3)Cl$ was used in place of $HAuCl_4{\cdot}3H_2O$, the selectivity declined to some degree (Table 1, entry 4). We also tested the effect of temperature on this offline reaction progress. We found that it was easier to form sulfone at a higher temperature (Table 1, entry 5). By contrast, under bulk solution-phase conditions the reactant could not be fully consumed and the selectivity was not good (Table 1, entry 6).

Received: December 14, 2020
Published: March 3, 2021

https://dx.doi.org/10.1021/acs.joc.0c02942
J. Org. Chem. 2021, 86, 5011−5015

Table 1. Optimization of Thioanisole Oxidation Using Offline Collection



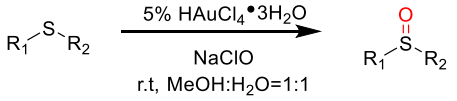
		yield (%)[a]	
entry	catalyst	2	3
1	5% $HAuCl_4{\cdot}3H_2O$	91	9
2	1% $HAuCl_4{\cdot}3H_2O$	66	34
3		57	43
4	5% $Au(PPh_3)Cl$	76	24
5[b]	5% $HAuCl_4{\cdot}3H_2O$	85	15
6[c]	5% $HAuCl_4{\cdot}3H_2O$	35	10

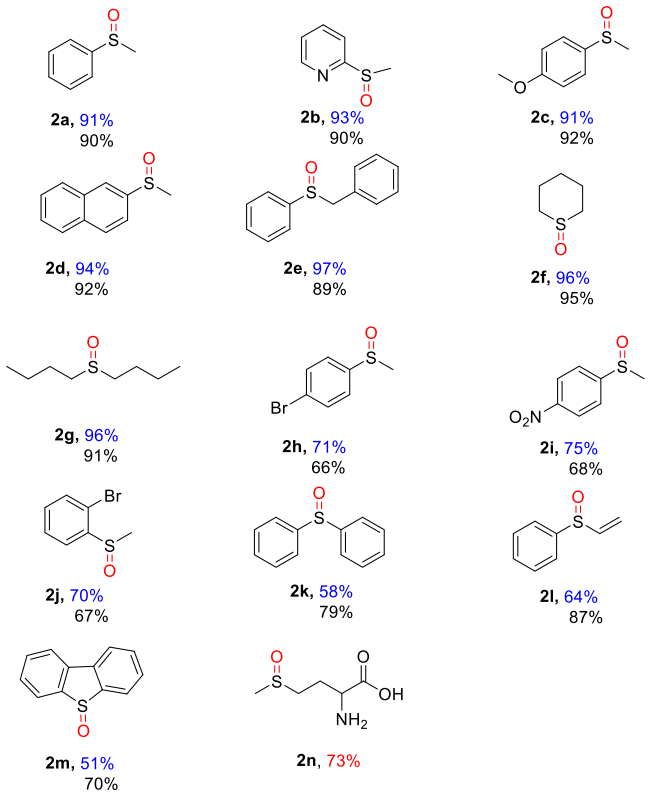
[a]Yield (%) was determined by NMR ($-CH_3$) from the crude reaction mixture. [b]Heated at 85 °C. [c]The bulk reaction was carried out for 2 min at room temperature.

