Green Chemistry

Accessing the Sustainable Multicomponent Sulfonamide Synthesis Through Deep Eutectic Solvent Design

Journal:	*Green Chemistry*
Manuscript ID	GC-ART-05-2019-001541.R1
Article Type:	Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	Marset, Xavier; Universidad de Alicante, Departamento de Química Orgánica Torregrosa-Crespo, Javier; University of Alicante, Departamento de Agroquímica y Bioquímica Martínez-Espinosa, Rosa; University of Alicante, Departamento de Agroquímica y Bioquímica Guillena, Gabriela; University of Alicante, Organic Chemistry Ramón, Diego; Universidad de Alicante, Química Orgánica
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
ga.cdx	

Article type: Full paper

Website www.rsc.org/greenchem
Impact factor* 8.586

Journal expectations To be suitable for publication in *Green Chemistry* articles must report innovative research on the development of alternative sustainable technologies demonstrating a significant advance in green and sustainable chemistry.

Article type: Full paper Original scientific work that has not been published previously. Full papers do not have a page limit and should be appropriate in length for scientific content.

Journal scope Visit the *Green Chemistry* website for additional details of the journal scope and expectations.

Green Chemistry provides a unique forum for the publication of innovative research on the development of alternative sustainable technologies. The scope of *Green Chemistry* is based on, but not limited to, the definition proposed by Anastas and Warner (Green Chemistry: Theory and Practice, P T Anastas and J C Warner, Oxford University Press, Oxford, 1998). Green chemistry is the utilisation of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.

Green Chemistry is at the frontiers of this interdisciplinary science and publishes research that attempts to reduce the environmental impact of the chemical enterprise by developing a technology base that is inherently non-toxic to living things and the environment. Submissions on all aspects of research relating to the endeavour are welcome.

The journal publishes original and significant cutting-edge research that is likely to be of wide general appeal. Coverage includes the following, but is not limited to:

- the application of innovative technology to establish industrial procedures
- the development of environmentally improved routes, synthetic methods and processes to important products
- the design of new, greener and safer chemicals and materials
- the use of sustainable resources
- the use of biotechnology alternatives to chemistry-based solutions
- methodologies and tools for measuring environmental impact and application to real world examples
- chemical aspects of renewable energy

All items must be written so as to be widely accessible (conceptually) to chemists and technologists as well as, for example, final year undergraduates.

Reviewer responsibilities Visit the Reviewer responsibilities website for additional details of the reviewing policy and procedure for Royal of Society of Chemistry journals.

When preparing your report, please:

- Focus on the originality, importance, impact and reliability of the science. English language and grammatical errors do not need to be discussed in detail, except where it impedes scientific understanding.
- Use the journal scope and expectations to assess the manuscript's suitability for publication in *Green Chemistry.*
- State clearly whether you think the article should be accepted or rejected and include details of how the science presented in the article corresponds to publication criteria.
- Inform the Editor if there is a conflict of interest, a significant part of the work you cannot review with confidence or if parts of the work have previously been published.

Thank you for evaluating this manuscript, your advice as a reviewer for *Green Chemistry* is greatly appreciated.

Dr Katie Lim Executive Editor
Royal Society of Chemistry, UK

Professor Philip Jessop Editorial Board Chair
Queen's University, Canada

ARTICLE

Multicomponent Synthesis of Sulfonamides from Triarylbismuthines, Nitro Compounds and Sodium Metabisulfite in Deep Eutectic Solvents

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Xavier Marset,[a] Javier Torregrosa-Crespo,[b] Rosa M. Martínez-Espinosa,[b] Gabriela Guillena,*[a] Diego J. Ramón*[a]

A sustainable synthesis of sulfonamides using a copper-catalysed process starting from triarylbismuthines, $Na_2S_2O_5$ and nitro compounds is described, in a Deep Eutectic Solvent (DES) as reaction medium. Thus, triarylbismuthines are used as reagents for the incorporation of SO_2 into organic motifs. The bismuth salts formed as by-product can be easily removed from the crude reaction mixture by precipitation with water, while the use of volatile organic compounds (VOCs) as solvents is avoided in the entire process. The eutectic mixture employed as solvent is fully characterised, with the preliminary results proving its low toxicity. The designed DES also allows for a novel multicomponent reaction which saves time, reduces purification steps, energy and cost.

Introduction

The manufacturing of active pharmaceutical ingredients (APIs) generates more waste than any other process within the existing chemical sectors.[1] The sulfonamide functional group is one of the most used moieties found in pharmacologically active compounds,[2] which include those related to new research[3] on anticancer active molecules.[4] Despite its undeniable interest, traditional methods for its synthesis are still prevailing.[5] For more than a century, sulfonamides have been mostly prepared from amines and activated sulfonyl derivatives,[6] usually sulfonyl chlorides. This method is efficient but relies entirely on the use of stoichiometric sulfonyl chlorides, which are not stable or commercially affordable and generate stoichiometric amounts of corrosive HCl. For this reason, new methodologies avoiding the use of unstable and toxic reagents, harsh reaction conditions or dry volatile organic compounds (VOCs) as solvents are demanded.

Multicomponent methods[7] have also been explored using SO_2 surrogates under transition metal catalysis.[8] Recently, we reported the efficient multicomponent synthesis of sulfones from aryl boronic acids, sodium metabisulfite (a food additive) and electrophiles as alkylating reagents catalysed by Pd nanoparticles.[9] The use of sodium metabisulfite possess some advantages, since it is an inexpensive reagent used in food industry. It is known to yield SO_2 under heating or in the presence of water,[10] generating only Na_2SO_3 as waste, thus avoiding the generation of toxic organic by-products. In this case, a DES was used as green reaction medium to carry out the sulfone synthesis, benefitting from the enhanced SO_2 solubility in this type of medium.[11]

DESs are solvents formed by combining a hydrogen-bond donor and an acceptor, affording a mixture with strong interactions. As a consequence, a depression of the melting point of the mixture is observed.[12] Since its discovery, hundreds of mixtures have been found to form a eutectic phase, with more than ten million low-transition-temperature mixtures being available.[13] Changing one of the DES components can modify dramatically its properties. Thus, DESs can be designed for each reaction by choosing carefully the eutectic components. In addition, most of the components are naturally-occurring, bio-renewable, biodegradable or can be bio-assimilated, which makes these solvents an interesting alternative to traditional hazardous organic solvents.[14]

Despite the obvious sustainable advantages of DESs as reaction media, there is still controversy about their potential toxicity; several reports support the theory that DESs are non-toxic, eco-friendly, biodegradable and benign solvents, whilst other similar studies demonstrate exactly the opposite.[15] For this reason, a rigorous analysis of the real toxicity of each new mixture must be performed.

In this study, a new multicomponent reaction using triarylbismuth reagents as starting materials to generate sulfonamides was planned. Triarylbismuthines are non-toxic,[16] and unlike other organometallic reagents (such as boron or tin derivatives) can react with 3 equivalents of an electrophilic reagent (in this case SO_2), increasing the atom economy of the process. As the Bi-C bond energy is quite low, the reactivity displayed by these reagents would be enhanced.[17] The reaction

[a] Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica. Facultad de Ciencias. Universidad de Alicante. Apdo. 99, E-03080-Alicante, Spain.
[b] Departamento de Agroquímica y Bioquímica. División de Bioquímica y Biología Molecular. Facultad de Ciencias. Universidad de Alicante. Apdo. 99, E-03080-Alicante, Spain.
Emails: djramon@ua.es, gabriela.guillena@ua.es

† Electronic supplementary information (ESI) available: DSC analyses, characterisation data, and ^{1}H-NMR and ^{13}C-NMR data.
See DOI: 10.1039/x0xx00000x

of triarylbismuth reagents with $Na_2S_2O_5$ as SO_2 source, would provide aryl sulfinates that could react in situ with nitro compounds.[18] The Na_2SO_3 by-product formed during the first sulfonylation step, reacts with hydrogen donor compounds giving $NaHSO_3$, a potential reductant.[19] The corresponding reaction intermediate would afford, after reduction, a sulfonamide as product. This strategy reduces the by-product formation, meeting the Green Chemistry criteria.[20]

Results and discussion

The study was started by optimising the reaction conditions to yield *N*-phenylbenzenesulfonamide (**4a**), using triphenylbismuthine (**1a**), $Na_2S_2O_5$ (**2**), and nitrobenzene (**3a**) as the model reaction (Table S1). Using choline chloride (ChCl):acetamide (1:2) as solvent, different copper sources were analysed. The use of just 1 mol% of CuCl yielded the desired product in 43% yield without the need of any external ligand or base. Next, different DESs and conventional organic solvents were tested. However, none of them afforded better results. The reaction did not take place in organic solvents or water. Although the reaction did not proceed in ChCl:Urea (1:2) or chlorocholine chloride (ClChCl):Urea (1:2), yields around 50% were obtained both, in ChCl:Acetamide (1:2) and acetyl choline chloride (AcChCl):Urea (1:2). Therefore a new mixture, AcChCl:Acetamide (1:2), was deemed the most suitable reaction medium. This mixture was found to form a eutectic phase (according to DSC analysis, Fig. 1). To the best of our knowledge, this mixture has not been described previously in the literature.

By using this novel DES as medium, 99% yield was obtained, proving that both components of the DES mixture have an important effect in the reaction course (Fig 2).

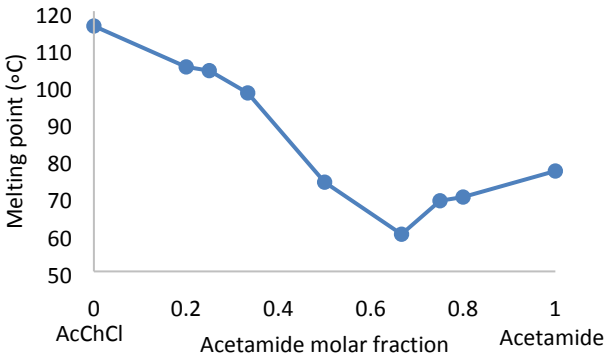


Figure 1. Phase diagram of the mixture acetylcholine chloride:Acetamide.

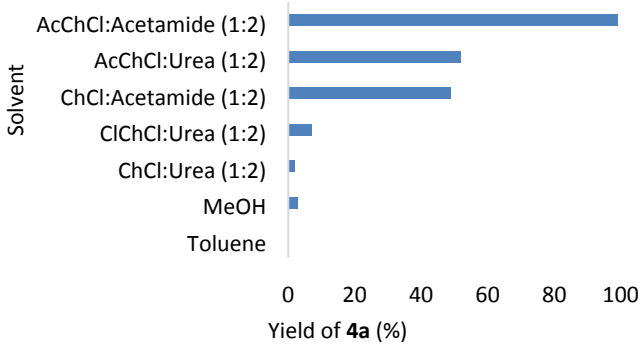


Figure 2. Solvent optimisation.

With these optimised conditions in hand, the scope of nitro compounds was evaluated (Chart 1). No effect on the electronic properties of the substituents of the nitro arene was observed. Good to excellent yields were obtained for all kind of nitro arenes bearing neutral, electron-donating or electron-withdrawing groups. The reaction was chemoselective, as no Suzuki-type by-product was observed.[21] This transformation was also compatible with nitro alkanes, although the product was obtained in lower yield (**4m**). The reaction could also take place twice in the same substrate by using 1,3-dinitrobenzene as starting material (**4i**).

Then, the scope of Ar_3Bi was evaluated (Table 1). The reaction worked with good to excellent yields for triarylbismuth reagents bearing neutral or electron donating groups (**5a-5e**) and lower yields were obtained with electron-withdrawing groups (**5f-5i**). The use of more complex structures and functional groups is also compatible, making the synthesis of biologically active compounds in a single step possible (Scheme 1).[22]

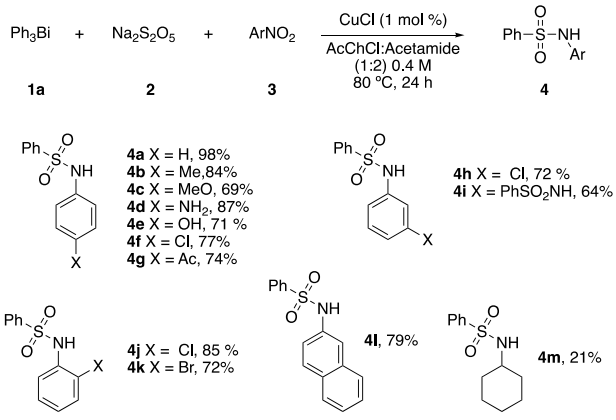
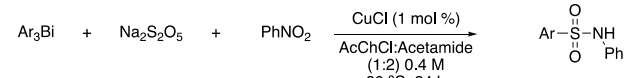


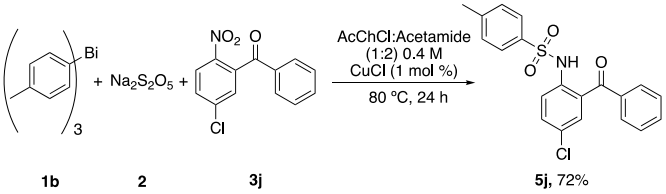
Chart 1. Scope of nitro compounds.

Table 1. Scope of triarylbismuthines.[a]



Entry	Ar	Product	Yield[b]
1	4-MeC_6H_4	**5a**	82%
2	1-naphtyl	**5b**	75%
3	4-MeOC_6H_4	**5c**	71%
4	3,4,5-MeOC_6H_2	**5d**	72%
5	4-$Me_2NC_6H_4$	**5e**	78%
6	4-FC_6H_4	**5f**	49%
7	4-BrC_6H_4	**5g**	62%
8	2-$CF_3C_6H_4$	**5h**	28%
9	3-$CF_3C_6H_2$	**5i**	48%

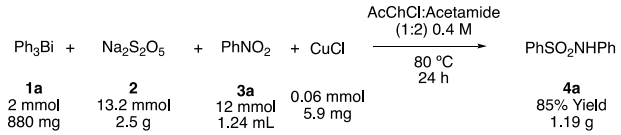
[a] Reaction conditions: Ar_3Bi (0.2 mmol), $Na_2S_2O_5$ (1.32 mmol, 251 mg), CuCl (0.59 mg, 1 mol%) and $PhNO_2$ (1.2 mmol, 123 μL) in 1.5 mL of DES were stirred at 80 °C for 24 h. [b] Isolated yields based on the consumption of the three aryl groups attached to Bi.



Scheme 1. Synthesis of anti-leprosy compound **5j**.

The recycling of the DES and catalyst was attempted by the extraction of the product using immiscible organic solvents, and subsequent addition of fresh reagents to perform a new reaction cycle.[23] However, the use of 2-MeTHF as extraction solvent for this purpose was unsuccessful, since the reaction yield dropped from 98% to 27% in the second cycle. This was probably due to the salts formed during the process affecting the DES structure and therefore limiting its recyclability. Alternatively, in order to avoid the use of VOC solvents in the process, a gram-scale reaction was performed. At the end of the reaction process, a solution of HCl (0.5 M) was added in order to remove the bismuth-waste, obtaining product **4a** as a precipitate which was filtered and rinsed with water. In this case, the use of VOC solvents was completely avoided during the whole process, obtaining 1.19 g of compound **4a** with high purity (85% yield, see Fig S1 for ^{1}H NMR). A similar result was obtained through VOC extraction using EtOAc as solvent (Scheme 2). When the reaction was quenched with only water and the organic products were extracted with EtOAc, the formation of a precipitate containing bismuth salts was observed. After removal of the precipitate, an ICP-mass analyses of both, the organic and aqueous layer, showed only a presence of 0.02% and 2.3% of bismuth, respectively.

To have some insights in the reaction mechanism, several control experiments were performed (see supporting information).



Scheme 2. Gram-scale reaction without using VOC solvents.

The first step involved the disaggregation of $Na_2S_2O_5$ through a homolytic cleavage of the S-S bond. This step includes the formation of radical intermediates,[24] in accordance with our radical-trapping experiments. Running the reaction in the presence of TEMPO (2,2,6,6-etramethylpiperidine 1-oxyl) completely inhibits the product formation. However, when TEMPO was added to the pre-formed sodium sulfinate, CuCl, nitrobenzene and $NaHSO_3$, the reaction proceeded, although with lower yields. These radical intermediates suffer a disproportionation to afford electrophilic SO_2 and the by-product Na_2SO_3. Next, SO_2 undergoes insertion between C-Bi bond.[25] Given that a large excess of chloride anions is present in the medium, $BiCl_3$ may be released, alongside the corresponding sulfinate. Finally, the sulfinate reacts with the nitro arene, being reduced by $NaHSO_3$[19d] (generated from Na_2SO_3 and moisture) to yield sulfonamide, in a process catalysed by copper (Scheme 3).

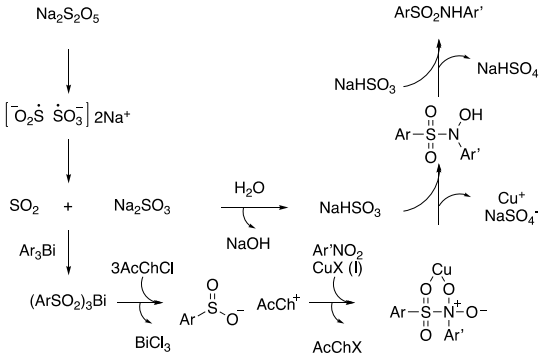
DES physicochemical characterisation.

Since the eutectic mixture employed in this study has not been described previously, a complete physicochemical characterisation was performed. First, the density was measured employing a 50 mL pycnometer (equation 1).

$$\rho_{DES} = \frac{m_{DES}}{m_{water}}\rho_{water} = 1.09\ g/mL\ (28\ ^{\circ}C)$$

Equation 1. Density of DES.

The pH value is a very important parameter to be measured for a new solvent. It can be crucial for the corrosion, catalytic or dissolution properties of the solvent, limiting its industrial applicability. In non-aqueous solutions, pH depends on temperature and on the chemical potential of hydrogen.



Scheme 3. Plausible reaction mechanism.

The chemical potential depends on the presence of ions and hydrogen-bonding with other species.[26] It was observed that the pH value decreased linearly with the acetamide molar fraction (Fig. 3); meaning that the more hydrogen bonds available, the lower the chemical potential of hydrogen was and the lower pH value was obtained. The phase diagram (Fig 1) was plotted using the individual differential scanning calorimetry analyses of several mixtures containing different proportions of the two DES components (Fig S4).

Finally, the potential toxicity of this novel eutectic mixture was studied. Preliminary studies carried out with strains of mesophilic bacteria showed that the DES is non-toxic for concentrations below 300 mM. Nevertheless, further studies will be carried out in order to completely assess the DES toxicity.

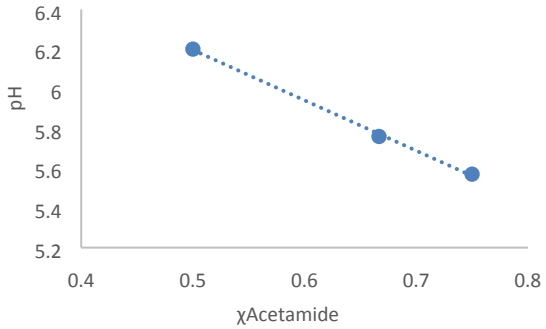


Figure 3. pH values depending on the acetamide molar fraction.

