Electronic Supplementary Information

1,3,5-Trimethoxybenzene (TMB) as a new quencher for preserving redox-labile disinfection byproducts and for quantifying free chlorine and free bromine

Stephanie S. Lau[a§], Ryan P. Dias[b], Kayla R. Martin-Culet[b], Nicholas A. Race[b‡], Marella H. Schammel[b], Keith P. Reber[b], A. Lynn Roberts[a], John D. Sivey[*b]

[a] Department of Environmental Health and Engineering, Johns Hopkins University, 313 Ames Hall, 3400 North Charles Street, Baltimore, Maryland 21218, United States

[b] Department of Chemistry, Towson University, 8000 York Road, Towson, Maryland 21252, United States

[§] Current affiliation: Department of Civil and Environmental Engineering, Stanford University, 473 Via Ortega, Stanford, CA 94305, United States

[‡] Current affiliation: Department of Chemistry, College of William and Mary, Integrated Science Center, Williamsburg, VA, 23187

* Corresponding author contact information: phone: (410) 704-6087; e-mail: jsivey@towson.edu

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Reagent information

Table S1. List of Reagents and Their Associated Purity and Vendor Information

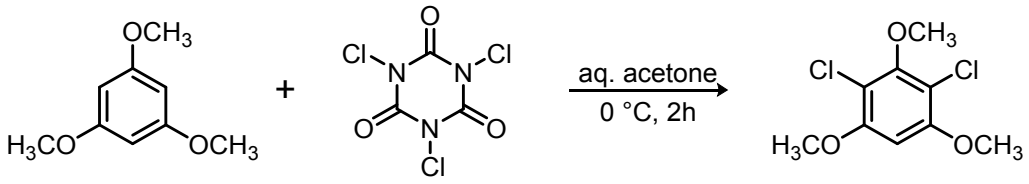
Chemical	Purity / Grade	Vendor
1,2-dibromopropane	98%	TCI America
1,3,5-trimethoxybenzene	≥ 99.0 %	Sigma-Aldrich or Fisher Scientific
2-bromo-1,3,5-trimethoxybenzene	98%	Oakwood Chemical
2-chloro-1,3,5-trimethoxybenzene	98%	Sigma-Aldrich
2,4-dichlorophenol	99%	Acros Organics
2,4,6-trichlorophenol	98%	Aldrich
2-bromoanisole	97%	Sigma-Aldrich
2-chlorobenzonitrile	≥ 98%	Sigma-Aldrich or Acros Organic
4-bromoanisole	99%	Sigma-Aldrich
acetone	certified ACS	Fisher Scientific
acetonitrile	Optima	Fisher Scientific
ammonium chloride	99.5%	Sigma-Aldrich
anisaldehyde	99+%	Acros Organics
anisole	99.7%	Sigma-Aldrich
bromine	99.6%	Acros Organics
bromoacetonitrile	97%	Sigma-Aldrich
chloral hydrate	99%	Supelco
chloroacetonitrile	99%	Sigma-Aldrich
chloroform	certified ACS	Fisher Scientific
chloropicrin	97%	Supelco
dibromoacetonitrile	93%	Supelco
dichloroacetonitrile	98%	Supelco
dichloromethane	certified ACS	Fisher Scientific
diethyl ether	laboratory grade	Fisher Scientific
dimethenamid-P [a]	95.4%	ChemService Inc.
ethanol	>99%	PHARMCO-AAPER
ethyl acetate	certified ACS	Fisher Scientific
hexanes	certified ACS	Fisher Scientific
L-ascorbic acid	reagent grade	Sigma
magnesium sulfate	anhydrous, ACS grade	Fisher Scientific
methanol	99.9%	Fisher Scientific
methyl tert-butyl ether (MTBE)	CHROMASOLV Plus	Sigma-Aldrich
N-bromosuccinimide	99%	Acros Organics

[a] Dimethenamid is a chiral compound. All experiments, syntheses, and analyses involving dimethenamid performed herein were conducted with the dimethenamid-P enantiomer due to its greater commercial availability (and greater use in agriculture[1]) compared to the racemate. All experiments, syntheses, and analyses conducted herein are ostensibly achiral; using dimethenamid-P instead of racemic dimethenamid is not anticipated to influence the conclusions drawn in this work.

Table S1. (continued)

Chemical	Purity / Grade	Vendor
N-chlorosuccinimide	98%	Oakwood Chemical
nitric acid	70%	Fisher Scientific
pentane	certified ACS	Fisher Scientific
potassium phosphate monobasic	ACS reagent	J. T. Baker
silica gel	technical grade, 60 Å	Sigma-Aldrich
sodium bicarbonate	≥ 99.7%	Acros Organics
sodium bromide	99.5%	Acros Organics
sodium chloride	99.999%	Acros Organics
sodium hydroxide	certified ACS pellets	Fisher Scientific
sodium hypochlorite solution	5.65-6%	Fisher Scientific
sodium nitrate	≥ 99.0 %	Sigma-Aldrich
sodium phosphate dibasic	ACS reagent	J. T. Baker
sodium sulfate	anhydrous, ACS grade	Fisher Scientific
sodium sulfite	99.99%	Aldrich
sodium tetraborate decahydrate	99.5%	Acros
sodium thiosulfate pentahydrate	99.5–101.0%	Alfa Aesar
tetrahydrofuran	anhydrous, 99.5%	Acros Organics
toluene	99.9%	Fisher Scientific
trichloroisocyanuric acid	90+%	Alfa Aesar
trifluoroacetic acid	99%	Oakwood Chemical

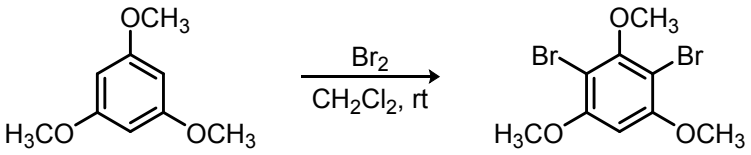
Synthesis of 2,4-dichloro-1,3,5-trimethoxybenzene



The synthesis was carried out according to the procedure reported by Maraš and Kočevar.[2] To a 50-mL round bottom flask equipped with a magnetic stirring bar was added a solution of 1,3,5-trimethyoxybenzene (500 mg, 2.97 mmol, 1.00 eq.) in 3.5 mL of acetone and 6 mL of water. This solution was cooled to 0 °C in an ice bath, and a solution of trichloroisocyanuric acid (482 mg, 2.08 mmol, 0.70 eq.) in 4 mL of acetone was added dropwise over five minutes. The reaction was stirred at 0 °C for two hours before the addition of 9 mL of 3% aqueous sodium hydroxide solution. After stirring for ten minutes, the liquid phase had turned bright yellow. The precipitated solids were collected by vacuum filtration and washed with three 25 mL portions of water to give the crude product as a white solid. This compound was purified by recrystallization from absolute ethanol to give 2,4-dichloro-1,3,5-trimethoxybenzene as white crystals (489 mg, 70% yield). Purity as determined by GC-MS was >98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (3H, s), 3.91 (6H, s), 6.38 (1H, s)

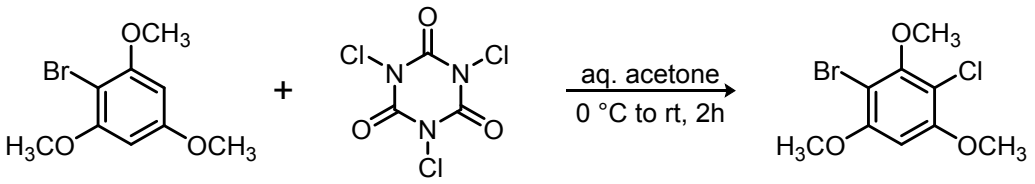
Synthesis of 2,4-dibromo-1,3,5-trimethoxybenzene



The synthesis was carried out according to the procedure reported by Kiehlmann and Lauener.[3] To a 50 mL flask equipped with a magnetic stirring bar was added a solution of 1,3,5-trimethoxybenzene (500 mg, 2.97 mmol, 1.00 eq.) in 10 mL of dichloromethane. A solution of bromine (1.43 g, 8.92 mmol, 3.00 eq.) in 10 mL of dichloromethane was then added dropwise over the course of one hour. Initially, the orange/red color rapidly faded over the course of 5-10 seconds after the addition of each drop of the bromine solution. However, after the addition of approximately 1/3 of the bromine solution, the orange / red color persisted for several minutes before fading. A dark red color persisted after addition of the bromine solution was complete, and thin layer chromatography (3:1 hexanes / ethyl acetate, UV / anisaldehyde visualization) showed complete consumption of 1,3,5-trimethoxybenzene (R_f = 0.5, stains red) and clean formation of the desired dibromide (R_f = 0.32, stains faintly purple). The reaction was quenched with 10% aqueous sodium sulfite solution, the layers were separated, and the aqueous phase was extracted once with diethyl ether before the combined organic layers were dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to give 950 mg of the crude dibromide as a white solid (98%). This material was then recrystallized from 3:1 pentane / chloroform to afford 368 mg of pure dibromide as dense white needles (40%). Purity as determined by GC-MS was >98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (3H, s), 3.91 (6H, s), 6.35 (1H, s).

Synthesis of 2-bromo-4-chloro-1,3,5-trimethoxybenzene



To a 25 mL round bottom flask equipped with a magnetic stirring bar was added a solution of 2-bromo-1,3,5-trimethyoxybenzene (150 mg, 607 μmol, 1.00 eq.) in 4.5 mL of acetone and 3 mL of water. This solution was cooled to 0 °C in an ice bath, and solid trichloroisocyanuric acid (46.6 mg, 201 μmol, 0.33 eq.) was added in a single portion. The reaction was stirred at 0 °C for one hour (a precipitate formed) and then for one additional hour at room temperature. After this time, the reaction was quenched with 4.5 mL of 1 M aqueous sodium hydroxide solution, and the mixture was stirred vigorously before the solid was collected by vacuum filtration. The resulting amorphous white solid was washed with water before drying under high vacuum to give 150 mg of the crude product (88%). This material was recrystallized from absolute ethanol to afford 94.2 mg of pure 2-bromo-4-chloro-1,3,5-trimethoxybenzene as shiny white flakes (55%).

m.p. 128.1–129.1 °C

IR: 2984, 2948, 1574, 1458, 1431, 1390, 1342, 1212, 1195, 1109, 1078, 1010, 807, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, Fig. S1): δ 3.88 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 6.37 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$, Fig. S2): δ 56.7, 56.8, 60.7, 93.3, 99.1, 109.8, 154.9, 155.82, 155.84.