Additionally, we took advantage of online mass spectrometry analysis to assess these reaction conditions using 1 mM 4-methoxyphenyl sulfoxide, which had a similar ionization efficiency as that of the internal standard we used. First, the capillary temperature was varied from 50 to 250 °C, the travel distance was fixed at 2 cm, and the solution sample was diluted ten times to 1 mM. The droplets were generated using the ESSI setup under 120 psi N_2 and high voltage (+3.0 kV). The reaction occurred during the travel distance, and the yield was calculated from I_p/I_s, where I_p was the intensity of product and I_s was the intensity of the internal standard. The yield decreased as the temperature increased, indicating that a lower temperature was favorable for this reaction. Consequently, offline collections were finished at room temperature. Second, we found that the pH of the diluted NaClO had a marked effect on this reaction. When the pH was 7 or lower, the reaction performed poorly. The highest peak appeared near pH 12 in which the yield of product was 79%. When the distance from the sprayer to the collection surface was varied from 0.2 to 5 cm under the conditions of 50 °C and pH 12 of the diluent NaClO, we found that the best distance was 3.5 cm. The variations with temperature, flight distance, and the NaClO pH value are presented in Figures S2−S4, respectively. For this setting, the yield was 87%. Because a velocity of 84 m/s was reported for charged droplets under 120 psi, the time scale was so short that a highly accelerated reaction in the microdroplets must have been involved.[28−30] To verify this idea, we investigated the first-order reaction kinetics of online experiments and the reaction in the bulk solution and plotted the ln C_t/C_o function of the reaction time (Figure S5). For the microdroplets, the reaction time was the distance divided by 84 m/s. For the bulk, the reaction time was controlled within 0.5−10 min. The rate acceleration factor was 10^6 for the two-slopes ratio. Thus, we conclude that the reaction rate for product formation is much faster in the microdroplets than in the bulk.

Encouraged by this outcome, we continued to examine this method using a variety of substituted thioanisoles (Table 2). Based on the results obtained from the EASI experiments, we applied the ultrasonic nebulizing setup to scale up the reaction (Figure S1b). When using reactants with 1.0 equiv of NaClO and a catalytic amount of $HAuCl_4{\cdot}3H_2O$ (5%), the reactions were conducted over 2 min with good isolated yields (**2a−2g**). We attribute this performance to the effect of the electron-donating groups that make sulfides more readily oxidized. The highest rate of product formation was 48 mg/min (**2e**). However, in the case of electron-withdrawing groups (**2h−2j**), the oxidation process was reduced, and the amount of oxidizing reagent had to be doubled for the same reaction time to obtain a higher yield. The yields reached moderate levels with single sulfoxides products. We also investigated the condition where sulfur connects to more than one aromatic group. Instead of doubling the oxidant, we prolonged the reaction time to 10 min under the same conditions to obtain the appropriate yields (**2k−2m**). Finally, we tested the sulfur-containing amino acid methionine (Met), which could prevent oxygen radical damage in living organisms. We found that Met could be converted to sulfoxide by 1 equiv of NaClO and 5% $HAuCl_4{\cdot}3H_2O$ within 2 min, which provided a relative yield of 73%. All the products in Table 2 were characterized by NMR spectroscopy and MS. We also tested this reaction on a millimolar scale with a substrate of benzyl phenyl sulfide. The parallel device of the ultrasonic nebulization system made up of four similar reaction cells and used in this step under the same concentration of reactant, obtaining the final sulfoxide

Table 2. Scope of Sulfide Oxidation Reactions[a]





[a]Yield (%) in blue was determined by ^1H NMR on the liquid by EASI within 2 min and yield (%) in black was the isolated yield of UN reactions. **2h−2j** was 2.0 equiv NaClO and 5% $HAuCl_4{\cdot}3H_2O$ over 2 min. **2k−2m** was 1.0 equiv NaClO and 5% $HAuCl_4{\cdot}3H_2O$ over 10 min by UN reactions.

https://dx.doi.org/10.1021/acs.joc.0c02942
J. Org. Chem. 2021, 86, 5011−5015

(**2e**) at a rate of 195 mg/min. To further evaluate the oxidation method, we designed a protein fingerprinting experiment to achieve a specific modification of the adrenocorticotropic hormone (ACTH, human 1−24). There are many strategies to modify protein structure, such as post-translational modification and interactions, and chemical modification. The fast photochemical oxidation of proteins was developed by Chance and co-worker using synchrotron radiolysis to produce hydroxyl radicals that could label a protein on the millisecond or shorter time scale.[31−36] The use of MS for proteomics and metabolomics is in full swing, and electrosonic spray ionization (ESSI) technology provides more efficient desolvation and makes droplets more abundantly charged, both of which enhance the MS sensitivity and increase the resolution.[37,38] Recently, our group had developed a technology for the ultrafast enzymatic digestion of proteins using trypsin, and we have applied this to digest ACTH within 0.24 ms and obtain nearly 100% sequence coverage.[39]