Experimental

General

Melting points were obtained with a Reichert Thermovar apparatus. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$ as a solvent and TMS as internal standard for ^{1}H and ^{13}C; chemical shifts are given in δ (parts per million) and coupling constants (*J*) in Hertz. FT-IR spectra were obtained on a JASCO 4100LE (Pike Miracle ATR) spectrophotometer. Mass spectra (EI) were obtained at 70 eV on a Himazdu QP-5000 spectrometer, giving fragment ions in m/z with relative intensities (%) in parentheses. The mass spectrometry analyses of high resolution (HRMS) were performed in the unit of Mass Spectrometry of the Technical Services Research at the University of Alicante with a spectrometer Finnigan MAT95-S. DIP analyses were performed using an Agilent mass spectrometer, model Network 5973 Mass Selective with direct sample introduction to the ion source through the SIS (Scientific Instrument Services) probe Direct Insertion Probe (73DIP-1).The chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and 12 m HP-1 capillary column (0.2 mm diam, 0.33 mm film thickness, OV-1 stationary phase), using nitrogen (2 mL/min) as a carrier gas, $T_{injector}$ = 275 ºC, $T_{detector}$ = 300 ºC, T_{column} = 60 ºC (3 min) and 60-270 ºC (15 ºC/min), P = 40 kPa. Thin layer chromatography (TLC) was carried out on Schleicher&Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light. DSC analysis were carried out on a METTLER TOLEDO equipment, model TGA/SDTA851e/LF/1600, and EM analysis on a PFEIFFER VACUUM, model THERMOSTAR GSD301T. pH measurements were performed using a Mettler Toledo SevenEasy S20 pH-meter. Reactions carried out under microwave irradiation were performed on a MW CEM Discovery 908010 apparatus. Column chromatography was performed using silica gel 60 of 40-63 mesh. All reagents were commercially available (Acros, Aldrich, Fluorochem) and were used as received.

Synthesis of Ar_3Bi.

For commercially available organomagnesium reagents: a solution of the $BiCl_3$ in dry THF (1M) was added dropwise over a solution of ArMgBr in THF or Et_2O (1M) under argon atmosphere with magnetic stirring. Once the addition was completed, the solution was heated to reflux for 12 h. Then, the reaction was allowed to reach room temperature and poured slowly over a cold saturated aqueous solution of NH_4Cl. Product was extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure.[27]

For non-commercially available organomagnesium reagents: the corresponding aryl iodide (6.2 mmol) was dissolved in dry THF and cooled to -78 ºC in an acetone bath. A *n*-butyllithium solution (2.5 M, 6.2 mmol) was added dropwise and the mixture was stirred at that temperature for 1 h. Then, a solution of $BiCl_3$ (2 mmol) in dry THF was added dropwise and the mixture was slowly allowed to reach room temperature. The corresponding mixture was stirred overnight at rt and then quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (15 mL x 3) and the combined organic layers washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and reduced under reduced pressure. Ar_3Bi were usually purified by recrystallization from hot EtOH or by flash chromatography using a mixture of EtOAc and hexanes.[30]

Synthesis of sulfonamides.

A solution of Ar_3Bi (0.2 mmol), sodium metabisulfite (1.32 mmol), CuCl (0.006 mmol) and the corresponding nitro compound (1.2 mmol) in 1.5 mL of DES was stirred for 24 h at 80 °C in a reaction vessel opened to air. Once the reaction was completed, water was added to dissolve the DES phase. A precipitate containing the bismuth waste was formed. The bismuth by-product was only soluble in acidic aqueous solutions. The aqueous suspension was extracted three times with EtOAc. The sulfonamide product and the excess of nitro compound were dissolved in EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products **4/5**.

Alternatively, product could be isolated by quenching the reaction mixture with HCl (0.5 M) and filtering the suspension. The filtrate was rinsed with distilled water to afford products **4/5** in high purity, although with lower yields than in the previous method due to the slight solubility of sulfonamides in water. Isolated yields are based on the consumption of the three aryl groups attached to Bi.

Conclusions

In summary, an efficient one-pot, one-step synthesis of sulfonamides is described in this study; starting from unactivated reagents such as nitro compounds and triarylbismuthines, with $Na_2S_2O_5$ as SO_2 source and reductant. This process, catalysed by copper chloride in a ligand-free fashion has been demonstrated to be chemoselective, simple, and air and moisture insensitive. In addition, in this study non-toxic reagents are used, and the excess of by-product formation is reduced, following most of the Green Chemistry principles. The resulting bismuth salts are easily removed from the reaction crude mixture by precipitation with water. The eutectic mixture here described has been characterised, with preliminary analyses showing low toxicity.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the University of Alicante (VIGROB-173 and VIGROB-309) and the Spanish Ministerio de Economía, Industria y Competitividad (CTQ2015-66624-P and PGC2018-096616-B-I00). X.M. and J.T.C. thank Generalitat Valenciana (ACIF/2016/057 and ACIF/2016/077) for their fellowships. We gratefully acknowledge the polishing of our English by Mrs. Oriana C. Townley.

Notes and references

1. M. C. Bryan, P. J. Dunn D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chem.*, 2018, **20**, 5082–5103.
2. J. Engel, A. Kleemann, B. Kutscher and D. Reichert, *Pharmaceutical Substances*, Thieme, Stuttgart, 5th edn., 2014.
3. M. Feng, B. Tang, S. H. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200-1216.
4. K. P. Rakesh, S.-M. Wang, J. Leng, L. Ravindar, A. M. Asiri, H. M. Marwani and H.-L. Qin, *Anti-Cancer Agents Med. Chem.*, 2018, **18**, 488-505.
5. K. Hofman, N.-W. Liu and G. Manolikakes, *Chem. Eur. J.*, 2018, **24**, 11852-11863.
6. (a) K. K. Anderson, *Comprehensive Organic Chemistry*, Pergamon Press, Oxford, 1979; (b) S. Caddick, J. D. Wilden and D. B. Judd, *J. Am. Chem. Soc.*, 2004, **126**, 1024-1025; (c) J. Jiang, S. Zeng, D. Chen, C. Cheng, W. Deng and J. Xiang, *Org. Biomol. Chem.*, 2018, **16**, 5016-5020.
7. (a) T. J. J. Müller, *Multicomponent Reactions*, Science of Synthesis, Stuttgart, 2014; (b) H. Eckert, *Molecules*, 2017, **22**, 349.
8. (a) A. Shavnya, S. B. Coffey, A. C. Smith and V. Mascitti, *Org. Lett.*, 2013, **15**, 6226-6229; (b) M. W. Johnson, S. W. Bagley, N. P. Mankad, R. G. Bergman, V. Mascitti and F. D. Toste, *Angew. Chem., Int. Ed.*, 2014, **53**, 4404-4407; (c) Smith, *Angew. Chem., Int. Ed.*, 2015, **54**, 13571-13575; (d) E. F. Flegeau, J. M. Harrison and M. C. Willis, *Synlett*, 2016, **27**, 101-105. (e) H. Konishi, H. Tanaka and K. Manabe, *Org. Lett.*, 2017, **19**, 1578-1581; (f) M. Wang, Q. Fan and X. Jiang, *Green Chem.*, 2018, **20**, 5469-5473; (g) Y. Chen, P. R. D. Murray, A. T. Davies and M. C. Willis, *J. Am. Chem. Soc.*, 2018, **140**, 8781-8787; (h) D. Yang, P. Sun, W. Wei, F. Liu, H. Zhang and H. Wang, *Chem. Eur. J.*, 2018, **24**, 4423-4427; (i) M. Wang, J. Zhao and X. Jiang, *ChemSusChem*, 2019, DOI: 10.1002/cssc.201802919, Ahead of Print.
9. X. Marset, G. Guillena and D. J. Ramón, *Chem. Eur. J.*, 2017, **23**, 10522-10526.
10. H. Zhu, Y. Shen, Q. Deng, J. Chen and T. Tu, *ACS Catal.*, 2017, **7**, 4655-4659.
11. D. Yang, M. Hou, H. Ning, J. Zhang, J. Ma, G. Yang and B. Han, *Green Chem.*, 2013, **15**, 2261-2265.
12. (a) J. García-Álvarez, *Eur. J. Inorg. Chem.*, 2015, DOI: 10.1002/ejic.201500892, 5147-5157; (b) D. Rengstl, V. Fischer and W. Kunz, *Phys. Chem. Chem. Phys.*, 2014, **16**, 22815-22822.
13. O. S. Hammond, D. T. Bowron and K. J. Edler, *Angew. Chem., Int. Ed.*, 2017, **56**, 9782-9785.
14. I. Juneidi, M. Hayyan and M. A. Hashim, *RSC Adv.*, 2015, **5**, 83636-83647.
15. (a) K. Radošević, M. Cvjetko Bubalo, V. Gaurina Srček, D. Grgas, T. Landeka Dragičević and I. Radojčić Redovniković, *Ecotoxicol. Environ. Saf.*, 2015, **112**, 46-53; (b) M. Hayyan, C. Y. Looi, A. Hayyan, W. F. Wong and M. A. Hashim, *PLoS One*, 2015, **10**, e0117934/0117931-e0117934/0117918.
16. Y. M. Hitomi Suzuki, *Organobismuth Chemistry*, ELSEVIER, Amsterdam, 2001.
17. B. D. Jadhav and S. K. Pardeshi, *Appl. Organomet. Chem.*, 2017, **31**, e3591.
18. (a) H. Tian, A. Cao, L. Qiao, A. Yu, J. Chang and Y. Wu, *Tetrahedron*, 2014, **70**, 9107-9112; (b) B. Yang, C. Lian, G. Yue, D. Liu, L. Wei, Y. Ding, X. Zheng, K. Lu, D. Qiu and X. Zhao, *Org. Biomol. Chem.*, 2018, **16**, 8150-8154; (c) N. Eid, I. Karame and B. Andrioletti, *Eur. J. Org. Chem.*, 2018, 5016-5022.
19. (a) W. Zhang, J. Xie, B. Rao and M. Luo, *J. Org. Chem.*, 2015, **80**, 3504-3511; (b) M. Abbasi, M. R. Mohammadizadeh and Z. Moradi, *Tetrahedron Lett.*, 2015, **56**, 6610-6613; (c) H. Gao, B. Hu, W. Dong, X. Gao, L. Jiang, X. Xie and Z. Zhang, *ACS Omega*, 2017, **2**, 3168-3174; (d) Z.-H. Guan, Z.-Y. Zhang, Z.-H. Ren, Y.-Y. Wang and X. Zhang, *J. Org. Chem.*, 2011, **76**, 339-341.
20. P. T. Anastas and J. C. Warner, *Green chemistry : theory and practice*, Oxford University Press, Oxford, 1998.
21. (a) M. Hebert, P. Petiot, E. Benoit, J. Dansereau, T. Ahmad, A. Le Roch, X. Ottenwaelder and A. Gagnon, *J. Org. Chem.*, 2016, **81**, 5401-5416; (b) M. L. N. Rao, O. Yamazaki, S.

Shimada, T. Tanaka, Y. Suzuki and M. Tanaka, *Org. Lett.*, 2001, **3**, 4103-4105.
22. M. M. V. Ramana, R. S. Lokhande, U. J. Joshi, G. V. Gadre and A. J. Joshi, *Int. J. Pharm. Sci. Rev. Res.*, 2014, **26**, 134-139, 136.
23. F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati and A. Salomone, *Chem. Commun.*, 2018, **54**, 8100-8103.
24. E. G. Janzen, *J. Phys. Chem.*, 1972, **76**, 157-162.
25. B. C. Smith and C. B. Waller, *J. Organometal. Chem.*, 1971, **32**, C11-C12.
26. B. Jibril, F. Mjalli, J. Naser and Z. Gano, *J. Mol. Liq.*, 2014, **199**, 462-469.
27. H. El Ghaoui, M. Raihane, B. Rhouta, N. Bitinis, A. Carlmark, M. Arroyo, R. Verdejo, M. A. Lopez-Manchado and M. Lahcini, *Polym. Int.*, 2014, **63**, 709-717.
28. (a) J. Luan, L. Zhang and Z. Hu, *Molecules*, 2011, **16**, 4191-4230; (b) J.-Q. Liu, J.-J. Yang, J.-F. Li, K. Li, X.-D. Xiao, Y.-L. Bai and J.-W. Wang, *Mol. Catal.*, 2017, **443**, 125-130.

Dear Prof. Dr. Han,

Please, find attached our revised manuscript entitled "*Multicomponent Synthesis of Sulfones from Triarylbismuthines, Nitro Compounds and Sodium Metabisulfite in Deep Eutectic Solvents*", Manuscript ID: GC-ART-05-2019-001541, which has been changed (highlighted in yellow) according to the reviewers' comments as follows:

Referee 1:

- Referee comment: Page 5, right column: …disaggregation of Na2S2O5 throw…
- Answer: The spelling mistake has been corrected (Page 3, line 2).

- Referee comment: Compound 4j: There should be ten signals. Nine signals could be noticed in 13C NMR spectrum, and two signals overlap. In the revised version, three overlaps are noted, yielding 12 signals in total.
- Answer: Compound **4j** should have 10 signals, but only 9 signals can be noticed. This fact is due to an overlap of two signals, as it has been previously reported (*J. Org. Chem.*, 2017, **82**, 5810-5818; Synthetic Communications, **2018**, *48*, 1436-1442). In the characterisation data, there are 3 signals which are noted as "(2C)". One of these signals correspond to an overlap of two signals. The other two signals correspond to the two couples of chemically equivalent carbons of the phenyl group.

Referee 2:

- Referee comment: Since DESs have been known and similar DES has been reported, this reviewer had suggested that the description of "Through Deep Eutectic Solvent Design" in the title is over-selling and not suitable, but the authors did not revise it.
- Answer: The title has been completely revised.

- Referee comment: The revised abstract is still too redundant and not well organized. Actually it can be revised in a much more concise and more readable way. In the abstract, the authors' comment that "This one-pot synthetic method is extremely advantageous from an atom economy point of view" is over-selling. As it is clear that the method requires at least 2 equiv. of sodium metabisulfite and nitro compounds that can lead to waste of the reactants and byproduct generation is inevitable, which mean the method is not atom economic, and are obviously contradictory with the description "extremely advantageous from an atom economy point of view".
- Answer: The abstract has been carefully revised and reorganised. The concept of atom economy has been removed throughout the manuscript.

- Referee comment: In Results and discussion section, in "The study started by optimising", "was" is missing. The "organic conventional solvents" should be "conventional organic solvents". There are still many other English issues.
- Answer: English has been revised along the manuscript, and revised by a English-native speaker. All "over-selling" concepts have been removed:
    - Page 1, left column, line 15: "volatile organic compunds"
    - Page 1, right column, line 9: "As a consequence, a depression of the melting point of the mixture is observed"
    - Page 1, right column, line 13: "Changing one of the DES components can modify dramatically its properties. Thus, DESs can be designed for each reaction by choosing carefully the eutectic components"
    - Page 2, left column, line 7: "This strategy reduces the by-product formation, meeting the Green Chemistry criteria"
    - Page 2, left column, line 10: "study was started"
    - Page 2, left column, line 17: "Next, different DESs and conventional organic solvents were tested. However, none of them afforded better results. The reaction did not take place in organic…"
    - Page 2, left column, line 25: "reaction médium"
    - Page 2, right column, line 4: "Good to excellent yields were obtained for all kind of nitro arenes"
    - Page 2, right column, line 7: "…by-product was observed.[21] This transformation was also compatible…"
    - Page 2, right column, line 16: "…with electron-withdrawing groups (**5f-5i**)."
    - Page 3, left column, line 18: "When the reaction…"
    - Page 3, right column, line 2: "through a homolytic cleavage"
    - Page 4, right column, line 8: "…saturated aqueous solution of NH_4Cl."
    - Page 5, left column, line 11: "…source and reductant. This process, catalyzed..."
    - Page 5, left column, line 16: "…excess of by-product formation is reduced."
    - Page 5, left column, line 30: "We gratefully acknowledge the polishing of our English by Mrs. Oriana C. Townley."

- Referee comment: in the charts and tables, it unclear on which reactant the isolated yields of the products are based.
- Answer: A footnote has been added to Table 1 and it has been explained as well in the experimental section.
    - Page 5, left column, line 6: "Isolated yields are based on the consumption of the three aryl groups attached to Bi."
- Referee comment: Since the synthesis of sulfones and sulfides by similar Pd-catalyzed reactions of boronic acids, Na2S2O5 with halides or nucleophiles have been reported by the authors themselves using another DES, which may make

the method less novel, this reviewer suggests the authors should focus on sulfonamide synthesis.

- Answer: The synthesis of sulfones and arylsulfides has been removed from the manuscript according to the referee's suggestion.

Finally, we would like to thank the reviewers for their careful work and helpful comments.

Sincerely yours,

Diego J. Ramón
Departamento de Química Orgánica
Universidad de Alicante
03080-Alicante
Spain

Supporting Information

Multicomponent Synthesis of Sulfonamides from Triarylbismuthines, Nitro Compounds and Sodium Metabisulfite in Deep Eutectic Solvents

Xavier Marset[a], Javier Torregrosa-Crespo[b], Rosa María Martínez-Espinosa[b] Gabriela Guillena[a]*, Diego J. Ramón[b]*

[a] Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica. Facultad de Ciencias. Universidad de Alicante. Apdo. 99, E-03080-Alicante, Spain.

[b] Departamento de Agroquímica y Bioquímica. División de Bioquímica y Biología Molecular. Facultad de Ciencias. Universidad de Alicante. Apdo. 99, E-03080-Alicante, Spain.

Corresponding authors: gabriela.guillena@ua, djramon@ua.es

Table of Contents

1. Procedures.

General

Melting points were obtained with a Reichert Thermovar apparatus. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$ as a solvent and TMS as internal standard for ^{1}H and ^{13}C; chemical shifts are given in δ (parts per million) and coupling constants (*J*) in Hertz. FT-IR spectra were obtained on a JASCO 4100LE (Pike Miracle ATR) spectrophotometer. Mass spectra (EI) were obtained at 70 eV on a Himazdu QP-5000 spectrometer, giving fragment ions in *m/z* with relative intensities (%) in parentheses The mass spectrometry analyses of high resolution (HRMS) were performed in the Mass Spectrometry Unit of the Technical Services Research at the University of Alicante with a spectrometer *Finnigan MAT95-S.* DIP analyses were performed using an Agilent mass spectrometer, model Network 5973 Mass Selective with direct sample introduction to the ion source through the SIS (Scientific Instrument Services) probe Direct Insertion Probe (73DIP-1) The chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and 12 m HP-1 capillary column (0.2 mm diam, 0.33 mm film thickness, OV-1 stationary phase), using nitrogen (2 mL/min) as a carrier gas, $T_{injector}$ = 275 ºC, $T_{detector}$ = 300ºC, T_{column} = 60ºC (3 min) and 60-270 ºC (15 ºC/min), *P* = 40 kPa. Thin layer chromatography (TLC) was carried out on Schleicher&Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light. DSC analysis were carried out on a *METTLER TOLEDO* equipment, model *TGA/SDTA851e/LF/1*600, and EM analysis on a *PFEIFFER VACUUM*, model *THERMOSTAR GSD301T*. pH measurements were performed using a *Mettler Toledo SevenEasy S20* pH-meter. Reactions carried out under microwave irradiation were performed on a *MW CEM Discovery 908010* apparatus. Column chromatography was performed using silica gel 60 of 40-63 mesh. All reagents were commercially available (Acros, Aldrich, Fluorochem) and were used as received.

Deep Eutectic Solvents preparation.

DESs were prepared by mixing the corresponding components in the appropriate molar ratio and heating the mixture at 80 ºC under Ar atmosphere until a clear solution was obtained. Since some of the components of DESs are very hygroscopic, they were always stored under Ar atmosphere, although the reactions employing DESs as solvents were carried out in opened to air reaction vessels.

Synthesis of Ar_3Bi.

For commercially available organomagnesium reagents: a solution of the $BiCl_3$ in dry THF (1M) was added dropwise over a solution of ArMgBr in THF or Et_2O (1M) under argon atmosphere with magnetic stirring. Once the addition was completed, the solution was heated to reflux for 12h. Then, the reaction was allowed to reach room temperature and poured slowly over a cold solution of NH_4Cl (sat. aq.). Product was extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure.[1]

For non-commercially available organomagnesium reagents: the corresponding aryl iodide (6.2 mmol) was dissolved in dry THF and cooled to -78 ºC in an acetone bath. A *n*-butyllithium solution (2.5 M, 6.2 mmol) was added dropwise and the mixture was stirred at that temperature for 1h. Then, a solution of $BiCl_3$ (2 mmol) in dry THF was added dropwise and the mixture was slowly allowed to reach room temperature. The corresponding mixture was stirred overnight at rt and then quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (15 x 3 mL) and the combined organic layers washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and reduced under reduced pressure.

Ar_3Bi were usually purified by recrystallization from hot EtOH or by flash chromatography using a mixture of EtOAc and hexanes.[2]

Synthesis of sulfonamides.

