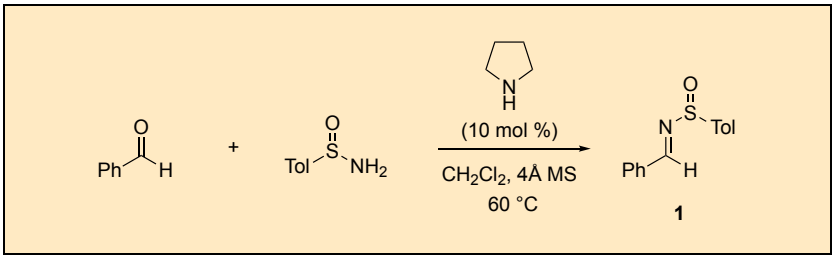
Organic Syntheses

Preparation of *N*-Sulfinyl Aldimines using Pyrrolidine as Catalyst *via* Iminium Ion Activation

Sara Morales, Alfonso García Rubia, Eduardo Rodrigo, José Luis Aceña, José Luis García Ruano, and M. Belén Cid*[1]

Department of Organic Chemistry, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Checked by Gabrielle St-Pierre, Christopher J. Borths, and Margaret M. Faul



Procedure (Note 1)

A. N-Benzylidene-p-*toluenesulfinamide (**1**).* An oven-dried, 100 mL one-necked round-bottomed flask is charged with a Teflon-coated magnetic stir bar (2.5 x 0.5 cm), *p*-toluenesulfinamide (5.00 g, 32.2 mmol) (Note 2), 4Å molecular sieves (6.5 g) (Note 3), dichloromethane (40 mL) (Note 4), benzaldehyde (3.42 g, 3.3 mL, 32.2 mmol) (Note 5), and pyrrolidine (230 mg, 265 μL, 3.22 mmol) (Note 6). The flask is connected to a reflux condenser fitted with a calcium sulfate-filled drying tube (30 g) (Note 7) and heated to 60 ºC (Figure 1). The mixture is stirred at 500 rpm for 5 h, resulting in a brown heterogeneous suspension (Note 8) (Figure 2). The reaction is allowed to cool to room temperature and diluted by addition of EtOAc (50 mL). The mixture is filtered through a pad of silica gel (Note 9) and washed with EtOAc (3 x 50 mL). The filtrate is concentrated under reduced pressure using a rotary evaporator (25 ºC, 30 mmHg) to give a white solid. The solid is washed with hexane (20 mL) and collected *via* vacuum filtration into a 100 mL ceramic Buchner funnel equipped with filter paper of moderate

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porosity to yield 6.31–6.40 g (81–82%) of *N*-benzylidene-*p*-toluenesulfinamide (**1**) as a white crystalline solid (Note 10) (Figure 3).