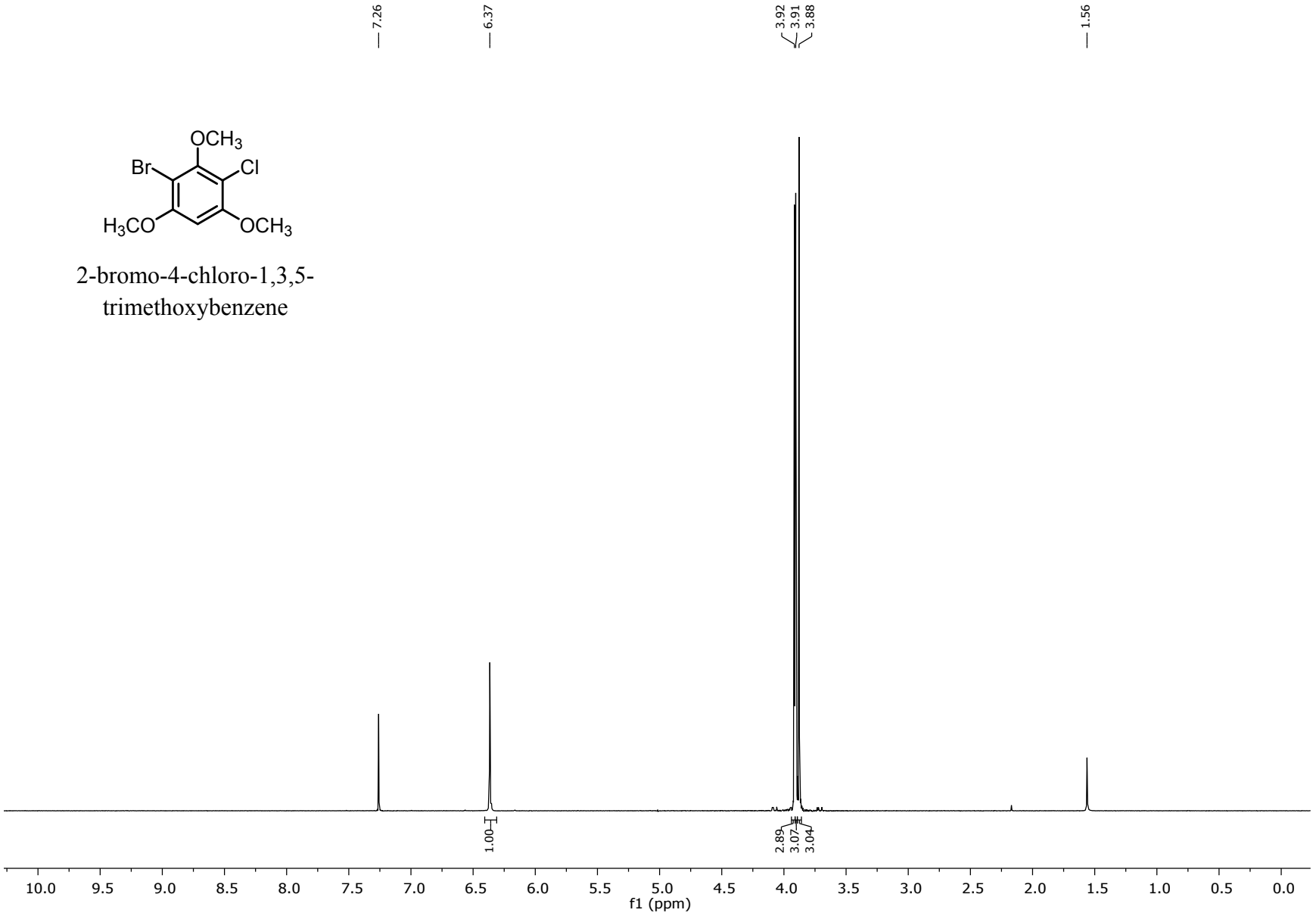


Fig. S1. ^{1}H NMR spectrum of 2-bromo-4-chloro-1,3,5-trimethoxybenzene (400 MHz, $CDCl_3$).

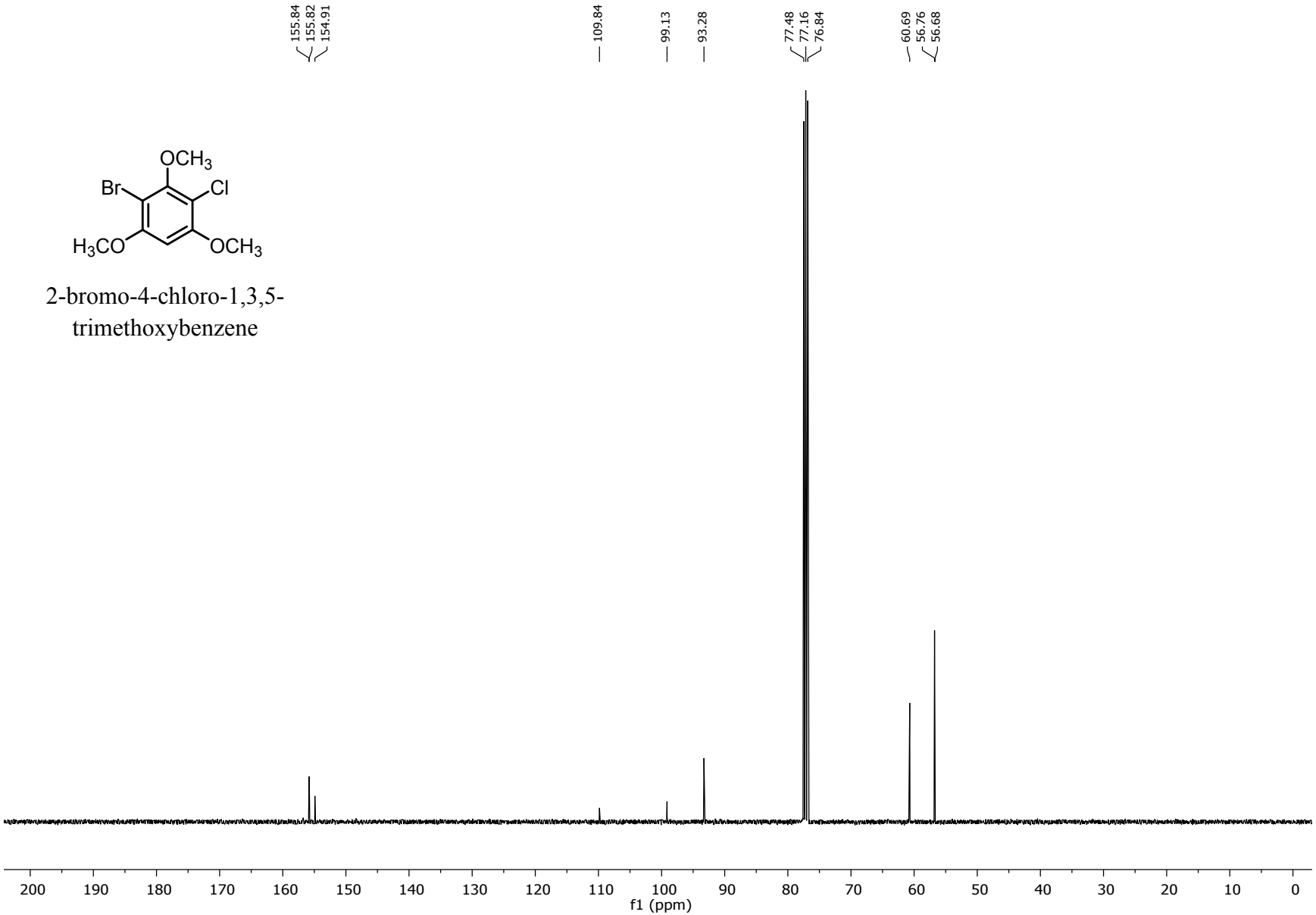
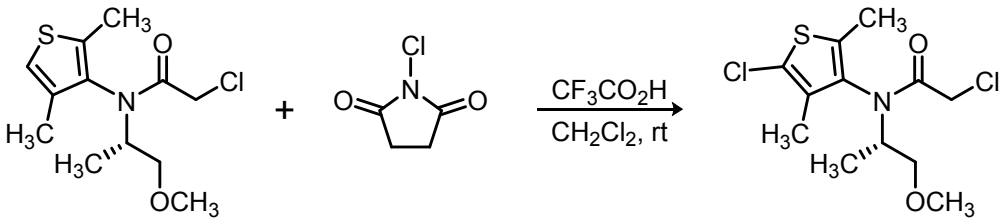


Fig. S2. ^{13}C NMR spectrum of 2-bromo-4-chloro-1,3,5-trimethoxybenzene (100 MHz, $CDCl_3$).

Synthesis of chloro-dimethenamid-P



To a flame-dried 25 mL flask under argon equipped with a magnetic stirring bar was added a solution of dimethenamid-P (70.0 mg, 0.254 mmol, 1.00 eq.) in 10 mL of anhydrous dichloromethane. Solid *N*-chlorosuccinimide (37.3 mg, 0.279 mmol, 1.10 eq.) was added in a single portion followed by neat trifluoroacetic acid (194 μL, 2.54 mmol, 10.0 eq.), and the reaction mixture was stirred at room temperature for 24 h. Thin layer chromatography (plate eluted three times in 3:1 hexanes / ethyl acetate, UV / anisaldehyde visualization) showed a small amount of unreacted dimethenamid-P (UV-active and stains white) and formation of chloro-dimethenamid-P (UV-active but does not stain) of slightly higher R_f. An additional portion of *N*-chlorosuccinimide (15.0 mg, 0.112 mmol, 0.44 eq.) was added, and the reaction mixture was stirred at room temperature for a further 24 hours, at which point all of the dimethenamid-P had been consumed. The trifluoroacetic acid was quenched by the dropwise addition of saturated aqueous sodium bicarbonate solution until no more carbon dioxide evolution was observed. The layers of the resulting biphasic mixture were separated, the organic phase was dried over anhydrous sodium sulfate, and the drying agent was removed by vacuum filtration. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (4:1 hexanes / ethyl acetate) to give pure chloro-dimethenamid-P as a colorless oil (60 mg, 76%).