A solution of Ar_3Bi (0.2 mmol), sodium metabisulfite (1.32 mmol), CuCl (0.006 mmol) and the corresponding nitro compound (1.2 mmol) in 1.5 mL of DES was stirred for 24 h at 80 °C in a reaction vessel opened to air. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products **4/5**.

Alternatively, product could be retrieved by quenching the reaction mixture with $NaHCO_3$ and filtering the suspension. The filtrate was rinsed with distilled water to afford products **4** in high purity, although with lower yields than in the previous method due to the slight solubility of sulfonamides in water (Fig S1).

Microbial strain, culture media and incubation conditions.

The microorganism used in this study to test the toxicity, tolerance and the potential assimilation of the DESs here described was *Escherichia coli* BL21 (DE3) (Novagen). The incubation experiments were conducted in 250 mL Erlenmeyer with 50 mL of Luria-Bertani medium (LB). In all cases, the cells were grown at 37 °C with constant shaking (180 rpm). The growth of the bacterium was monitored by measuring the absorbance at 600 nm. All the physiological studies were done in triplicate. In order to test the toxicity/tolerance of the DES, the media were supplemented with it at final concentrations between 0 (control) and 750 mM.

2. Gram-Scale Reaction.

a)

Ph_3Bi	+	$Na_2S_2O_5$	+	$PhNO_2$	+	CuCl	AcChCl:Acetamide (1:2), 80°C	$PhSO_2NHPh$
2 mmol 880 mg		13.2 mmol 2.5 g		12 mmol 1.24 mL		0.06 5.9 mg		85% Yield 1.19 g

b)

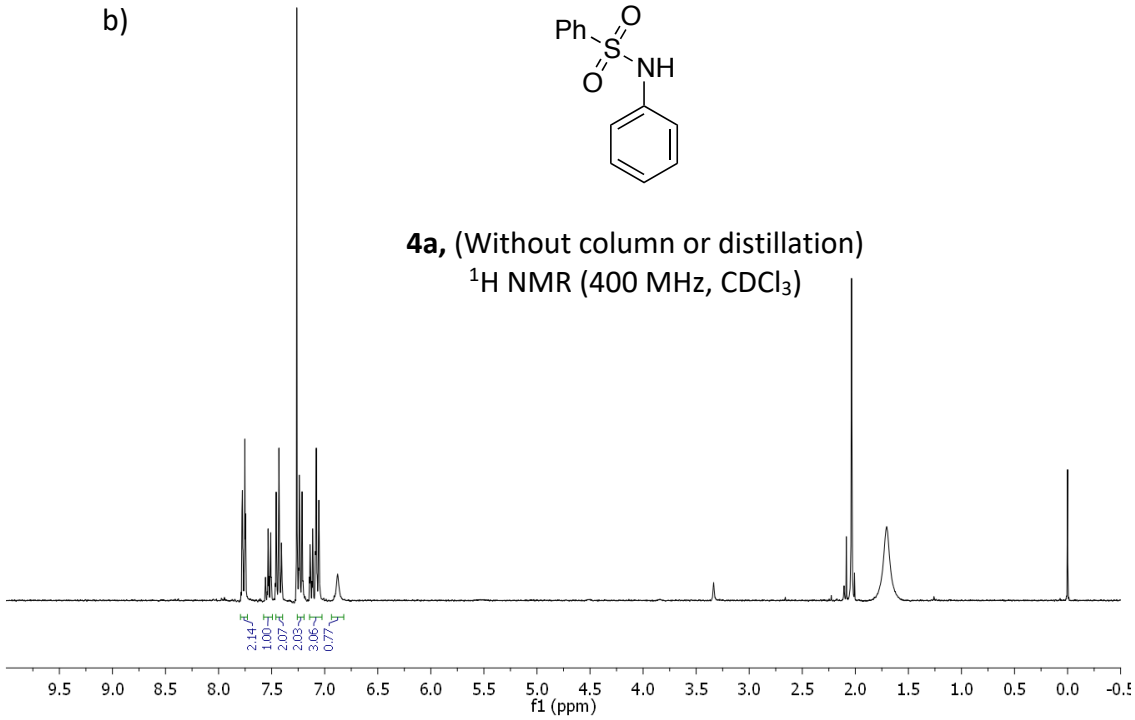
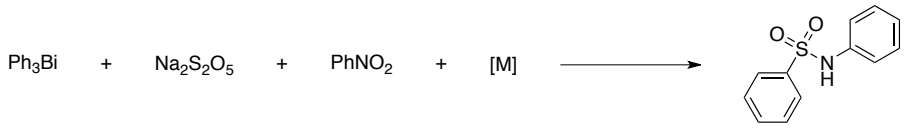


Fig. S1. a) Gram-scale reaction. b)^{1}H NMR spectra of compound **4a** directly filtered from the reaction media without any purification step.

3. Optimisation Studies.

Table S1. Optimisation of reaction conditions.[a]



Entry	DES (molar ratio)	[M] (1 mol%)	Ligand (mol%)	T (ºC)	t (h)	Yield (%)[b]
1	ChCl:Acetamide (1:2)	$CuCl_2$	-	50	15	-
2	ChCl:Acetamide (1:2)	$CuCl_2$	-	80	15	21%
3	ChCl:Acetamide (1:2)	$CuCl_2$	-	80	1	35[c]
4	ChCl:Acetamide (1:2)	$CuCl_2$	**L1** (1)	80	24	18
5	ChCl:Acetamide (1:2)	$CuCl_2$	**L2** (2)	80	24	31
6	ChCl:Acetamide (1:2)	$CuCl_2$	**L3** (2)	80	24	61
7	ChCl:Acetamide (1:2)	CuCl	-	80	24	43
8	ChCl:Acetamide (1:2)	CuI	-	80	24	29
9	ChCl:Acetamide (1:2)	CuO	-	80	24	20
10	ChCl:Acetamide (1:2)	Cu_2O	-	80	24	47
11	ChCl:Acetamide (1:2)	CuBr	-	80	24	27
12	ChCl:Acetamide (1:2)	Cu	-	80	24	8
13	ChCl:Acetamide (1:2)	CuCl	**L3** (2)	80	24	26
14	ChCl:Glycerol (1.2)	CuCl	-	80	24	5
15	Ph_3PMeBr:Glycerol (1:2)	CuCl	-	80	24	12
16	ChCl:$(HOCH_2)_2$ (1:2)	CuCl	-	80	24	18
17	ChCl:Urea (1:2)	CuCl	-	80	24	2
18	ChCl:Glucose (2:1)	CuCl	-	80	24	1
19	ChCl:Formic Ac (1:2)	CuCl	-	80	24	0
20	ChCl:Sorbitol (1:1)	CuCl	-	80	24	0
21	DecA:Menthol (1:2)	CuCl	-	80	24	0
22	Urea:Acetamide (1:2)	CuCl	-	80	24	19
23	Betaine:$PhCO_2H$ (2:3)	CuCl	-	80	24	43
24	Betaine:Acetamide (1:2)	CuCl	-	80	24	28
25	AcChCl:Acetamide (1:2)	CuCl	-	80	24	66
26	AcChCl:Acetamide (1:2)	CuCl	-	80	24	72[d]
27	AcChCl:Acetamide (1:2)	CuCl	-	80	24	99[e]
28	ChCl:Acetamide (1:2)	CuCl	-	80	24	49[e]
29	AcChCl:Urea (1:2)	CuCl	-	80	24	52[e]
30	AcChCl:Acetamide (1:2)	$FeCl_2$	-	80	24	43[e]
31	AcChCl:Acetamide (1:2)	$NiCl_2$	-	80	24	6[e]
32	AcChCl:Acetamide (1:2)	CuCl	-	80	24	22[e,f]
33	AcChCl:Acetamide (1:2)	CuCl	-	80	24	40[e,g]
34	AcChCl:Acetamide (1:2)	CuCl	-	60	24	49[e]
35	AcChCl:Acetamide (1:2)	CuCl	-	100	24	99[e]
36	H_2O	CuCl	-	80	24	0[e]
37	PhMe	CuCl	-	80	24	0[e]
38	MeOH	CuCl	-	80	24	3[e]

[a] Conditions: Ph_3Bi (0.2 mmol), $Na_2S_2O_5$ (1.32 mmol), $PhNO_2$ (0.6 mmol) in 1.5 ml of DES. [b] Yields determined by GC using tridecane as standard. [c] Reaction carried out under MW irradiation. [d] Reaction carried out using 1.5 eq of $PhNO_2$ [e] Reaction carried out using 2.0 eq of $PhNO_2$ [f] Reaction carried out using 1.0 eq of $Na_2S_2O_5$ [g] Reaction carried out using 1.6 eq of $Na_2S_2O_5$.

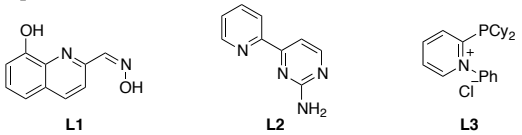


Fig S2. Ligands

Table S2. Study of SO_2 surrogates.[a]

Entry	SO_2 source	Yield (%)[b]
1	$Na_2S_2O_5$	99
2	$K_2S_2O_5$	95
3	DABSO	63
4	$Na_2S_2O_4$	15
5	S_8	0
6	NaO_2SCH_2OH	0

[a] Reaction carried out using compounds 1**a** (0.2 mmol), sulphur source (1.32 mmol) and **3a** (1.2 mmol) in 1.5 mL of DES. [b] Yield determined by GC using tridecane as internal standard.

Table S3. Study of aryl sources.[a]

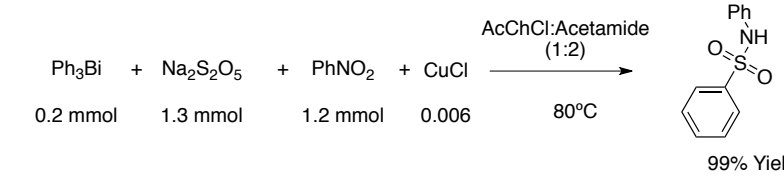
Entry	Aryl source	Yield (%)[b]
1	Ph_3Bi	99
2	$PhB(OH)_2$	16
3	PhMgBr	0
4	Ph_3Al	0
5	PhZnBr	0

[a] Reaction carried out using compounds **1** (1 eq mmol), $Na_2S_2O_5$ (2.2 equivalents) and **3a** (2 equivalents) in DES (0.4 M). [b] Yield determined by GC using tridecane as internal standard.

4. Control Experiments

A series of control experiments were carried out in order to shed some light about the reaction mechanism. Scheme a) shows the optimised reaction conditions, with the subsequent schemes showing modified conditions.

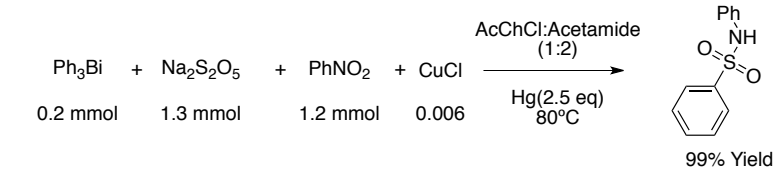
a)



99% Yield

The reaction was not catalysed by copper nanoparticles, since adding in 2.5 eq of Hg did not affect the reaction outcome (scheme b).

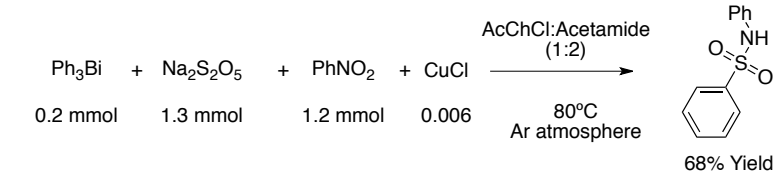
b)



99% Yield

When the reaction was run under argon atmosphere, a slightly decrease on the product yield was observed. Therefore, a role for molecular oxygen and/or moisture can be expected (scheme c). Oxygen can be involved in copper oxidation or in the oxidation of bismuth by-product to form Bi_2O_3, while moisture can interact with the DES (very hygroscopic) and act as a source of protons in the reduction step.

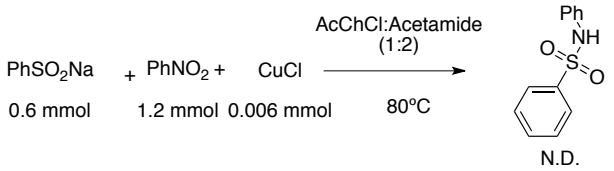
c)



68% Yield

Since Ar_3Bi and SO_2 produce sodium phenylsulfinate, several reactions were tested with this reagent. Running the reaction with sodium benzenesulfinate without sodium metabisulfite did not yield the final product, confirming the dual role of sodium metabisulfite as SO_2 source and reductant (scheme d).

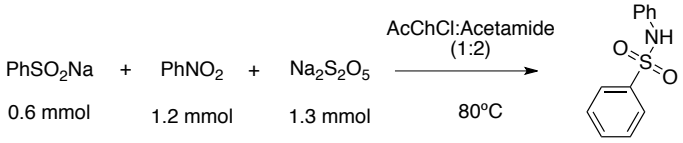
d)



N.D.

Surprisingly, reaction worked without adding the copper catalyst, although a very low yield was obtained (scheme e).

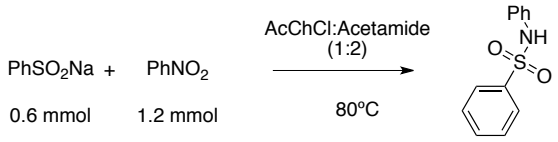
e)



16% Yield

As in scheme d, the absence of the reductant prevented the product formation (scheme f).

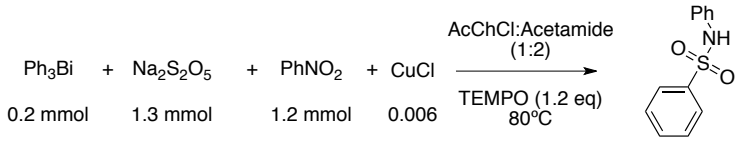
f)



N.D.

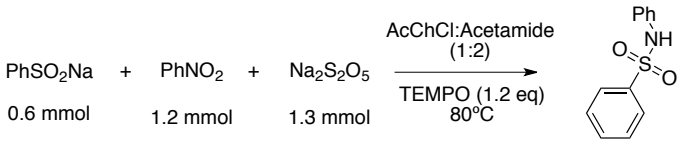
The reaction was inhibited by the use of a radical scavenger (TEMPO), involving a possible radical mechanism (schemes g and h).

g)



N.D.

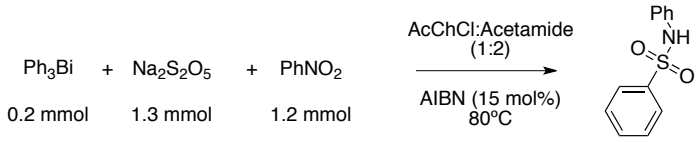
h)



N.D.

Using a catalytic amount of a radical initiator (AIBN) without using copper, product **4a** was obtained with 38% yield.

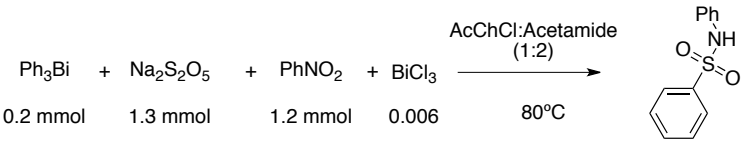
i)



38% Yield

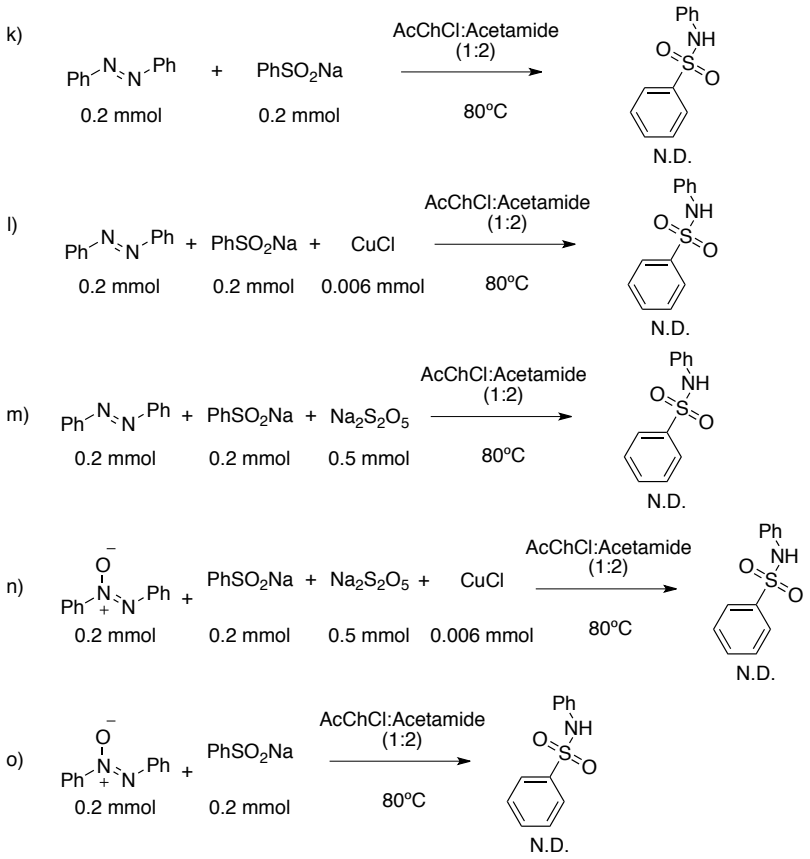
The possibility the actual catalyst was the $BiCl_3$ released during the reaction course was contemplated. Nevertheless, the same range of yield that in the absence of CuCl was obtained (scheme j).

j)



18% Yield

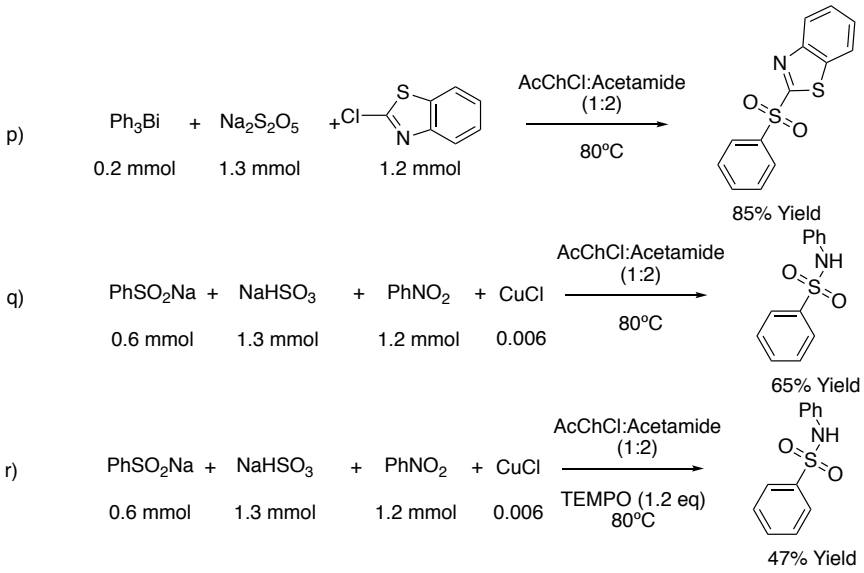
The reduction of nitro compounds usually takes place *via* a dimer. Therefore, several reactions were tested with some dimeric nitrogen species, but no product was obtained in any of them (schemes k-o).



The reaction of triphenylbismuthine with sodium metabisulfite to yield sodium benzenesulfinate and its subsequent reaction with an electrophile took place smoothly without the need of a copper catalyst. This result suggested that CuCl was only involved in the reduction step (scheme p).

