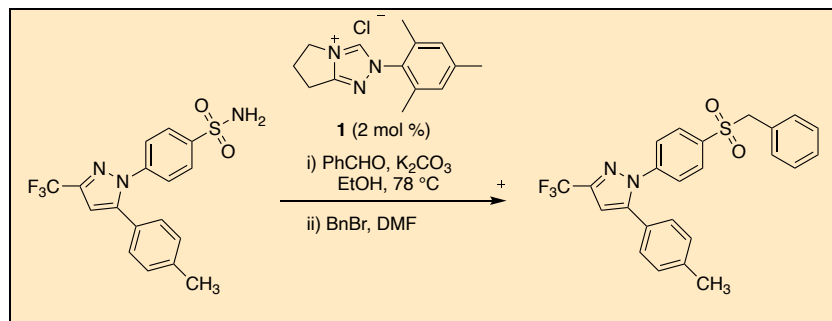


Deaminative Functionalization of Primary Sulfonamides

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Checked by Melissa A. Hardy and Richmond Sarpong



Procedure (Note 1)

A. 1-(4-(Benzylsulfonyl)phenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (2). To a 500 mL three-necked, round-bottomed flask equipped with an overhead stirrer (Note 2), nitrogen inlet line (Note 3), thermocouple, and reflux condenser (Figure 1) is added celecoxib (7.00 g, 18.4 mmol, 1 equiv), potassium carbonate powder (5.07 g, 36.7 mmol, 2.00 equiv) (Note 4), 2-mesityl-1,2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride (1) (97 mg, 0.37 mmol, 2.0 mol %), and anhydrous ethanol (70 mL) (Note 5).

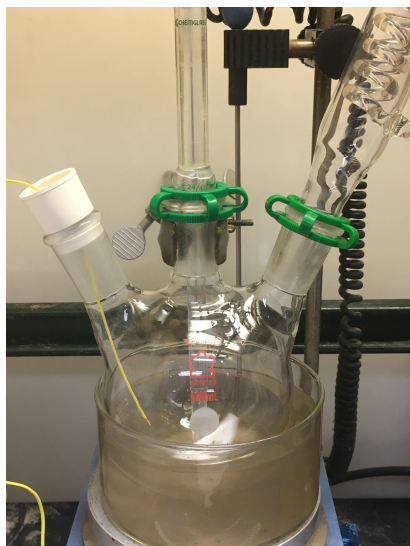


Figure 1. Reaction set-up (photo provided by checkers)

The reaction mixture is stirred and the vessel is degassed with three vacuum/nitrogen purge cycles. Benzaldehyde is added via syringe (2.25 mL, 2.33 g, 22.0 mmol, 1.20 equiv) (Note 4) in one portion, and the resulting reaction mixture is heated at an internal temperature of 70 °C for 16 h, during which time the reaction mixture turns yellow (Figure 2).

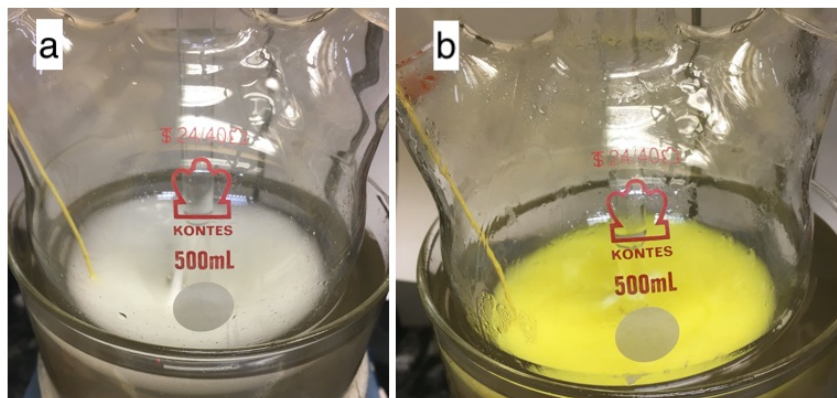


Figure 2. Reaction mixture (a) upon addition of benzaldehyde and (b) after heating for 14 h (photos provided by checkers)