In this step, we sprayed a room-temperature sample solution that consisted of 10 μM human ACTH and a 10 μM NaClO dilution with or without adding trypsin. Microdroplets were generated using our homemade ESSI sprayer setup under a +3.0 kV voltage, a flow rate of 20 μL/min, and a N_2 pressure of 120 psi. Initially when fixing the distance to inlet at 20 mm and keeping the stream spraying for 1 min, we observed that the oxidized fragment peak at m/z 738.7 (z = 4) increased as the flight distance of the microdroplets increased, corresponding to longer reaction times. When comparing the MS/MS fragments with the control experiment, we observed peaks at m/z 675.6 (z = 4), m/z 871.5 (z = 3), and m/z 900.5 (z = 3) (Figure 1a), which corresponded to adding one O atom to the peaks at m/z 671.6 (z = 4), m/z 866.2 (z = 3), and m/z 895.2 (z = 3) found in the control experiment (Figure 1b).

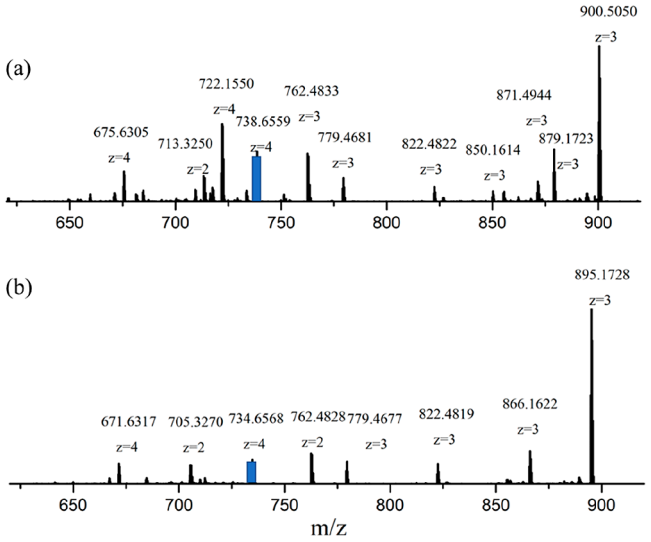


Figure 1. MS/MS spectra of ACTH for m/z 738.559 (z = 4) and 734.6568 (z = 4) showing (a) the oxidized fragmentation pattern and (b) the unmodified fragmentation pattern.

To determine where the location of the oxidation point is on the peptide, 5 mM ammonium bicarbonate containing 5 μg/mL trypsin was added to the prepared mixture. We found the m/z 1072 peak increased markedly after adding one oxygen compared to the fragment at m/z 1056. Moreover, we used the energy of CID (23−30 eV) to confirm the MS MS fragments after online digestion. The masses of the fragments had an added value 16 Da compared to the corresponding fragments before oxidation (Table S1).

CONCLUSIONS

In summary, we have used microdroplets containing sodium hypochlorite and chloroauric acid to synthesize sulfoxides from sulfides within 2 min, which is a very short time compared to traditional bulk reactions. A series of substrates was investigated by this method, and the yields were found to be good. In addition, we demonstrated that this reaction can be scaled up using an ultrasonic nebulizing system. We applied this approach to protein fingerprinting to determine specific methionine sites. This enables us to extend the ability to perform protein sequencing by combining it with the previously introduced method for the ultrafast enzymatic digestion of proteins using microdroplet mass spectrometry. The initial results appear to offer a new method for the preparation of sulfoxides from sulfides and allow the oxidative fingerprinting of proteins.