At room temperature in $CDCl_3$, chloro-dimethenamid-P exists as a ~1.25:1.00 mixture of atropisomers due to restricted rotation about the bond connecting the amide nitrogen atom to the thiophene ring. Fractional integration values represent the contributions of each atropisomer to the total proton count for one molecule of dimethenamid-P.

IR: 2980, 2923, 1669, 1567, 1449, 1396, 1350, 1236, 1200, 1146, 1109, 1029, 994, 942, 793, 720, 680 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, Fig. S3): δ 1.09 (1.64H, d, J = 7.0 Hz), 1.17 (1.26H, d, J = 7.0 Hz), 1.98 (1.59H, s), 2.00 (1.29H, s), 2.28 (1.19H, s), 2.30 (1.64H, s), 3.25 (1.28H, s), 3.28 (1.65H, s), 3.29-3.37 (1H, m), 3.46-3.53 (1H, m), 3.62-3.70 (2H, m), 4.46 (0.46H, m), 4.56 (0.57H, m).

^{13}C NMR (100 MHz, $CDCl_3$, Fig. S4): δ 12.5, 12.9, 13.1, 13.6, 15.0, 15.6, 42.7, 54.0, 54.8, 58.58, 58.63, 74.1, 74.3, 122.17, 122.21, 132.4, 132.5, 132.6, 133.1, 134.6, 135.0, 167.05, 167.09.

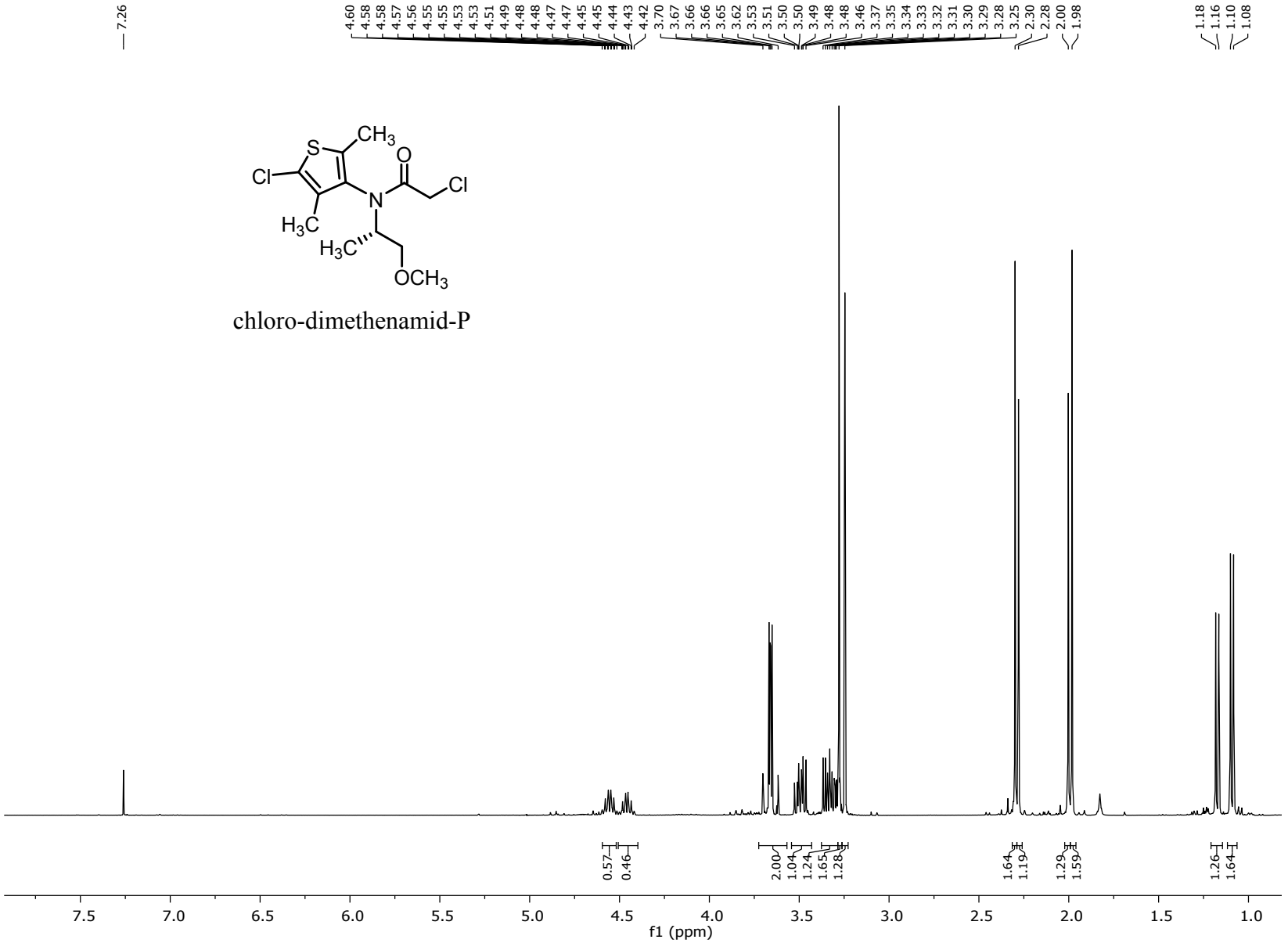


Fig. S3. ^{1}H NMR spectrum of chloro-dimethenamid-P (400 MHz, $CDCl_3$).

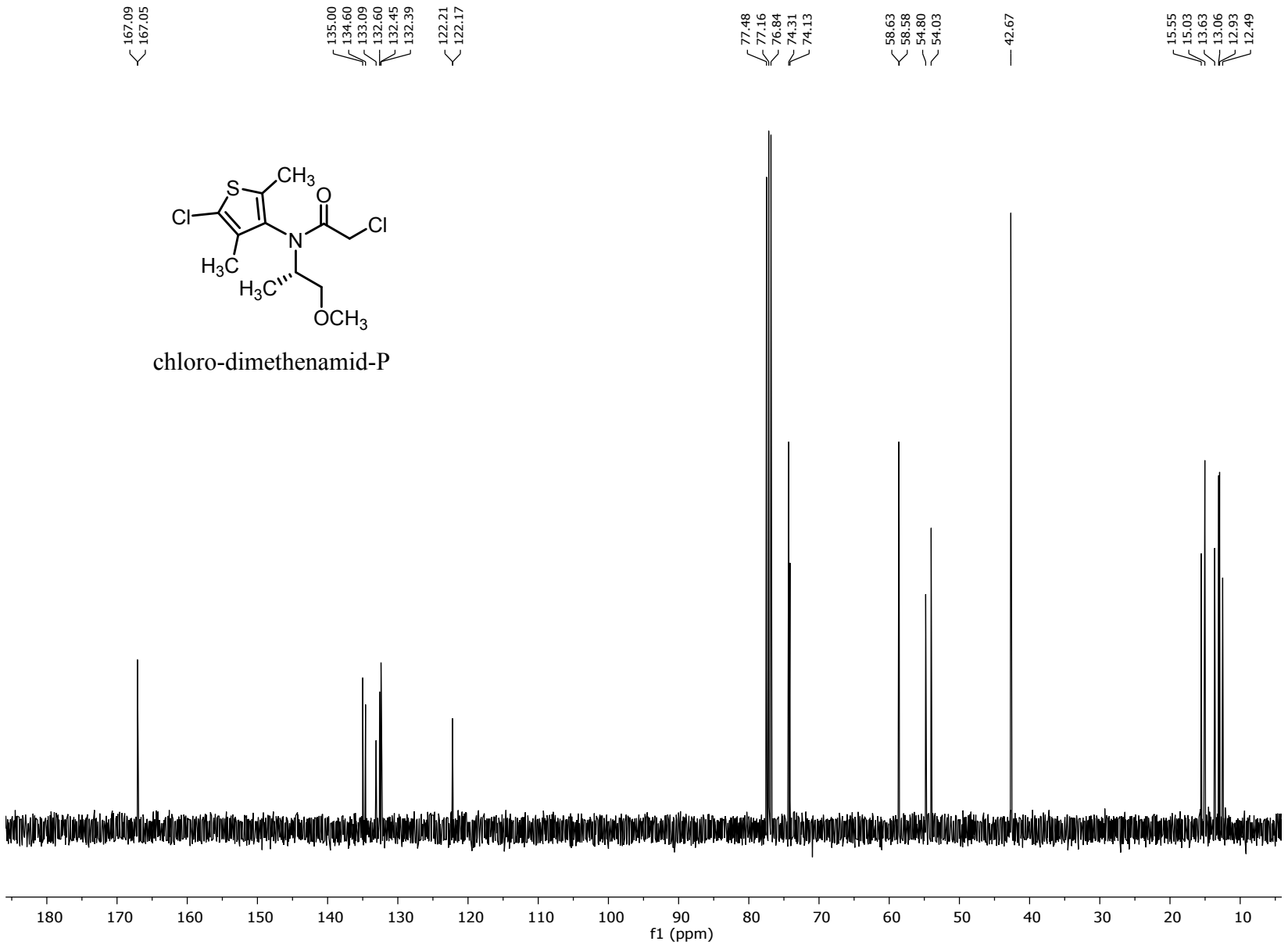
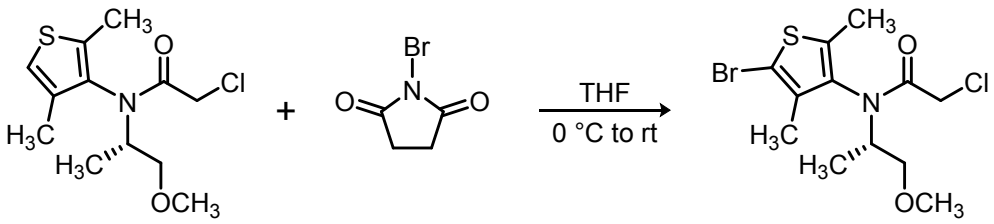


Fig. S4. ^{13}C NMR spectrum of chloro-dimethenamid-P (100 MHz, $CDCl_3$).