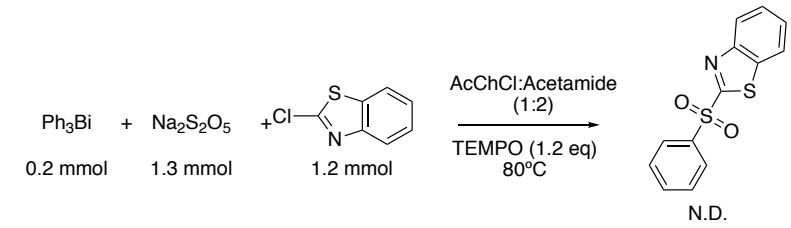
To further prove the role of CuCl as catalyst for the reduction step, the sodium benzenesulfinate was mixed with nitrobenzene and sodium bisulfite in the presence of CuCl, obtaining the corresponding sulphonamide in 65% yield (scheme q). However, the reaction took place with very low yield without copper (scheme e).

Performing the same reaction in the presence of a radical scavenger also afford the product, although a slight drop in yield was observed (scheme r). The reaction did take place with the sodium sulfinate, but not when Ph_3Bi was used as reagent (scheme g), confirming that the radical species are present in the sulfinate formation from $Na_2S_2O_5$ and Ph_3Bi.



The synthesis of sulfones under optimal conditions but in the presence of TEMPO did not afford the product, confirming that there are radical species involved in the sulfinate formation (scheme q).

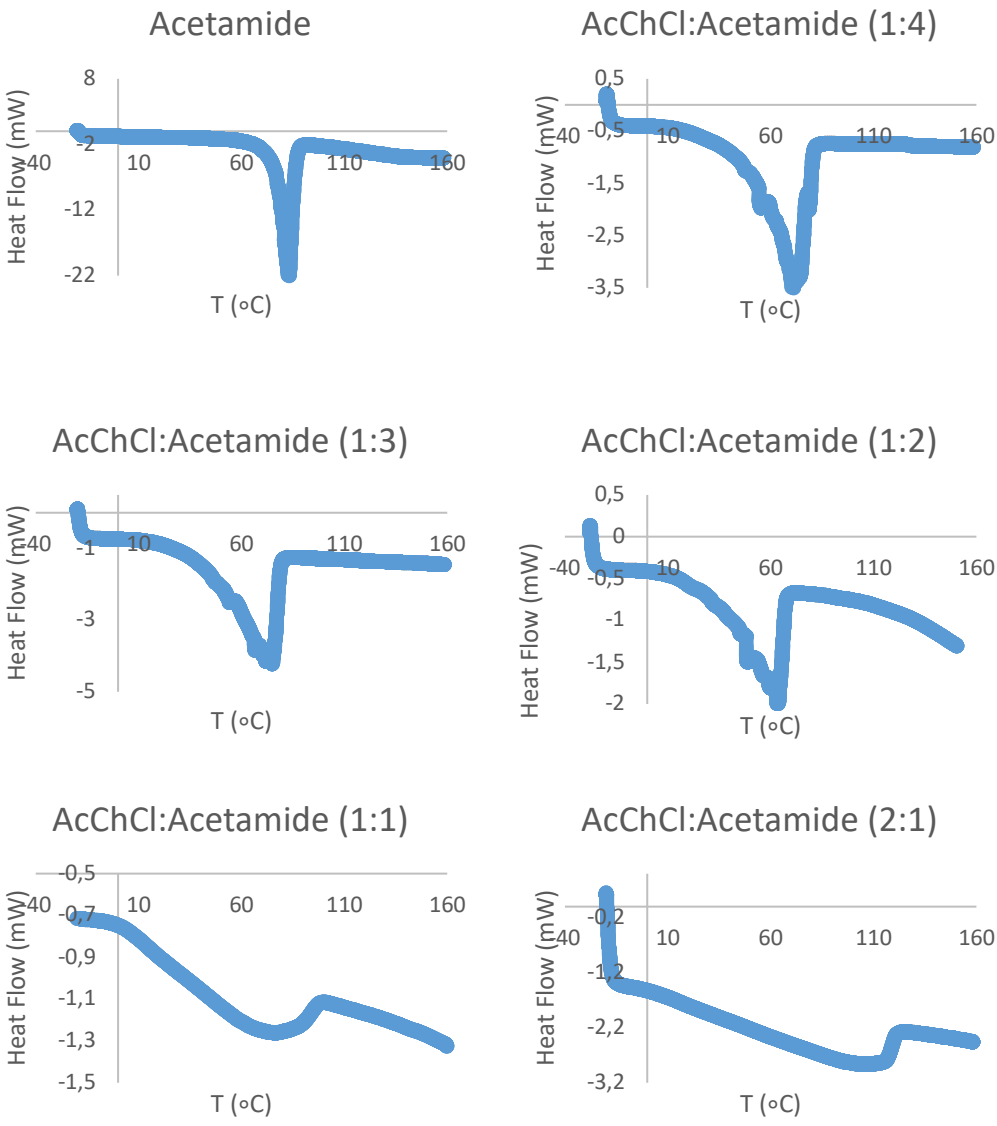
s)



5. DES Characterization

5.1. DSC

Samples were prepared by mixing the two components (AcChCl and acetamide) and grinding them together until an intimate mixture was obtained.



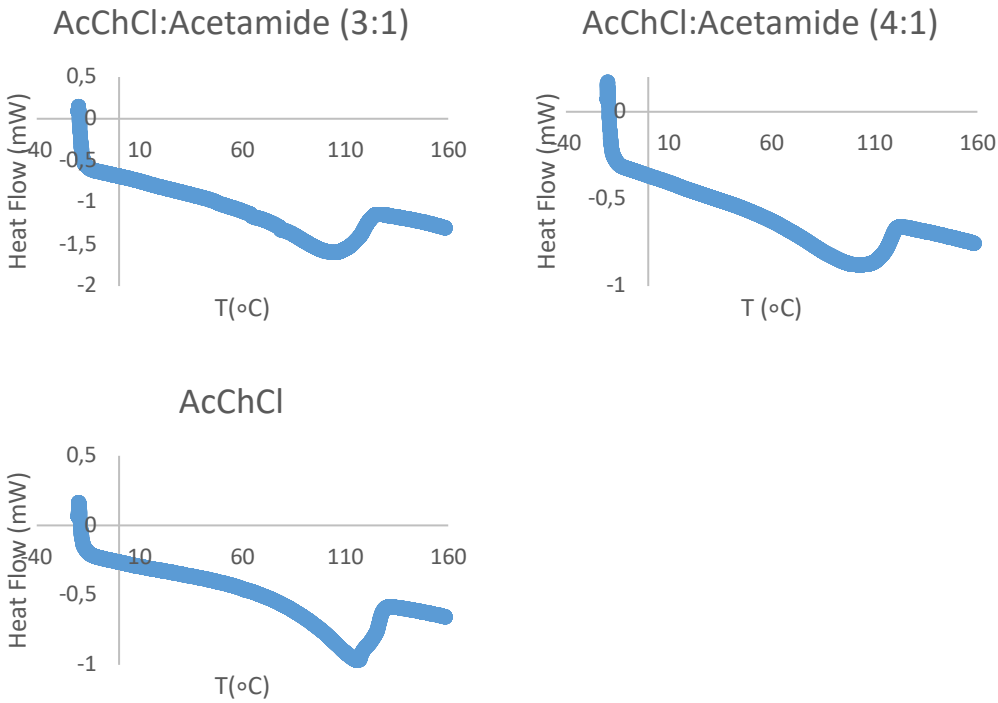


Fig S3. DSC analyses of different mixtures of AcChCl:Acetamide.

Despite of having a melting point around 60°C, the mixture did not return to solid state when cooled to room temperature.[3] Nevertheless, this eutectic mixture was very viscous at rt, making the nucleation and crystal growth process more difficult to happen. [4]

A second cycle in the DSC measurement was performed by cooling the sample to -90°C and heating it up again to 160 °C. In this second cycle, no melting point was observed. Instead, a glass transition temperature can be observed, confirming the glass nature of the mixture (Fig. S5).

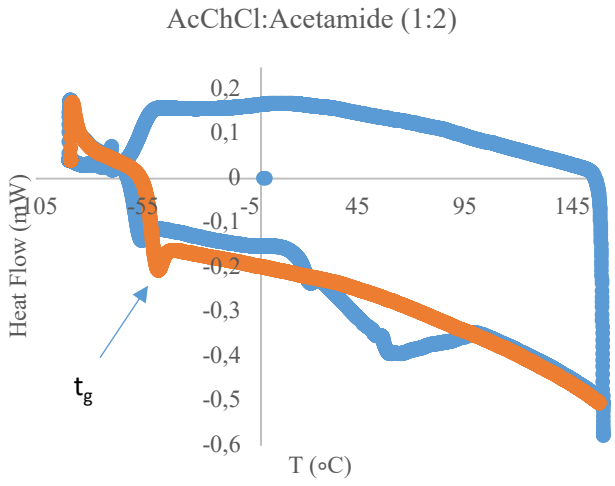


Fig. S4. DSC of the mixture AcChCl:acetamide (1:2) with 2 consecutive cycles of heating/cooling.

6. Characterization data.

***N*-phenylbenzenesulfonamide (4a)**:[5] Cream solid; m.p. 101-103 °C; R_f = 0.63 (hexane/ethyl acetate: 1/1); t_r = 15.00 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.80 (m, 2H, ArH), 7.55-7.50 (m, 1H, NH), 7.45-7.40 (m, 2H, ArH), 7.30-7.20 (m, 3H, ArH), 7.15-7.05 (m, 3H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.0, 136.5, 133.1, 129.4 (2C), 129.2 (2C), 127.3 (2C), 125.5, 121.8 (2C); IR (ATR): ν = 3204, 1302, 1151, 723 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 234 (M^++1, 12%), 233 (M^+, 86), 168 (40), 141 (24), 93 (12), 92 (100), 77 (51), 65 (33).

***N*-(p-tolyl)benzenesulfonamide (4b)**:[5] White solid; m.p. 101-103 °C; R_f = 0.23 (hexane/ethyl acetate: 4/1); t_r = 15.77 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80-7.75 (m, 2H, ArH), 7.55-7.45 (m, 1H, ArH), 7.45-7.35 (m, 2H, ArH), 7.24 (br s, 1H, NH), 7.05-6.95 (m, 4H, ArH), 2.25 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.1, 135.5, 133.8, 133.0, 129.9 (2C), 129.1 (2C), 127.4 (2C), 122.4 (2C), 20.9; IR (ATR): ν = 3256, 1328, 1159, 687cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 247 (M^+, 57 %), 106 (100), 79 /18), 77 (36), 51 (10).

***N*-(4-methoxyphenyl)benzenesulfonamide (4c)**:[6] Brown solid; m.p. 87-89 °C; R_f = 0.63 (hexane/ethyl acetate: 1/1); t_r = 16.86 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75-7.70 (m, 2H, ArH), 7.60-7.50 (m, 1H, ArH), 7.45-7.40 (m, 2H, ArH), 7.05-6.95 (m, 2H, ArH), 6.86 (s, 1H, NH), 6.80-6.70 (m, 2H, ArH), 3.74 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.1, 139.0, 133.0, 129.1 (2C), 128.9, 127.4 (2C), 125.6 (2C), 114.5 (2C), 55.5; IR (ATR): ν = 3259, 1508, 1326, 1155 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 263 (M^+, 22%), 122 (100).

***N*-(4-aminophenyl)benzenesulfonamide (4d)**:[7] White solid; m.p. 168-170 °C; R_f = 0.30 (hexane/ethyl acetate: 1/1); t_r = 13.41 min; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (s, 1H, NH), 7.65-7.60 (m, 2H, ArH), 7.60-7.50 (m, 3H, ArH), 6.70-6.65 (m, 2H, ArH), 6.45-6.35 (m, 2H, ArH), 5.15 (br s, 2H, NH_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 146.1, 139.7, 132.4, 128.9 (2C), 126.7 (2C), 125.5, 124.6 (2C), 114.2 (2C); IR (ATR): ν = 3395, 1653, 1260, 1160 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 248 (M^+, 15%), 107 (100), 80 (13).

***N*-(4-hydroxyphenyl)benzenesulfonamide (4e)**:[8] White solid; m.p. 156-158 °C; R_f = 0.40 (hexane/ethyl acetate: 1/1); t_r = 17.95 min; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.73 (br s, 1H, NH), 9.31 (br s, 1H, OH), 7.70-7.65 (m, 2H, ArH), 7.60-7.45 (m, 3H, ArH), 6.85-6.75 (m, 2H, ArH), 6.65-6.55 (m, 2H, ArH); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.9, 139.5, 132.6, 129.0 (2C), 128.4, 126.7 (2C), 124.1 (2C), 115.5 (2C); IR (ATR): ν = 3243, 1320, 1190, 686 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 249 (M^+, 36%), 108 (100), 81 (15), 77 (14).

***N*-(4-chlorophenyl)benzenesulfonamide (4f)**:[9] White solid; m.p. 116-118 °C; R_f = 0.57 (hexane/ethyl acetate: 1/1); t_r = 16.36 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (ddd, *J* = 7.1, 3.1, 1.8 Hz, 2H, ArH), 7.60-7.50 (m, 2H, ArH + NH), 7.50-7.40 (m, 2H, ArH), 7.20-7.15 (M, 2H, ArH), 7.10-7.00 (M, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7, 135.1, 133.4, 131.1, 129.5 (2C), 129.3 (2C), 127.3 (2C), 123.1 (2C); IR (ATR): ν = 3241, 1374, 1160, 688 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 269 (M^+ Cl^{37}, 27%), 267 (M^+ Cl^{35}, 71), 141 (15), 128 (33), 126 (100), 101 (10), 99 (28), 77 (40), 51 (16).

***N*-(4-acetylphenyl)benzenesulfonamide (4g)**:[10] Brown solid; m.p. 125-127 °C; R_f = 0.43 (hexane/ethyl acetate: 1/1); t_r = 18.17 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90-7.80 (m, 4H, ArH), 7.63 (s, 1H, NH), 7.60-7.55 (m, 1H, ArH), 7.50-7.45 (m, 2H, ArH), 7.25-7.15 (m, 2H, ArH), 2.53 (s, 3H, CH_3CO); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1, 141.2, 138.9, 133.6, 133.5, 130.1 (2C), 129.4 (2C), 127.3 (2C), 119.2 (2C), 26.6; IR (ATR): ν = 3347, 1429, 1129, 695 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 275 (M^+, 53%), 261 (15), 260 (100), 119 (12), 77 (38).

***N*-(3-chlorophenyl)benzenesulfonamide (4h)**:[9] White solid; m.p. 114-116 °C; R_f = 0.67 (hexane/ethyl acetate: 1/1); t_r = 16.22 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.85 (m, 2H, ArH), 7.74 (s, 1H, NH), 7.60-7.55 (m, 1H, ArH), 7.50-7.45 (m, 2H, ArH), 7.20-7.10 (m, 2H, ArH), 7.10-7.00 (m, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.6, 137.9, 135.0, 133.5, 130.4, 129.3 (2C), 127.3 (2C), 125.4, 121.1, 119.1; IR (ATR): ν = 3195, 1312, 1152, 683 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 269 (M^+ Cl^{37}, 21%), 267 (M^+ Cl^{35}, 57), 203 (12), 202 (17), 168 (25), 167 (11), 141 (59), 126 (25), 99 (24), 91 (11), 78 (11), 77 (100).

***N*-*N*-(1,3-phenylene)dibenzenesulfonamide (4i)**: White solid; m.p. 162-165 °C; R_f = 0.37 (hexane/ethyl acetate: 1/1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.30 (s, 2H, 2xNH), 7.70-7.65 (m, 4H, ArH), 7.60 (*ap* t, *J* = 7.4 Hz, 2H, ArH), 7.51 (*ap* t, *J* = 7.6 Hz, 4H, ArH), 7.11 (t, *J* = 1.0 Hz, 1H, ArH), 7.02 (t, *J* = 8.1 Hz, 1H, ArH), 6.69 (dd, *J* = 8.1, 1.9 Hz, 2H, ArH); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 139.3 (2C), 138.5 (2C), 132.9 (2C), 129.8, 129.2 (4C), 126.6 (4C), 115.2 (2C), 110.8; IR (ATR): ν = 3404, 1324, 1152, 688 cm^{-1}; MS (DIP): *m*/*z* (%): 388 (M^+, 43%), 183 (100), 182 (35), 181 (11), 167 (19), 166 (39), 156 (26), 141 (13), 125 (13), 105 (15), 79 (14), 78 (17), 77 (83), 51 (18); HRMS calcd. (%) for $C_{18}H_{16}N_2O_4S_2$: 388.0551; found: 388.0549.

***N*-(2-chlorophenyl)benzenesulfonamide (4j)**:[9] White solid; m.p. 146-148 °C; R_f = 0.63 (hexane/ethyl acetate: 1/1); t_r = 15.16 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80-7.75 (m, 2H, ArH), 7.67 (dd, *J* = 8.5, 1.5 Hz, 1H, ArH), 7.60-7.50 (m, 1H, ArH), 7.45-7.40 (m, 2H, ArH), 7.30-7.20 (m, 2H, ArH), 7.10-7.05 (m, 1H, ArH), 7.00 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.0, 133.4, 129.5, 129.2 (2C), 128.1 (2C), 127.4 (2C), 126.2, 125.4, 122.8; IR (ATR): ν = 3247, 1332, 1157 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 269 (M^+ Cl^{37}, 32%), 267 (M^+ Cl^{35}, 96), 168 (13), 167 (18), 141 (54), 128 (33), 126 (100), 102 (15), 99 (45), 90 (11), 77 (87), 63 (12).

***N*-(2-bromophenyl)benzenesulfonamide (4k)**:[11] White solid; m.p. 113-115 °C; R_f = 0.43 (hexane/ethyl acetate: 7/3); t_r = 16.08 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80-7.75 (m, 2H, ArH), 7.68 (dd, *J* = 8.2, 1.5 Hz, 1H, ArH), 7.60-7.50 (m, 1H, ArH), 7.45-7.35 (m, 3H, ArH), 7.28 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H, ArH), 6.99 (br s, 1H, NH), 6.98 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.9, 134.7, 133.4, 132.7, 129.2 (2C), 128.7, 127.4 (2C), 126.6, 123.1, 116.1; IR (ATR): ν = 1333, 1159, 722 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 314 (M^+ Br^{81}+1 , 14%), 313 (M^+ Br^{81}, 98), 312 (M^+ Br^{79}+1,

13), 311 (M^+Br^{79}, 95), 172 (98), 170 (100), 145 (13), 143 (17), 141 (58), 125 (29), 91 (86), 90 (13), 77 (96), 65 (10), 64 (19), 63 (22), 51 (31).

***N*-(naphtalen-2-yl)benzenesulfonamide (4l):**[9] White solid; m.p. 96-98 °C; R_f = 0.63 (hexane/ethyl acetate: 1/1); t_r = 18.82 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90-7.80 (m, 2H, ArH), 7.75-7.65 (m, 3H, ArH), 7.58 (br s, 1H, NH), 7.56 (d, J = 2.2 Hz, 1H, ArH), 7.50-7.35 (m, 5H, ArH), 7.25 (dd, J = 8.9, 2.2 Hz, 1H, ArH);^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.0, 134.1, 133.7, 133.2, 131.2, 129.5, 129.2 (2C), 127.7, 127.6, 127.4 (2C), 126.8, 125.6, 121.2, 118.6; IR (ATR): ν = 3189, 1321, 1148, 648 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 283 (M^+, 51%), 142 (72), 115 (100), 110 (11), 77 (16).

***N*-cyclohexylbenzenesulfonamide (4m)**:[12] White solid; m.p. 81-83 °C; R_f= 0.67 (hexane/ethyl acetate: 1/1); t_r = 14.83 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95-7.85 (m, 2H, ArH), 7.60-7.50 (m, 3H, ArH), 4.46 (d, J = 6.3 Hz, 1H, C*H*NH), 3.17 (br s, 1H, NH), 1.80-1.75 (m, 2H, CH_2NH), 1.70-1.60 (m, 2H, CH_2Cy), 1.55-1.50 (m, 1H, CH_2Cy), 1.30-1.10 (m, 5H, CH_2Cy); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.6, 132.6, 129.2 (2C), 127.0 (2C), 52.8, 34.1 (2C), 25.3, 24.8; IR (ATR): ν = 3278, 2929, 1707, 1322, 1159 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 239 (M^+, 32%), 197 (12), 196 (100), 141 (44), 98 (15), 77 (46).