The progress of the reaction is monitored for the disappearance of celecoxib (Note 6). The reaction mixture is cooled to room temperature (22–24 °C internal temperature) and diluted with 70 mL of anhydrous DMF, which is added via syringe. Benzyl bromide (3.27 mL, 4.70 g, 27.5 mmol, 1.50 equiv) (Note 4) is then added in one portion via syringe, after which a mild exotherm of approximately 1 °C occurs over the first 5 min. The resulting reaction mixture is stirred at ambient temperature (20–24 °C) for a total of 3 h, during which time product formation is monitored (Note 7). The reflux condenser is replaced with a 500-mL addition funnel filled with 350 mL of water. The water is added via the addition funnel over approximately 30 min, during which time the product precipitates as a pale-yellow solid (Figure 3).

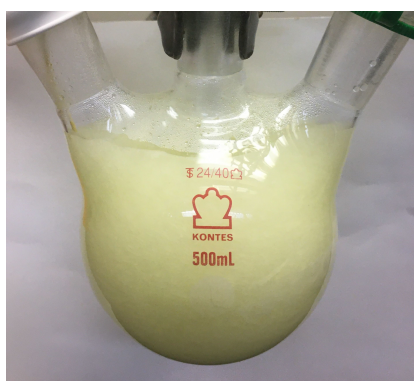


Figure 3. Reaction mixture upon addition of water
(photo provided by checkers)

The slurry is stirred at room temperature for 1 h, the product is isolated via filtration, and the solid is washed with water (2 x 50 mL), followed by heptane (2 x 50 mL) (Note 8). The solid is dried under vacuum at 300 mmHg with a nitrogen sparge for 18 h with occasional agitation (Figure 4) (Note 9) to afford compound **2** (7.23 g, 86%, 99% purity) (Notes 10 and 11) as a white solid (Note 12).

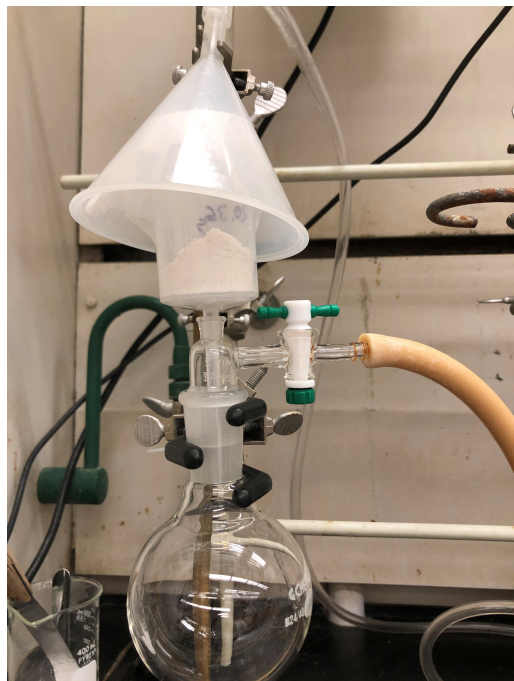


Figure 4. Filtration and drying of isolated product (photo provided by submitters)

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 celecoxib, potassium carbonate, 2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride, ethanol, benzaldehyde, *N,N*-dimethylformamide, and benzyl bromide.