EXPERIMENTAL SECTION

General Information. All mass spectrometry (MS) experiments were performed using an LTQ Orbitrap Velos mass spectrometer (Thermo Fisher Scientific, San Jose, CA). The temperature of the MS inlet capillary varied between 50 and 275 °C, the S-lens voltage was set at 55 V, and a high voltage (+3.0 kV) supplied from an external high-voltage power source. A collision energy of 20−30 eV was selected for tandem mass spectrometry (MS/MS). The easy ambient sonic-spray ionization (EASI) and electrosonic spray ionization (ESSI) instruments were constructed of an inner fused silica capillary (o.d. 148 μm and i.d. 74 μm) and an outer capillary (o.d. 360 μm and i.d. 250 μm). Dry N_2 with a pressure of either 60 or 120 psi was used as nebulization gas. An ultrasonic nebulizer (Model 402AI, Yuwell Medical Equipment & Supply Corp., Suzhou, China) was used. The sodium hypochlorite (NaClO, 11−14%) solution was purchased from Energy Alfa Aesar Co., Inc., and other reagents and solvents were purchased from Adamas Reagent Co., Ltd. (Shanghai, China) and used as received without further purification. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$; δ values were given in ppm, and coupling constants (J) were given in hertz (Hz). The high-resolution mass spectra (HRMS) were recorded on a LTQ Orbitrap Elite mass spectrometer with a FTMS.

General Procedure: Microdroplet Reactions by EASI. First, 100 μL of 100 mM methyl phenyl sulfide (also called thioanisole) in methanol, 50 μL of 200 mM commercial 11−14% NaClO in water, and 5 μL of 100 mM chloroauric acid in water were mixed, and an extra 400 μL of methanol and 445 μL of water were added to the system. The sprayed droplets were collected by a vial containing 100 μL of a saturated solution of $Na_2S_2O_3$ for 2 min under 60 psi N_2. The flow rate was 100 μL/min, and the reaction distance was 3.5 cm. After collection, the mixture was extracted by 1 mL of ethyl acetate, transferred into a new vial, dried for NMR analysis. The bulk reaction was performed by mixing the same concentration of liquids at room temperature for 2 min, followed by adding 100 μL of a saturated solution of $Na_2S_2O_3$. After extraction and drying, the collected sample was prepared for NMR analysis. The relative yield was calculated by the integration of the product of interest. Other sulfides were reacted following the same steps as those for thioanisole.

Scaling-Up Reactions Using the UN System. First, 0.5 mmol sulfides in 5 mL of methanol, 0.5 mmol commercial 11−14%NaClO in 2.5 mL of water, and 250 μL of 100 mM chloroauric acid in water were added into the UN cell. To the cell were added 7.5 mL methanol and 9.75 mL water to make a total volume of 25 mL. Nebulization was maintained for 2 or 10 min, then 1 mL of a saturated solution of $Na_2S_2O_3$ was added to quench the reaction. After extraction and

https://dx.doi.org/10.1021/acs.joc.0c02942
J. Org. Chem. 2021, 86, 5011−5015

drying with Na_2SO_4, the mixture was concentrated under vacuum, and the residue was purified by flash column chromatography with petroleum and ethyl acetate as the eluent to give the desired sulfoxide products. All products were characterized by NMR spectroscopy and high-resolution MS.

To further test this method, we tested four parallel devices using the same reactant concentration of benzyl phenyl sulfide (Figure S5). After nebulizing for 2 min, the mixture was combined, and 4 mL of a saturated solution of $Na_2S_2O_3$ was added to quench the reaction. After extraction and drying by Na_2SO_4, the mixture was concentrated under vacuum before the residue was purified by flash column chromatography. The isolated yield was 90% with 389 mg of product, which was similar to the one batch with a yield of 89%.

Oxidation of Adrenocorticotropic Hormone (ACTH). At room temperature, 10 μM human ACTH (1−24) and 10 μM dilute NaClO solution were mixed and sprayed for 1 min under +3.0 kV and 120 psi N_2. The flow rate was 20 μL/min. For online digestion, a 5 μg/mL trypsin solution was added to the spray solution. The control experiments were done without a NaClO oxidant, which allowed us to confirm the sequences either with or without the addition of an oxygen (16 Da) atom in the tandem MS with CID 23−30 eV. Using the same procedure, we scaled up the reactions to obtain products **2a−2m** using the UN system.

Methyl Phenyl Sulfoxide (2a). Colorless oil, 90% yield (63 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.66 (m, 2H), 7.60−7.51 (m, 3H), 2.76 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 145.7, 131.1, 1 29.4, 123.5, 44.0. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_7H_8NaOS^+$ 163.0188, found 163.0189.