Synthesis of bromo-dimethenamid-P



To a flame-dried 25 mL flask under argon equipped with a magnetic stirring bar was added a solution of dimethenamid-P (75.0 mg, 0.272 mmol, 1.00 eq.) in 8 mL of anhydrous tetrahydrofuran. This solution was cooled to 0 °C in an ice bath, and solid *N*-bromosuccinimide (53.2 mg, 0.299 mmol, 1.10 eq.) was added in a single portion. The initially colorless reaction mixture immediately turned bright yellow. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 15 min. Thin layer chromatography (3:1 hexanes / ethyl acetate, UV / anisaldehyde stain visualization) showed that the brominated product was copolar with dimethenamid-P (R_f = 0.27) but stained light blue whereas dimethenamid-P stained white. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (4:1 hexanes / ethyl acetate) to give pure bromo-dimethenamid-P as a colorless oil (95 mg, 98%).

At room temperature in $CDCl_3$, bromo-dimethenamid-P exists as a ~1.15:1.00 mixture of atropisomers due to restricted rotation about the bond connecting the amide nitrogen atom to the thiophene ring. Fractional integration values represent the contributions of each atropisomer to the total proton count for one molecule of dimethenamid-P.

IR: 2979, 2922, 1668, 1561, 1448, 1394, 1378, 1348, 1239, 1200, 1145, 1109, 1010, 977, 940, 793, 767, 716, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, Fig. S5): δ 1.11 (1.60H, d, *J* = 7.0 Hz), 1.19 (1.43H, d, *J* = 7.0 Hz), 2.00 (1.56H, s), 2.02 (1.39H, s), 2.30 (1.37H, s), 2.32 (1.58H, s), 3.26 (1.37H, s), 3.30 (1.58H, s), 3.31-3.39 (1H, m), 3.48-3.54 (1H, m), 3.63-3.72 (2H, m), 4.48 (0.48H, m), 4.59 (0.56H, m).

^{13}C NMR (100 MHz, $CDCl_3$, Fig. S6): δ 13.3, 13.9, 14.2, 14.6, 15.1, 15.6, 42.8, 54.1, 54.9, 58.6, 58.7, 74.2, 74.4, 106.67, 106.71, 133.1, 133.6, 135.19, 135.23, 137.4, 137.8, 167.1, 167.2.

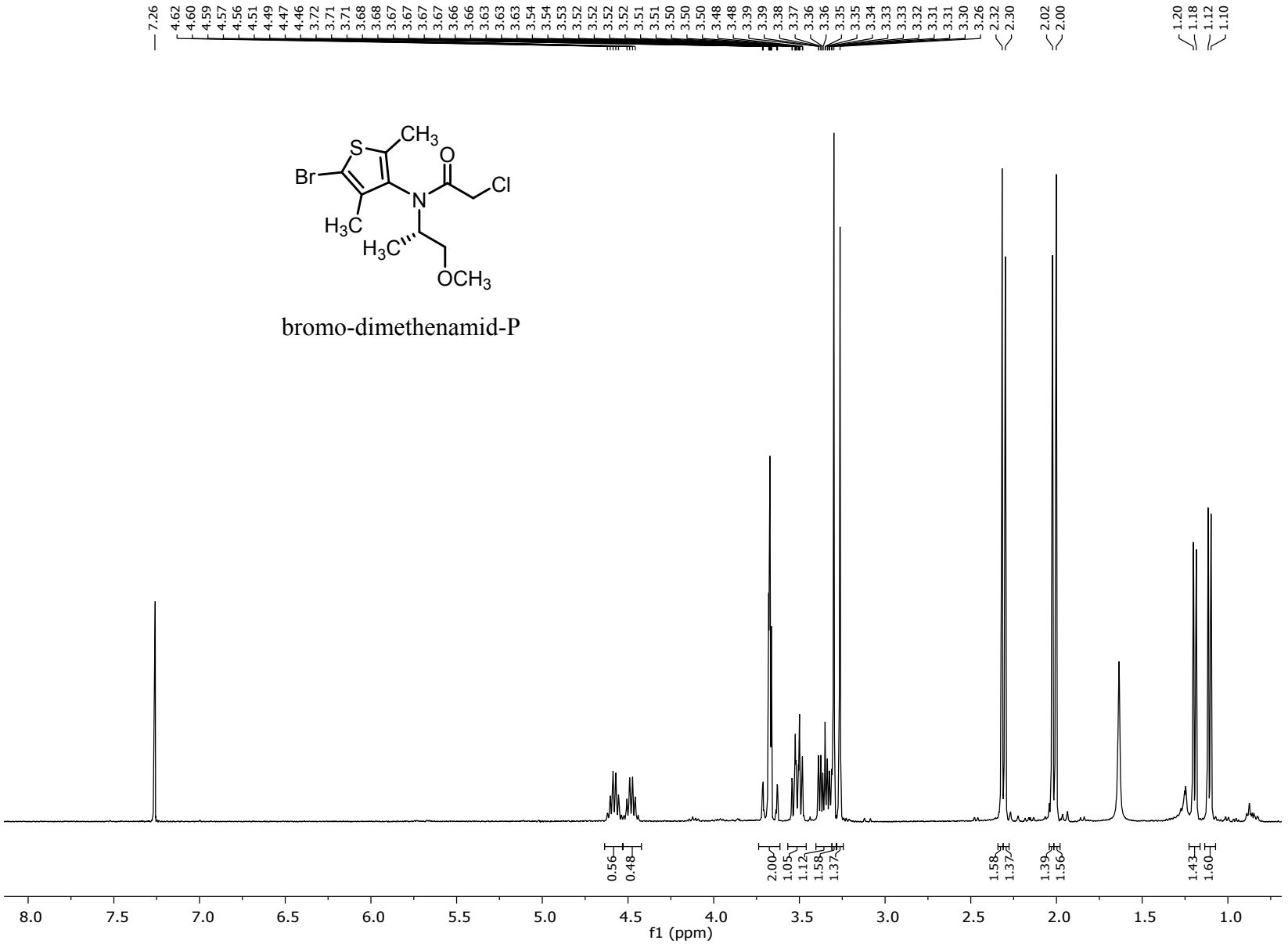


Fig. S5. ^{1}H NMR spectrum of bromo-dimethenamid-P (400 MHz, $CDCl_3$).

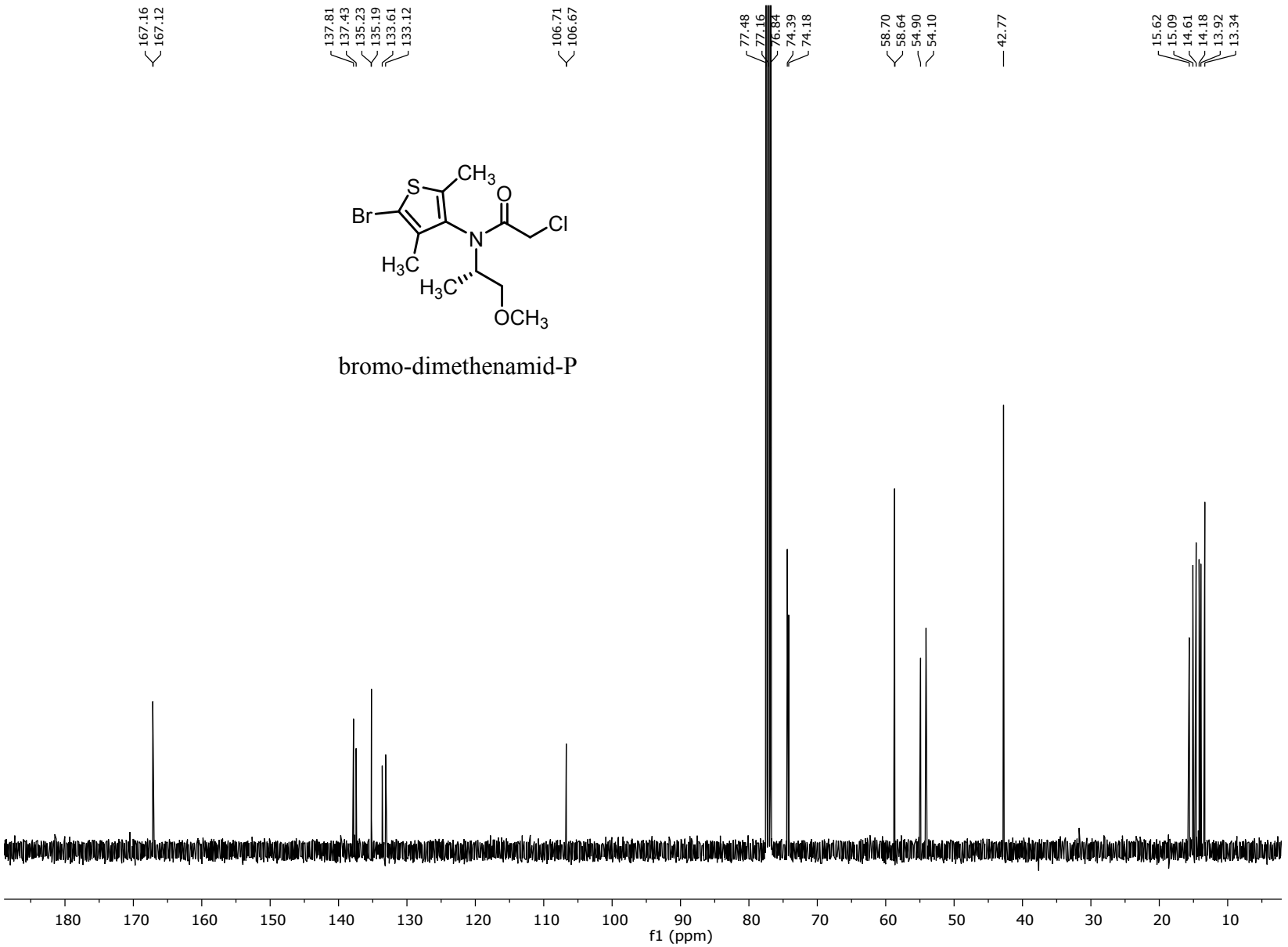


Fig. S6. ^{13}C NMR spectrum of bromo-dimethenamid-P (100 MHz, $CDCl_3$).

NMR data for dimethenamid-P

NMR data for dimethenamid-P is not readily available in the literature and is therefore reproduced below for reference (Fig. S7 and S8). At room temperature in $CDCl_3$, dimethenamid-P exists as a ~1.15:1.00 mixture of atropisomers due to restricted rotation about the bond connecting the amide nitrogen atom to the thiophene ring. Fractional integration values represent the contributions of each atropisomer to the total proton count for one molecule of dimethenamid-P.