2. Dimensions of the stir paddle: 5.8 cm diameter, 2.5 cm height, 3 mm thickness.
3. The reaction is not sensitive to water, however the sulfinic acid intermediate is moderately sensitive to oxygen and will slowly oxidize to the corresponding sulfonate if run under air (~5% oxidation over the course of the reaction).
4. Potassium carbonate, Benzaldehyde, and Benzyl bromide were used in excess to ensure >98% conversion within 18 h.
5. Checkers: Celecoxib (98%) was purchased from Combi-Blocks, potassium carbonate powder (≥98%) was purchased from Sigma-Aldrich, 2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride (97%) was purchased from Sigma-Aldrich, anhydrous ethanol (≥99.5%) was purchased from Sigma-Aldrich, benzaldehyde (≥99%) was purchased from Sigma-Aldrich, DMF (99.8%) was purchased from Sigma-Aldrich, and benzyl bromide (98%) was purchased from Sigma-Aldrich. All reagents and solvents were used as received.
6. The checkers monitored the reaction by ¹H NMR (700 MHz) and deemed the reaction complete when celecoxib could no longer be observed. The submitters monitored the reaction by HPLC using the following conditions: Waters Acquity UPLC BEH C18 (100 mm × 2.1 mm × 1.7 μm). Gradient of 10-95% MeCN in 0.1% aqueous H₃PO₄ over 4 min, then hold at 95% MeCN for 3 min. Flow rate of 0.5 mL/min. Temperature: 40 °C. The reaction was deemed complete when less than 2% of celecoxib remained versus the sulfinic acid intermediate when monitored at 210 nm. Retention time of celecoxib: 4.89 min. Retention time of sulfinic acid: 4.71 min. Retention time of sulfone 2: 5.58 min.
7. The checkers monitored the reaction by ¹H NMR (700 MHz) and deemed the reaction complete when the sulfinic acid intermediate could no longer be observed. The submitters monitored the reaction using the HPLC conditions described in Note 6. The reaction was deemed complete when less than 2% of the sulfinic acid intermediate remained versus product 2 when monitored at 210 nm.

8. During each wash, the wash solvent was added to the cake and agitated with a spatula to generate a uniform slurry, then sucked to dryness under vacuum. During the washes with heptane, the yellow color from the solid was washed into the filtrate. The checkers used a 150 mL funnel with a glass fritted filter of porosity C.

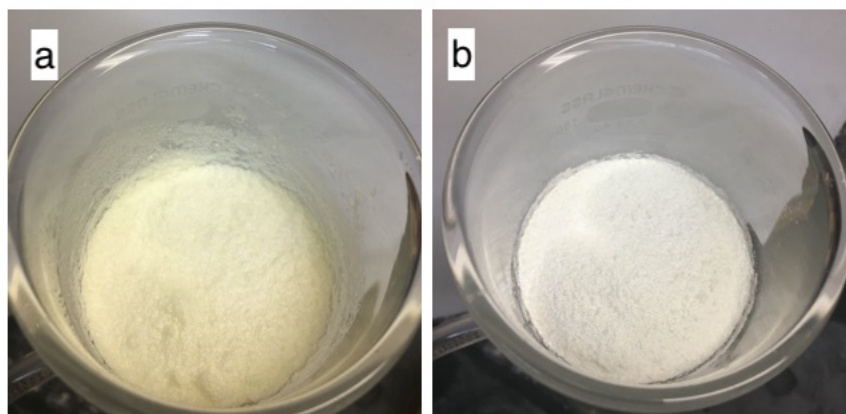


Figure 5. Solid on filter (a) before and (b) after heptane wash (photos provided by checkers)

9. In cases where ^1H NMR analysis revealed remaining solvent, the solid was transferred to a closed system and dried under vacuum (0.1 mmHg) with stirring for an additional 4 h.
10. The product purity was determined by qNMR with 1,3,5-trimethoxybenzene as an internal standard. 1,3,5-Trimethoxybenzene was purchased from Sigma-Aldrich and used as received (purity: $\geq 99\%$).
11. When the reaction was carried out on half-scale, 3.57 g (85%, 98% purity) of the product was obtained.
12. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ : 2.34 (s, 3H), 4.75 (s, 2H), 7.19 – 7.25 (m, 3H), 7.12 – 7.18 (m, 4H), 7.27 – 7.35 (m, 3H), 7.51 – 7.55 (m, 2H), 7.72 – 7.76 (m, 2H). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ : 20.8, 60.5, 106.2, 118.6, 120.3, 122.1, 123.9, 125.2, 126.0, 128.3, 128.4, 128.5, 128.7, 129.4, 129.4, 130.9, 137.9, 139.2, 142.0, 142.3, 142.5, 142.6, 142.8, 145.4. ^{19}F NMR (565 MHz, $\text{DMSO}-d_6$) δ : –61.1 (s) (referenced against fluorobenzene internal standard, ppm = –113.15). IR (film): 3151, 3064, 3033, 2973, 2924, 1161, 1149, 1125, 806, 561 cm^{-1} . HRMS (ESI+) m/z calcd for $\text{C}_{24}\text{H}_{20}\text{O}_2\text{N}_2\text{F}_3\text{S}^+$