2-(Methylsulfinyl)pyridine (2b). Colorless oil, 90% yield (63 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64−8.59 (d, J = 4.6, 1H), 8.04−7.99 (d, J = 7.7, 1H), 7.94 (td, J = 7.7, 1.6 Hz, 1H), 7.41−7.35 (m, 1H), 2.84 (s, 3H). ^{13}C{1H} NMR (101 MHz, CDCl3): δ 165.9, 149.6, 138.2, 124.6, 119.3, 41.3. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_6H_8NOS^+$ 142.0321, found 142.0322.

4-Methoxypheny Methyl Sulfoxide (2c). Colorless oil, 92% yield (78 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.72 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 162.0, 136.6, 125.5, 114.9, 55.5, 44.0. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_{11}O_2S^+$ 171.0474, found 171.0475.

2-(Methylsulfinyl)naphthalene (2d). White solid, 92% yield (88 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.84 (m, 3H), 7.59−7.41 (m, 3H), 2.70 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ142.7, 134.5, 133.0, 129.6, 128.5, 128.1, 127.9, 127.4, 124.1, 119.5, 43.8. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{11}OS^+$ 191.0525, found 191.0526.

Benzyl Phenyl Sulfoxide (2e). White solid, 89% yield (96 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.33 (m, 1H), 7.28−7.18 (m, 1H), 6.99−6.90 (m, 1H), 4.08 (d, J = 12.6 Hz, 1H), 3.97 (d, J = 12.6 Hz, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ142.8, 131.2, 130.4 (2C), 129.2, 128.9 (2C), 128.5 (2C), 128.3, 124.5 (2C), 63.60 (s). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{13}OS^+$ 217.0682, found 217.0683.

Thiane-1-oxide (2f). Yellow liquid, 95% yield (56 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01−2.68 (m, 4H), 2.26 (m, 2H), 1.78−1.55 (m, 4H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 48.9 (2C), 24.6 (2C), 19.1. HRMS (ESI): m/z [M + K]$^+$ calcd for $C_5H_{10}KOS^+$ 157.0084, found 157.0098.

1-(Butylsulfinyl)butane (2g). Yellow liquid, 91% yield (74 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (m, 4H), 1.77−1.73 (m, 4H), 1.51−1.46 (m, 4H), 1.02−0.97 (t, J = 4.0 Hz, 6H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 52.1, 24.6, 22.1, 13.7. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_{19}OS^+$ 163.1151, found 163.1153.

1-Bromo-4-(methylsulfinyl)benzene (2h). Yellow oil, 66% yield (72 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77−7.62 (m, 2H), 7.62−7.49 (m, 2H), 2.74 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 144.8, 132.6, 125.5, 125.1, 43.9. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_8BrOS^+$ 218.9474, found 218.9476.

1-(Methylsulfinyl)-4-nitrobenzene (2i). White solid, 68% yield (63 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47−8.32 (m, 2H), 7.92−7.77 (m, 2H), 2.79 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 153.3, 149.5, 124.7 (2C), 124.5 (2C), 43.9. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_8NO_3S^+$ 186.0219, found 186.0221.

1-Bromo-2-(methylsulfinyl)benzene (2j). Yellow oil, 67% yield (73 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, J = 7.8, 1.6 Hz, 1H), 7.68−7.55 (m, 2H), 7.39 (td, J = 7.8, 1.6 Hz, 1H), 2.84 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 145.4, 132.9, 132.3, 128.8, 125.7, 118.4, 41.9. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_8BrOS^+$ 218.9474, found 218.9476.

Sulfinyldibenzene (2k). Yellow oil, 79% yield (80 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.65 (m, 4H), 7.52−7.43 (m, 6H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 145.6 (2C), 131.1 (2C), 129.3 (4C), 124.8 (4C). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{11}OS^+$ 203.0525, found 203.0527.