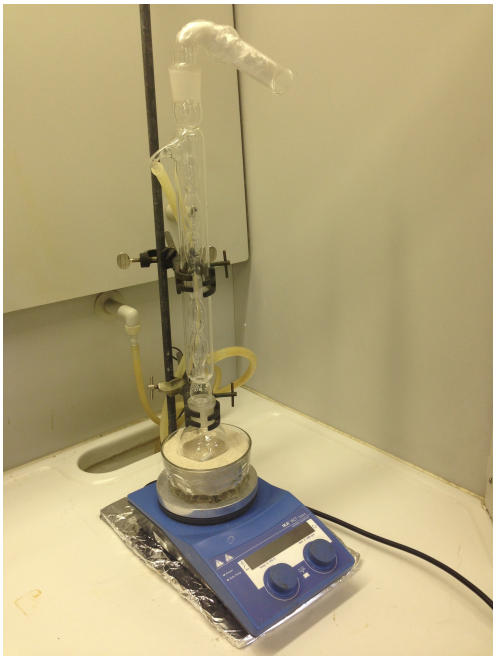

Figure 1. Reaction apparatus

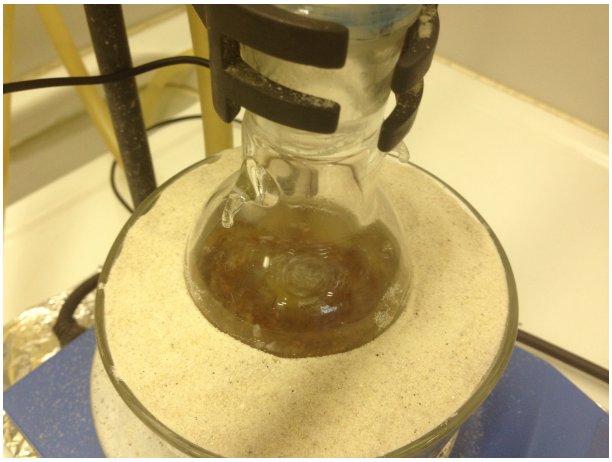

Figure 2. Reaction mixture heated to 60 °C

Figure 3. Product (1) as a white solid

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 *p*-toluene sulfonamide, calcium sulfate, dichloromethane, benzaldehyde, molecular sieves, and pyrrolidine.

2. Both enantiomerically pure forms of *p*-toluenesulfinamide are available from Sigma Aldrich Chemical Co. However, the racemic material was best prepared at a much lower cost according to a known procedure.[2] (*S*)-(+)-*p*-Toluenesulfinamide (98 %, Sigma Aldrich Chemical Co) was used by the checkers.
3. 4Å Molecular sieves (1.6 mm of particle size) were purchased from Sigma Aldrich Chemical Co. and activated by drying in a vacuum oven at 220 °C for 24 h. The submitters activated 4Å Molecular sieves (1.6-2.5 mm of particle size), purchased from Carlo Erba (ref. P1820017), by using microwaves (700W, 3 x 30 s) and subsequent cycles of vacuum/argon.
4. Dichloromethane (anhydrous, ≥99.8%, contains 40-150 ppm amylene as stabilizer) was purchased from Sigma Aldrich Chemical Co. (ref. 270997) and stored over activated 4Å molecular sieves.
5. Benzaldehyde (purified by redistillation, ≥99.5%) was purchased from Sigma Aldrich Chemical Co. and used as received.
6. Pyrrolidine (http://www.sigmaaldrich.com/catalog/product/sial/83240 puriss. p.a., ≥99.0%) was purchased from Sigma Aldrich Chemical Co. and used as received.
7. Calcium sulfate (Drierite™) was used by the checkers. The submitters used calcium chloride (irregular granules, purissimum, 95%) purchased from Panreac and used as received. The drying tube contained cotton wool as stopper.
8. The reaction was monitored by TLC on silica gel using cyclohexane:EtOAc (4:1) as eluent and visualization with UV light. Benzaldehyde had R_f= 0.60, *p*-toluenesulfinamide had R_f= 0.04 and the final product **1** had R_f= 0.43.
9. Filtration was carried out in a medium porosity 200 mL filter funnel with a 6 cm I.D. charged with 30 g of silica gel (40-63 μm) that was purchased from Merck and used as received.
10. Physical and spectroscopic characteristics of *N*-benzylidene-*p*-toluenesulfinamide (**1**): White solid, mp: 72–74 °C (lit.[3] mp: 73–75 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.36 (s, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.38–7.49 (m, 3H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 6.8 Hz, 2H), 8.74 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 124.8, 128.9, 129.6, 129.9, 132.6,

133.9, 141.7, 141.8, 160.7 ppm. MS (ES+): *m/z* (%): 266 ([M+Na]+, 78), 244 ([M+H]+, 100). HRMS: Found: 244.0794 (–1.4 ppm); $C_{14}H_{14}NOS$ $[M+H]^+$ requires 244.0796. The purity of the product was determined using quantitative NMR: A mixture of 21.0 mg of **1** and 17.9 mg of 1,3,5-trimethoxybenzene (99%, purchased from Sigma Aldrich Chemical Co. and used as received) was dissolved in 0.6 mL of $CDCl_3$. ^1H NMR (300 MHz) gave a product purity of 100%.

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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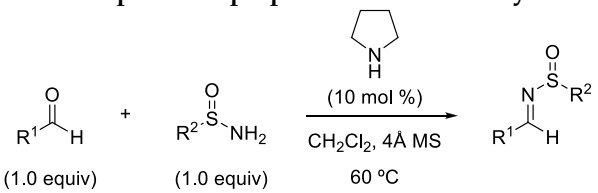
Discussion

N-Sulfinyl imines[4] are valuable intermediates for the synthesis of a wide range of nitrogen-containing molecules, due to the presence of an electron-withdrawing group on the nitrogen atom that significantly enhances the electrophilicity of the C=N bond. Moreover, the chiral nature of the sulfinyl moiety allows the access to enantiomerically enriched amines, usually achieving a high degree of stereocontrol.[5] The preparation of *N*-sulfinyl imines typically occurs through the direct condensation of carbonyl compounds with sulfinamides. However, the low reactivity of the latter reagents requires somewhat harsh reaction conditions that involves activation of the carbonyl group with Lewis acids and/or the use of dehydrating agents.[6] Therefore, the development of milder, more sustainable synthetic protocols is of great interest.