^{1}H NMR (400 MHz, $CDCl_3$, Fig. S7): δ 1.12 (1.73H, d, J = 7.0 Hz), 1.20 (1.46H, d, J = 6.9 Hz), 2.06 (1.62H, s), 2.08 (1.32H, s), 2.33 (1.41H, s), 2.35 (1.52H, s), 3.27 (1.52H, s), 3.30 (1.41H, s), 3.32-3.40 (1H, m), 3.51-3.59 (1H, m), 3.61-3.70 (2H, m), 4.47 (0.46H, m), 4.57 (0.53H, m), 6.81 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$, Fig. S8): δ 13.5, 14.0, 14.4, 14.7, 15.2, 15.7, 42.9, 54.0, 54.8, 58.6, 58.7, 74.3, 74.5, 118.4, 118.5, 133.8, 134.3, 135.2, 135.3, 137.0, 137.3, 167.17, 167.22.

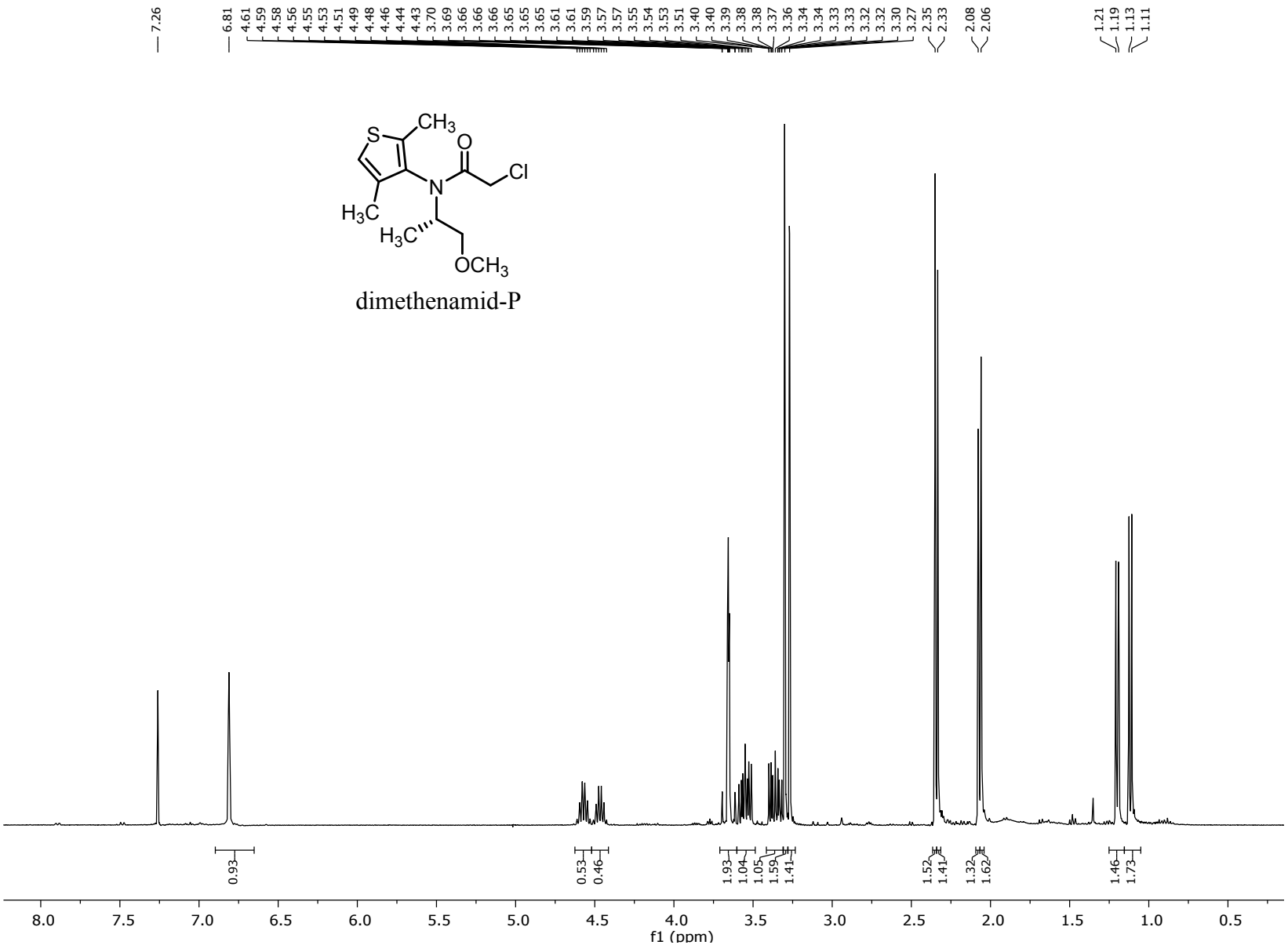


Fig. S7. ^{1}H NMR spectrum of dimethenamid-P (400 MHz, $CDCl_3$).

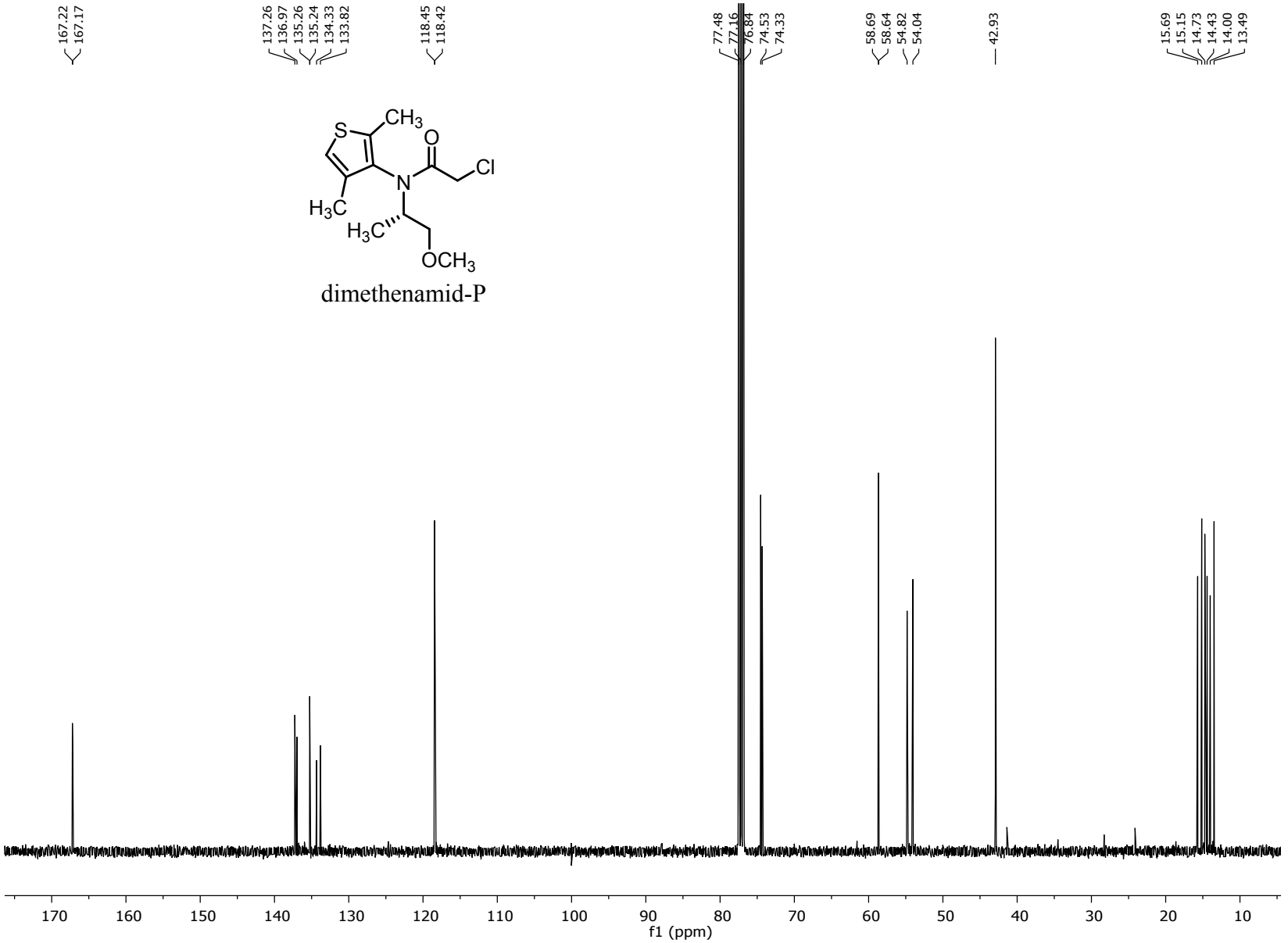


Fig. S8. ^{13}C NMR spectrum of dimethenamid-P (100 MHz, $CDCl_3$).

Additional experimental methods

Analytical methods for (1) stoichiometry of TMB + free chlorine or free bromine experiments and (2) experiments examining TMB as a quencher for bromination reactions of anisole. Toluene samples (1.0 μL) containing anisole, TMB, as well as their chlorinated and brominated products were analyzed on an Agilent 7890A gas chromatograph (GC) interfaced with an Agilent 5975C mass spectrometer (MS). An Agilent DB-5MS+DG column (30 m + 10 m DuraGuard, 0.250 mm inner diameter, 0.25 μm film thickness) was used. The GC inlet was set to 280 ^{o}C and operated in splitless mode. The total column flow was constant at 1 mL min^{-1}. The oven temperature program included an initial temperature of 70 ^{o}C (no hold), ramp at 10 ^{o}C min^{-1} to 125 ^{o}C (no hold), ramp at 32 ^{o}C min^{-1} to 285 ^{o}C (1 min final hold); the total analysis time was 17 min. The transfer line was fixed at 290 ^{o}C. Retention times and ions detected in selected ion monitoring mode for each analyte are shown in **Table S2**.