$[M+H]^+$: 457.1192, found: 457.1197. mp: 148–151 °C. TLC R_f = 0.35 (20% ethyl acetate in hexanes, visualized by UV).

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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Sulfonamides and related sulfonyl compounds are pervasive in drug discovery and development. Yet, no methods existed for the mild, late-stage transformation of sulfonamides to other valuable pharmacophores (sulfones,

sulfonic acids, other sulfonamides, etc.). As such, we were interested in developing a method wherein sulfonamides could be applied as generally useful synthetic handles within drug discovery. Recently, we developed conditions for the conversion of primary sulfonamides to sulfinates under mild reaction conditions in the presence of virtually any other functional group.² The reactions occur under mildly basic conditions (K_2CO_3) in the presence of an NHC catalyst, and benzaldehyde acts as the terminal reductant, forming benzonitrile as the stoichiometric byproduct. The sulfinate esters that are formed as the immediate products can be derivatized in the same reaction vessel to sulfones, other sulfonamides, sulfonic acids, as well as non-sulfur containing products through radical desulfonylation or Pd-catalyzed desulfonylative cross-coupling.

References

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2. Fier, S. P.; Maloney, K. M. *J. Am. Chem. Soc.* **2019**, *141*, 1441–1445.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

Celecoxib: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (169590-42-5)
Potassium carbonate (584-08-7)
2-Mesityl-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride (862893-81-0)
Ethanol (64-17-5)
Benzaldehyde (100-52-7)
DMF: N,N-Dimethylformamide (68-12-2)
Benzyl bromide (100-39-0)



Kevin M. Maloney earned a Ph.D. in organic chemistry from the Massachusetts Institute of Technology in 2007 under the guidance of Professor Rick Danheiser, where his research focused on developing novel iminoacetone nitrile cycloadditions as a general strategy for natural product synthesis. After completing his graduate studies, he joined the Department of Process Research & Development at Merck & Co., Inc., Rahway, NJ, USA, where he is currently a Director in Process Chemistry. Kevin's group is responsible for the discovery and development of green, robust, and safe synthetic routes to active pharmaceutical ingredients (APIs) from early development through NDA filings in support of the company's pipeline.