We recently described an unprecedented aminocatalytic method for the synthesis of several classes of imines that consists of the activation of the carbonyl compound through the formation of an iminium ion using a secondary amine in a catalytic amount.[7] In the case of *N*-sulfinyl imines, the best results were achieved employing equimolecular amounts of both reactants and 10 mol % of pyrrolidine in the presence of 4Å molecular sieves as water scavenger. This procedure was applied to differently substituted aromatic, heteroaromatic and unsaturated aldehydes, as well as ethyl glyoxylate, and using both *p*-toluene- or *t*-butylsulfinamides in racemic form (Table 1). Thus prepared *N*-sulfinyl imines were obtained in similar or higher yields compared to previously reported procedures,[2a,7,8] after a simple filtration through a short pad of silica with no need of further purification steps. This process was also tested with enantiomerically pure sulfinamides, proving that the reaction conditions did not affect the stereochemical integrity at the sulfur atom.

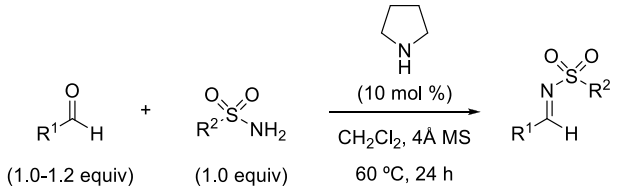
Table 1. Scope of the preparation of *N*-sulfinyl imines



entry	R^1	R^2	reaction time (h)	yield (%)
1	4-$NO_2C_6H_4$	Tol	2.5	93
2	4-$MeOC_6H_4$	Tol	2.0	96
3	4-CNC_6H_4	Tol	4.0	92
4	4-ClC_6H_4	Tol	3.0	95
5	2-$NO_2C_6H_4$	Tol	5.0	90
6	2-HOC_6H_4	Tol	3.0	89
7	2-BrC_6H_4	Tol	4.0	96
8	2-$MeOC_6H_4$	Tol	3.0	99
9	3-$MeOC_6H_4$	Tol	3.0	91
10	2-naphthyl	Tol	4.0	90
11	2-pyridyl	Tol	4.0	88
12	2-pyrrolyl	Tol	4.0	91
13	2-methylindolyl	Tol	8.0	70
14	5-nitrothiophenyl	Tol	4.0	90
15	PhCH=CH	Tol	4.0	99
16	4-$NO_2C_6H_4$CH=CH	Tol	3.0	97
17	4-$MeOC_6H_4$CH=CH	Tol	3.5	88
18	2-$MeOC_6H_4$CH=CH	Tol	3.5	98
19	EtO_2C	Tol	5.0	93
20	Ph	*t*-Bu	4.0	99
21	4-$NO_2C_6H_4$	*t*-Bu	4.0	91
22	4-$MeOC_6H_4$	*t*-Bu	4.0	99

Current preparation methods for the parent *N*-sulfonyl imines[2a,9,10] have to deal with their lower stability towards hydrolysis, and hence the reaction conditions may not be compatible with the structural integrity of the final compounds. In this case, our organocatalytic method proceeded in analogous manner, although longer reaction times (24 h) were required, and in most cases a slight excess of aldehyde was employed (Table 2). The corresponding *N*-sulfonyl imines were isolated in high yields after filtration through celite instead of silica.