Table S2. GC-MS Selected Ion Monitoring (SIM) Method Details for Analyzing Anisole, TMB, and their Halogenated Products

Analyte	*SIM Group*	*Retention Time (min)*	*Quantitation Ion*	*Monitoring Ion*	*Extraction Efficiency*
anisole	A	5.35	108 $M^{+\bullet}$	none [a]	104%
2-chlorobenzonitrile (internal standard)	B	9.85	137 $M^{+\bullet}$	102 $(M - Cl)^{+}$	not determined [b]
4-bromoanisole	C	10.47	186 $M^{+\bullet}$	171 $(M - CH_3)^{+}$	91%
2-bromoanisole		10.59	186 $M^{+\bullet}$	171 $(M - CH_3)^{+}$	89%
1,3,5-trimethoxybenzene	D	13.43	168 $M^{+\bullet}$	137 $(M - OCH_3)^{+}$	103%
2-chloro-1,3,5-trimethoxybenzene	E	14.74	202 $M^{+\bullet}$	204 $M^{+\bullet}$ (^{37}Cl)	104%
2-bromo-1,3,5-trimethoxybenzene		15.14	246 $M^{+\bullet}$	231 $(M - CH_3)^{+}$	95%

[a] Background ions (likely originating from the solvent toluene) were detected with mass-to-charge ratios identical to the major daughter ions of anisole; therefore, no monitoring ions were recorded for this analyte. Interfering ions did not, however, preclude accurate quantitation of the molecular ion of anisole.

[b] The raw peak areas of various analytes were normalized to the peak area of the internal standard before the concentrations of the analytes were computed. The extraction efficiency of the internal standard was not determined as it was not used in our computations.

TMB as a quencher for chlorination reactions of 2,4-dichlorophenol. Toluene samples (1.0 μL) containing 2,4-dichlorophenol, TMB, as well as their chlorinated products (with 2-chlorobenzonitrile as the internal standard) were analyzed on an Agilent 7890B GC interfaced with an Agilent 5977A MS. An Agilent HP-5MS UI column (30 m × 0.25 mm, film thickness = 0.25 μm) was used. The GC inlet was set to 280 °C and operated in split mode (split ratio = 15:1). The total column flow was constant at 1 mL min^{-1}. The oven temperature program included an initial temperature of 70 °C (no hold), ramp at 10 °C min^{-1} to 100 °C (no hold), ramp at 30 °C min^{-1} to 290 °C (1.667 min final hold); the total analysis time was 11 min. The transfer line temperature was fixed at 290 °C. Retention times and ions detected in selected ion monitoring mode for each analyte are shown in **Table S3**.

Table S3. GC-MS Selected Ion Monitoring (SIM) Method Details for Analyzing 2,4-Dichlorophenol, TMB, and their Chlorinated Products

Analyte	*SIM* Group	*Retention Time (min)*	*Quantitation Ion*	*Monitoring Ion*	*Extraction Efficiency*
2,4-dichlorophenol	A	5.11	162 $M^{+\bullet}$	126 $(M - H - Cl)^+$	96%
2-chlorobenzonitrile (internal standard)		5.15	137 $M^{+\bullet}$	102 $(M - Cl)^+$	not determined [a]
2,4,6-trichlorophenol	B	6.22	196 $M^{+\bullet}$	160 $(M - H - Cl)^+$	93%
1,3,5-trimethoxybenzene		6.46	168 $M^{+\bullet}$	137 $(M - OCH_3)^+$	103%
2-chloro-1,3,5-trimethoxybenzene	C	7.45	202 $M^{+\bullet}$	204 $M^{+\bullet}$ (^{37}Cl)	104%
2,4-dichloro-1,3,5-trimethoxybenzene		7.87	236 $M^{+\bullet}$	238 $M^{+\bullet}$ (^{37}Cl)	99%

[a] The raw peak areas of various analytes were normalized to the peak area of the internal standard before the concentrations of the analytes were computed. The extraction efficiency of the internal standard was not determined as it was not used in our computations.

Experimental design for chlorination and bromination reactions of dimethenamid-P. The performance of TMB as a quencher was investigated for kinetic experiments involving chlorination and bromination of the herbicide dimethenamid-P (structure shown in **Fig. S7**) using batch reactors. The experimental setup is similar to that described previously.[4, 5] Briefly, reaction solutions (total volume = 25 mL) were prepared in 40-mL amber glass vials and contained borate buffer (10 mM adjusted to pH 8.0 using HNO_3), $NaNO_3$ (98.5 mM), NaCl (1.3 mM), NaBr (up to 130 μM), and dimethenamid-P (10.0 μM). Reactors were incubated in a circulating water bath at 20.00 ± 0.01 °C for several minutes and then dosed with NaOCl (305 μM) at t = 0. Following addition of NaOCl, vials were capped, shaken manually for 10 s, and returned to the water bath. Aliquots of reaction solution (0.90 mL) were obtained periodically and transferred to 4-mL amber glass vials pre-amended with TMB (0.156 mL at 3.38 mM in methanol) or sodium thiosulfate (42 μL at 10.1 mM in 18 MΩ cm water); 4-mL vials containing a quencher and an aliquot of a reaction solution were capped and shaken manually for 10 s.

After all samples from a time course were quenched, toluene (0.45 mL, containing 2-chlorobenzonitrile at 10.2 μM as the internal standard) was added to each 4-mL vial as the extraction solvent. Vials were capped and shaken manually for 30 s. After phase separation was re-established, a portion of the toluene phase (0.2 mL) from each sample was transferred to a 0.3-mL glass insert seated inside an amber glass 2-mL autosampler vial, which was subsequently secured with a screw-top plastic cap fitted with a PTFE-lined septum. Dimethenamid-P, TMB, as well as their halogenated products were analyzed concurrently via GC-MS (**Table S4**).

Analytical method for (1) competitive halogenation experiments and (2) experiments examining TMB as a quencher for chlorination and bromination reactions of dimethenamid-P. Toluene samples (1.0 μL) containing dimethenamid-P, TMB, as well as their halogenated products, were analyzed on an Agilent 7890A GC interfaced with an Agilent 5975C MS. An Agilent DB-35MS UI column (30 m, 0.250 mm inner diameter, 0.25 μm film thickness) was used to effect separations. The GC inlet was set to 260 °C and operated in splitless mode. The total column flow was constant at 1.0 mL min^{-1}. The oven temperature program included an initial temperature of 70 °C (0.5 min hold), ramp at 20 °C min^{-1} to 190 °C (no hold time), ramp at 10 °C min^{-1} to 290 °C (no hold time); the total analysis time was 16.5 min. The transfer line was fixed at 280 °C. Retention times and ions quantified in selected ion monitoring mode for each analyte are shown in **Table S4**.

Table S4. GC-MS Selected Ion Monitoring (SIM) Method Details for Analyzing Dimethenamid-P, TMB, and their Halogenated Products

Analyte	*SIM Group*	*Retention time (min)*	*Quantitation Ion*	*Monitoring Ion*	*Extraction Efficiency*
2-chlorobenzonitrile (internal standard)	A	5.60	137 $M^{+\bullet}$	102 $(M - Cl)^+$	not determined [a]
1,3,5-trimethoxybenzene	B	7.20	168 $M^{+\bullet}$	137 $(M - OCH_3)^+$	103%
2-chloro-1,3,5-trimethoxybenzene	C	9.18	202 $M^{+\bullet}$	204 $M^{+\bullet}$ (^{37}Cl)	104%
2,4-dichloro-1,3,5-trimethoxybenzene	D	10.03	236 $M^{+\bullet}$	238 $M^{+\bullet}$ (^{37}Cl)	99%
2-bromo-1,3,5-trimethoxybenzene			246 $M^{+\bullet}$	248 $M^{+\bullet}$ (^{81}Br)	95%
2-bromo-4-chloro-1,3,5-trimethoxy-benzene	E	10.90	282 $M^{+\bullet}$ (^{35}Cl, ^{81}Br)	280 $M^{+\bullet}$ (^{35}Cl, ^{79}Br)	111%
dimethenamid-P	F	11.14	154 [b]	203 [b]	110%
2,4-dibromo-1,3,5-trimethoxybenzene	G	11.90	326 $M^{+\bullet}$ (^{79}Br, ^{81}Br)	324 $M^{+\bullet}$ (^{79}Br, ^{79}Br)	112%
chloro-dimethenamid-P	H	12.11	188 [b]	237 [b]	100%
bromo-dimethenamid-P	I	13.10	232 [b]	234 [b]	109%

[a] The raw peak areas of various analytes were normalized to the peak area of the internal standard before the concentrations of the analytes were computed. The extraction efficiency of the internal standard was not determined as it was not used in our computations.

[b] Based on the method reported in ref [5]

Table S5. Instrumental and Method Limits of Detection (LOD) and Limits of Quantitation (LOQ) for TMB and its Halogenated Derivatives [a]

Analyte	*Instrumental LOD (μM)*	*Instrumental LOQ (μM)*	*Method LOD (μM)*	*Method LOQ (μM)*
TMB	1.5	5	0.8	2
Cl-TMB	0.15	0.5	0.08	0.2
Br-TMB	0.06	0.2	0.03	0.10
diCl-TMB	0.11	0.4	0.05	0.2

[a] Instrumental LOD/LOQ values are based on the GC-MS methods described above. Method LOD/LOQ values include corrections for liquid-liquid extraction efficiency and preconcentration.

Determination of liquid-liquid extraction efficiencies

The extraction efficiencies listed in **Tables S2–S4** were assessed by spiking each analyte of interest into an aqueous solution with the same matrix as the reaction solution used in the corresponding halogenation experiments. Toluene (containing 2-chlorobenzonitrile as internal standard) was then added to the aqueous solution containing a known concentration of the analyte for liquid-liquid extraction. For the analytes listed in **Tables S2 and S4**, the volumes of aqueous solution and toluene and the extraction procedure are the same as those described in Section 2.3 of the main text. For the analytes listed in **Table S3**, the extraction procedure is identical to that described in Section 2.2. Samples were analyzed using GC-MS according to the methods described on p. S19, S20, and S22.

Concentrations of the analytes of interest in the toluene extracts were quantified through the use of external calibration standards and were corrected for the detector response of the internal standard. The extraction efficiency of each analyte was computed using the following equation:

$$\text{extraction efficiency} = \frac{\text{measured concentration}}{\text{nominal concentration}} \times 100\%$$

The extraction efficiencies listed in **Tables S2–S4** were taken into account when calculating concentrations in the aqueous phase from concentrations measured in toluene extracts.