4-methyl-*N*-phenylbenzenesulfonamide (5a):[9] White solid; m.p. 98-100 °C; R_f= 0.37 (hexane/ethyl acetate: 1/1); t_r = 15.99 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.60 (m, 2H, ArH), 7.30-7.20 (m, 5H, ArH + NH), 7.15-7.05 (m, 3H, ArH), 2.37 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.0, 136.7, 136.3, 129.8 (2C), 129.4 (2C), 127.4 (2C), 125.5, 121.7 (2C), 21.7; IR (ATR): ν = 3236, 1335, 1153, 753 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 248 (M^+1, 11%), 247 (M^+, 69), 182 (22), 168 (14), 155 (47), 92 (55), 91 (100), 65 (41).

***N*-phenylnaphtalene-1-sulfonamide (5b)**:[13] White solid; m.p. 149-151 °C; R_f= 0.43 (hexane/ethyl acetate: 7/3); t_r = 20.62 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (dd, J = 8.7, 0.7 Hz, 1H, ArH), 8.04 (d, J = 8.3 Hz, 1H, ArH), 7.94 (d, J = 8.1 Hz, 1H, ArH), 7.68 (ddd, J = 8.6, 7.0, 1.1 Hz, 1H, ArH), 7.61 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H, ArH), 7.46 (dd, J = 8.1, 7.5 Hz, 1H, ArH), 7.22 (s, 1H, NH), 7.15-7.10 (m, 2H, ArH), 7.05-7.00 (m, 1H, ArH), 7.00-6.95 (m, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.4, 134.8, 134.3, 134.1, 130.5, 129.3 (3C), 128.7, 128.3, 127.0, 125.4, 124.3, 124.2, 121.7 (2C); IR (ATR): ν = 3234, 1322, 1160, 692 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 283 (M^+, 29%), 219 (16), 218 (56), 217 (15), 128 (20), 127 (100), 92 (14).

4-methoxy-*N*-phenylbenzenesulfonamide (5c):[9] White solid; m.p. 105-107 °C; R_f = 0.60 (hexane/ethyl acetate: 1/1); t_r = 17.32 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.6 Hz, 2H, ArH), 7.22 (ap t, J = 7.6 Hz, 2H, ArH), 7.15-7.05 (m, 3H, ArH), 6.87 (d, J = 8.6 Hz, 2H, ArH), 3.81 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.2, 136.8, 130.7, 129.6 (2C), 129.4 (2C), 125.3, 121.7 (2C), 114.3 (2C), 55.7; IR (ATR): ν = 3255, 1336, 1152, 695 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 263 (M^+, 61%), 171 (100), 123 (21), 107 (50), 92 (35), 77 (32), 65 (20), 64 (12).

3,4,5-trimethoxy-*N*-phenylbenzenesulfonamide (5d): White solid; m.p. 121-123 °C; R_f = 0.50 (hexane/ethyl acetate: 1/1); t_r = 20.43 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H, NH), 7.30-7.20 (m, 2H, ArH), 7.15-7.10 (m, 3H, ArH), 7.01 (s, 2H, ArH), 3.84 (s, 3H, OCH_3), 3.74 (s, 6H, 2xOCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.2 (2C), 141.8, 136.7, 133.4, 129.4 (2C), 125.7, 122.1 (2C), 104.6 (2C), 61.0, 56.4 (2C);IR (ATR): ν = 3259, 1312, 1148, 1125 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 324 (M^++1, 14%), 323 (M^+, 81), 244 (11), 231 (19), 183 (25), 168 (14), 167 (100), 137 (13), 109 (11), 92 (15), 81 (11), 77 (12), 66 (12), 65 (14). HRMS calcd. (%) for $C_{15}H_{17}NO_5S$: 323.0827; found: 323.0824.

4-(dimethylamino)-*N*-phenylbenzenesulfonamide (5e): White solid; m.p. 172-174 °C; R_f= 0.27 (hexane/ethyl acetate: 7/1); t_r = 20.49 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.55 (m, 2H, ArH), 7.25-7.20 (m, 2H, ArH), 7.10-7.00 (m, 3H, ArH), 6.72 (s, 1H, NH), 6.60-6.55 (m, 2H, ArH), 3.00 (s, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.0, 137.3, 129.3 (2C), 129.2 (2C), 124.9, 124.5, 121.3 (2C), 111.0 (2C), 40.2 (2C); IR (ATR): ν = 3253, 1315, 1137, 1090 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 277 (M^++1, 13%), 276 (M^+, 70), 184 (67), 136 (100), 120 (69), 119 (11), 105 (16), 104 (16), 91 (11), 77 (20), 65 (14), 64 (18); HRMS calcd. (%) for $C_{14}H_{16}N_2O_2S$: 276.9032; found: 276.0942.

4-fluoro-*N*-phenylbenzenesulfonamide (5f):[9] White solid; m.p. 106-108 °C; R_f = 0.47 (hexane/ethyl acetate: 7/1); t_r = 15.99 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85-7.75 (m, 2H, ArH), 7.30-7.20 (m, 3H, ArH + NH), 7.25-7.05 (m, 5H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4 (d, J = 255.4 Hz), 136.3, 135.0 (d, J = 3.3 Hz), 130.1 (d, J = 9.5 Hz, 2C), 129.5 (2C), 125.8, 122.0 (2C), 116.4 (d, J = 22.6 Hz, 2C); IR (ATR): ν = 1334, 1149, 840 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 251 (M^+, 64%), 186 (21), 159 (18), 95 (33), 92 (100), 75 (12), 65 (33).

4-bromo-*N*-phenylbenzenesulfonamide (5g):[9] White solid; m.p. 106-109 °C; R_f= 0.57 (hexane/ethyl acetate: 1/1); t_r = 16.85 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.60 (m, 2H, ArH), 7.55-7.50 (m, 2H, ArH), 7.40 (s, 1H, NH), 7.30-7.20 (m, 2H, ArH), 7.15-7.05 (m, 3H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.0, 136.2, 132.5 (2C), 129.6 (2C), 128.9 (2C), 128.2, 125.9, 121.9 (2C); IR (ATR): ν = 3250, 1335, 1155, 741 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 313 (M^+Br^{81}, 32%), 311 (M^+Br^{79}, 31%), 220 (12), 218 (11), 168 (21), 157 (19), 155 (19), 92 (100), 76 (11), 75 (11), 65 (32).

***N*-phenyl-2-(trifluoromethyl)benzenesulfonamide (5h)**: White solid; m.p. 97-99 °C; R_f = 0.37 (hexane/ethyl acetate: 7/3); t_r = 15.95 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.9 Hz, 1H, ArH), 7.87 (d, J = 7.6 Hz, 1H, ArH), 7.64 (t, J = 7.6 Hz, 1H, ArH), 7.56 (td, J = 7.9, 0.8 Hz, 1H, ArH), 7.25-7.20 (m, 2H, ArH), 7.15-7.10 (m, 1H, ArH), 7.10-7.00 (m, 2H, ArH), 6.75 (s, 1H, NH);^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.3, 125.7, 133.2, 132.6, 132.3, 129.5 (2C), 128.6 (q, J = 6.3 Hz), 127.8 (q, J = 32.9 Hz), 126.1, 123.1 (q, J = 273.8 Hz), 122.32 (2C); IR (ATR): ν = 3278, 1497, 1352, 1160 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 301 (M^+, 53%), 207 (15), 145 (31), 92 (100), 65 (37); HRMS calcd. (%) for $C_{13}H_{10}F_3NO_2S$: 301.0384; found: 301.0381.

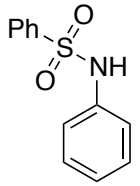
***N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (5i)**: White solid; m.p. 79-81 °C; R_f = 0.43 (hexane/ethyl acetate: 7/3); t_r = 15.56 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H, NH), 7.96 (d, J = 7.9 Hz, 1H, ArH), 7.78 (d, J = 7.9 Hz, 1H, ArH), 7.58 (t, J = 7.9 Hz, 1H, ArH), 7.30-7.25 (m, 3H, ArH), 7.20-7.15 (m, 1H, ArH), 7.10-7.05 (m, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.2, 135.8, 131.8 (q, J =33.5 Hz), 130.5, 130.0, 129.8 (q, J = 6.6 Hz), 129.6 (2C), 126.2, 124.2 (q, J = 7.2 Hz),

122.3 (2C), 120.45 (q, J = 272.9 Hz); IR (ATR): ν = 3231, 1322, 1165, 1155 cm^{-1}; MS (70 eV, EI): m/z (%): 301 (M^+, 52%), 145 (22), 92 (100), 65 (28); HRMS calcd. (%) for $C_{13}H_{10}F_3NO_2S$: 301.0384; found: 301.0382.

***N*-(2-benzoyl-4-chlorophenyl)-4-methylbenzenesulfonamide (5j)**:[14] Yellow solid; m.p. 114-116 °C; R_f = 0.53 (hexane/ethyl acetate: 7/1); t_r = 28.14 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1H, NH), 7.76 (d, J = 8.8 Hz, 1H, ArH), 7.65-7.55 (m, 1H, ArH), 7.53 (d, J = 8.3 Hz, 2H, ArH), 7.48 (dd, J = 8.8, 2.5 Hz, 1H, ArH), 7.45-7.40 (m, 2H), 7.40-7.35 (m, 2H), 7.32 (d, J = 2.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H, ArH), 2.22 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1, 144.1, 137.4, 136.9, 135.6, 133.6, 133.3, 132.3, 130.0 (2C), 129.8 (2C), 129.4, 128.4 (2C), 128.0, 127.3 (2C), 125.2, 21.5; IR (ATR): ν = 3265, 1636, 1379, 1183 cm^{-1}; MS (70 eV, EI): m/z (%): 387 (M^+ Cl^{37}, 29%), 385 (M^+ Cl^{35}, 29%), 232 (33), 230 (100), 195 (54), 167 (24), 166 (14), 155 (15), 139 (12), 91 (66), 77 (21).

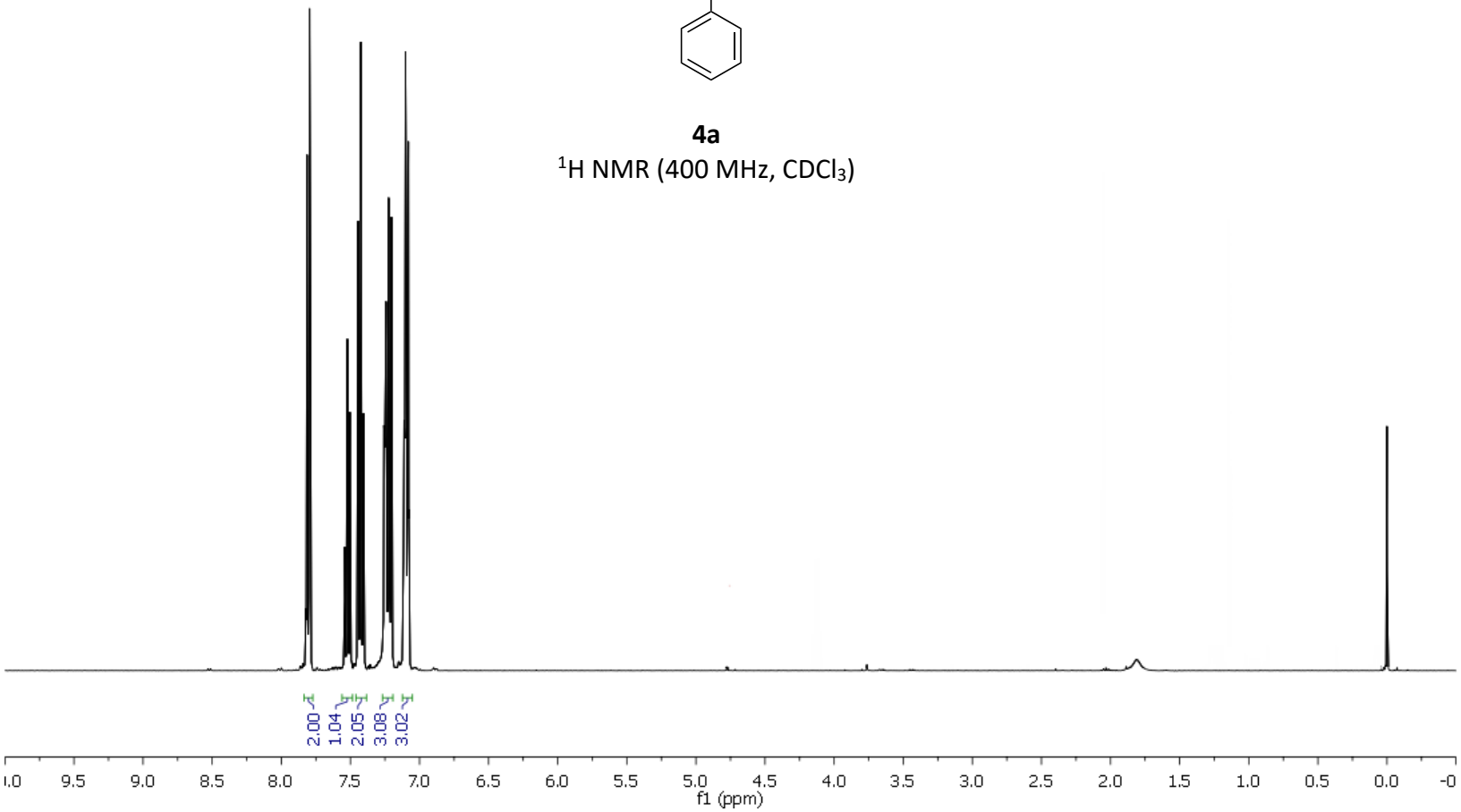
1. H. El Ghaoui, M. Raihane, B. Rhouta, N. Bitinis, A. Carlmark, M. Arroyo, R. Verdejo, M. A. Lopez-Manchado and M. Lahcini, *Polym. Int.*, 2014, **63**, 709-717.
2. (a) J. Luan, L. Zhang and Z. Hu, *Molecules*, 2011, **16**, 4191-4230; (b) J.-Q. Liu, J.-J. Yang, J.-F. Li, K. Li, X.-D. Xiao, Y.-L. Bai and J.-W. Wang, *Mol. Catal.*, 2017, **443**, 125-130.
3. D. Rengstl, V. Fischer and W. Kunz, *Phys. Chem. Chem. Phys.*, 2014, **16**, 22815-22822.
4. H. G. Morrison, C. C. Sun and S. Neervannan, *Int. J. Pharm.*, 2009, **378**, 136-139.
5. S. W. Youn, T. Y. Ko and Y. H. Jang, *Angew. Chem., Int. Ed.*, 2017, **56**, 6636-6640.
6. J. L. Garcia Ruano, A. Parra, L. Marzo, F. Yuste and V. M. Mastranzo, *Tetrahedron*, 2011, **67**, 2905-2910.
7. A. Yasuhara, A. Kasano and T. Sakamoto, *J. Org. Chem.*, 1999, **64**, 2301-2303.
8. F. Baragona, T. Lomberget, C. Duchamp, N. Henriques, E. Lo Piccolo, P. Diana, A. Montalbano and R. Barret, *Tetrahedron*, 2011, **67**, 8731-8739.
9. Y. Jiang, Y. You, W. Dong, Z. Peng, Y. Zhang and D. An, *J. Org. Chem.*, 2017, **82**, 5810-5818.
10. C.-C. Zeng, X.-M. Li, H. Yan and R.-G. Zhong, *Chin. J. Chem.*, 2007, **25**, 1174-1182.
11. V. M. Vlasov, M. I. Terekhova, E. S. Petrov, V. D. Sutula and A. I. Shatenshtein, *Zh. Org. Khim.*, 1982, **18**, 1672-1679.
12. W. Wei, C. L. Liu, D. Yang, J. Wen, J. You and H. Wang, *Adv. Synth. Catal.*, 2015, **357**, 987-992.
13. S.-Y. Moon, J. Nam, K. Rathwell and W.-S. Kim, *Org. Lett.*, 2014, **16**, 338-341.
14. S. Lu, J.-Y. Ong, S. B. Poh, T. Tsang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2018, **57**, 5714-5719.

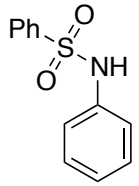
7. NMR Spectra



4a

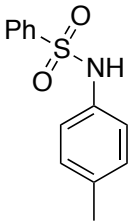
^{1}H NMR (400 MHz, $CDCl_3$)





4a

^{13}C NMR (101 MHz, $CDCl_3$)

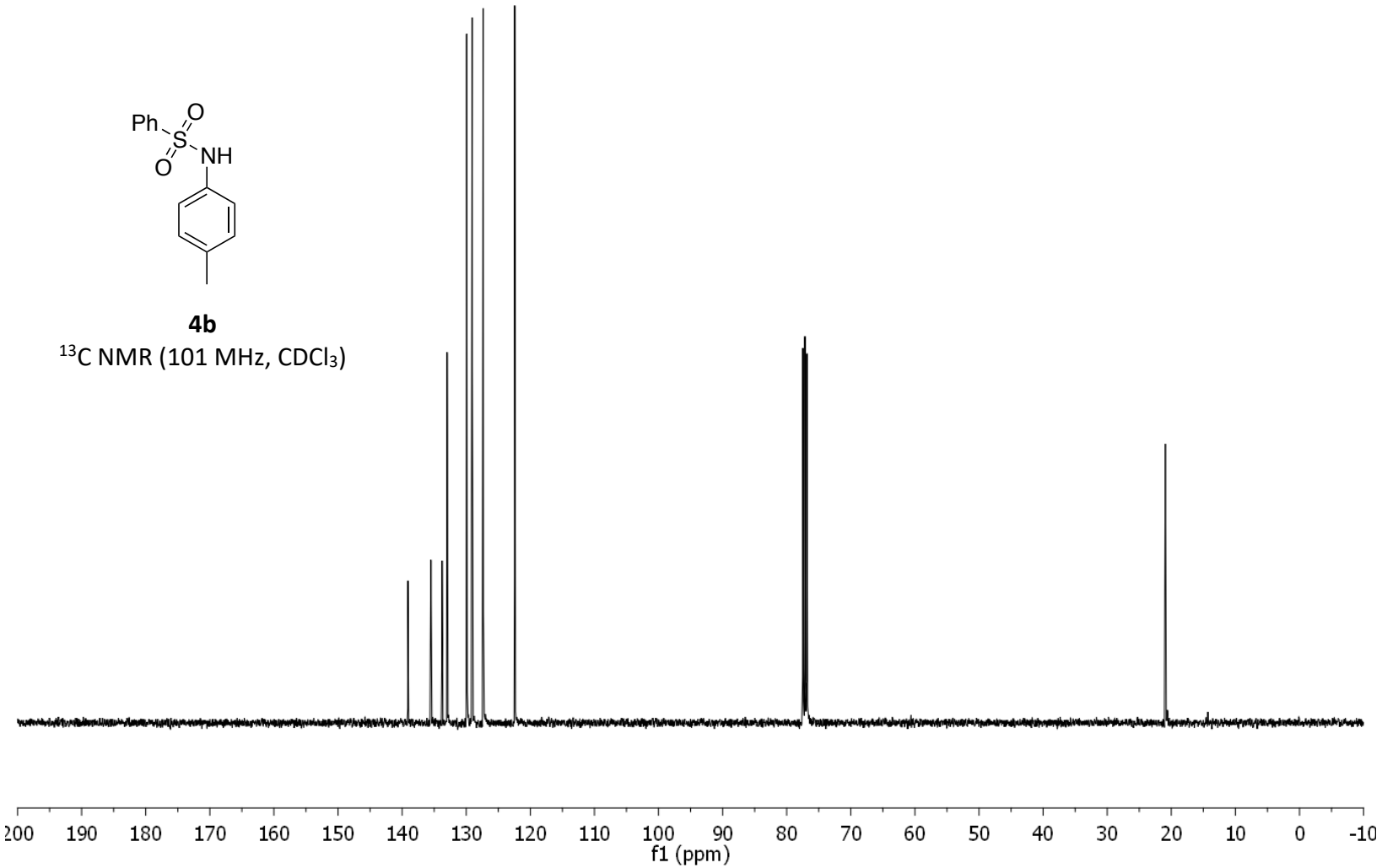


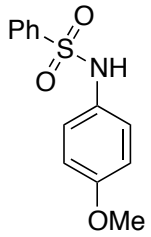
4b

^{1}H NMR (300 MHz, $CDCl_3$)

