Organic Syntheses

Large Scale Oxidative Cyclization of (*E*)-Hex-3-en-1-yl (4-Methoxyphenyl)sulfamate

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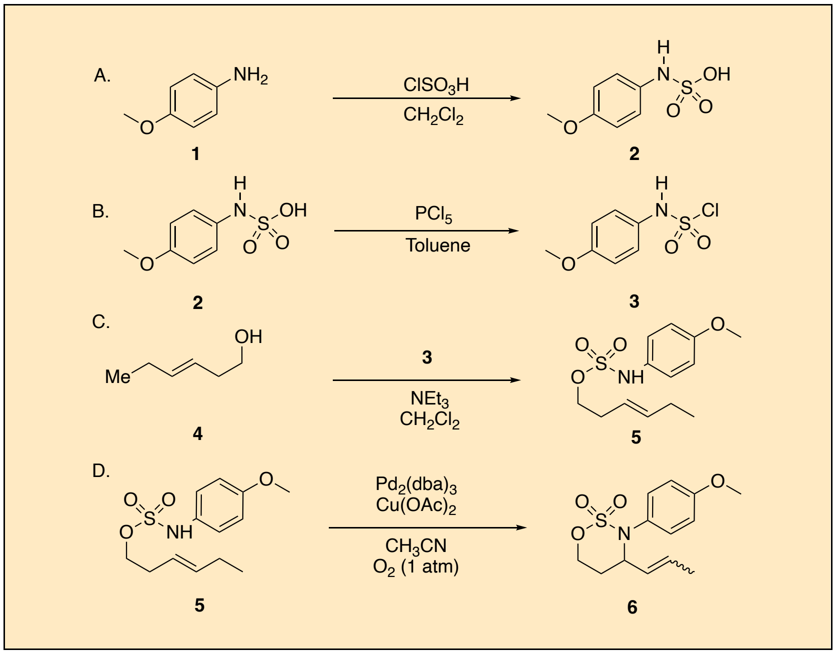
Checked by Jacob P. Sorrentino and Neil Garg



Procedure (Note 1)

A. *(4-Methoxyphenyl)sulfamic acid* (**2**). A flame-dried 500 mL three-necked (24/40 joint) round-bottomed flask is equipped with a 4 cm x 1 cm teflon-coated magnetic stir bar. The necks are then equipped with a thermometer, a glass stopper, and a three-way glass stopcock, which is then connected to a Schlenk line (Figure 1A). To this flask is added 4-methoxyaniline (**1**) (12.32 g, 100 mmol, 2 equiv) (Note 2). The flask is then evacuated for 5 min and backfilled with N_2 three times before dichloromethane (100 mL) (Note 3) is added in two portions using a 60 mL syringe. The flask is then lowered into a 0 °C ice-water bath and allowed to cool for 10 min. A separate flame-dried 50 mL pear-shaped flask (14/20 joint) is sealed with a rubber septum and connected to a nitrogen inlet line by an 18 gauge x 1.5 in needle, providing a positive pressure of N_2, before being charged with chlorosulfonic acid (3.32 mL, 50 mmol, 1 equiv) (Note 4) and dichloromethane (25 mL) by syringe. The 500 mL flask and 50 mL flask are connected via an 18 gauge x 18 in cannula needle, and the 500 mL flask is additionally equipped with an exhaust bubbler via an 18 gauge needle (Figure 1A). This solution of chlorosulfonic acid in dichloromethane is added dropwise by positive pressure via cannula into the solution of **1** in dichloromethane over a period of 30 min. The reaction mixture is stirred (600 rpm) for another 30 min at 0 °C after which the flask is removed from the ice water bath (Figure 1B). After stirring for an additional 1 h at room temperature, the reaction mixture is then diluted with diethyl ether (50 mL) and filtered through a medium porosity sintered glass funnel (Note 5). The solid residue is washed with dichloromethane (4 x 50 mL) (Note 3) (Figure 1C) before collecting the solid material retained on the filter and drying under high vacuum for 1 h (Note 6). The solid material is then washed with acetone (4 x 50 mL). The solid material retained on the filter is collected and dried under high vacuum (~760 mm Hg) to yield (4-methoxyphenyl)sulfamic acid (**2**) (9.35 g, 46 mmol, 92%) as a light purple solid (Figure 1D) (Notes 7, 8, and 9), which is used directly in the next step without further purification.

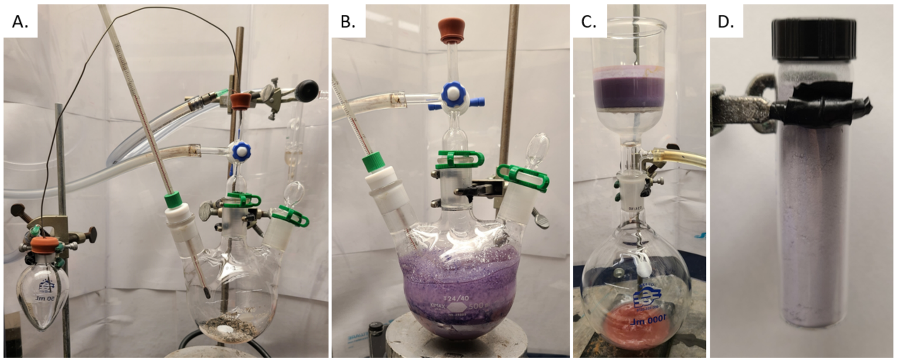


Figure 1. (A) Reaction set-up for Step A; (B) Reaction after ice-water bath removal; (C) Initial filtration of crude reaction mixture; (D) Compound 2 after filtration and drying (photos provided by checkers)

B. *(4-Methoxyphenyl)sulfamoyl chloride (**3**)*. A flame-dried 500 mL round-bottomed flask is equipped with a 4 cm x 1 cm Teflon-coated magnetic spin bar and charged with (4-methoxyphenyl)sulfamic acid (**2**) (7.5 g, 37 mmol, 1 equiv) and toluene (100 mL) (Note 10). Phosphorus pentachloride (10.4 g, 50 mmol, 1.25 equiv) (Note 11) is then added in one portion before equipping the flask with a flame-dried reflux condenser (24/40, 30 cm in length), which had been pre-sealed with a rubber septum and affixed with a nitrogen inlet line via an 18-gauge needle providing a positive pressure of nitrogen (Figure 1A). The reaction flask is then placed into an oil-bath preheated to 90 °C (Figure 2B). The reaction mixture is stirred (600 rpm) at this temperature for 2.5 h. Following this time, the reaction flask is carefully removed from the oil bath and allowed to cool to room temperature over a period of 20 min. Subsequently, the reaction mixture is filtered through a small plug of cotton placed in a funnel (Figures 2C and 2D); the plug of cotton is rinsed with dichloromethane (4 x 25 mL). Subsequently, the dark brown colored solution is concentrated under reduced pressure using a rotary evaporator (40 °C, 90 mmHg) before placing under high vacuum to afford 15 g of (4-methoxyphenyl)sulfamoyl chloride as a brown oil (Note 12) (Figure 2E). The crude brown oil is used without further purification in Step C.

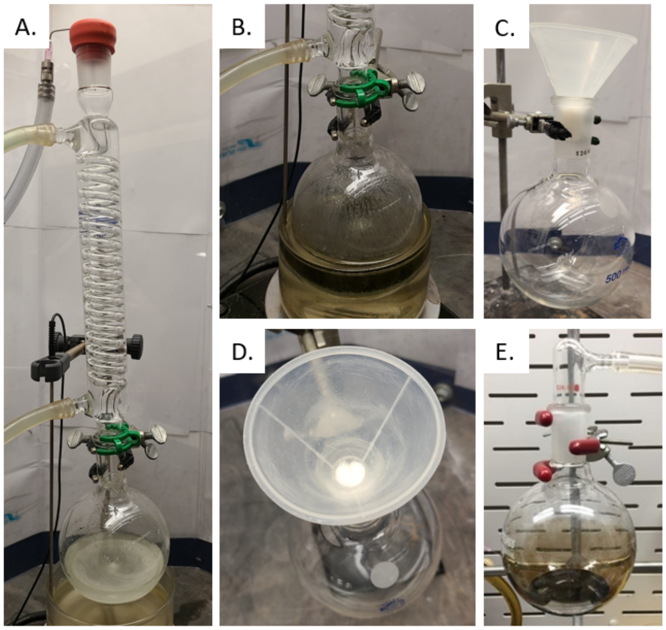


Figure 2. (A) Reaction set-up for Step B; (B) Reaction mixture after heating; (C) Cotton filter, side view; (D) Cotton filter, top view; (E) Unpurified brown oil product (photos 2A-2D provided by checkers, photo 2E provided by submitter)

C. *(E)-Hex-3-en-1-yl (4-methoxyphenyl)sulfamate* (**5**). A flame-dried three-necked 250 mL round-bottomed flask is equipped with a 4 cm x 1 cm Teflon coated magnetic stir bar, and the necks are then equipped with a thermometer, a glass stopper, and a three-way glass stopcock which is then connected to a Schlenk line (Figure 3A). The flask is evacuated for 5 min and backfilled with N_2 three times, and the flask is charged with **3** (15 g crude mixture diluted in 10 mL of dichloromethane). Dichloromethane (90 mL) is added by syringe. To this mixture is added (*E*)-hex-3-en-1-ol (**4**) (3.68 mL, 30 mmol, 1 equiv) (Note 13) by dropwise addition over 3 min, and the flask is then immersed in a 0 °C ice-water bath and allowed to stir for 10 min. Triethylamine (4.6 mL, 33 mmol, 1.1 equiv) (Note 14) is then added dropwise over 5 min to this reaction mixture using a 10 mL Luer-lock plastic syringe with constant stirring (~600 rpm). The reaction flask is then lifted from the ice-water bath and allowed to warm to room temperature (23 °C) over a period of 3 h. Following this time, the flask is immersed in a 0 °C ice-water bath for 10 min before the reaction mixture is quenched by careful dropwise addition of 1M aqueous HCl (60 mL) over 10 min (Note 15). The reaction mixture is diluted with additional dichloromethane (50 mL) and transferred to a 500 mL separatory funnel. The organic layer is removed, and the remaining aqueous layer is extracted with dichloromethane (3 x 60 mL each time). The organic fractions are pooled, dried with anhydrous sodium sulfate (3 g) (Note 16), filtered, and concentrated under reduced pressure on a rotary evaporator (30 °C, 150 mmHg) to yield a dark brown oil (Figure 3B). This brown oil is mixed with silica gel (22 g) (Note 17) and dichloromethane (15 mL), and the mixture is evaporated to dryness. This dried silica is added to the top of a chromatography column (60 cm (length) x 4 cm (width) column containing an additional 90 g of silica gel (silica height 20 cm), and the product purified by column chromatography (Note 18) using hexanes and ethyl acetate (Note 19) as the eluents to yield **5** as a light brown oil (3.24 g, 11.4 mmol, 38%) (Figure 3C) (Notes 20, 21, and 22).