Mass balance on TMB

In the presence of free chlorine and free bromine, TMB is transformed into 2-chloro-1,3,5-trimethoxybenzene (Cl-TMB) and 2-bromo-1,3,5-trimethoxybenzene (Br-TMB), respectively. When free chlorine is present in sufficient excess, Cl-TMB and Br-TMB can be further chlorinated into 2,4-dichloro-1,3,5-trimethoxybenzene (Cl_2-TMB) and 2-bromo-4-chloro-1,3,5-trimethoxybenzene (BrCl-TMB), respectively. When free bromine is present in excess, Cl-TMB and Br-TMB can be further brominated to form BrCl-TMB and 2,4-dibromo-1,3,5-trimethoxybenzene (Br_2-TMB), respectively. Thus, the TMB mass balance in our quenched samples can be computed as follows:

$$[TMB]_{tot} = [TMB] + [Cl - TMB] + [Br - TMB] + \left[Cl_2 - TMB\right] + [BrCl - TMB] + [Br_2 - TMB]$$

Under the conditions employed in our halogenation experiments, dihalogenation of TMB did not occur to any significant extent ($\leq 0.3\%$ of $[TMB]_o$). Thus, the TMB mass balance can be approximated by the following expressions:

Chlorination: $[TMB]_{tot} = [TMB] + [Cl - TMB]$

Chlorination and bromination: $[TMB]_{tot} = [TMB] + [Cl - TMB] + [Br - TMB]$

Determination of bromination rate constants for TMB

For all of the competition kinetics experiments performed herein, $[TMB]_o = [HOBr]_{tot,o} =$ 10 μM and $[\text{dimethenamid-P}]_o$ = 100 μM, such that TMB and dimethenamid-P (DM) were in competition for the available free bromine. A greater concentration of DM relative to TMB was employed to compensate for the lesser reactivity of DM and thereby facilitate quantifiable levels of transformation for both DM and TMB. The extent of TMB bromination relative to that of DM bromination can be used to calculate apparent second-order rate constants for bromination of TMB ($k_{app,TMB}$, M^{-1} s^{-1}) as described below, noting that apparent second-order rate constants can be calculated for bromination of DM ($k_{app,DM}$, M^{-1} s^{-1}) for each set of solution conditions based on previously reported second-order rate constants.[4]

The bromination rate of DM can be expressed as:

$$\frac{-d[DM]}{dt} = k_{app,DM}[DM][HOBr]_{tot} \tag{S1}$$

Rearranging **eqn S1** and integrating gives:

$$\int_{[DM]_o}^{[DM]_f} \frac{-d[DM]}{[DM]} = k_{app,DM}\int_0^t [HOBr]_{tot}\,dt \tag{S2}$$

Solving the definite integral on the left-hand side yields:

$$-\left(\ln [DM]_f - \ln [DM]_o\right) = k_{app,DM}\int_0^t [HOBr]_{tot}\,dt \tag{S3}$$

Rearranging the logarithmic terms:

$$\ln \frac{[DM]_o}{[DM]_f} = k_{app,DM}\int_0^t [HOBr]_{tot}\,dt \tag{S4}$$

Solving for $k_{app,DM}$: (S5)

$$k_{app,DM} = \frac{1}{\int_0^t [HOBr]_{tot}\,dt}\ln \frac{[DM]_o}{[DM]_f}$$

The bromination rate of TMB can be expressed as:

$$\frac{-d[TMB]}{dt} = k_{app,\,TMB}[TMB][HOBr]_{tot} \tag{S6}$$

Applying the mathematical manipulations depicted in **eqn S2 – S5** to **eqn S6** gives:

$$k_{app,\,TMB} = \frac{1}{\int_0^t [HOBr]_{tot}\,dt} \ln \frac{[TMB]_o}{[TMB]_f} \tag{S7}$$

Dividing **eqn S7** by **eqn S5**:

$$\frac{k_{app,\,TMB}}{k_{app,\,DM}} = \frac{\ln\left(\frac{[TMB]_o}{[TMB]_f}\right)}{\ln\left(\frac{[DM]_o}{[DM]_f}\right)} \tag{S8}$$

When modeling reactivity in systems containing a large excess of $[HOBr]_{tot}$ relative to the concentration of organic nucleophiles, apparent second-order rate constants (k_{app}, $M^{-1}\ s^{-1}$) can be converted to pseudo-first-order rate constants (k_{obs}, s^{-1}) by multiplying k_{app} by $[HOBr]_{tot,o}$. Under such conditions:

$$\frac{k_{app,\,TMB}[HOBr]_{tot,o}}{k_{app,\,DM}[HOBr]_{tot,\,o}} = \frac{k_{obs,\,TMB}}{k_{obs,\,DM}} = \frac{\ln\left(\frac{[TMB]_o}{[TMB]_f}\right)}{\ln\left(\frac{[DM]_o}{[DM]_f}\right)} \tag{S9}$$

Initial and final concentrations of TMB and DM, along with calculated values of $k_{obs,\,DM}$ (based on reactivity data reported previously[4]), were used to determine the value of $k_{obs,\,TMB}$ for each set of experimental conditions. Initial concentrations were calculated based on gravimetric measurements of spiking and buffer solutions added to each reactor. Final concentrations were obtained from GC-MS analyses of aliquots of reaction solutions that were quenched after 1 min of reaction time. Experiments examining the effects of reaction time (at 1, 3, and 5 min) on calculated values of $k_{obs,\,TMB}$ indicate that 1 min was sufficient to permit ~100% consumption of free bromine (data not shown).

Influence of quenchers on the stability of disinfection byproducts (DBPs)

MTBE samples (1.0 μL) containing disinfection byproducts (DBPs) and 1,2-dibromopropane as the internal standard were analyzed on an Agilent 7890B GC interfaced with a micro-electron capture detector (μ-ECD). An Agilent HP-5 column (30 m × 0.32 mm, film thickness = 0.25 μm) was used. The methods used to analyze different DBPs are described below.

Table S6. GC-ECD Method Details for Analyzing Chloropicrin, Chloral Hydrate, and Tribromoacetaldehyde

	Chloropicrin	**Chloral hydrate**	**Tribromoacetaldehyde**
Injection mode	splitless	splitless	splitless
Inlet temperature	117 °C	250 °C	250 °C
Detector temperature	297 °C	250 °C	250°C
Carrier gas flow	1 mL/min	1 mL/min	1 mL/min
Oven temperature program	35 °C for 6 min 30 °C/min to 190 °C, hold for 1.5 min 40 °C/min to 280 °C, hold for 2.333 min	35°C for 2 min 10 °C/min to 100 °C, no hold time 35 °C/min to 285 °C, no hold time	35 °C for 2 min 10 °C/min to 100 °C, no hold time 35 °C/min to 285 °C, hold for 3 min
Total run time	17.250 min	13.786 min	16.786 min
Extraction efficiency	92.2%	60.7%	38.1%

Table S7. GC-ECD Method Details for Analyzing Chloroacetonitrile, Dichloroacetonitrile, and Trichloroacetonitrile

	Chloroacetonitrile	**Dichloroacetonitrile**	**Trichloroacetonitrile**
Injection mode	split (15:1)	split (15:1)	split (15:1)
Inlet temperature	175 °C	175 °C	175 °C
Detector temperature	275 °C	275 °C	275 °C
Carrier gas flow	0.8 mL/min	0.8 mL/min	0.8 mL/min
Oven temperature program	27 °C for 4 min 15 °C/min to 75 °C, no hold time 35 °C/min to 185 °C, no hold time	27 °C for 4 min 15 °C/min to 75 °C, no hold time 35 °C/min to 185 °C, no hold time	27 °C for 4 min 15 °C/min to 75 °C, no hold time 35 °C/min to 185 °C, no hold time
Total run time	10.343 min	10.343 min	10.343 min
Extraction efficiency	58.2%	80.2%	78.1%

Table S8. GC-ECD Method Details for Analyzing Bromoacetonitrile and Dibromoacetonitrile

	Bromoacetonitrile	**Dibromoacetonitrile**
Injection mode	split (15:1)	split (15:1)
Inlet temperature	175 °C	175 °C
Detector temperature	275 °C	275 °C
Carrier gas flow	1 mL/min	1 mL/min
Oven temperature program	35 °C for 2 min 15 °C/min to 100 °C, no hold time 20 °C/min to 185 °C, no hold time	35 °C for 2 min 15 °C/min to 100 °C, no hold time 20 °C/min to 185 °C, no hold time
Total run time	10.583 min	10.583 min
Extraction efficiency	61.5%	79.3%

Chlorination of 2,4-dichlorophenol (2,4-DCP) with TMB as quencher

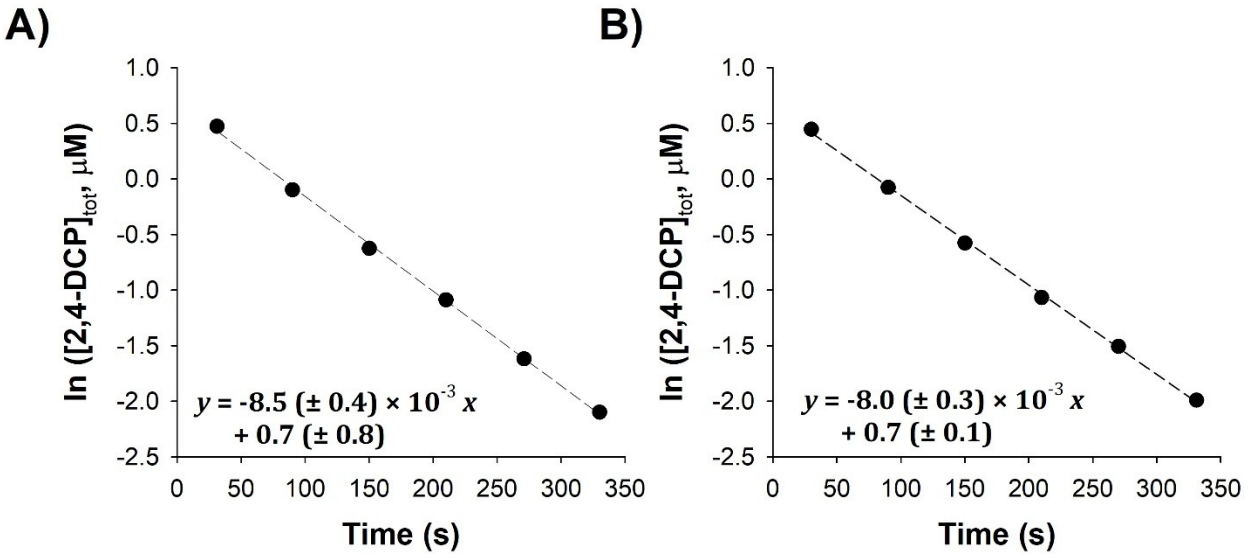


Fig. S9. Linear regressions of ln[2,4-DCP] versus time data from 2,4-DCP chlorination experiments using **(A)** TMB or **(B)** sodium thiosulfate to quench free chlorine. Reaction conditions: $[2,4\text{-DCP}]_{tot,o}$ = 2 μM, $[NaOCl]_o$ = 128 μM, pH = 7.08 (buffered with 10 mM phosphate), $[NaNO_3]$ = 95 mM, [NaCl] = 5 mM. Uncertainties in the equations indicate 95% confidence intervals.