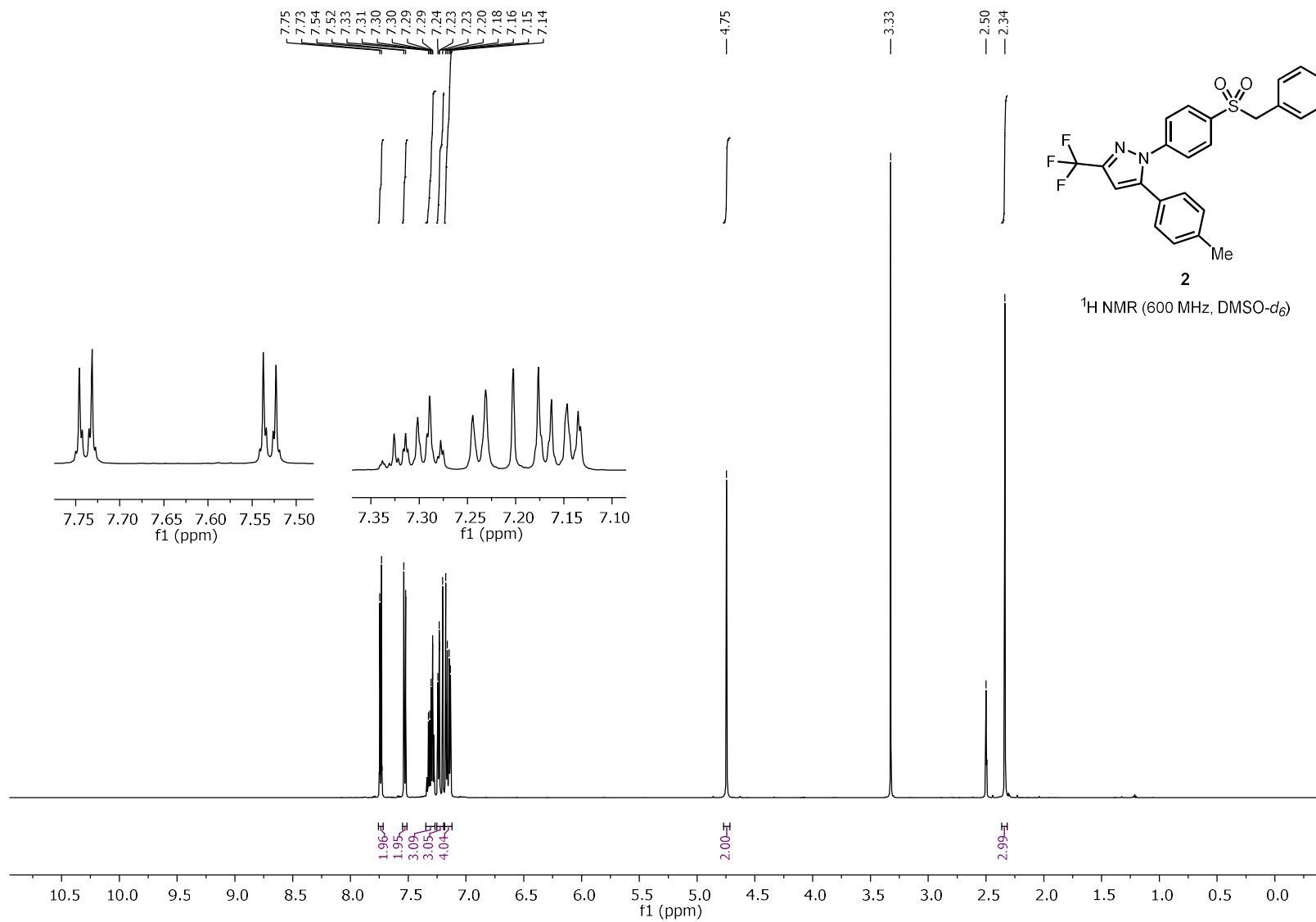


Patrick Fier was born and raised in Iowa, and he received his B.S. degree in chemistry from the University of Northern Iowa. He then obtained his Ph.D. in the group of Prof. John Hartwig from the University of California, Berkeley in 2014. As a graduate student, he developed several methods for the introduction of fluorine and fluorinated groups into organic molecules. He is currently an Associate Principal Scientist in the Department of Process Research & Development at Merck & Co., Inc., Rahway, NJ, USA. His research interests include the development, study, and applications of novel organic transformations.