4b

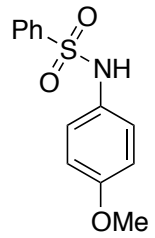
^{13}C NMR (101 MHz, $CDCl_3$)





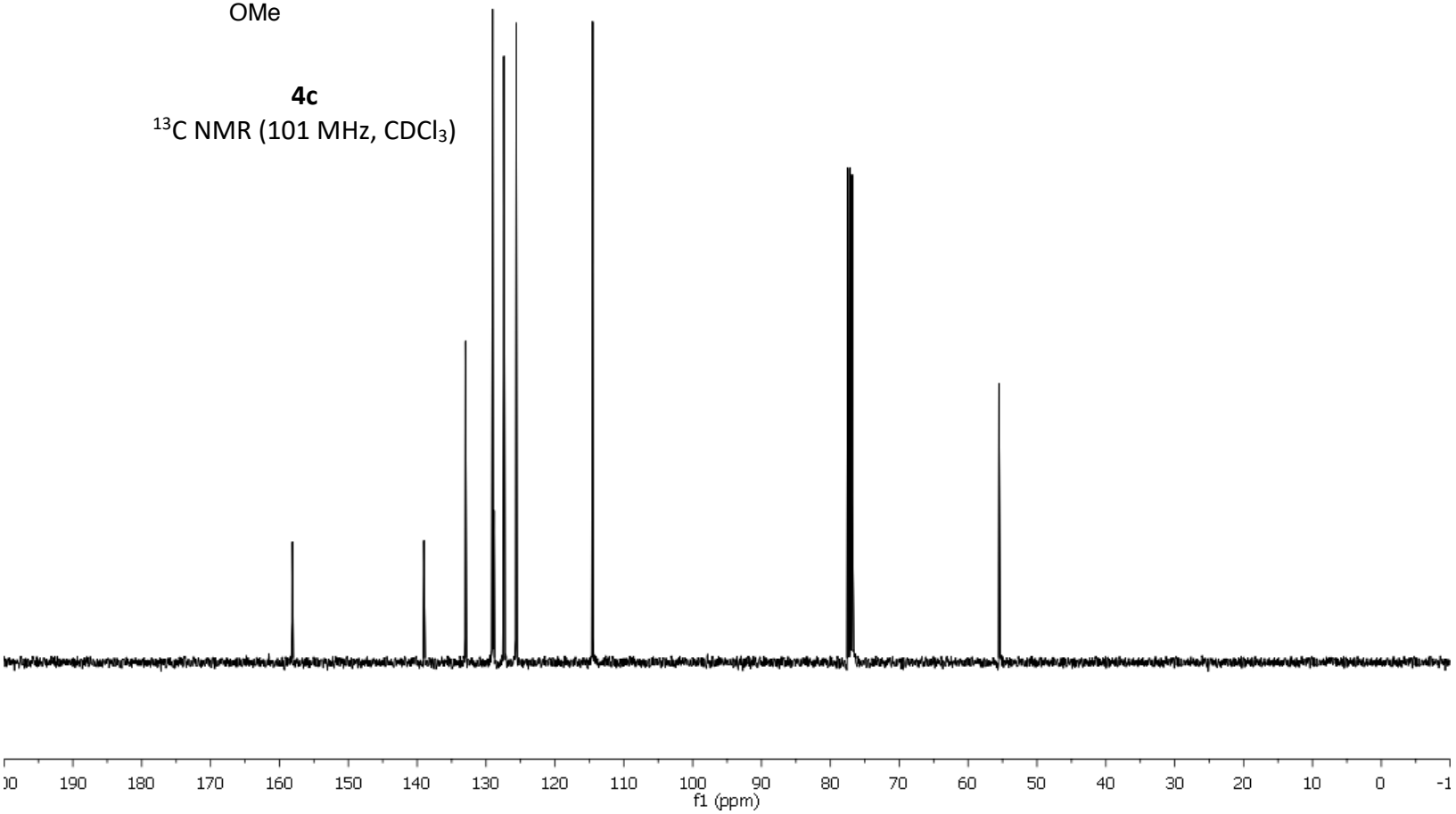
4c

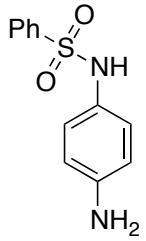
^{1}H NMR (300 MHz, $CDCl_3$)



4c

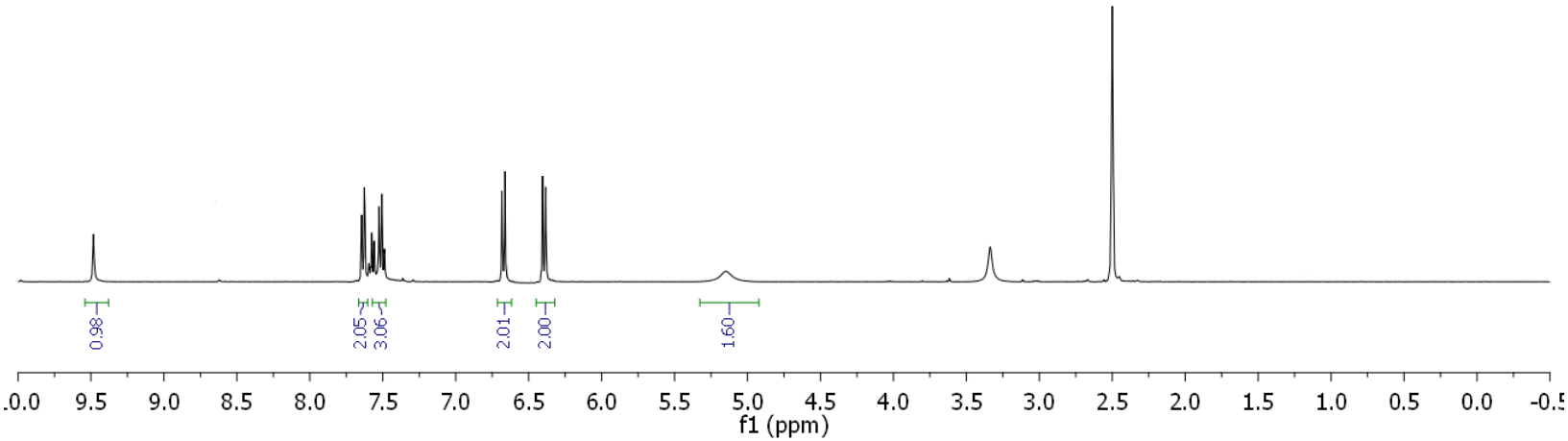
^{13}C NMR (101 MHz, $CDCl_3$)

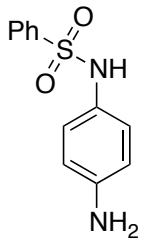




4d

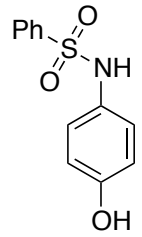
^{1}H NMR (400 MHz, DMSO-d_6)





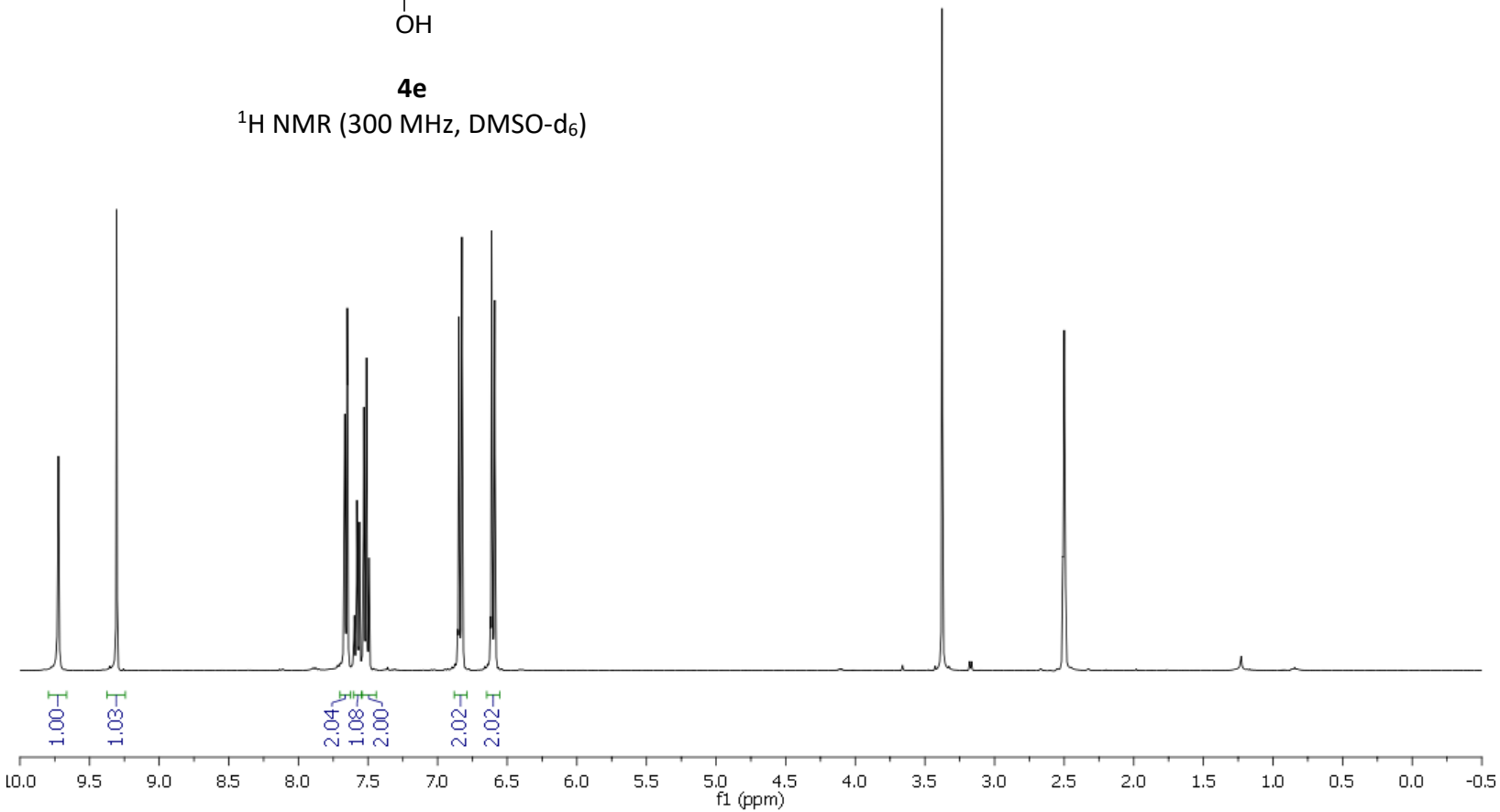
4d

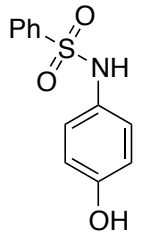
^{13}C NMR (101 MHz, DMSO-d_6)



4e

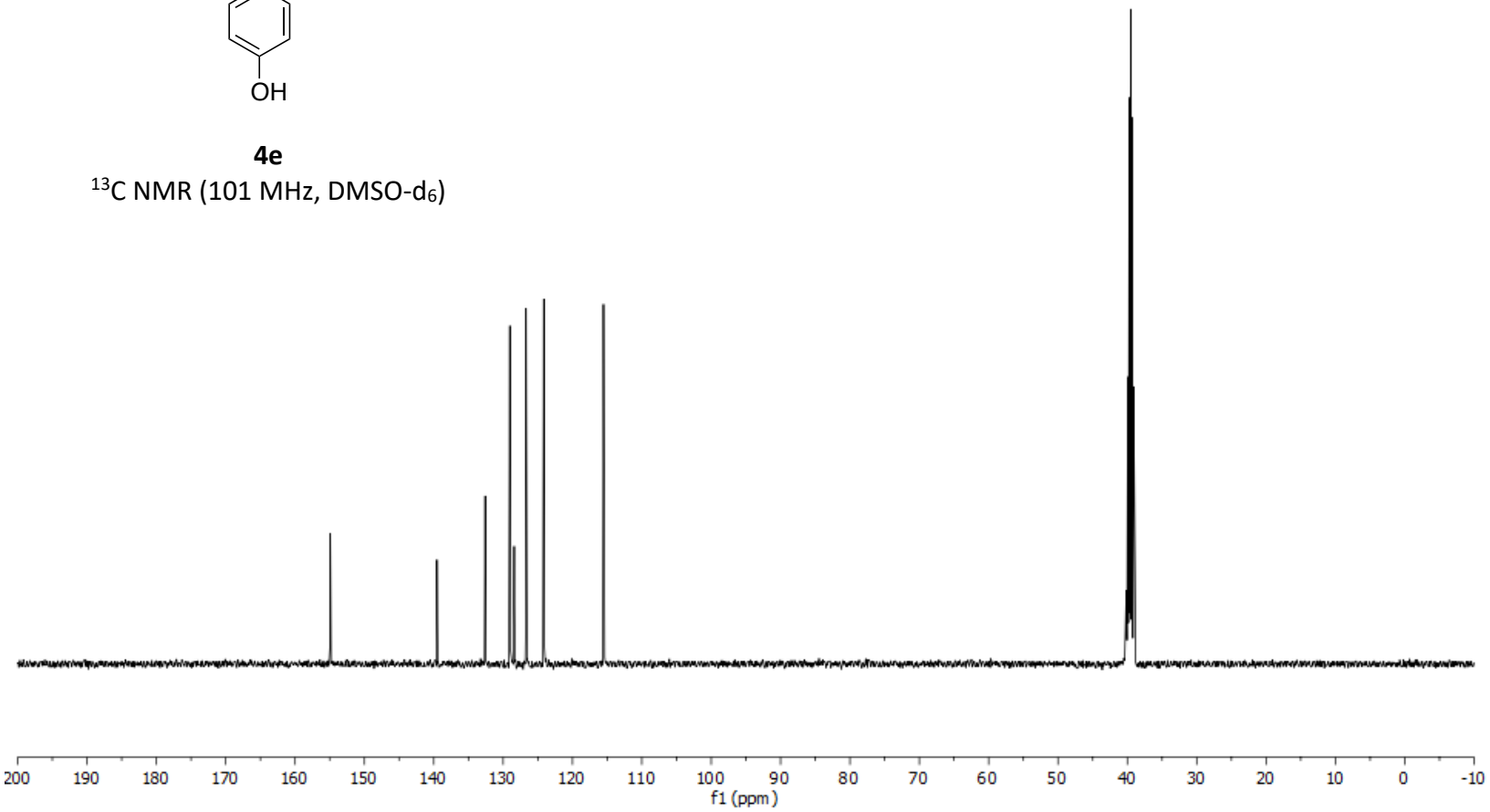
^{1}H NMR (300 MHz, DMSO-d_6)

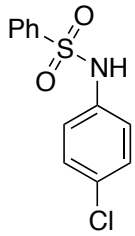




4e

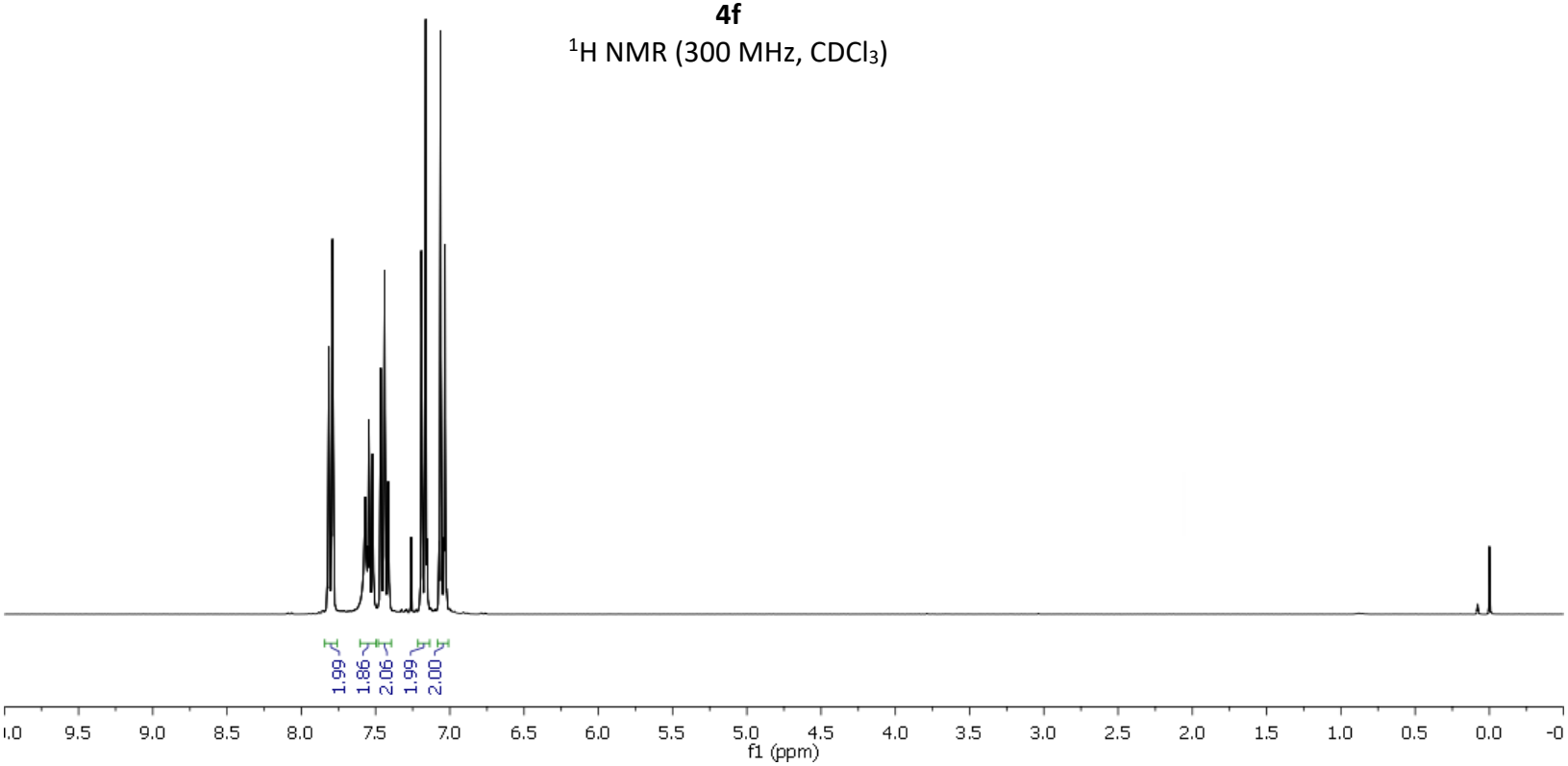
^{13}C NMR (101 MHz, DMSO-d_6)

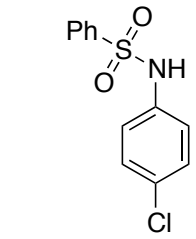




4f

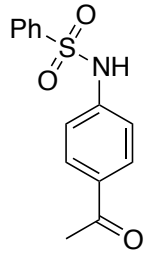
^{1}H NMR (300 MHz, $CDCl_3$)





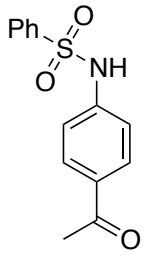
4f

^{13}C NMR (75 MHz, $CDCl_3$)



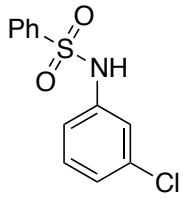
4g

^{1}H NMR (300 MHz, $CDCl_3$)