Reaction of 1,3,5-trimethoxybenzene (TMB) with free bromine

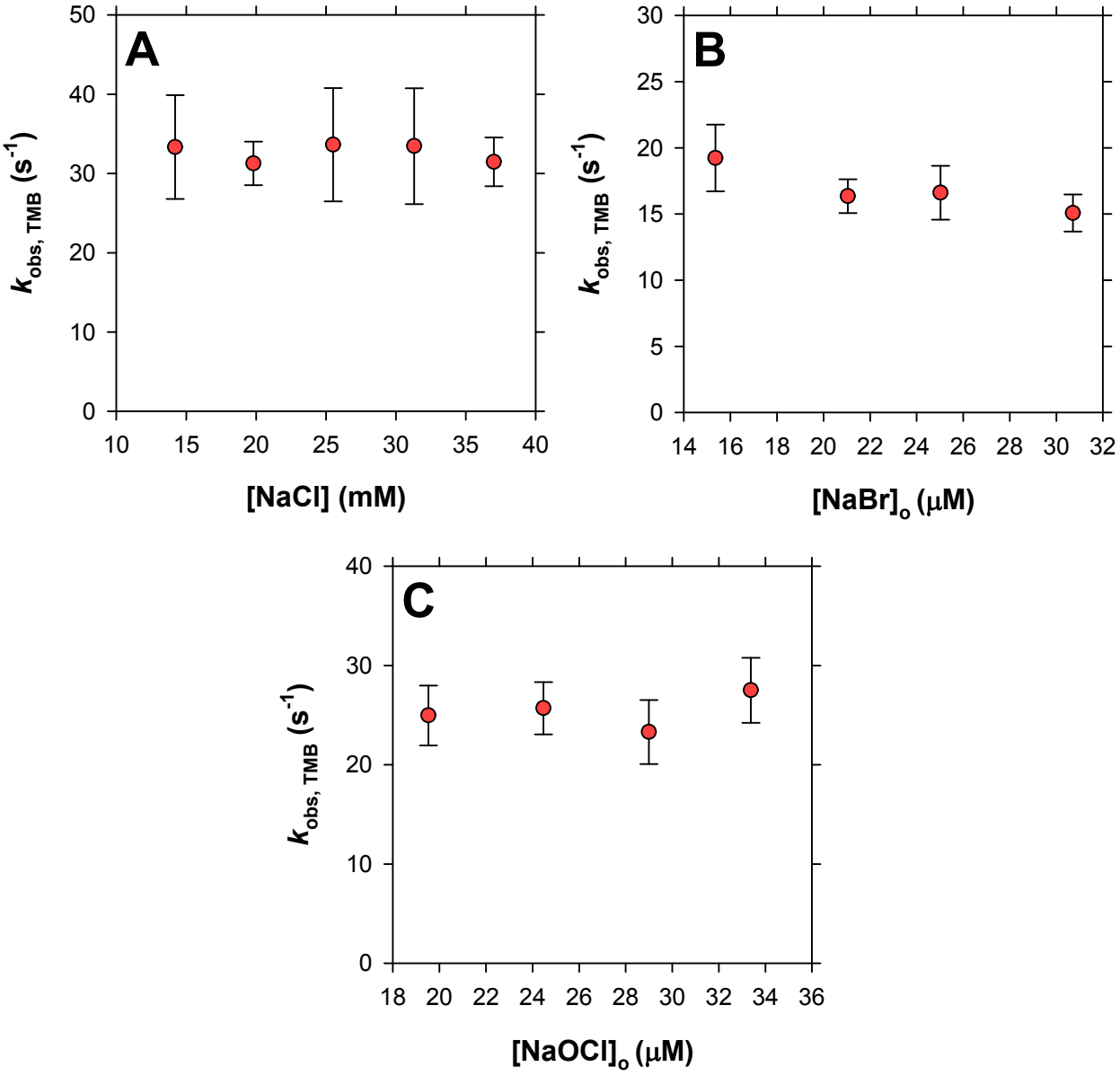


Fig. S10. Pseudo-first-order rate constants ($k_{obs,TMB}$) for the reaction of 1,3,5-trimethoxybenzene with free bromine as a function of the concentration of added **(A)** NaCl (pH 7.1, $[NaOCl]_o$ = 20 μM, [NaCl] = 14–37 mM), **(B)** NaBr (pH 7.0, $[NaOCl]_o$ = 10 μM, [NaBr] = 15–31 μM), and **(C)** NaOCl (pH 7.0, $[NaOCl]_o$ = 20–34 μM). Error bars denote 95% confidence intervals associated with experiments performed in triplicate. Values of k_{obs} were determined via competition kinetic experiments involving dimethenamid-P as a reference compound (see "Determination of bromination rate constants for TMB" above for additional details). Conditions applicable to all frames (unless specified otherwise): [borate buffer] = 20 mM, $[NaBr]_o$ = 10 μM, [NaCl] = 10 mM, $[NaNO_3]$ + [NaCl] = 0.100 M (excepting frame C, for which $[NaNO_3]$ + [NaCl] = 0.070 M), T = 20.0 °C.

Bromination of anisole

TMB and sodium thiosulfate were employed as quenchers for anisole bromination reactions at pH 7.48, 8.02, 8.50, and 9.02. Regiospecific pseudo-first-order rate constants corresponding to the formation of 4-bromoanisole (major product) and 2-bromoanisole (minor product) are shown in **Table S9**.

Table S9. Pseudo-First-Order Rate Constants for the Formation of 4-Bromoanisole ($k_{I,obs}$) and 2-Bromoanisole ($k_{II,obs}$) in Solutions of Free Bromine + Anisole Measured Using Thiosulfate or TMB as Quenchers [a]

Product	pH	Pseudo-first-order rate constant ± 95% confidence interval (s^{-1})		Percent Difference [d]	Significantly Different at 95% CI?
		Quencher = TMB [b]	Quencher = Thiosulfate [c]		
4-bromo-anisole	7.48	$(8.6 \pm 0.7) \times 10^{-4}$	$(7.3 \pm 1.5) \times 10^{-4}$	18%	No
	8.02	$(1.85 \pm 0.13) \times 10^{-4}$	$(2.0 \pm 0.4) \times 10^{-4}$	–9%	No
	8.50	$(6.34 \pm 0.13) \times 10^{-5}$	$(5.7 \pm 1.2) \times 10^{-5}$	12%	No
	9.02	$(1.19 \pm 0.02) \times 10^{-5}$	$(1.1 \pm 0.2) \times 10^{-5}$	8%	No
2-bromo-anisole	7.48	$(1.27 \pm 0.15) \times 10^{-4}$	$(1.03 \pm 0.12) \times 10^{-4}$	23%	Yes
	8.02	$(2.42 \pm 0.17) \times 10^{-5}$	$(2.7 \pm 0.3) \times 10^{-5}$	–10%	No
	8.50	$(7.25 \pm 0.09) \times 10^{-6}$	$(6.7 \pm 0.7) \times 10^{-6}$	8%	No
	9.02	$(1.13 \pm 0.03) \times 10^{-6}$	$(1.12 \pm 0.13) \times 10^{-6}$	0.7%	No

[a] Reaction conditions: $[NaBr]_o$ = 130 μM, $[anisole]_o$ = 6.0 μM, $[HOCl]_{tot,o}$ = 305 μM, [carbonate or borate buffer] = 20 mM, [NaCl] = 10 mM, $[NaNO_3]$ = 90 mM, T = 20.00 ± 0.01 °C.

[b] Determined experimentally based on the method reported in the main text.

[c] Calculated using eq. 3 (main text) and second-order rate constants reported in Sivey et al.[6] Confidence intervals were determined by propagating uncertainties associated with second-order rate constants and assuming an average uncertainty of ±0.1 for log(*K*) values (i.e., equilibrium constants used to calculate concentrations of brominating agents). This assumed average uncertainty for log(*K*) values is consistent with uncertainties reported for the pK_a of HOBr and the log(*K*) values associated with the hydrolysis of BrCl and Br_2 (see ref 7 and references therein).

[d] % difference = $\left(\frac{k_{obs,\ TMB} - k_{obs,\ thiosulfate}}{k_{obs,thiosulfate}}\right) \times 100\%$

Reaction of 1,3,5-trimethoxybenzene (TMB) with monochloramine

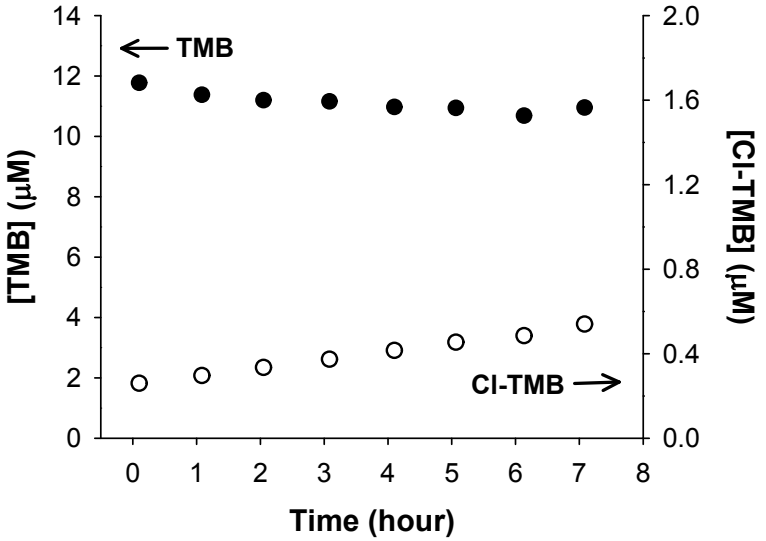


Fig. S11. The stability of TMB in the presence of monochloramine formed via free chlorine + excess NH_4Cl. Reaction conditions: pH 7.03, $[TMB]_o$ = 12 μM, $[NaOCl]_o$ = 154 μM, $[NH_4Cl]_o$ = 385 μM, [phosphate buffer] = 10 mM, T = 25°C.

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