Table 2. Scope of the preparation of *N*-sulfonyl imines



entry	R^1	R^2	yield (%)
1	4-$NO_2C_6H_4$	Tol	87
2	4-$MeOC_6H_4$	Tol	97
3	4-CNC_6H_4	Tol	95
4	2-$MeOC_6H_4$	Tol	86
5	PhCH=CH	Tol	99
6	4-$NO_2C_6H_4$CH=CH	Tol	98
7	4-$MeOC_6H_4$CH=CH	Tol	92
8	2,4-$(MeO)_2C_6H_3$	Tol	86
9	3,4,5-$(MeO)_3C_6H_2$	Tol	83
10	Ph	*t*-Bu	96

This efficient, inexpensive, simple, and sustainable method has been extended to other classes of C=N bond-containing molecules achieving comparable results. These include *N*-alkyl, *N*-aryl and *N*-phosphinoyl imines,[7] nitrones,[11] oximes and hydrazones.[12]

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Benzaldehyde; (100-52-7)
p-Toluenesulfinamide: Benzenesulfinamide, 4-methyl-; (6873-55-8)
Pyrrolidine; (123-75-1)
N-Benzylidene-*p*-toluenesulfinamide: Benzenesulfinamide, 4-methyl-*N*-(phenylmethylene)-; (66883-56-5)
p-Toluenesulfonamide: Benzenesulfonamide, 4-methyl-; (70-55-3)
N-Benzylidene-*p*-toluenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-(phenylmethylene)-; (13707-41-0)

Sara Morales received her Ph.D. degree in organic chemistry from Autónoma University of Madrid in 2015, studying the application of pyrrolidine as organocatalyst in the formation of C=N bonds, under the mentorship of Dr. M. Belén Cid and Professor José Luis García Ruano. She spent three months in the laboratory of Dr. Luca Bernardi at Bologna University (Italy), working on organocatalytic dynamic kinetic resolution processes. She is currently a post-doctoral researcher in the group of Dr. Andrés de la Escosura. Her research focuses on the self-replication and templated polymerization processes of nucleic acid analogues.

Alfonso García Rubia studied Chemistry at the University of Salamanca where he obtained his B.S. in Chemistry (2005) and M.S. in organic chemistry (2007). He completed his Doctoral Thesis at the Autónoma University of Madrid working on the palladium activation of C-H bonds, under the supervision of Prof. Juan Carlos Carretero (2012). After a post-doctoral stay in the same group, he is currently holding a research contract in the Translational Medicinal and Biological Chemistry laboratory at the Centro de Investigaciones Biológicas (CSIC).

Eduardo Rodrigo obtained his B.S. in Chemistry in 2009 and his M.S. in Organic Chemistry in 2011. In 2014, he was a visitor in the group of Prof. Petri M. Pihko in the University of Jyväskylä (Finland), working on the total synthesis of pectenotoxin-2. He finished his Ph.D. in 2016 at the Autónoma University of Madrid (Spain) in the field of organocatalysis under the supervision of Dr. M. Belén Cid. Currently, he works as a post-doctoral researcher at the Johannes Gutenberg University Mainz (Germany) in the group of Prof. Siegfried R. Waldvogel, in the field of organic electrosynthesis.