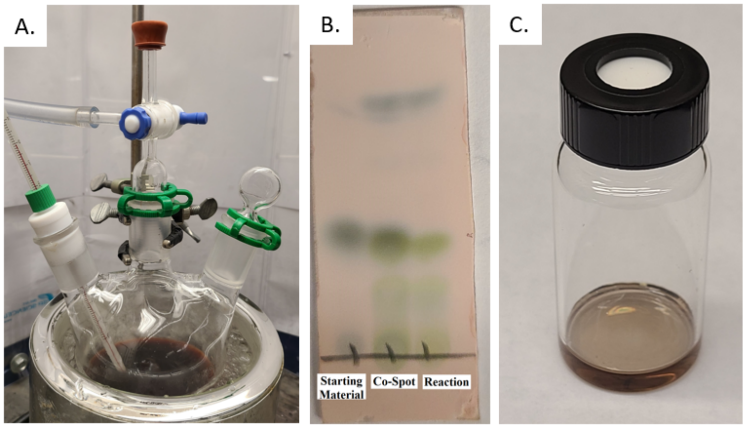


Figure 3. (A) Reaction set-up for Step C; (B) Thin-layer chromatography (4:1 hexanes/ethyl acetate) visualized by anisaldehyde stain (Note 18). Starting material (4) has $R_f = 0.36$ and product (5) has $R_f = 0.31$; (C) Compound 5 after purification (photos provided by checkers)

D. *(E)-3-(4-Methoxyphenyl)-4-(prop-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (**6**).* A flame-dried 250 mL round-bottomed flask is equipped with a 2 cm x 0.6 cm Teflon-coated magnetic stir bar and charged with (*E*)-hex-3-en-1-yl (4-methoxyphenyl)sulfamate (**5**) (2.85 g, 10 mmol, 1 equiv), Pd_2dba_3 (1.37 g, 1.5 mmol, 0.15 equiv) (Note 23) and $Cu(OAc)_2$ (1.82 g, 10 mmol, 1 equiv) (Note 24), followed by acetonitrile (200 mL for a final concentration of 0.05 M) (Note 25). The round-bottomed flask is sealed with a rubber septum, which is then equipped with an exhaust bubbler via an 18 gauge needle (Figure 4A). A balloon is inflated with O_2 and affixed with a disposable needle (Note 26). The reaction mixture is stirred (600 rpm), and the needle is lowered into the reaction solution and O_2 is bubbled for 10 min. Following this time, the balloon is raised such that the needle is slightly above the reaction solution and the 18 gauge needle connected to the exhaust bubbler is removed from the rubber septum. The reaction vessel is then submerged in an oil bath preheated to 55 °C and kept at this temperature for 17 h (Figure 4B). Following this time, the reaction flask is lifted from the oil bath and allowed to cool to room temperature over a period of 20 min. The reaction mixture is vacuum-filtered through a 2 cm pad of silica gel (Note 17) prepared on a medium-porosity sintered glass funnel (Note 27) to remove residual Pd and Cu salts (Figures 4C and 4D). The filter cake is rinsed with ethyl acetate (100 mL) (Note 19). After concentrating this solution under reduced pressure using a rotary evaporator (30 °C, 90 mmHg), the resulting brown oil (Figure 4b) is purified by column chromatography on silica (Notes 17 and 28) to yield ((*E*)-3-(4-methoxyphenyl)-4-(prop-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (**6**) as a light yellow solid (2.34 g, 8.3 mmol, 83%) (Figures 5A and 5B) (Notes 29, 30, and 31) as 6:1 mixture of *trans*/*cis* isomers.

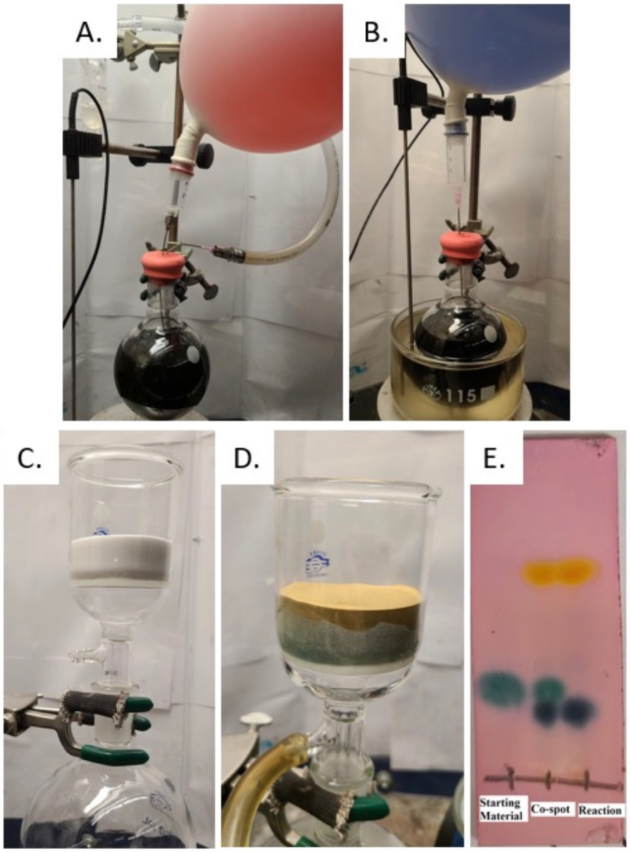


Figure 4. (A) Reaction set-up for Step D, sparging the system with O_2; (B) Reaction flask in 55 °C oil bath; (C) SiO_2 plug for filtration; (D) SiO_2 plug after filtration; (E) Thin-layer chromatography (4:1 hexanes/ethyl acetate) visualized by anisaldehyde stain. The starting material (5) has $R_f = 0.29$ and the product (6) has $R_f = 0.21$ (photos provided by checkers)

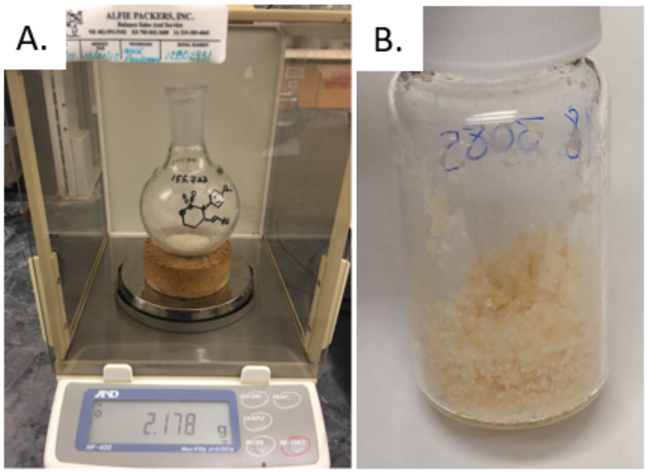


Figure 5. (A) Cyclization product 6 (photo provided by submitter); (B) Close-up image of product 6 (photo provided by checkers)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with 4-methoxyaniline, chlorosulfonic acid, diethyl ether, acetone, toluene, phosphorus pentachloride, (*E*)-hex-3-en-1-ol, triethylamine, aqueous HCl, anhydrous

sodium sulfate, silica gel, hexanes, ethyl acetate, anisaldehyde, ethanol, concentrated H_2SO_4, potassium permanganate, Pd_2dba_3, $Cu(OAc)_2$, dichloromethane, acetonitrile, and oxygen, as well as the proper procedures for handing molecular oxygen.