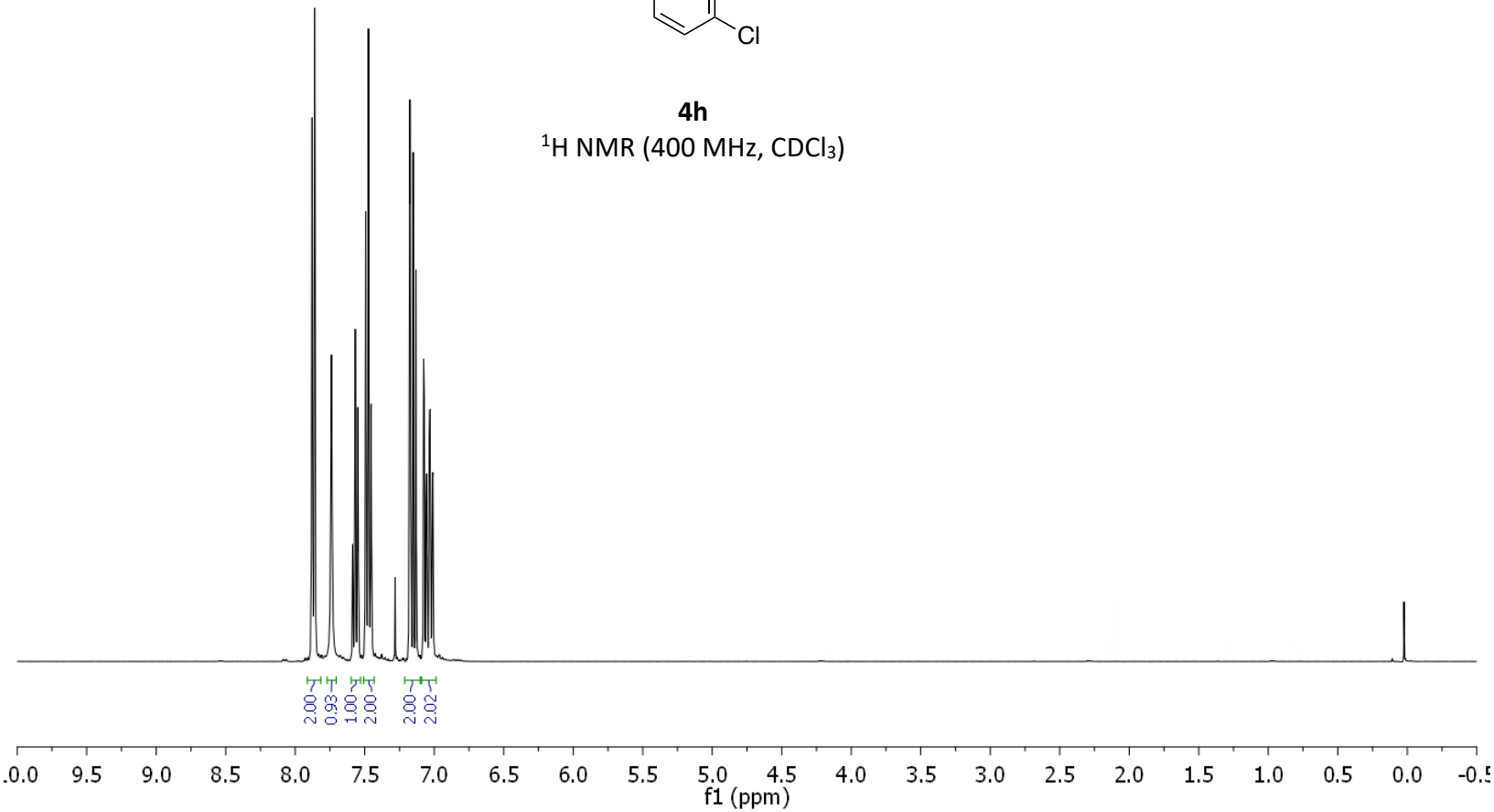
4g

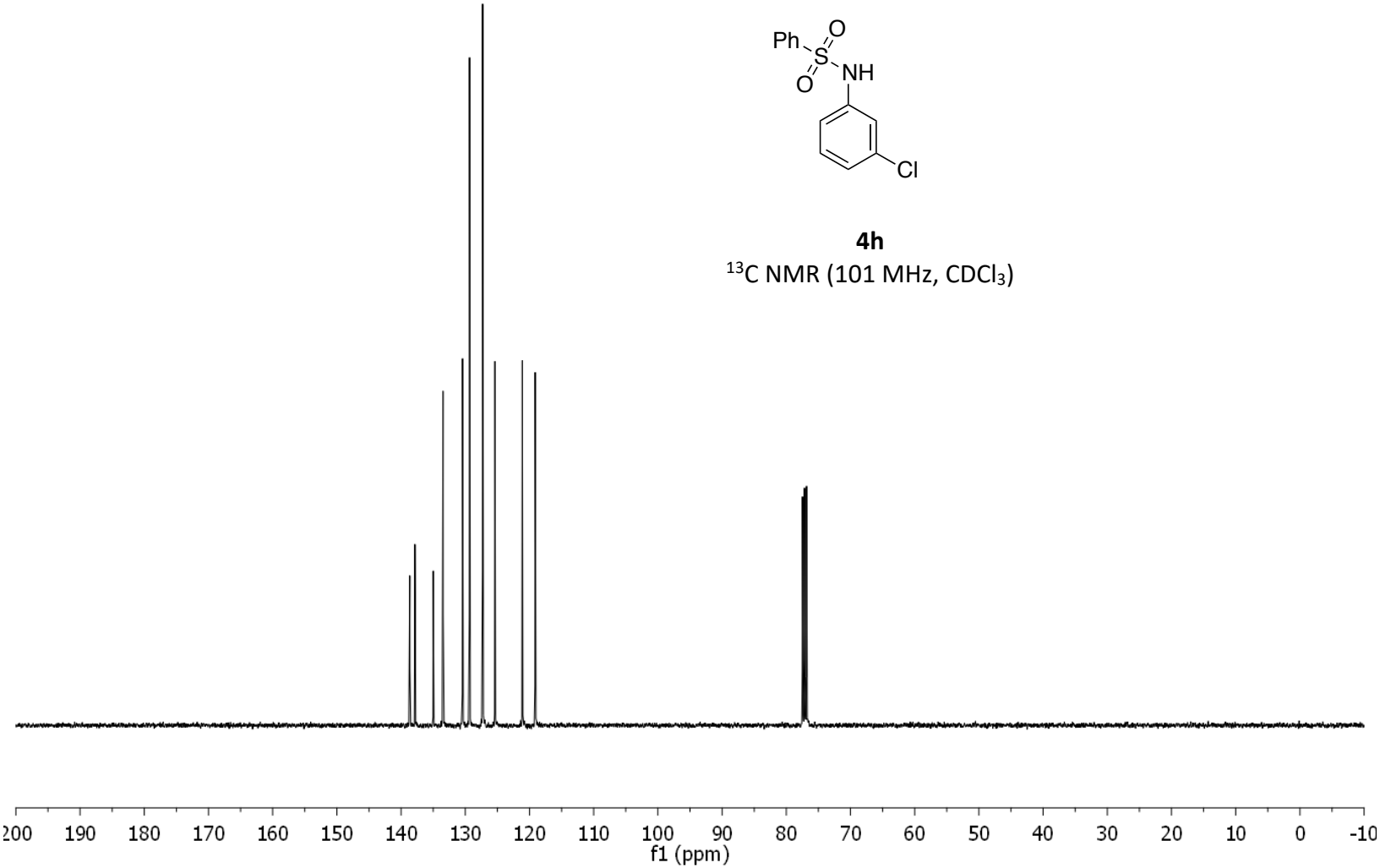
^{13}C NMR (101 MHz, $CDCl_3$)



4h

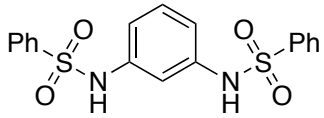
^{1}H NMR (400 MHz, $CDCl_3$)





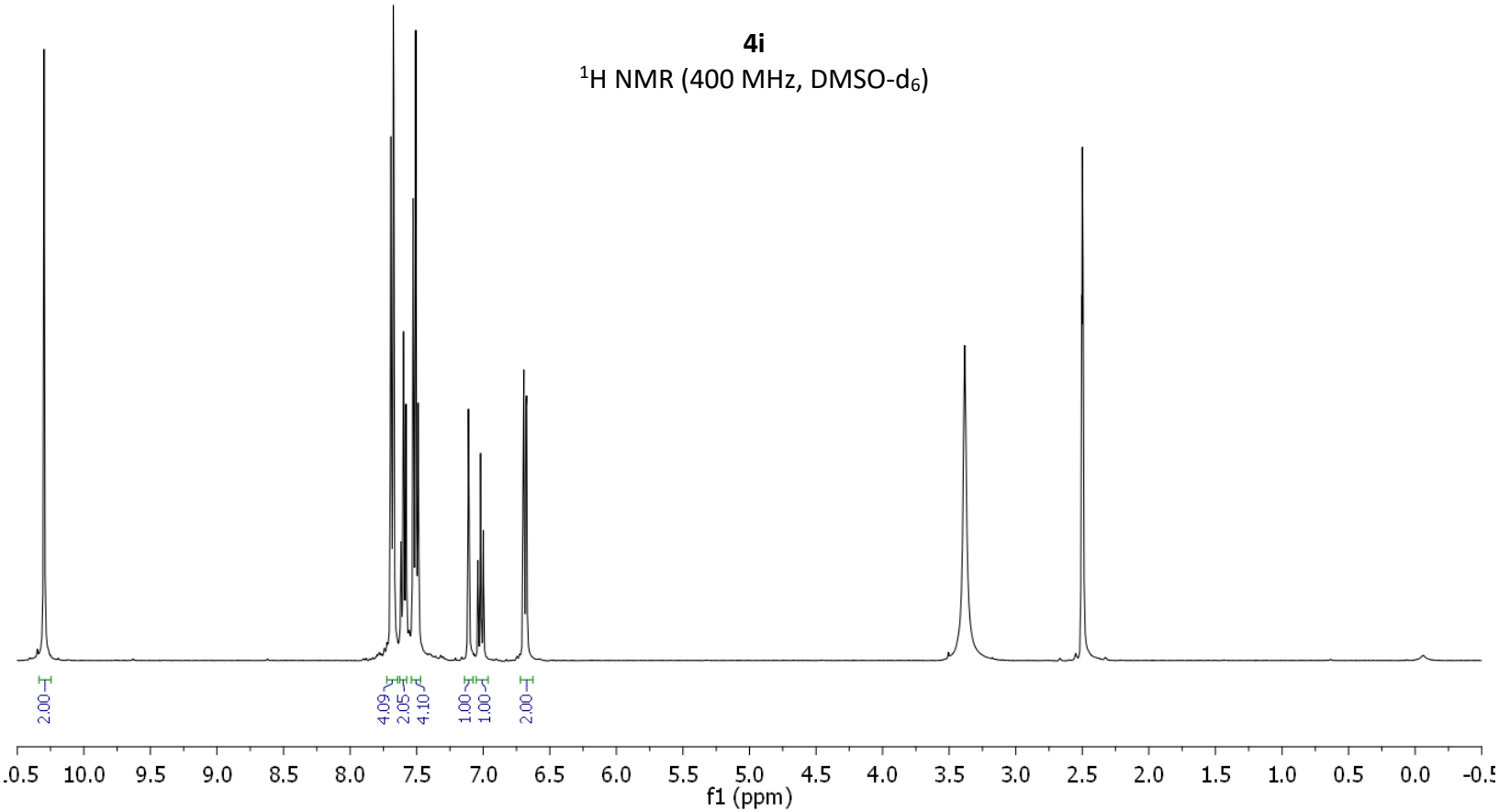
4h

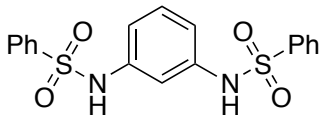
^{13}C NMR (101 MHz, $CDCl_3$)



4i

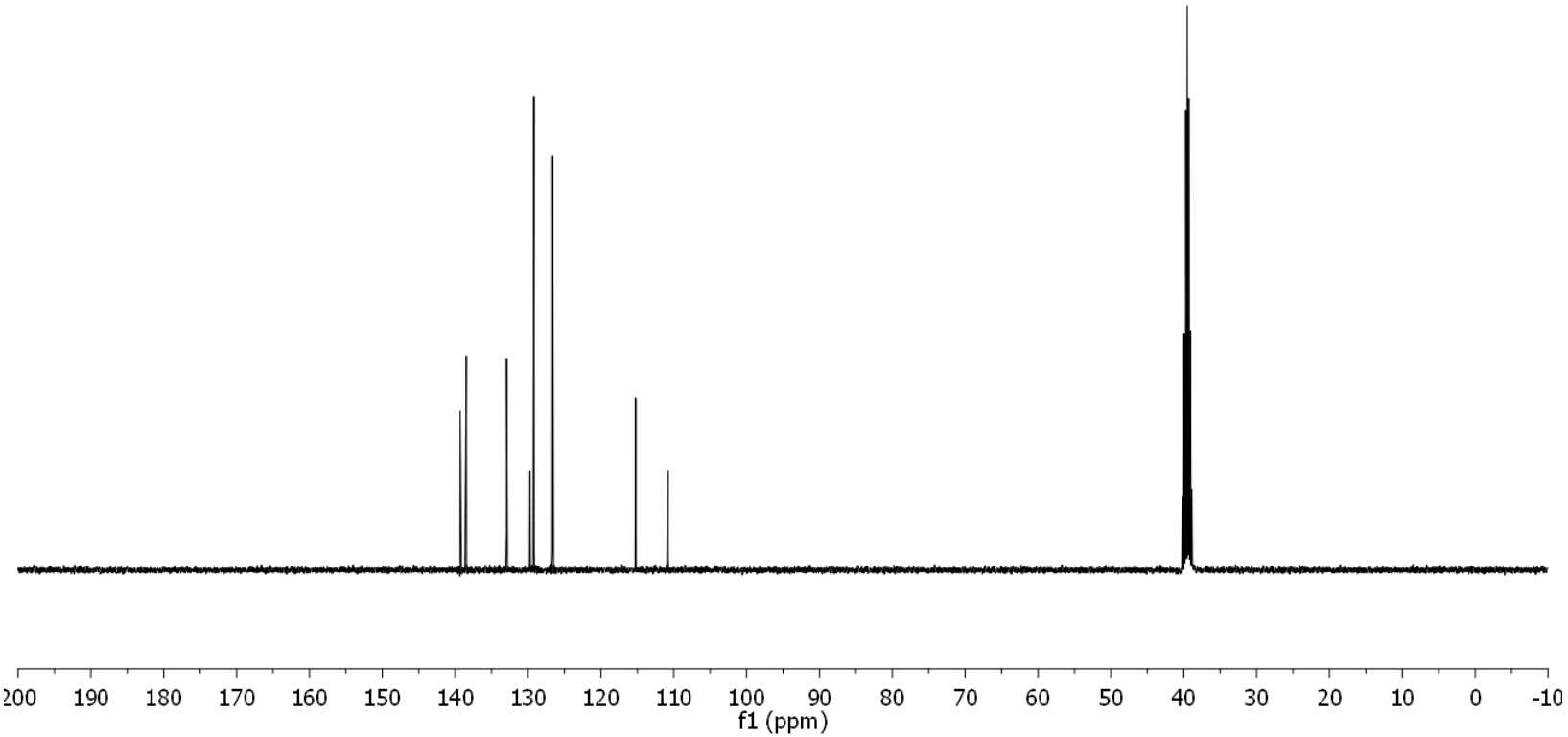
^{1}H NMR (400 MHz, DMSO-d_6)

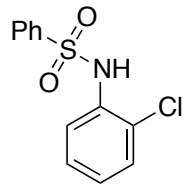




4i

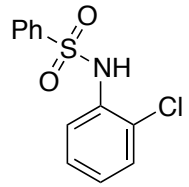
^{13}C NMR (101 MHz, DMSO-d_6)





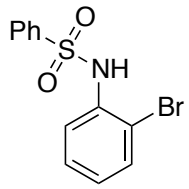
4j

^{1}H NMR (300 MHz, $CDCl_3$)



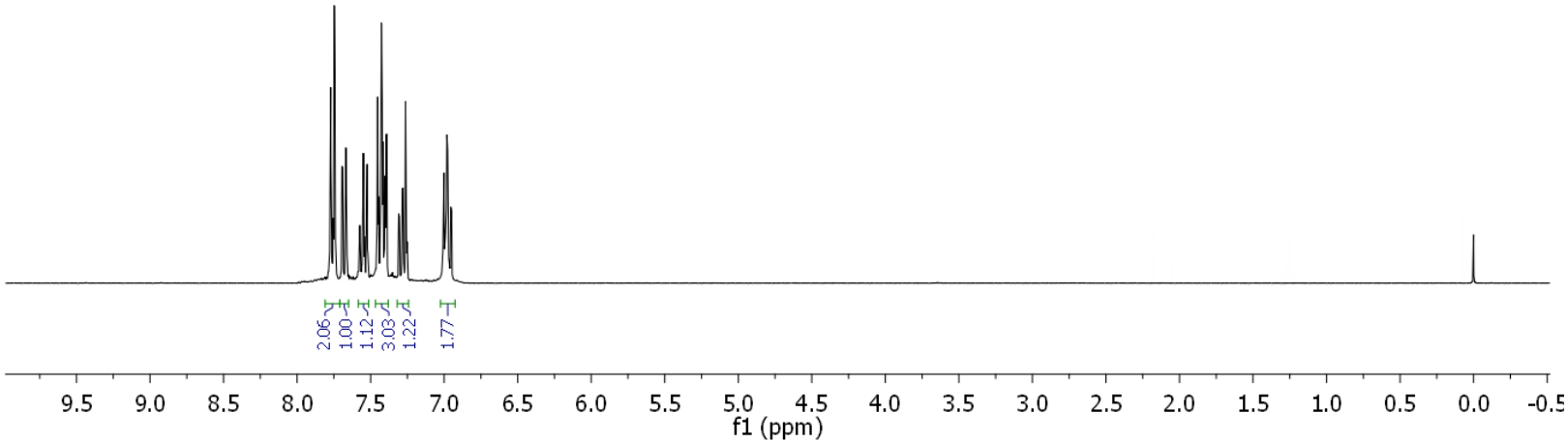
4j

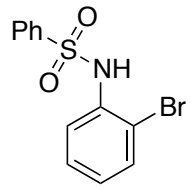
^{13}C NMR (101 MHz, $CDCl_3$)



4k

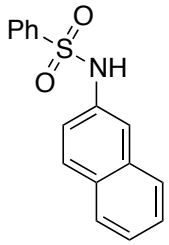
^{1}H NMR (300 MHz, $CDCl_3$)





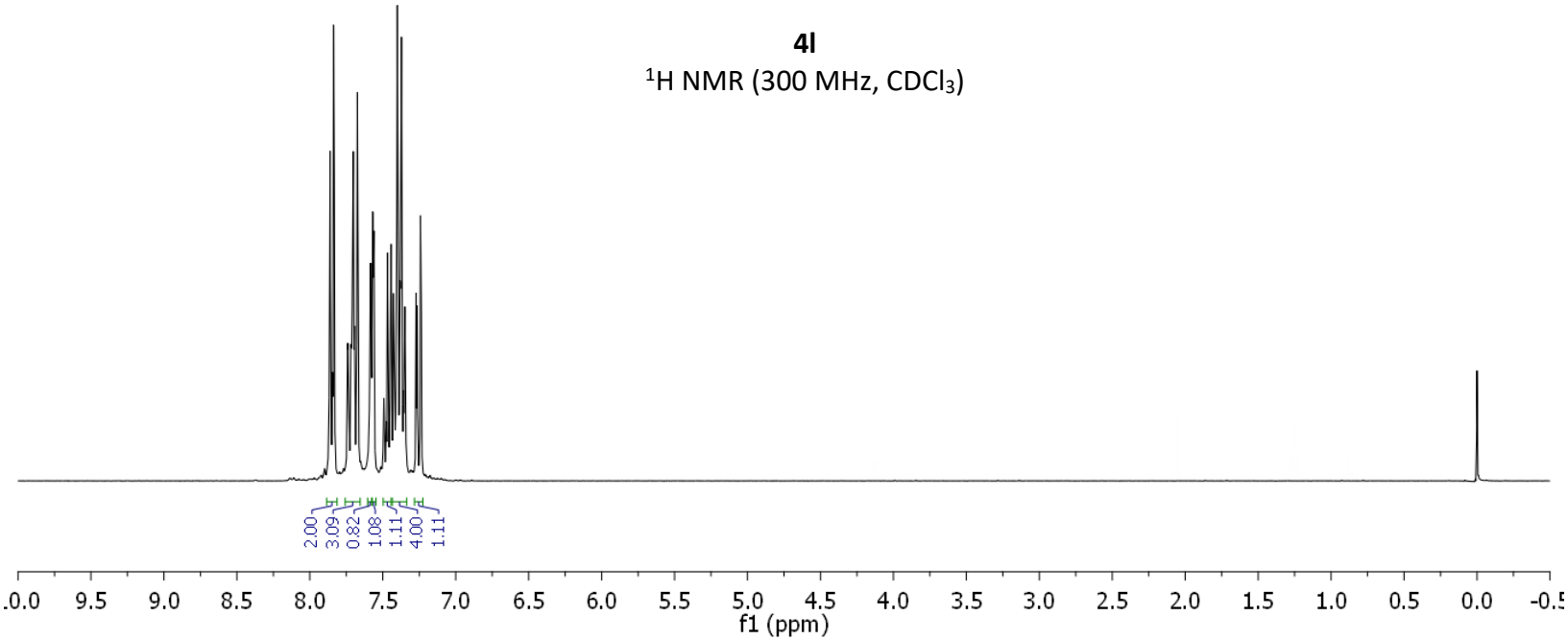
4k

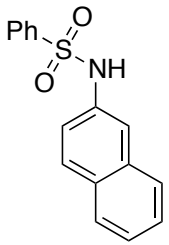
^{13}C NMR (101 MHz, $CDCl_3$)