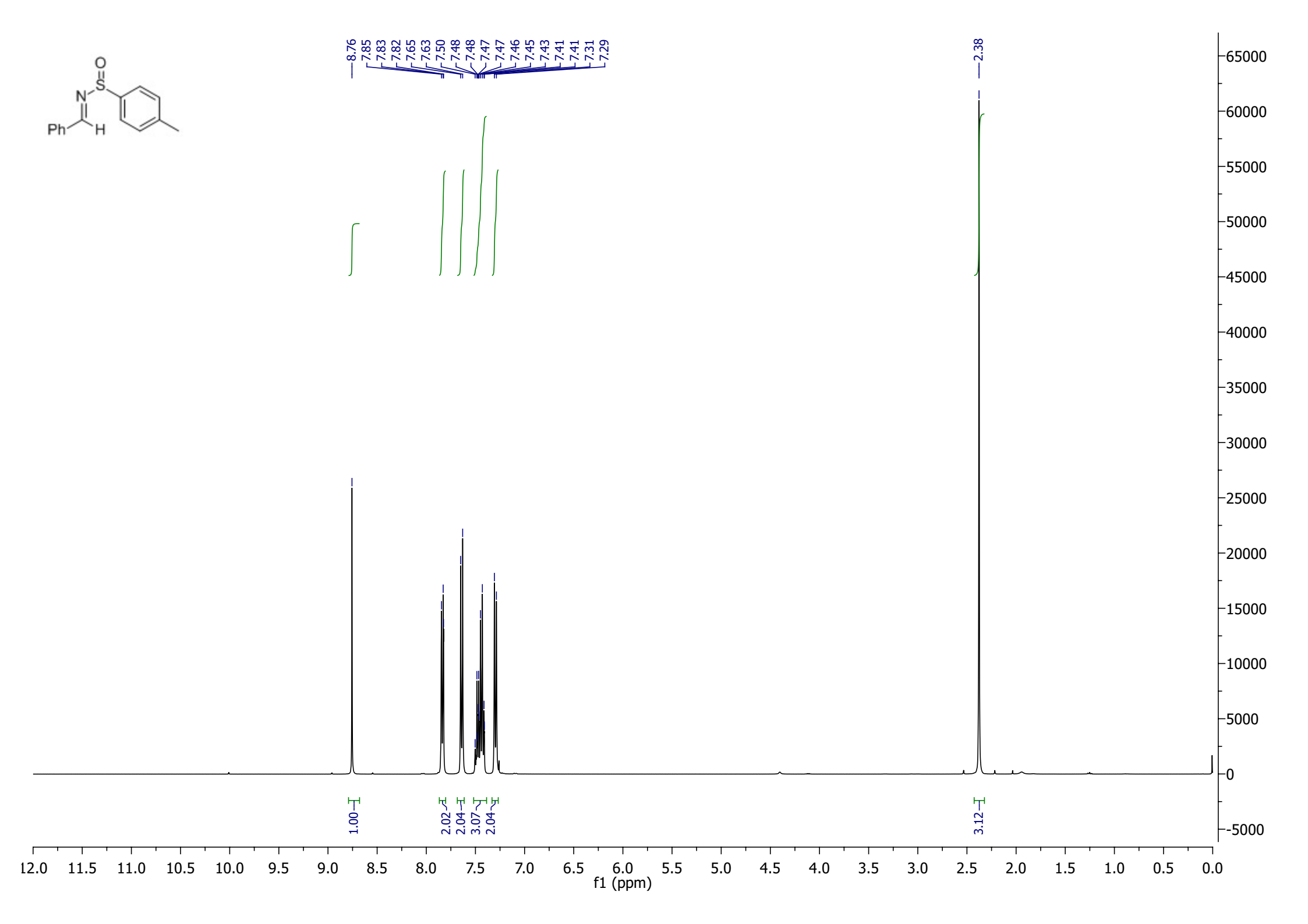
José Luis Aceña studied chemistry at the Complutense University (Madrid), where he obtained his B.Sc. in 1991 and Ph.D. in 1996. He carried out postdoctoral studies for nearly three years at the University of Cambridge (UK) under the supervision of Prof. Ian Paterson. After working for four years in the pharmaceutical industry, he returned to academia in the groups of Prof. Santos Fustero at the Príncipe Felipe Research Center (CIPF) in Valencia (2005-2011), Prof. Vadim Soloshonok at the University of the Basque Country (2012-2014), and Dr. M. Belén Cid at the Autónoma University of Madrid (2015-2016). Since October 2016 he holds a position as Assistant Professor at the University of Alcalá (Madrid).

José Luis García Ruano received his Ph.D. in 1973 at the Complutense University of Madrid, where he became full Professor in 1980. In 1983 he moved to the Autónoma University of Madrid where he was the Head of the Organic Chemistry Department for twelve years. He has been a visiting professor in the laboratories of Professors Walborsky (1992) and Padwa (2002). His activity has been mainly focused on the stereocontrolled reactions mediated by sulfoxides as well as organocatalytic processes involving sulfur compounds. He is co-author of more than three hundred papers and supervised more than 40 Ph.D. theses.

M. Belén Cid completed her Ph.D. in Organic Chemistry in 1995 at Autónoma University of Madrid (Prof. M. C. Carreño and. J. L. García Ruano). After postdoctoral stays at the Alcalá de Henares and Nottingham Universities and CSIC of Seville and Madrid, she returned as a *Ramón y Cajal* Researcher to the Autónoma University of Madrid where she was promoted to associate professor in 2009. She was visiting Professor in the laboratory of Prof. Karl Anker Jørgensen and supervised 6 doctoral theses. Her research interests focus on new organocatalytic transformations, organosulfur compounds, organic synthesis and applications of graphene in catalysts.