2. 4-Methoxyaniline (*p*-anisidine) was purchased from Sigma Aldrich (99%) and used without purification.
3. Dichloromethane was purchased from Sigma-Aldrich (≥99.5%, ACS reagent grade) and was used without further purification.
4. Chlorosulfonic acid ($ClSO_3H$) was purchased from Sigma-Aldrich (99%) and was used without further purification.
5. Medium Porosity: 10 to 15 µm size; the funnel capacity was 300 mL.
6. The material quickly decomposes into an uncharacterized brown oil if washed with acetone prior to drying under high vacuum for at least one hour.
7. (4-Methoxyphenyl)sulfamic acid: mp = 125 °C, ^{1}H NMR (300 MHz, DMSO) δ: 9.29 (s, 1H), 7.24 – 7.05 (m, 2H), 7.05 – 6.85 (m, 2H), 3.74 (s, 3H).^{13}C NMR (126 MHz, DMSO) δ: 156.9, 128.2, 122.3, 114.8, 55.4. IR (film): 3065, 2838, 1506, 1172, 1020, 878, 822, 596 cm^{-1}. HRMS [M - H] calcd for $C_7H_8NO_4S$: 202.0180. Found: 202.0178.
8. The purity of **2** was determined to be >97 wt% by qNMR using 1,3,5-trimethoxybenzene (Alfa Aesar 99%) as the internal standard.
9. A second reaction performed by the checker at half scale provided 4.57 g (90%) of the product.
10. Toluene was purchased from Sigma-Aldrich (≥99.5%, ACS reagent grade) and was used without further purification.
11. Phosphorous pentachloride (PCl_5) was purchased from Sigma-Aldrich (reagent grade, 95%) and used without further purification.
12. Due to its instability, compound **3** was used directly in the next step without further purification. Compound **3** was prepared following a procedure modified from that of Kloek and Leschinsky.[2] These authors note the marked instability of phenylsulfamoyl chlorides during any sort of purification procedure; we have independently noted this, as well. A second reaction performed on half-scale provided 7 g of the crude product.
13. *trans*-3-Hexen-1-ol was purchased from Sigma-Aldrich (97%, stabilized) and was used without further purification.
14. Triethylamine was newly purchased from Oakwood Chemicals and was used directly without further purification.

15. Hydrochloric acid (Certified ACS Plus, 36.5 to 38%) was purchased from Fisher chemical. A 1M solution was prepared by carefully adding 83 mL of this to 917 mL of deionized H_2O. *(Caution! This is significantly exothermic and should be performed in a fume hood with considerable care.)*
16. Sodium sulfate (anhydrous) was purchased from Oakwood Chemicals and was used directly without further purification.
17. Silica Gel (Grade 60, 230-400 mesh) was purchased from Fisher Chemical.
18. The eluent used during purification by chromatography was 95:5 hexanes/ethyl acetate (100 mL), 92:8 hexanes/ethyl acetate (100 mL), 88:12 hexanes/ethyl acetate (100 mL), 85:15 hexanes/ethyl acetate (100 mL), 83:17 hexanes/ethyl acetate (1000 mL). Fraction sizes of 14 mL were isolated. The column was monitored by thin-layer chromatography (4:1 hexanes/ethyl acetate) using anisaldehyde stain (Figure 6), which was prepared by mixing ethanol, concentrated H_2SO_4, and anisaldehyde in a 20:1:1 ratio. The TLC was stained by quick submersion into the stain before heating until fully developed. Compound 5 was found in fractions 58-80.

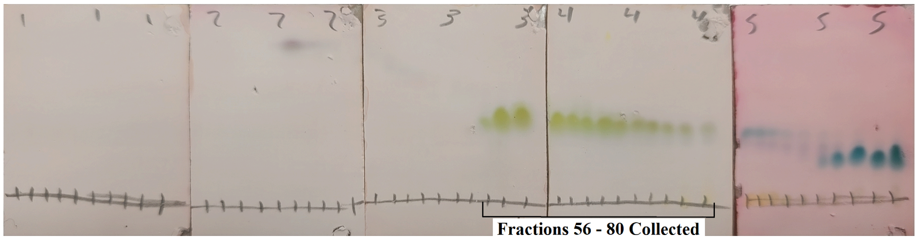


Figure 6. Thin-layer chromatography (4:1 hexanes/ethyl acetate) visualized using anisaldehyde stain

19. Hexanes (>98.5%) was purchased from Fisher Scientific and used as received. Ethyl acetate was purchased from Sigma-Aldrich (≥99.5%, ACS reagent grade) and was used without further purification.
20. (E)-Hex-3-en-1-yl (4-methoxyphenyl)sulfamate (**5**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.50 (s, 1H), 5.60 (dtt, J = 13.9, 6.3, 1.4 Hz, 1H), 5.33 (dtt, J = 15.2, 6.8, 1.5 Hz, 1H), 4.20 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.42 (q, J = 6.8 Hz, 2H), 2.02 (qdd, J = 7.4, 6.1, 1.2 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.6, 136.1, 128.9, 123.6, 122.7, 114.6, 71.3, 55.5, 32.0, 25.6, 13.5; IR (film): 3281, 2962, 2839, 1509, 1166, 920, 826, 648, 547 cm^{-1}. HRMS [M - H] calcd for $C_{13}H_{18}NO_4S$: 284.0962. Found: 284.0960.

21. The purity of **2** was determined to be >97 wt% by qNMR using 1,3,5-trimethoxybenzene (Alfa Aesar 99%) as the internal standard.
22. A second reaction performed by the checker at reduced scale provided 2.10 g (49%) of the product.
23. $Pd_2(dba)_3$ was purchased from Sigma-Aldrich (97%) and used without further purification.
24. $Cu(OAc)_2$ (anhydrous) was purchased from Sigma-Aldrich (98%) and used without further purification.
25. Acetonitrile was purchased from Sigma-Aldrich (≥99.5%, ACS reagent grade) and was used without further purification.
26. These needles (16 Gauge, Length of 4 in) were purchased from Grainger.
27. This pad of silica was made by wetting 10 g of silica gel (Note 17) with hexanes on a medium porosity sintered glass funnel (Note 6).
28. The compound was mixed with silica gel (16 g) (Note 17) and dichloromethane (15 mL) (Note 3). This suspension was evaporated to dryness, and the dried silica was added to the top of a chromatography column (60 cm (length) by 4 cm (width)) that contained an additional 90 g of silica gel. The column was eluted with 92:8 hexanes/ethyl acetate (250 mL), 85:15 hexanes/ethyl acetate (200 mL), and 82:18 hexanes/ethyl acetate (200 mL). The eluent was changed to 80:20 hexanes/ethyl acetate (950 mL), and fraction volumes of 16 mL were collected, which was continued as the eluent was changed to 78:22 hexanes/ethyl acetate (250 mL). Thin-layer analysis (4:1 hexanes/ethyl acetate), visualized using $KMnO_4$ stain, reveals product 6 was contained in fractions 38-60 (Figure 7) .

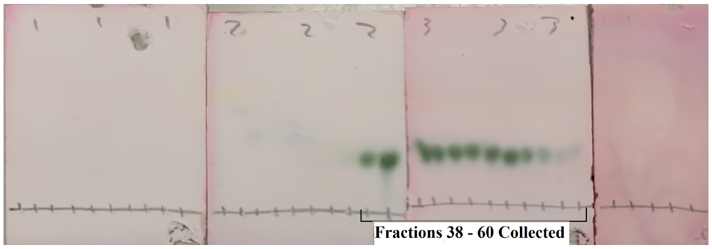


Figure 7. Thin-layer chromatography analysis reveals product 6 is contained in fractions 38-60 (photo provided by checkers)

29. (*E*)-3-(4-Methoxyphenyl)-4-(prop-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (**6**): mp = 118 °C, ^1H NMR (300 MHz, $CDCl_3$) δ: 7.31 – 7.25 (m, 2H), 6.92 – 6.84 (m, 2H), 5.57 (dq, *J* = 15.3, 6.5 Hz, 1H), 5.12 (ddq, *J* = 15.3,

8.3, 1.7 Hz, 1H), 4.88 (td, *J* = 12.4, 2.6 Hz, 1H), 4.66 (dd, *J* = 5.0, 2.2 Hz, 1H), 4.58 – 4.51 (m, 1H), 3.83 (s, 3H), 2.27 (dddd, *J* = 14.7, 13.5, 7.3, 4.2 Hz, 1H), 1.90 (dq, *J* = 14.5, 2.7 Hz, 1H), 1.54 (dd, *J* = 6.5, 1.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.4, 131.0, 130.6, 130.4, 128.1, 114.2, 71.5, 64.1, 55.4, 30.4, 17.6; IR (film): 2958, 2925, 2836, 1506, 1352, 1254, 1166, 1016, 885, 807, 779, 589, 554 cm^{-1}; HRMS calcd for $C_{13}H_{18}NO_4S^+$ calcd for $C_{13}H_{18}NO_4S$: 284.0951. Found: 284.0948.

30. The purity of **2** was determined to be >97 wt% by qNMR using 1,3,5-trimethoxybenzene (Alfa Aesar 99%) as the internal standard.
31. A second reaction was performed by the checker at reduced scale provided 1.11 g (78%) of the product.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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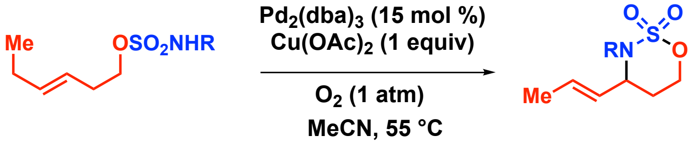
Discussion

The *aza*-Wacker cyclization is a very elegant but relatively under-explored alkene functionalization reaction.[3-5] Inspired by the early work of Åkermark, Bäckvall, Zetterberg[6-8] and Hegedus[9-11] and contemporary investigations of Stahl,[12-13] Stoltz,[14-15] and Zhang,[16-18] we envisioned developing an *aza*-Wacker cyclization of sulfamate esters as our entry into this field. To date, most *aza*-Wacker protocols have been developed with alkenyl amines or amides, thus requiring the nitrogen functionality to be native to the molecule. In addition, examples of *aza*-Wacker cyclization reactions that form rings >5 members remain very limited.[19-21] In our recently-disclosed reaction,[22] one large-scale example of which is described here, the sulfamate auxiliary can be appended to diverse alcohol containing substrates and oxidatively cyclized to form six-membered and larger rings (Table 1 and Table 2). The oxathiazinane moiety is a masked 1,3-amino alcohol, a motif found in a variety of biologically active compounds and is also an important synthetic intermediate (Scheme 1).[23-27] A highly unusual feature of our reaction is that it employs Pd (0) as a pre-catalyst; to our knowledge, all other disclosed protocols for *aza*-Wacker cyclizations directly utilize Pd (II) salts. A variety of *N*-alkyl and *N*-aryl substituents are tolerated in our reaction, allowing for a fairly general method of oxidative sulfamate cyclization.