(Vinylsulfinyl)benzene (2l). Yellow oil, 87% yield (66 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.61 (m, 2H), 7.61−7.49 (m, 3H), 6.62 (dd, J = 16.5, 9.6 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.92 (d, J = 9.6 Hz, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 143.3, 143.0, 131.3, 129.5, 124.7, 120.7. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_9OS^+$ 153.0369, found 153.0370.

Dibenzo[*b*,*d*]thiophene 5-Oxide (2m). White solid, 70% yield (70 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 7.6 Hz, 2H), 7.63 (td, J = 7.6, 1.0 Hz, 2H), 7.53 (td, J = 7.6, 1.0 Hz, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 145.2, 137.1, 132,6, 129.6, 127.6, 121.9. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_9OS^+$ 201.0369, found 201.0371.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02942.

Descriptions of the microdroplet generation setups and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Richard N. Zare − *Department of Chemistry, Fudan University, Shanghai 200438, China; Department of Chemistry, Stanford University, Stanford, California 94305, United States;* orcid.org/0000-0001-5266-4253; Email: rnz@fudan.edu.cn, rnz@stanford.edu

Authors

Jia Li − *Department of Chemistry, Fudan University, Shanghai 200438, China*

Chengyuan Liu − *National Synchrotron Radiation Laboratory, University of Science and Technology of China, Hefei 230029, China*

Hao Chen − *Department of Chemistry & Environmental Science, New Jersey Institute of Technology, Newark, New Jersey 07102, United States;* orcid.org/0000-0001-8090-8593

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02942

Author Contributions

⊥J.L. and C.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Scientific Research Startup Foundation of Fudan University (Grant IDH1615113) and the

National Natural Science Foundation of China (Grant 21974027).

REFERENCES

(1) Maezaki, N.; Yagi, S.; Yoshigami, R.; Maeda, J.; Suzuki, T.; Ohsawa, S.; Tsukamoto, K.; Tanaka, T. Pd-Catalyzed Sulfinylzincation of Activated Alkynes with 1-Alkynyl Sulfoxides as a Sulfinyl Source. *J. Org. Chem.* **2003**, *68*, 5550.

(2) Rademacher, P. M.; Woods, C. M.; Huang, Q.; Szklarz, G. D.; Nelson, S. D. Differential Oxidation of Two Thiophene-Containing Regioisomers to Reactive Metabolites by Cytochrome P450 2C9. *Chem. Res. Toxicol.* **2012**, *25*, 895.

(3) Kim, D. G.; Vershinina, E. A. e.; Sharutin, V. V. Synthesis, transformations and halocyclization of 8-(Prop-2-ynylsulfanyl)-quinoline and 8-(2-Bromoprop-2-enylsulfanyl)quinoline. *J. Sulfur Chem.* **2020**, *41*, 71.

(4) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. A Mild, Chemoselective Oxidation of Sulfides to Sulfoxides Using o-Iodoxybenzoic Acid and Tetraethylammonium Bromide as Catalyst. *J. Org. Chem.* **2003**, *68*, 5422.

(5) Wang, S. H.; Mandimutsira, B. S.; Todd, R.; Ramdhanie, B.; Fox, J. P.; Goldberg, D. P. Catalytic Sulfoxidation and Epoxidation with a Mn(III) Triazacorrole: Evidence for A "Third Oxidant" in High-Valent Porphyrinoid Oxidations. *J. Am. Chem. Soc.* **2004**, *126*, 18.

(6) Matteucci, M.; Bhalay, G.; Bradley, M. Mild and Highly Chemoselective Oxidation of Thioethers Mediated by $Sc(OTf)_3$. *Org. Lett.* **2003**, *5*, 235.

(7) Baig, N.; Madduluri, V. K.; Sah, A. K. Selective oxidation of organic sulfides to sulfoxides using sugar derived cis-dioxo molybdenum(vi) complexes: kinetic and mechanistic studies. *RSC Adv.* **2016**, *6*, 28015.

(8) Cao, J.-P.; Xue, Y.-S.; Li, N.-F.; Gong, J.-J.; Kang, R.-K.; Xu, Y. Lewis Acid Dominant Windmill-Shaped V_8 Clusters: A Bifunctional Heterogeneous Catalyst for CO_2 Cycloaddition and Oxidation of Sulfides. *J. Am. Chem. Soc.* **2019**, *141*, 19487.