Christopher J. Borths earned a Ph.D. in synthetic organic chemistry from the California Institute of Technology in 2004 for developing novel organocatalytic methods with Prof. David MacMillan. After completing his graduate studies, he joined the Chemical Process Research and Development Group at Amgen. He is currently a Principal Scientist in the Synthetic Technologies and Engineering group within the Pivotal Drug Substance Technology department where he works on the development of robust and safe manufacturing processes.

Gabrielle St-Pierre earned a M.Sc. in synthetic organic chemistry from the University of Montreal (Canada) in 2015 for developing glycosidation with minimal protection using pyridones as leaving groups and application on solid support with Prof. Stephen Hanessian and the synthesis of sialosides targeting CD22 cell surface receptors in collaboration with Ionis Pharmaceuticals. After completing her graduate studies, she joined Pivotal Drug Substance Technology department group at Amgen. She is currently a Senior Associate in the Synthetic Technologies and Engineering group within the Pivotal Drug Substance Technology department where she works on the development of robust and safe manufacturing processes.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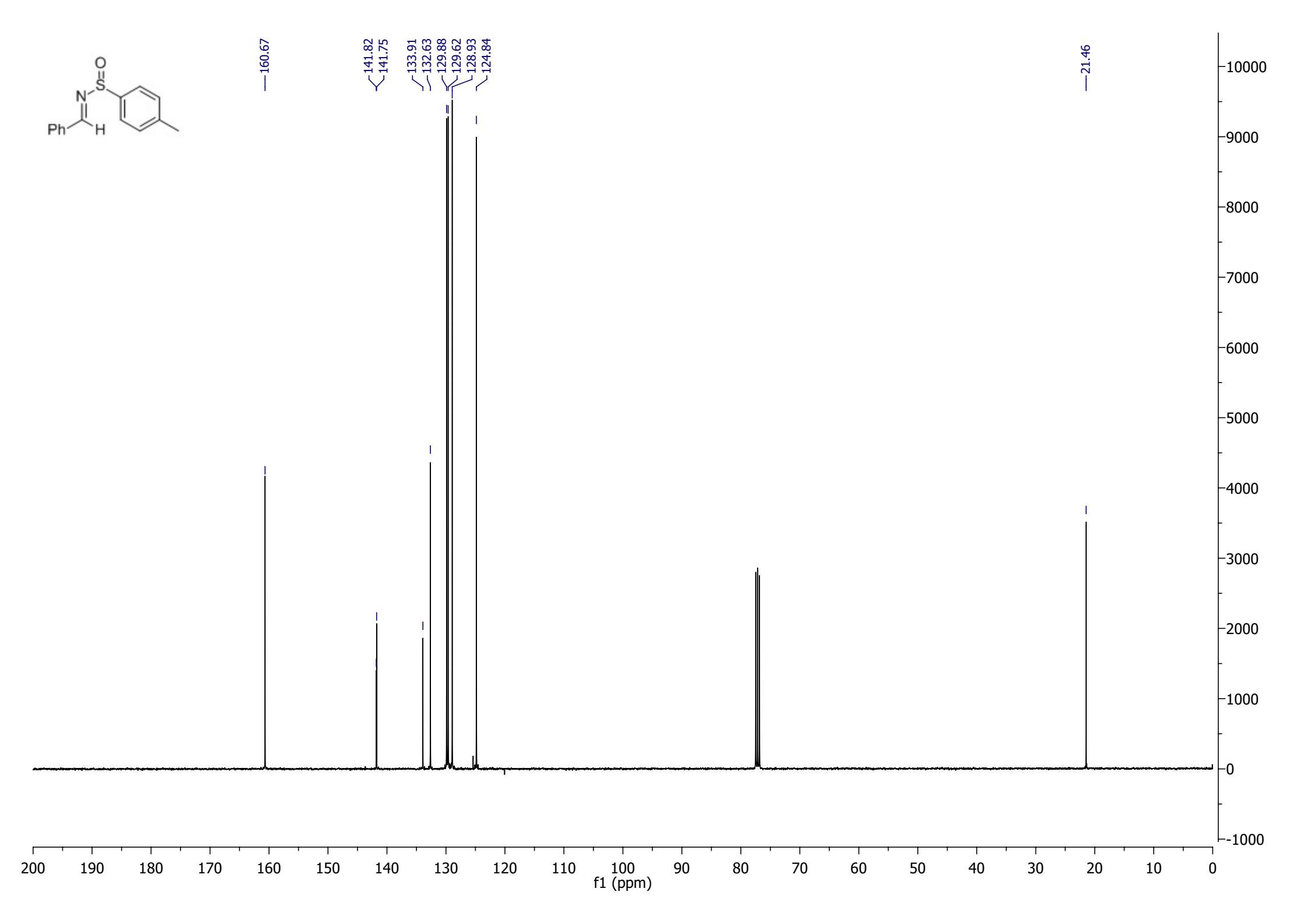
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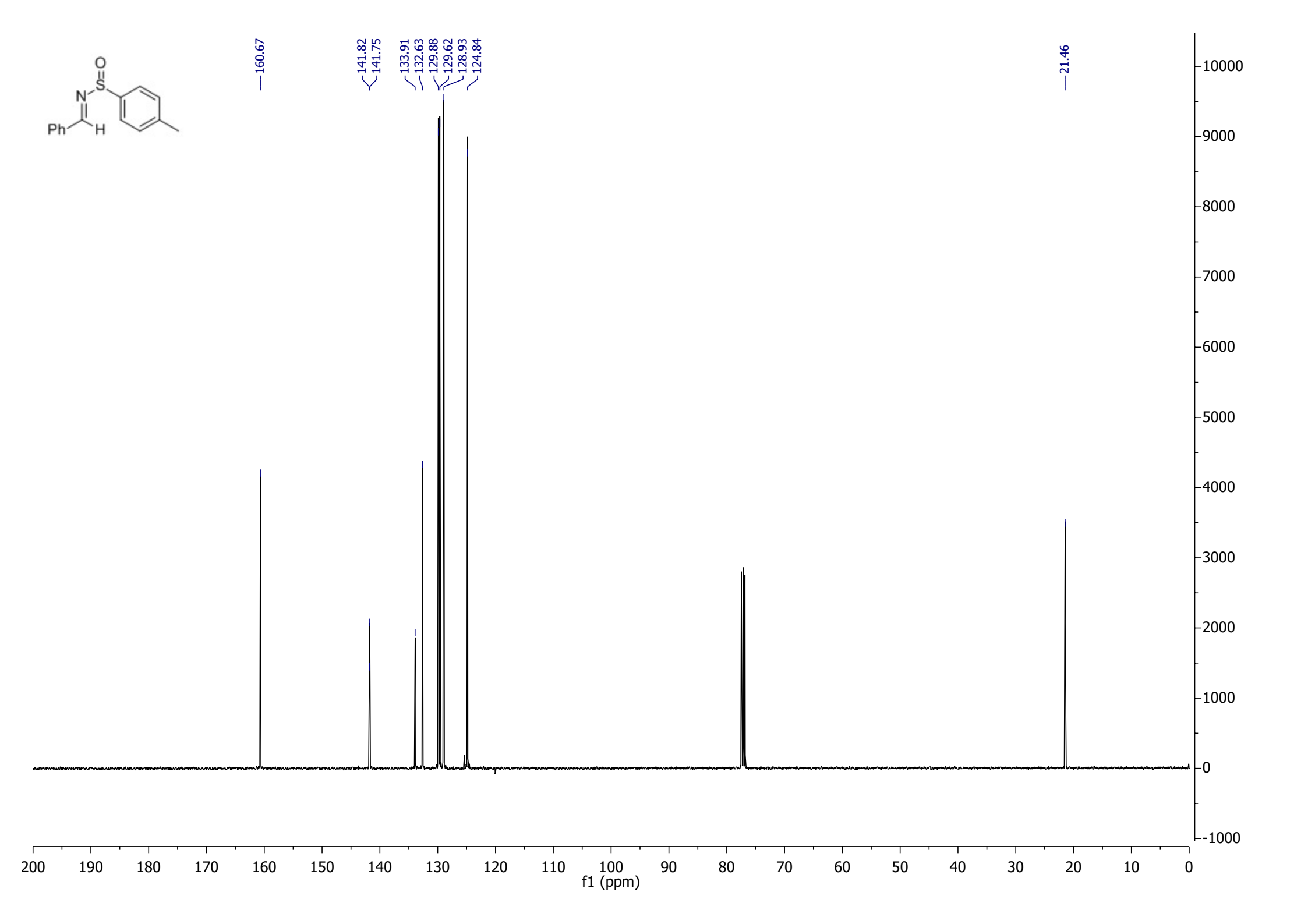
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