Table 1. ***N*-Alkyl and *N*-aryl sulfamate esters engage productively**



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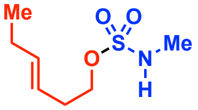
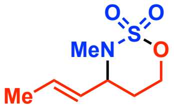
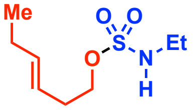
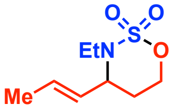
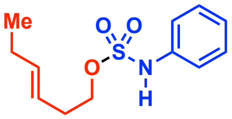
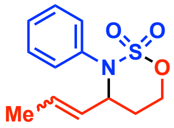
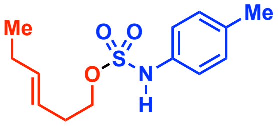
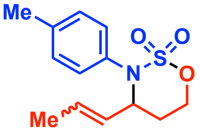
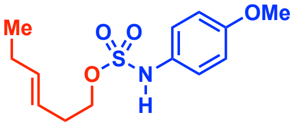
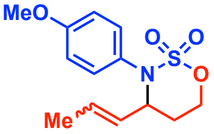
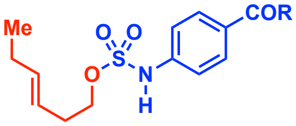
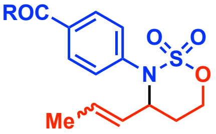
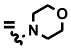
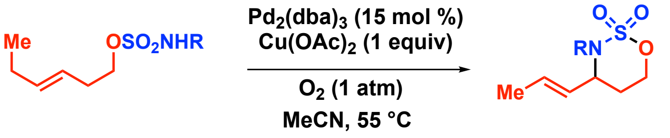
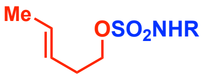
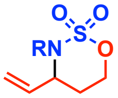
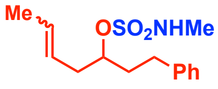
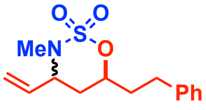
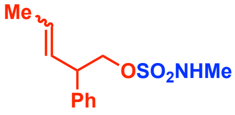
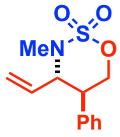
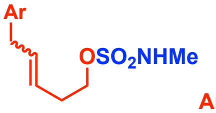
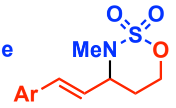
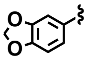
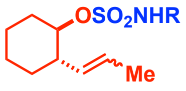
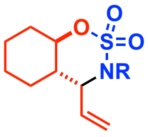
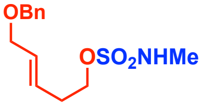
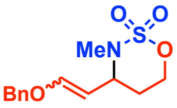
1			70
2			37[b]
3			55[c]
4			74[d]
5			73[c]
6			R = OEt 80[c] R =  70[c]

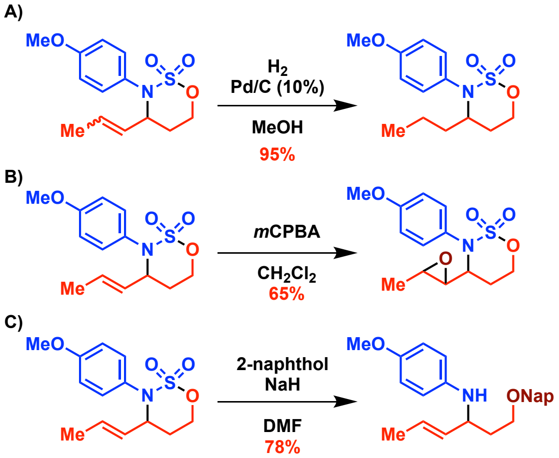
[a] isolated yield, unless otherwise mentioned [b] yield estimated by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene) [c] isolated as a 10:1 mixture of trans/cis isomers [d] isolated as a 5:1 mixture of trans/cis isomers

Table 2. Variety of alkenyl sulfamates



entry	substrate	product		yield (%)[a]
1			R = Me	68
			R = *p*-OMeC_6H_4	93
2[b]				83[c]
3[d]				67[e]
4[f]			Ar = Ph	94
			Ar = *p*-FC_6H_5	92
			Ar = 	73
5			R = Me	65
			R = p-OMeC_6H_4	70
6				56[g]

[a] isolated yield, unless otherwise mentioned [b] 1:1 mixture of cis/trans isomers [c] isolated as a 4:1 mixture of syn/anti diastereomers [d] 1:1 mixture of cis/trans isomers [e] isolated as a single diastereomer [f] Ar = Ph, 4.6:1 mixture of trans/cis isomers; Ar = *p*-FC_6H_5, 5.9:1 mixture of trans/cis isomers; Ar = 1,3-benzodioxole, 5:1 mixture of trans/cis isomers [g] isolated as a 1.6:1 mixture of trans/cis isomers



Scheme 1. Oxathiazinane heterocycles as synthetic starting materials

References

1. Corresponding author: Shyam Sathyamoorthi, ssathyam@ku.edu; https://orcid.ord/0000-0003-4705-7349. Address of all authors: Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66047 Funding: This work was supported by start-up funding provided jointly by the University of Kansas Office of the Provost and the Department of Medicinal Chemistry as well as a grant from the COBRE Protein Structure and Function Small Grants Program. Support for the NMR instrumentation was provided by the NIH Shared Instrumentation Grant #S10RR014767.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

p-Methoxyaniline: benzeneamine, 4-methoxy-; (104-94-9)
Chlorosulfonic acid: Chlorosulfuric acid; (7790-94-5)
trans-3-Hexen-1-ol: *trans*-3-Hexen-1-ol; (544-12-7)

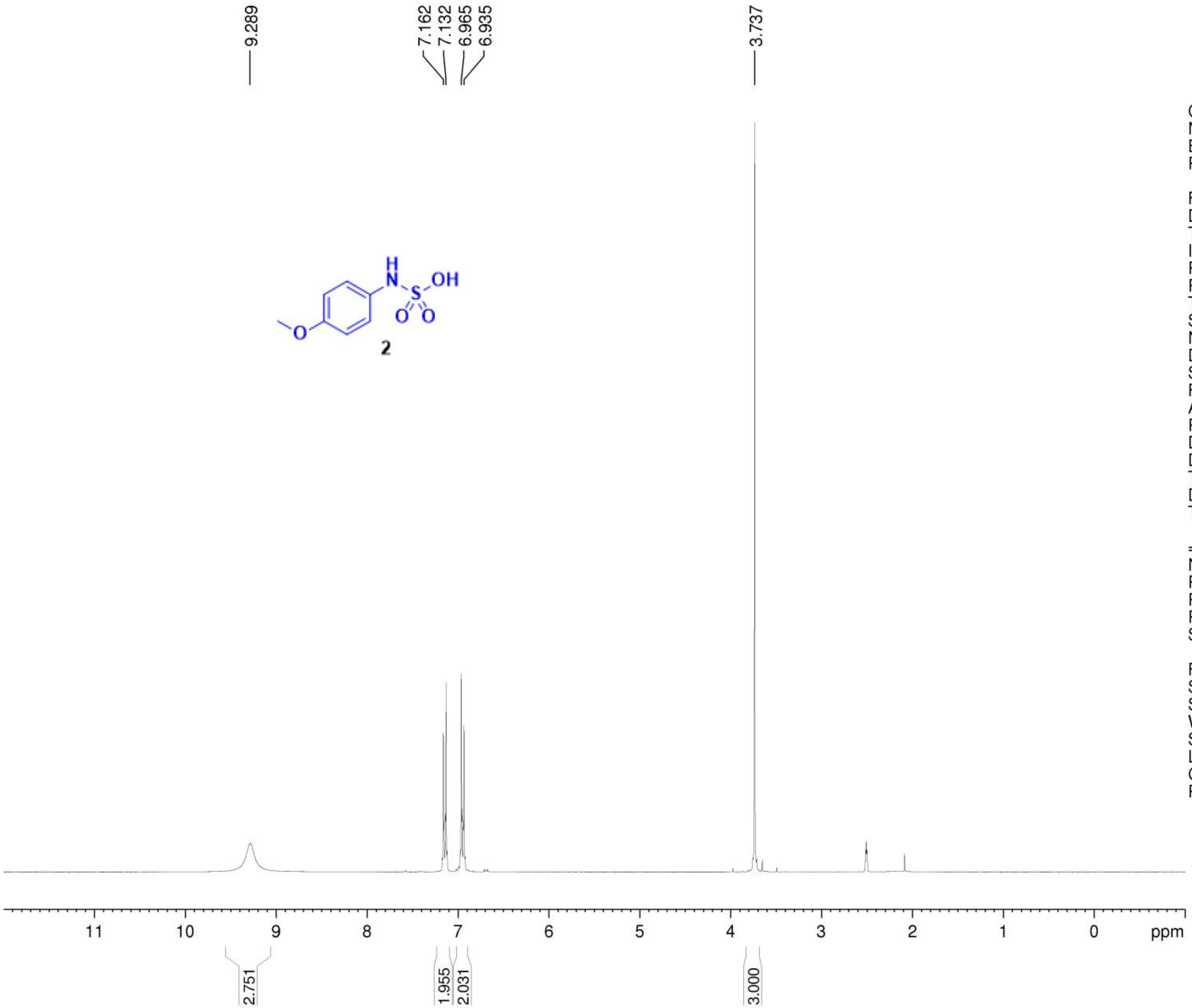
Triethylamine: Ethanamine, N,N-diethyl; (121-44-8)
$Pd_2(dba)_3$: Palladium, tris[μ-[(1,2-η:4,5-η)-(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one]]di-; (51364-51-3)
$Cu(OAc)_2$: Acetic acid, copper(2+) salt; (142-71-2)

Shyam Sathyamoorthi completed a B.S. degree in Cell and Molecular Biology with a minor in Chemistry at Tulane University, New Orleans, Louisiana, where he worked in the labs of Professor Ken Muneoka and Professor Robert A. Pascal, Jr. He then completed a Ph.D. in chemistry at Stanford University under the guidance of Professor Richard N. Zare (2018) as well as a Doctor of Medicine degree at the Stanford University School of Medicine (2019). Since July 2019, he is an assistant professor in the Department of Medicinal Chemistry at the University of Kansas, Lawrence, KS, USA.