(9) Pye, S. J.; Dalgarno, S. J.; Chalker, J. M.; Raston, C. L. Organic oxidations promoted in vortex driven thin films under continuous flow. *Green Chem.* **2018**, *20*, 118.

(10) Velusamy, S.; Kumar, A. V.; Saini, R.; Punniyamurthy, T. Copper catalyzed oxidation of sulfides to sulfoxides with aqueous hydrogen peroxide. *Tetrahedron Lett.* **2005**, *46*, 3819.

(11) Gu, X.; Li, X.; Chai, Y.; Yang, Q.; Li, P.; Yao, Y. A simple metal-free catalytic sulfoxidation under visible light and air. *Green Chem.* **2013**, *15*, 357.

(12) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S.-I. Flavin Catalyzed Oxidations of Sulfides and Amines with Molecular Oxygen. *J. Am. Chem. Soc.* **2003**, *125*, 2868.

(13) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. Oxidation of sulfides to sulfoxides and sulfones with 30% hydrogen peroxide under organic solvent- and halogen-free conditions. *Tetrahedron* **2001**, *57*, 2469.

(14) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A.; Riazymontazer, E. Metal-Free Chemoselective Oxidation of Sulfides to Sulfoxides by Hydrogen Peroxide Catalyzed byin situ Generated Dodecyl Hydrogen Sulfate in the Absence of Organic Co-Solvents. *Adv. Synth. Catal.* **2006**, *348*, 434.

(15) Fukuda, N.; Ikemoto, T. Imide-catalyzed oxidation system: sulfides to sulfoxides and sulfones. *J. Org. Chem.* **2010**, *75*, 4629.

(16) Kermanshahi, M. G.; Bahrami, K. Fe_3O_4@BNPs@SiO_2−SO_3H as a highly chemoselective heterogeneous magnetic nanocatalyst for the oxidation of sulfides to sulfoxides or sulfones. *RSC Adv.* **2019**, *9*, 36103.

(17) Liu, J.; Liu, G.; Liu, C.; Li, W.; Wang, F. Nano-sized mesoporous sodium iron hydroxyphosphate supported gold: an effective catalyst for the oxidation of sulfides. *Catal. Sci. Technol.* **2016**, *6*, 2055.

(18) Liu, K.-J.; Deng, J.-H.; Yang, J.; Gong, S.-F.; Lin, Y.-W.; He, J.-Y.; Cao, Z.; He, W.-M. Selective oxidation of (hetero)sulfides with molecular oxygen under clean conditions. *Green Chem.* **2020**, *22*, 433.

(19) Noguchi, T.; Hirai, Y.; Kirihara, M. Highly selective 30% hydrogen peroxide oxidation of sulfides to sulfoxides using micromixing. *Chem. Commun. (Cambridge, U. K.)* **2008**, 3040.

(20) Panda, M. K.; Shaikh, M. M.; Ghosh, P. Controlled oxidation of organic sulfides to sulfoxides under ambient conditions by a series of titanium isopropoxide complexes using environmentally benign H_2O_2 as an oxidant. *Dalton Trans.* **2010**, *39*, 2428.

(21) Wang, S.; Wang, L.; Đaković, M.; Popović, Z.; Wu, H.; Liu, Y. Bifunctional Ionic Liquid Catalyst Containing Sulfoacid Group and Hexafluorotitanate for Room Temperature Sulfoxidation of Sulfides to Sulfoxides Using Hydrogen Peroxide. *ACS Catal.* **2012**, *2*, 230.

(22) Zolfagharinia, S.; Kolvari, E.; Koukabi, N. A practical heteropolyacid nanocatalyst supported on nano-sized ceramic for the chemoselective oxidation of sulfides to sulfoxides through an experimental design approach. *Chemical Papers* **2017**, *71*, 2505.

(23) Khurana, J. M.; Panda, A. K.; Ray, A.; Gogia, A. Rapid Oxidation of Sulfides and Sulfoxides with Sodium Hypochlorite. *Org. Prep. Proced. Int.* **1996**, *28*, 234.