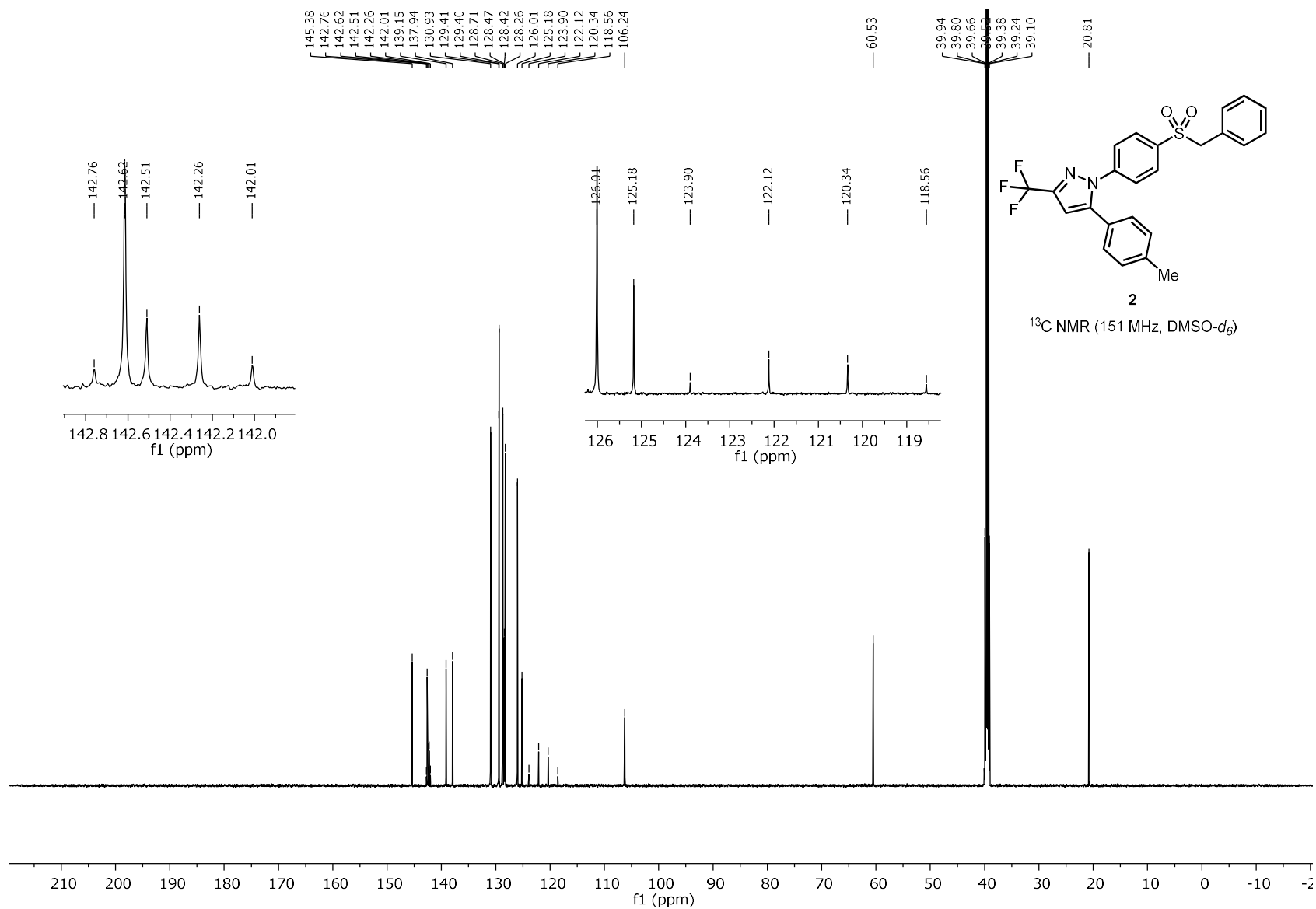


Melissa Hardy received her B.A. in Chemistry and French from Grinnell College in 2016. She is currently an NSF graduate fellow at the University of California, Berkeley with Professor Richmond Sarpong. Her Ph.D. studies focus on developing new strategies and methodologies for the synthesis of architecturally complex natural products.