Anand H. Shinde completed his M.Sc. in Organic Chemistry at Fergusson college (autonomous, then affiliated to University of Pune), Pune, Maharashtra, India. He then completed a Ph.D. in chemistry at Indian Institute of Technology Hyderabad (IITH), Hyderabad, India under the guidance of Professor Duddu S. Sharada (2017). Subsequently, he joined the Department of Chemistry, Stanford University as a postdoctoral scholar under the supervision of Professor Barry M. Trost (2018-19). Currently, he is working as a postdoctoral scholar in the Department of Medicinal Chemistry at the University of Kansas, Lawrence, KS, USA under the supervision of Professor Shyam Sathyamoorthi.

Jacob P. Sorrentino earned his B.S. in Biology with a minor in Chemistry at Nevada State College, Henderson, NV, USA in 2016, studying under Professor Zachary Woydziak. Jacob then went on to receive his Ph.D. in medicinal chemistry in 2022 from Department of Medicinal Chemistry at the University of Kansas, Lawrence, KS, USA working under Professor Ryan Altman. Jacob is currently working as a postdoctoral researcher in the laboratory of Professor Neil Garg in the Department of Chemistry and Biochemistry at the University of California, Los Angeles, CA, USA.

(4-Methoxyphenyl)sulfamic acid



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FIDRES	0.091480 Hz
AQ	5.4657025 sec
RG	362
DW	83.400 usec
DE	6.00 usec
TE	300.0 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 =====

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PL1	0 dB
PL1W	9.31909847 W
SFO1	300.1318008 MHz

F2 - Processing parameters

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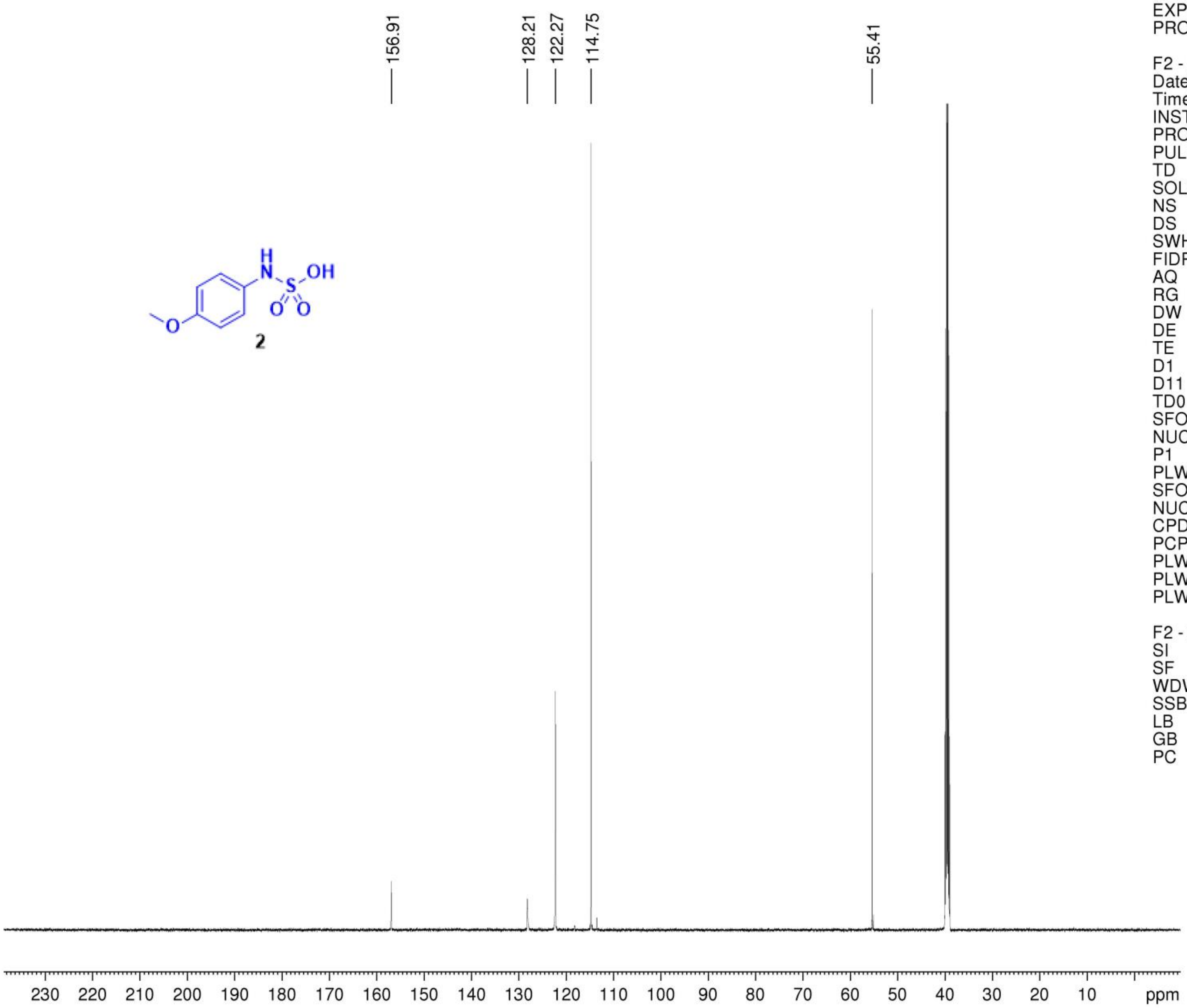
PC	1.40

(4-Methoxyphenyl)sulfamic acid



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DW	16.000 usec
DE	28.00 usec
TE	298.0 K
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D11	0.03000000 sec
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NUC1	13C
P1	10.50 usec
PLW1	23.00000000 W
SFO2	500.1330008 MHz
NUC2	1H
CPDPRG[2	waltz16
PCPD2	80.00 usec
PLW2	13.50000000 W
PLW12	0.21094000 W
PLW13	0.10610000 W

F2 - Processing parameters

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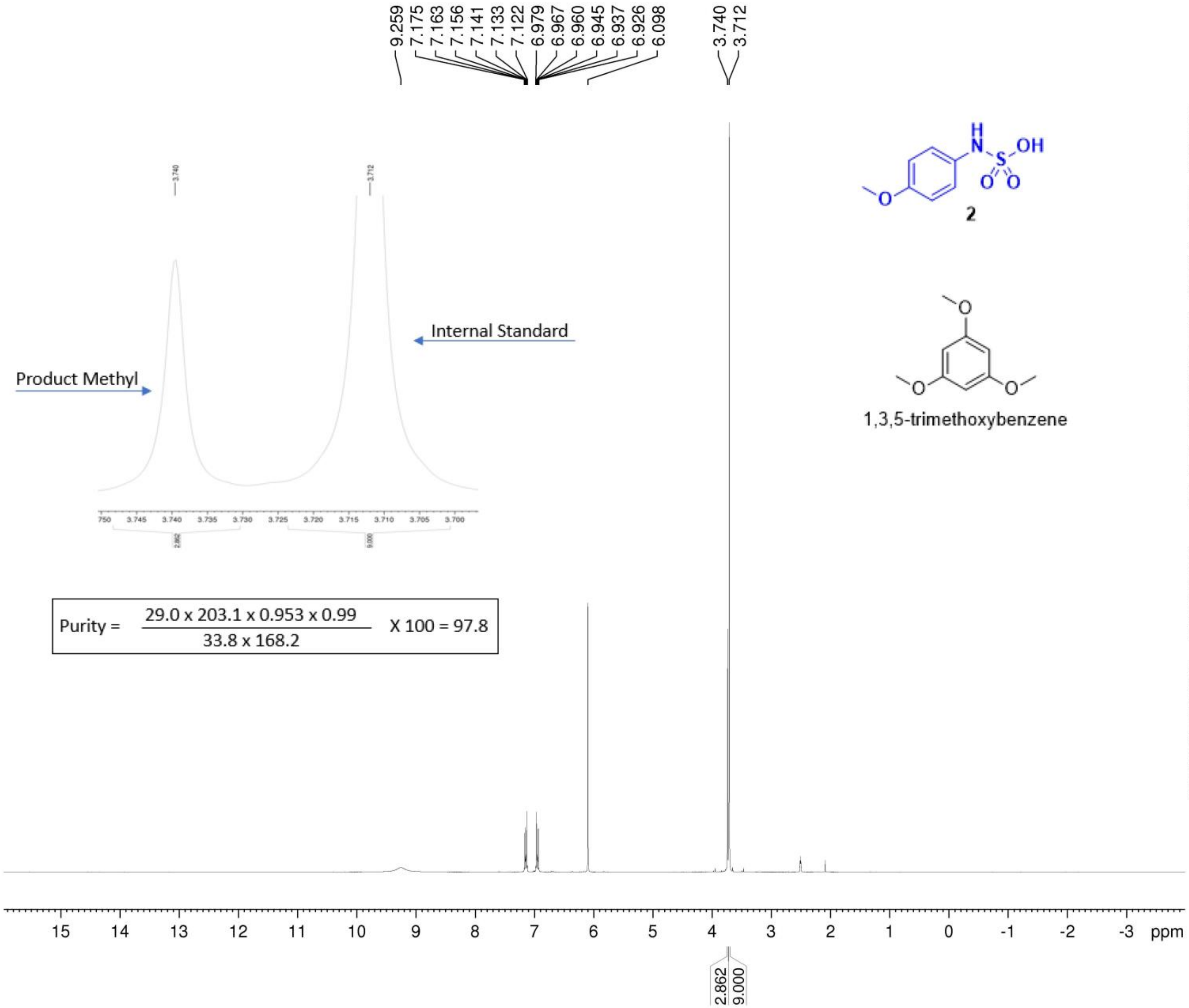
(4-Methoxyphenyl)sulfamic acid