(24) Teunissen, S. F.; Fernandes, A. M. A. P.; Eberlin, M. N.; Alberici, R. M. Celebrating 10 years of easy ambient sonic-spray ionization. *TrAC, Trends Anal. Chem.* **2017**, *90*, 135.

(25) Liu, C.; Li, J.; Chen, H.; Zare, R. N. Scale-up of microdroplet reactions by heated ultrasonic nebulization. *Chem. Sci.* **2019**, *10*, 9367.

(26) Luo, K.; Li, J.; Cao, Y.; Liu, C.; Ge, J.; Chen, H.; Zare, R. N. Reaction of chloroauric acid with histidine in microdroplets yields a catalytic Au−$(His)_2$ complex. *Chem. Sci.* **2020**, *11*, 2558.

(27) Yuan, Y.; Bian, Y. Gold(III) catalyzed oxidation of sulfides to sulfoxides with hydrogen peroxide. *Tetrahedron Lett.* **2007**, *48*, 8518.

(28) Lee, J. K.; Kim, S.; Nam, H. G.; Zare, R. N. Microdroplet fusion mass spectrometry for fast reaction kinetics. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 3898.

(29) Muller, T.; Badu-Tawiah, A.; Cooks, R. G. Accelerated carbon-carbon bond-forming reactions in preparative electrospray. *Angew. Chem., Int. Ed.* **2012**, *51*, 11832.

(30) Crawford, E. A.; Esen, C.; Volmer, D. A. Real Time Monitoring of Containerless Microreactions in Acoustically Levitated Droplets via Ambient Ionization Mass Spectrometry. *Anal. Chem.* **2016**, *88*, 8396.

(31) Maleknia, S. D.; Brenowitz, M.; Chance, M. R. Millisecond Radiolytic Modification of Peptides by Synchrotron X-rays Identified by Mass Spectrometry. *Anal. Chem.* **1999**, *71*, 3965.

(32) Shi, L.; Gross, M. L. Fast Photochemical Oxidation of Proteins Coupled with Mass Spectrometry. *Protein Pept. Lett.* **2019**, *26*, 27.

(33) Li, K. S.; Shi, L.; Gross, M. L. Mass Spectrometry-Based Fast Photochemical Oxidation of Proteins (FPOP) for Higher Order Structure Characterization. *Acc. Chem. Res.* **2018**, *51*, 736.

(34) Hambly, D. M.; Gross, M. L. Laser flash photolysis of hydrogen peroxide to oxidize protein solvent-accessible residues on the microsecond timescale. *J. Am. Soc. Mass Spectrom.* **2005**, *16*, 2057.

(35) Cheng, M.; Zhang, B.; Cui, W.; Gross, M. L. Laser-Initiated Radical Trifluoromethylation of Peptides and Proteins: Application to Mass-Spectrometry-Based Protein Footprinting. *Angew. Chem., Int. Ed.* **2017**, *56*, 14007.

(36) Chen, J.; Cui, W.; Giblin, D.; Gross, M. L. New protein footprinting: fast photochemical iodination combined with top-down and bottom-up mass spectrometry. *J. Am. Soc. Mass Spectrom.* **2012**, *23*, 1306.

(37) Orita, A.; Uehara, G.; Miwa, K.; Otera, J. Rate acceleration of organic reaction by immediate solvent evaporation. *Chem. Commun. (Cambridge, U. K.)* **2006**, No. 45, 4729.

(38) Banerjee, S.; Mazumdar, S. Electrospray ionization mass spectrometry: a technique to access the information beyond the molecular weight of the analyte. *Int. J. Anal. Chem.* **2012**, 282574.

(39) Zhong, X.; Chen, H.; Zare, R. N. Ultrafast enzymatic digestion of proteins by microdroplet mass spectrometry. *Nat. Commun.* **2020**, *11*, 1049.

https://dx.doi.org/10.1021/acs.joc.0c02942
J. Org. Chem. 2021, 86, 5011−5015