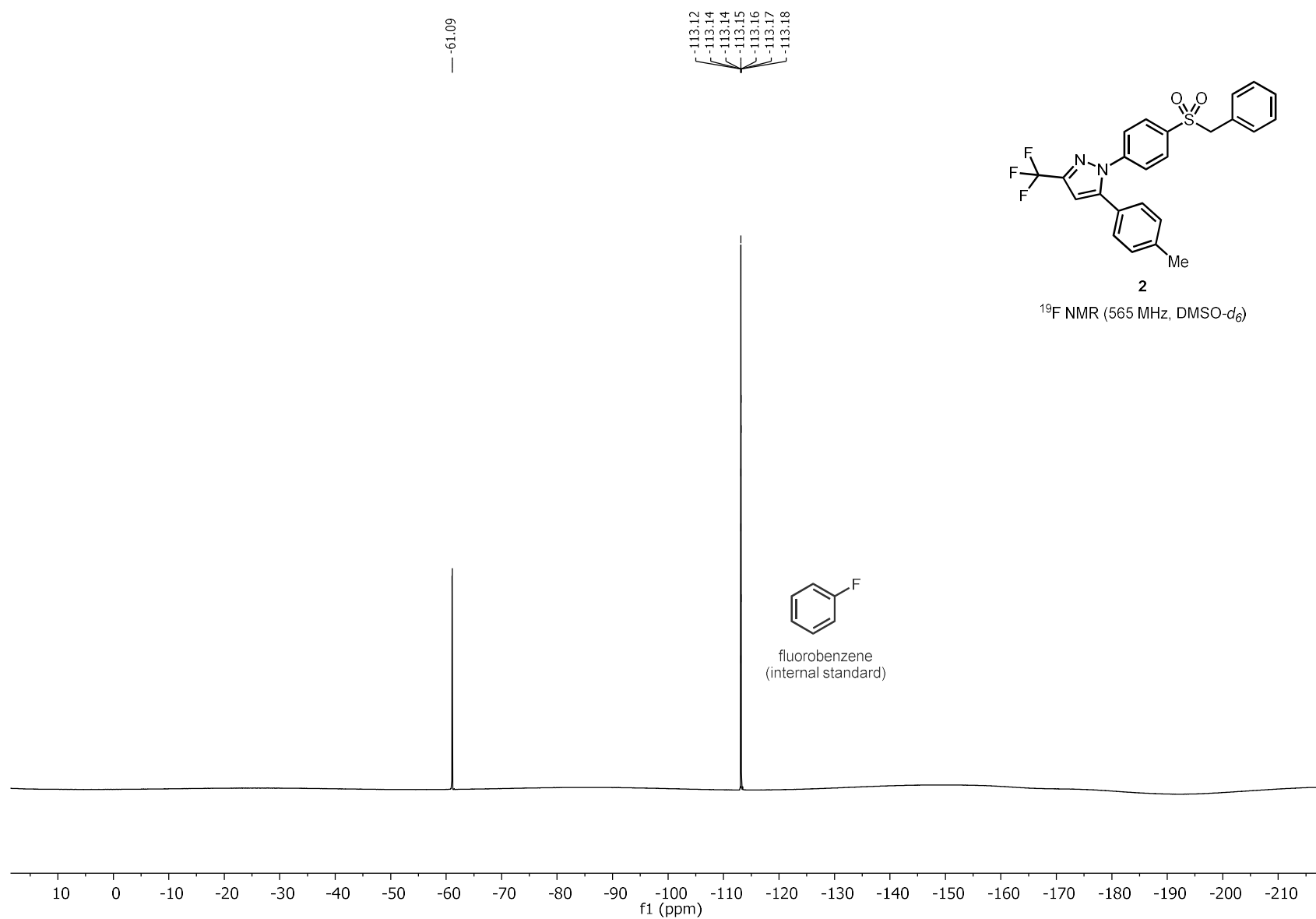
¹H NMR of 1-(4-(Benzylsulfonyl)phenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (**2**)



¹³C NMR of 1-(4-(Benzylsulfonyl)phenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (2)



¹⁹F NMR of 1-(4-(Benzylsulfonyl)phenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (**2**)



¹H qNMR of 1-(4-(Benzylsulfonyl)phenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (**2**) with 1,3,5-trimethoxybenzene (on half-scale)

mass of sample			12.4
MW analyte			456.48
#protons analyte			2
mass of TMB			11.1
ArH (3) integration			3
TMB/sample ratio by ¹ H NMR			3.7
Wt% purity	$((D6 \cdot D5 \cdot D3) / (168.19 \cdot D2 \cdot D4 \cdot D7)) \cdot 100$	equals	98.49459808