$$\text{Purity} = \frac{29.0 \times 203.1 \times 0.953 \times 0.99}{33.8 \times 168.2} \text{ X } 100 = 97.8$$

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PROCNO              1

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PULPROG           zg30
TD               65536
SOLVENT           DMSO
NS                  16
DS                   0
SWH        5995.204 Hz
FIDRES     0.091480 Hz
AQ       5.4657025 sec
RG                 256
DW          83.400 usec
DE            6.00 usec
TE             300.0 K
D1     30.00000000 sec
TD0                  1

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P1          15.20 usec
PL1               0 dB
PL1W      9.31909847 W
SFO1    300.1318008 MHz

F2 - Processing parameters
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SF      300.1300000 MHz
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PC                1.40
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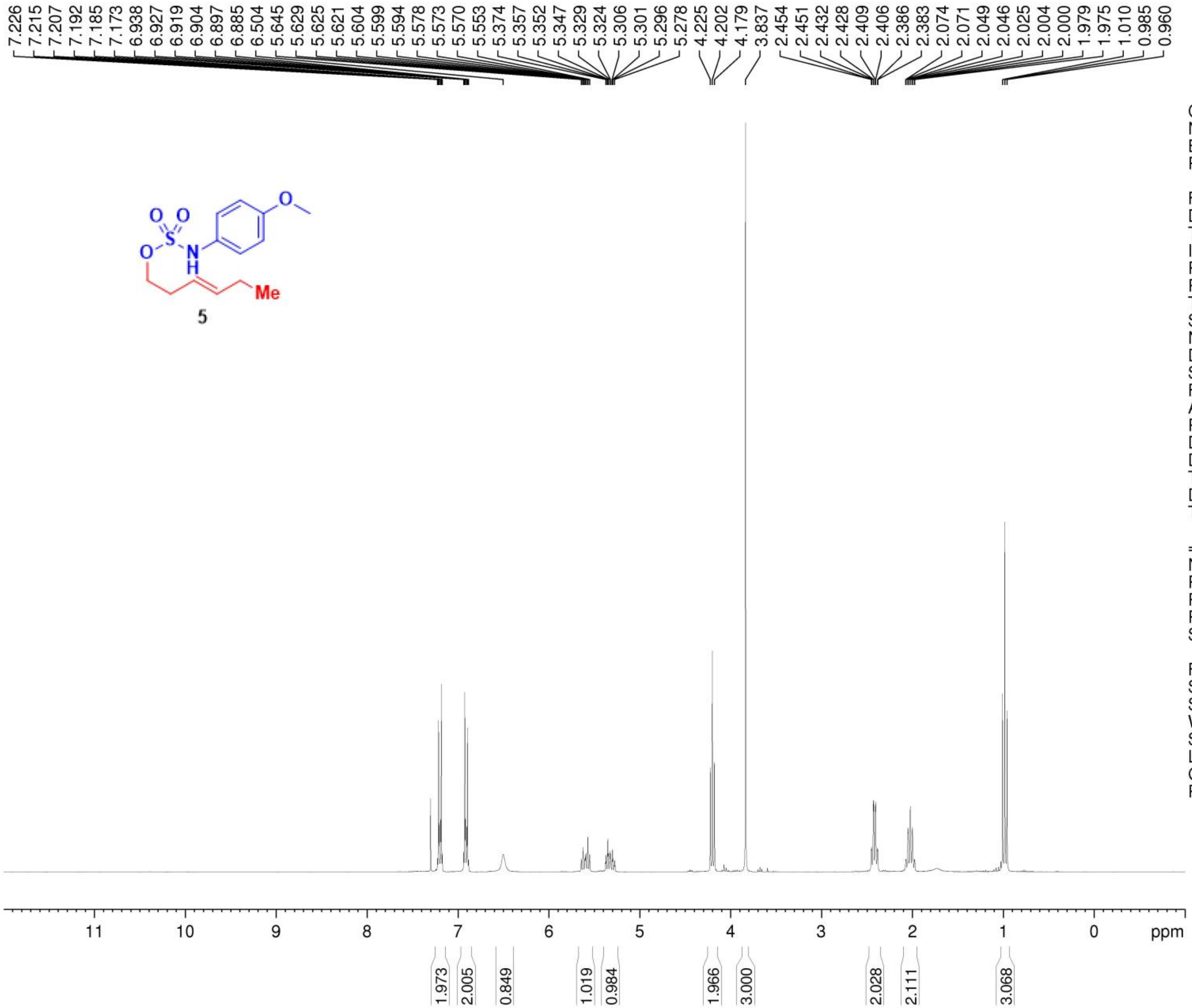
(E)-Hex-3-en-1-yl (4-methoxyphenyl)sulfamate

5



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D1 2.00000000 sec
TD0 1

======== CHANNEL f1 =====
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SFO1 300.1318008 MHz

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LB 0.30 Hz
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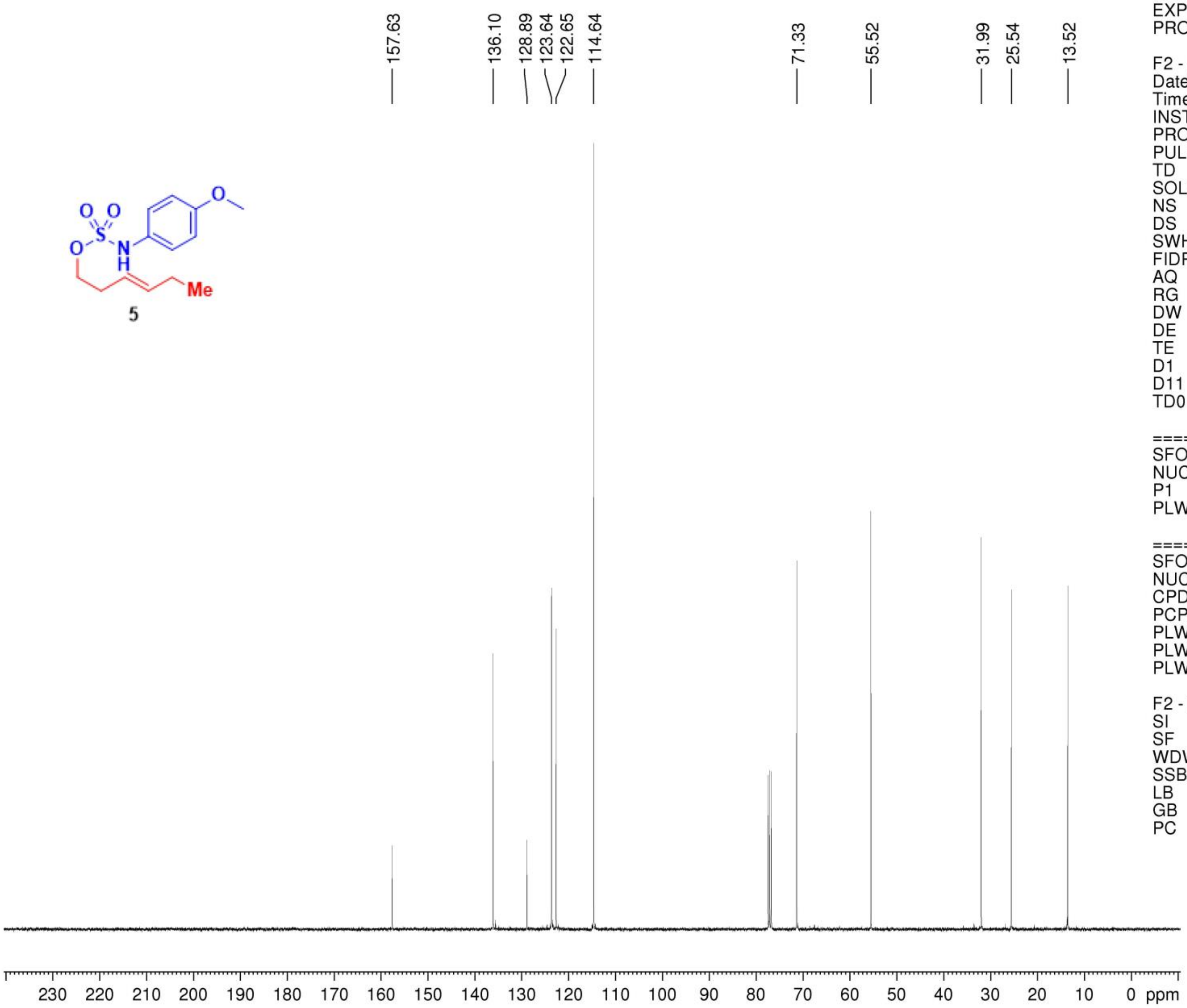
PC 1.40

(E)-Hex-3-en-1-yl (4-methoxyphenyl)sulfamate

5



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NS            512
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FIDRES     0.385323 Hz
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RG          189.85
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DE           6.50 usec
TE          298.1 K
D1        0.50000000 sec
D11       0.03000000 sec
TD0             1

======== CHANNEL f1 =====
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NUC1            13C
P1            10.00 usec
PLW1      52.00000000 W

======== CHANNEL f2 =====
SFO2     400.1324008 MHz
NUC2             1H
CPDPRG[2       waltz16
PCPD2          90.00 usec
PLW2      13.00000000 W
PLW12      0.36111000 W
PLW13      0.29249999 W

F2 - Processing parameters
SI          65536
SF        100.6127701 MHz
WDW             EM
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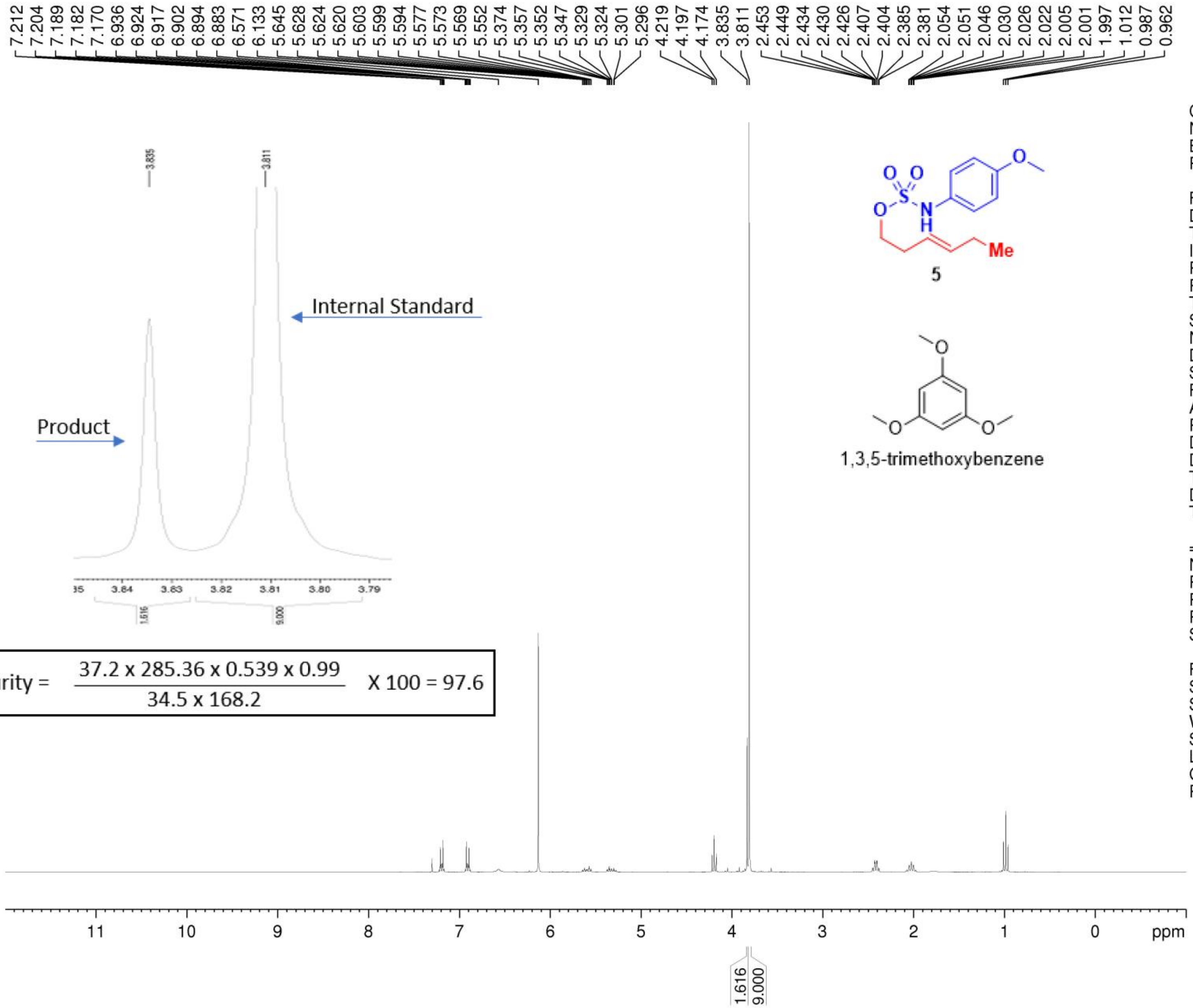
LB            1.00 Hz
GB               0
PC            1.40
```

(E)-Hex-3-en-1-yl (4-methoxyphenyl)sulfa



$$\text{Purity} = \frac{37.2 \times 285.36 \times 0.539 \times 0.99}{34.5 \times 168.2} \times 100 = 97.6$$

Current Data Parameters

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FIDRES	0.091480 Hz
AQ	5.4657025 sec
RG	256
DW	83.400 usec
DE	6.00 usec
TE	300.0 K
D1	30.00000000 sec
TD0	1

======== CHANNEL f1 =====

NUC1	1H
P1	15.20 usec
PL1	0 dB
PL1W	9.31909847 W
SFO1	300.1318008 MHz

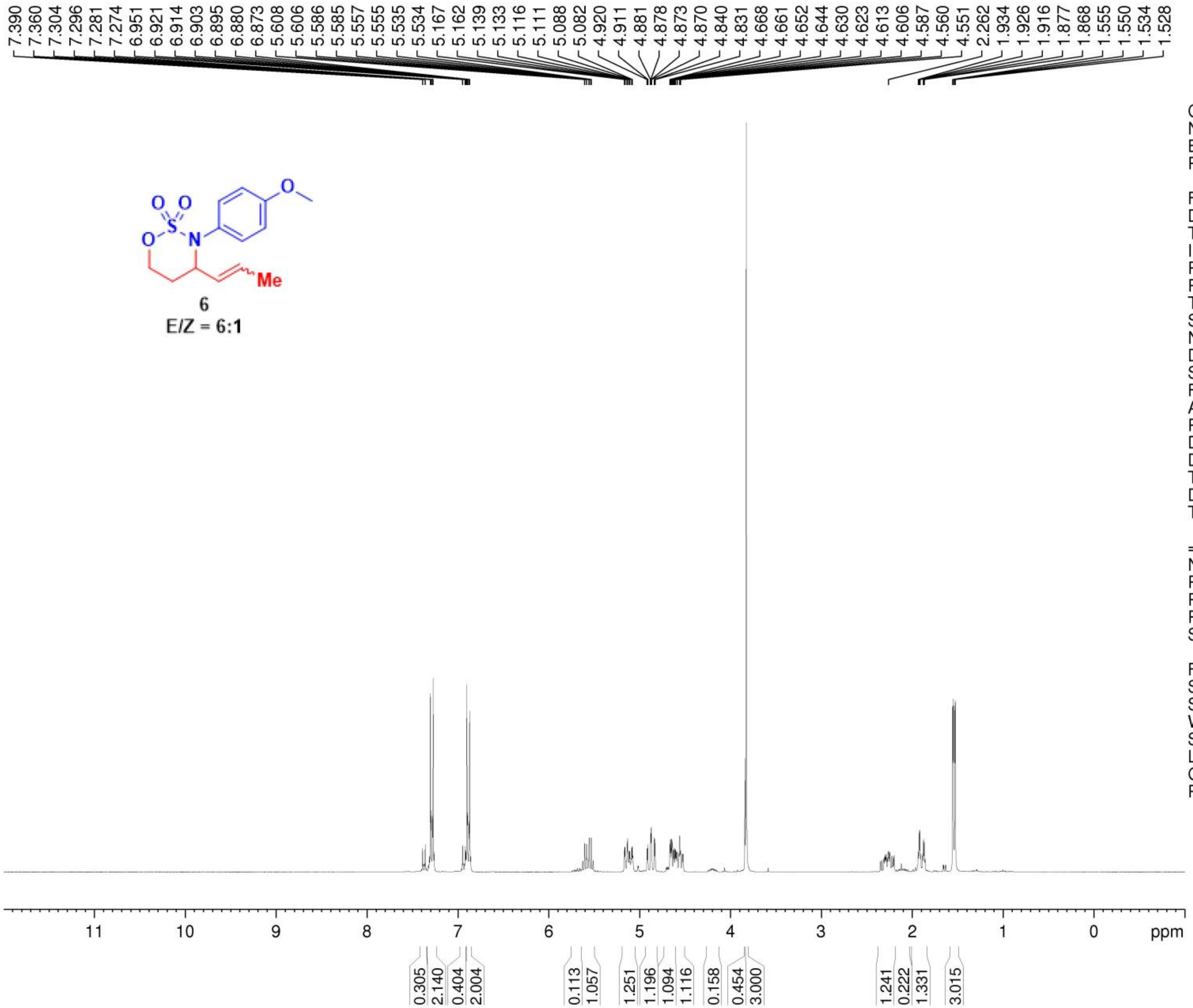
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

(E)-3-(4-Methoxyphenyl)-4-(prop-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide

6

E/Z = 6:1



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FIDRES	0.091480 Hz
AQ	5.4657025 sec
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DE	6.00 usec
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======== CHANNEL f1 =====

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PL1	0 dB
PL1W	9.31909847 W
SFO1	300.1318008 MHz

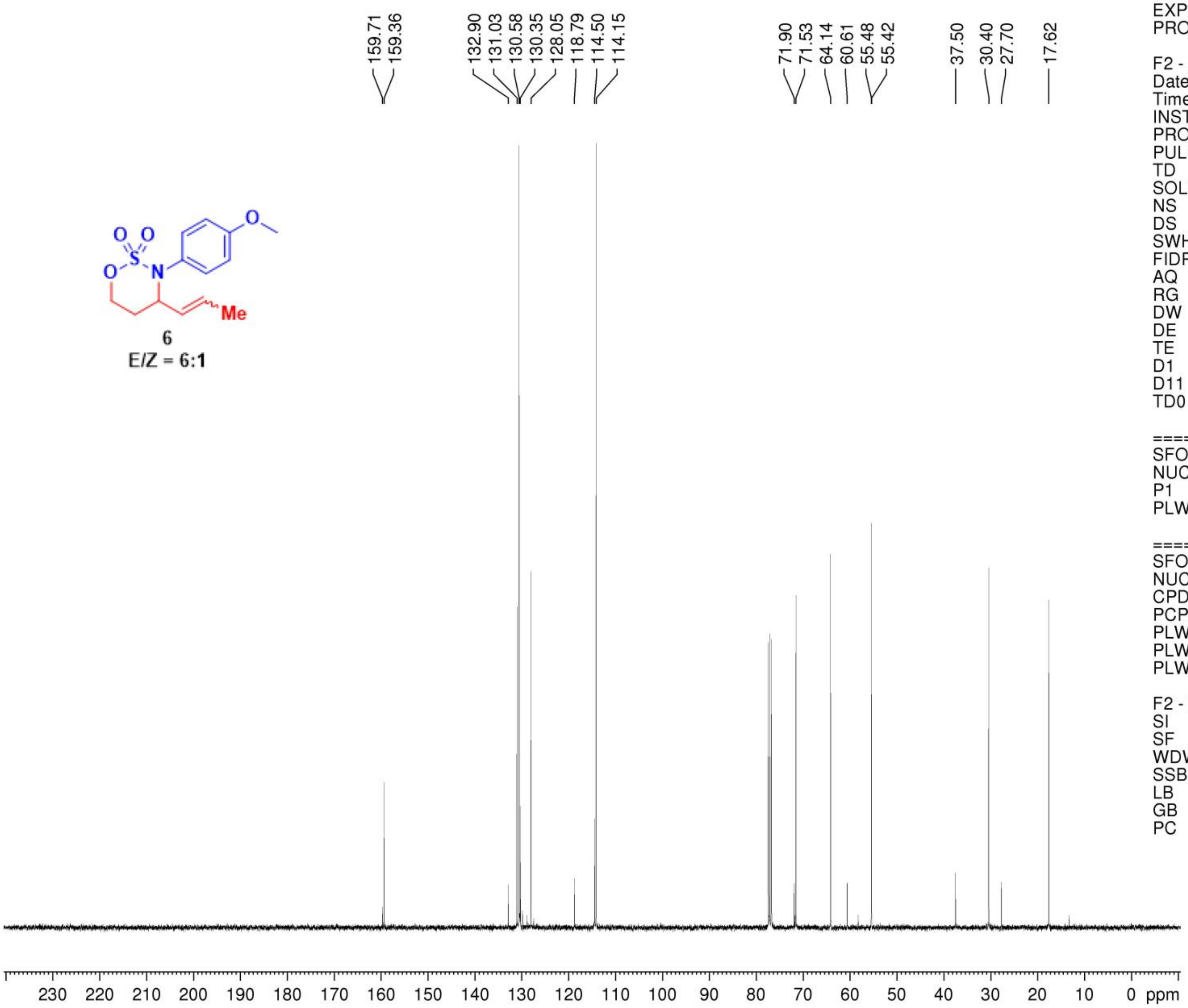
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

(E)-3-(4-Methoxyphenyl)-4-(prop-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide

6

E/Z = 6:1



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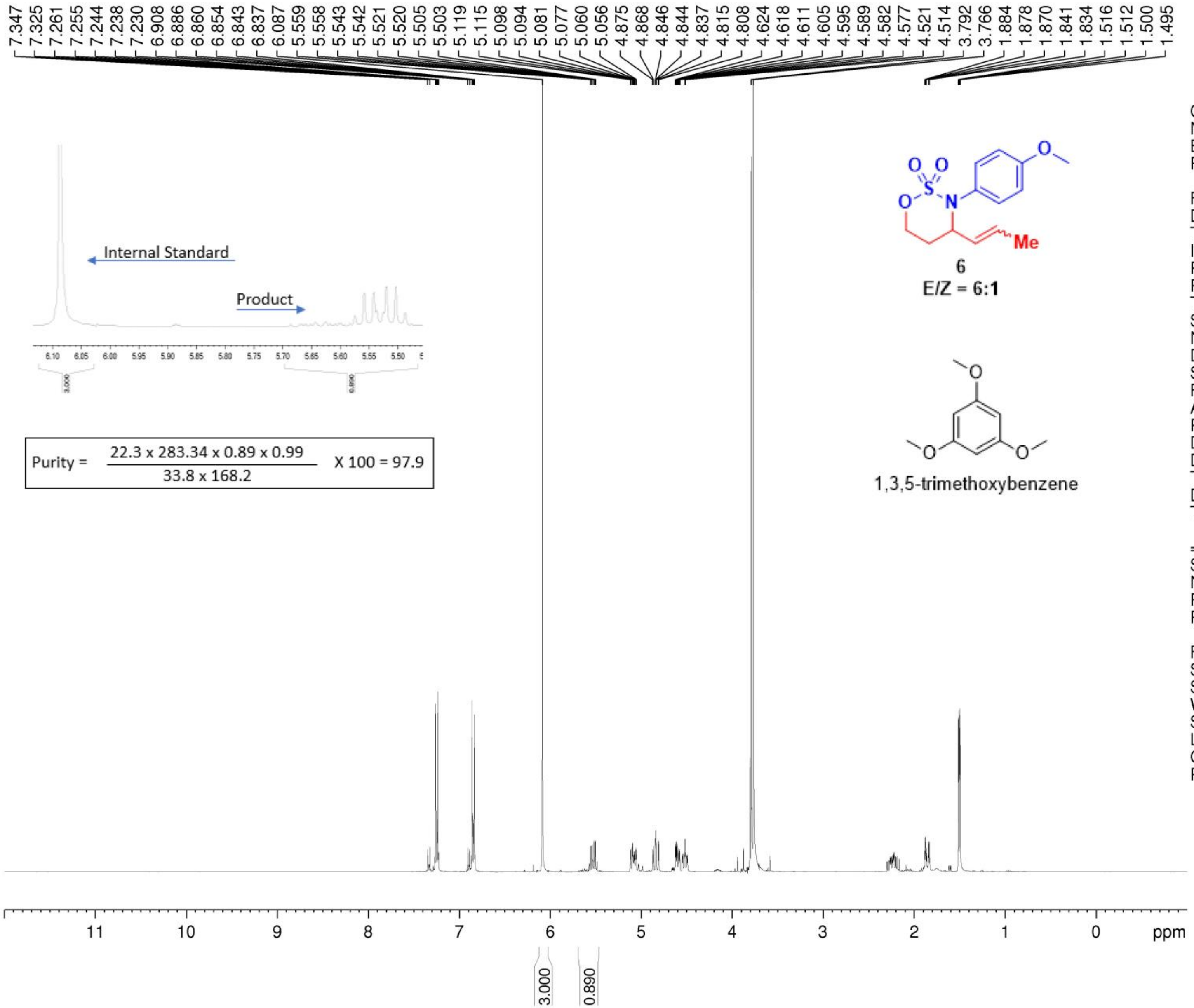
FIDRES 0.385323 Hz
AQ 1.2976128 sec
RG 189.85
DW 19.800 usec
DE 6.50 usec
TE 298.4 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 =====
SFO1 100.6243395 MHz
NUC1 13C
P1 10.00 usec
PLW1 52.00000000 W

======== CHANNEL f2 =====
SFO2 400.1324008 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 13.00000000 W
PLW12 0.36111000 W
PLW13 0.29249999 W

F2 - Processing parameters
SI 65536
SF 100.6127701 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

(E)-3-(4-Methoxyphenyl)-4-(prop-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide-qNMR



$$\text{Purity} = \frac{22.3 \times 283.34 \times 0.89 \times 0.99}{33.8 \times 168.2} \times 100 = 97.9$$

Current Data Parameters

NAME	Compound 6
EXPNO	110
PROCNO	1

F2 - Acquisition Parameters

Date_	20220914
Time	10.53
INSTRUM	av400
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	52882
SOLVENT	CDCl3
NS	16
DS	0
SWH	8012.820 Hz
FIDRES	0.151523 Hz
AQ	3.2998369 sec
RG	67.78
DW	62.400 usec
DE	6.50 usec
TE	297.6 K
D1	30.00000000 sec
TD0	1

======== CHANNEL f1 =====

SFO1	400.1324008 MHz
NUC1	1H
P1	15.00 usec
PLW1	13.00000000 W

F2 - Processing parameters

SI	65536
SF	400.1300184 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00