4l

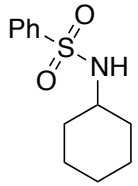
^{1}H NMR (300 MHz, $CDCl_3$)





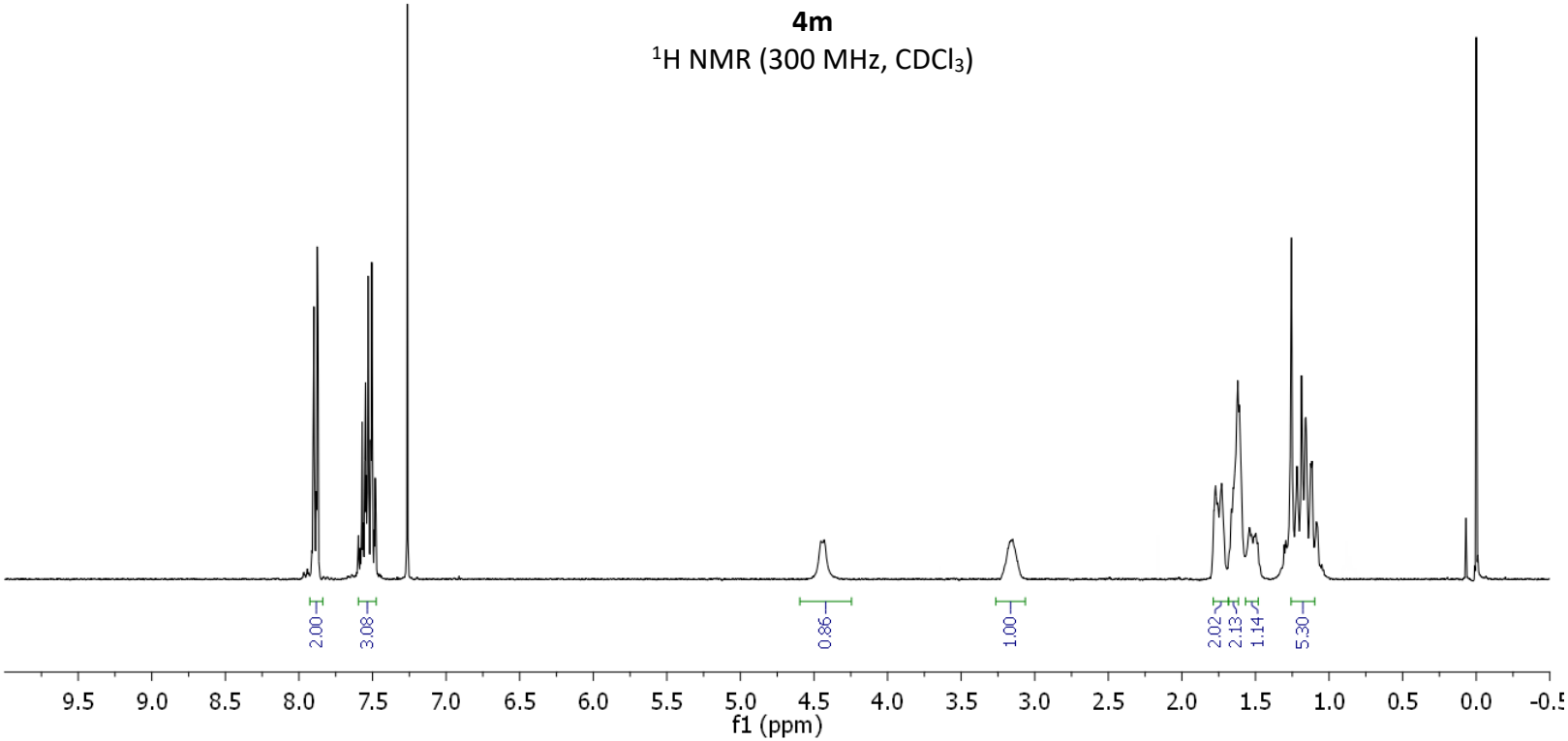
4l

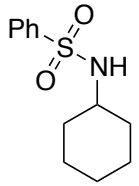
^{13}C NMR (101 MHz, $CDCl_3$)



4m

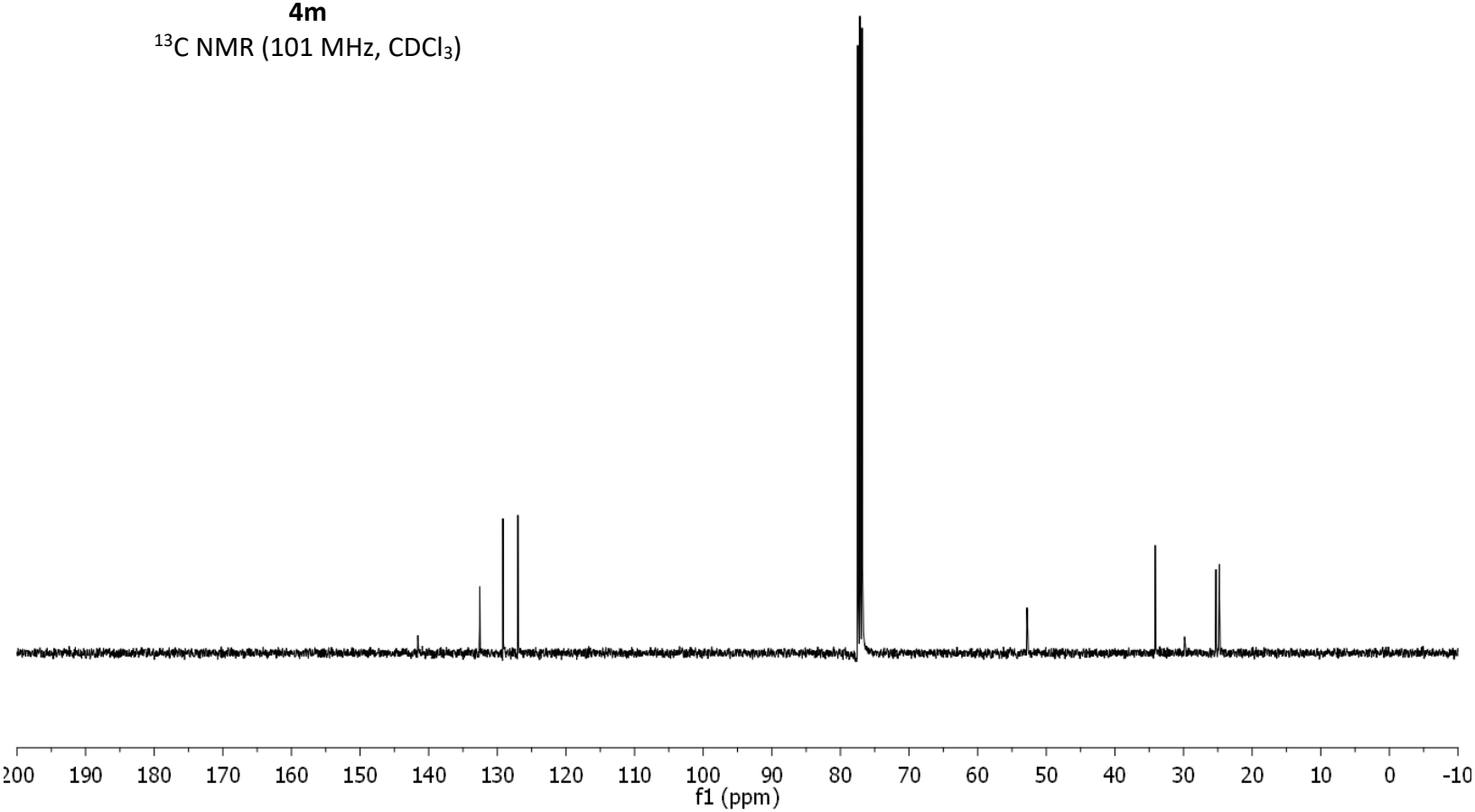
^{1}H NMR (300 MHz, $CDCl_3$)

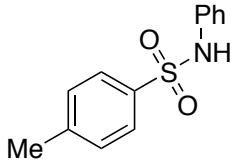




4m

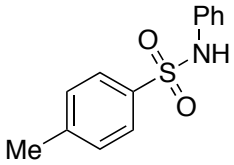
^{13}C NMR (101 MHz, $CDCl_3$)





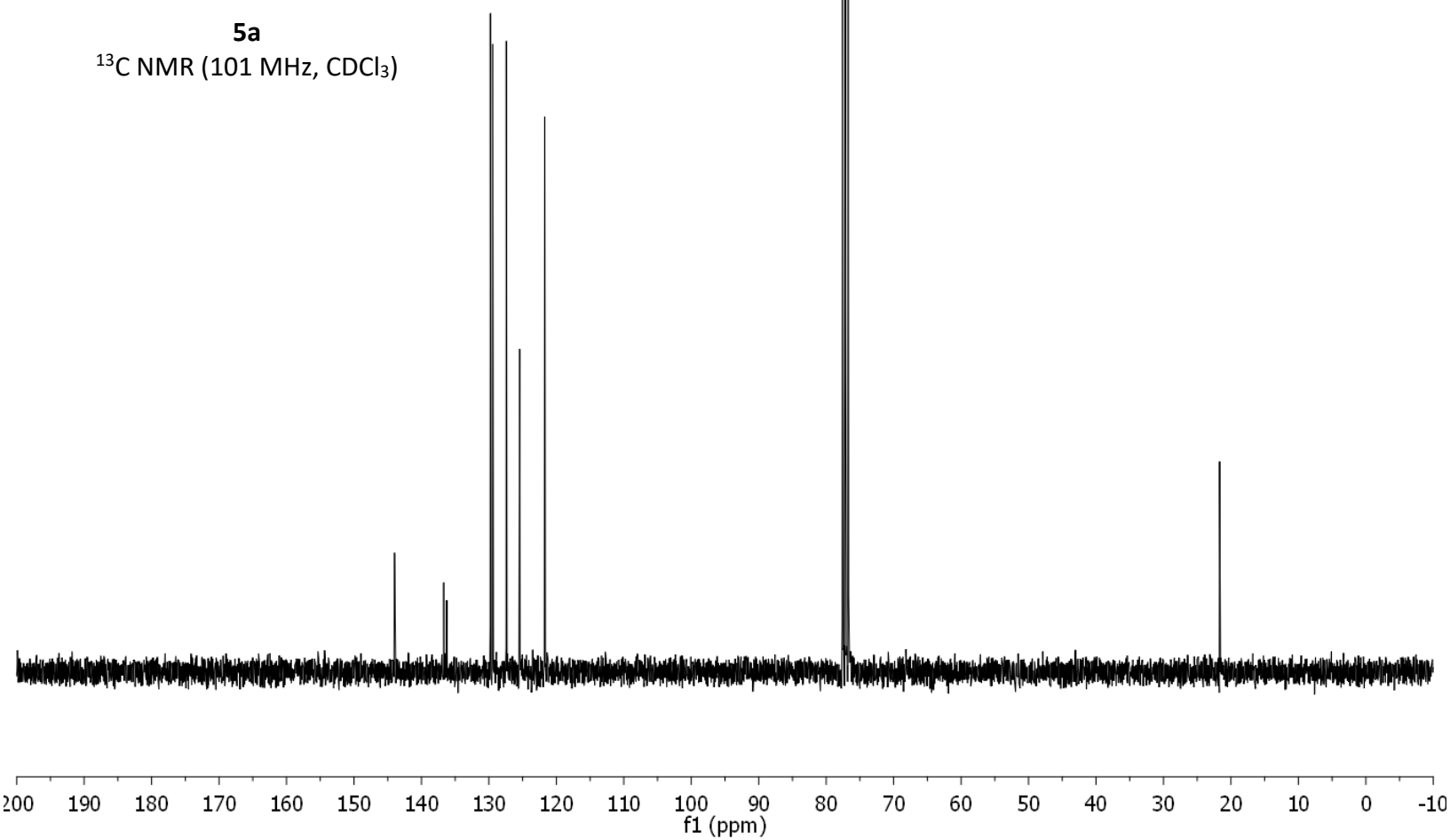
5a

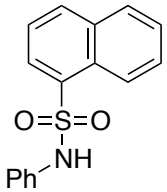
^{1}H NMR (300 MHz, $CDCl_3$)



5a

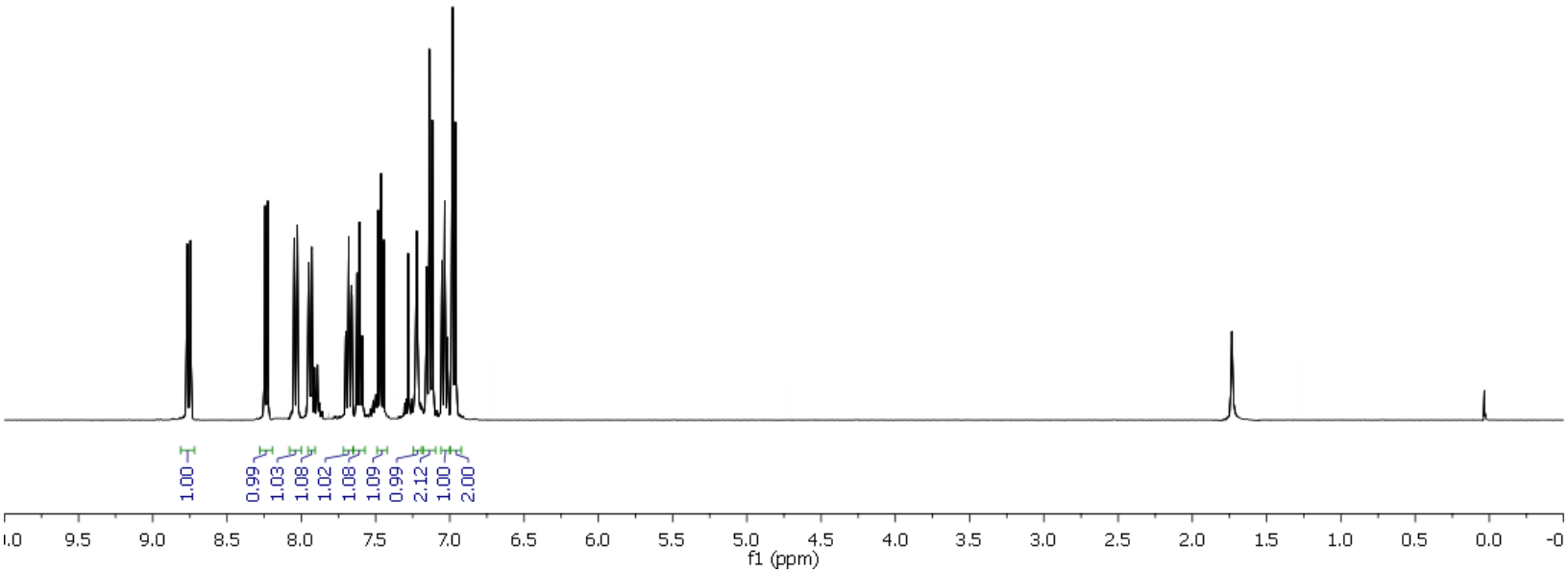
^{13}C NMR (101 MHz, $CDCl_3$)

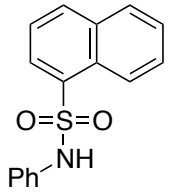




5b

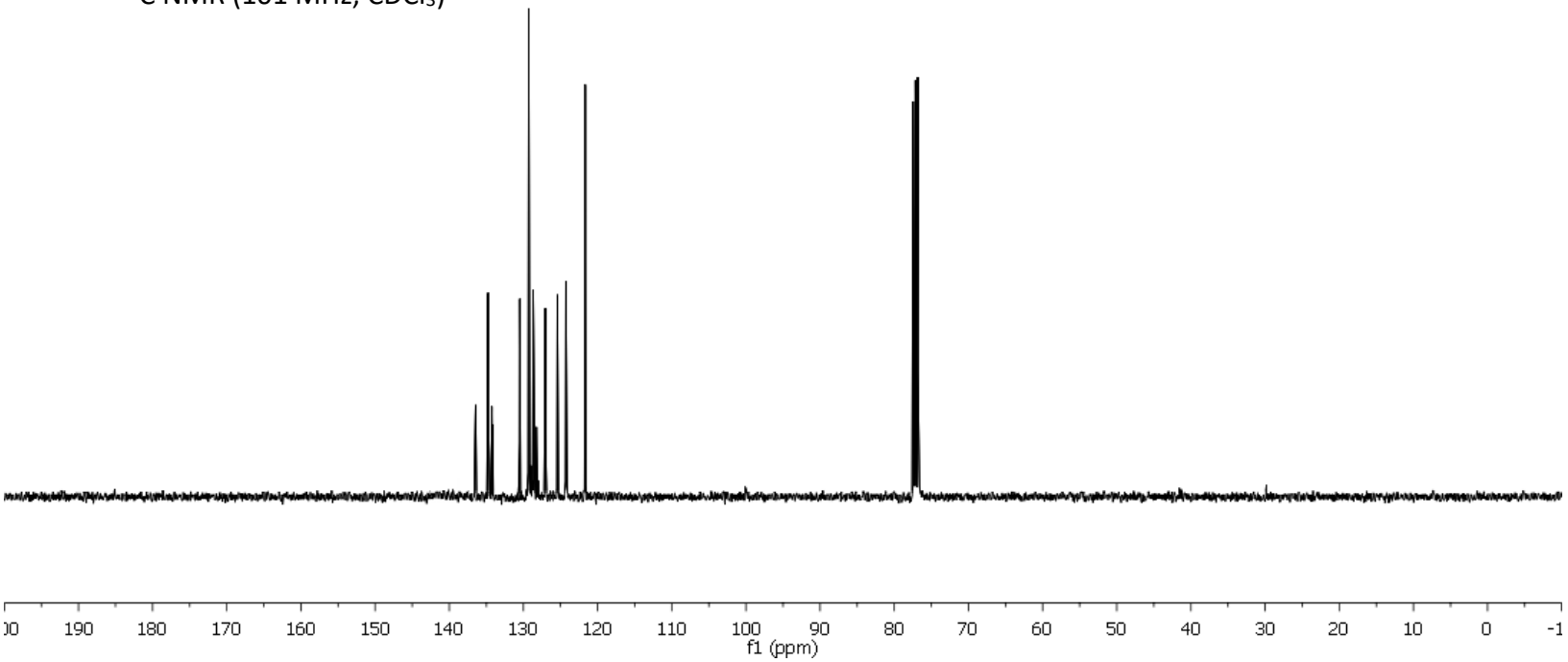
^{1}H NMR (300 MHz, $CDCl_3$)

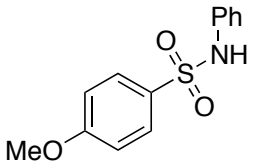




5b

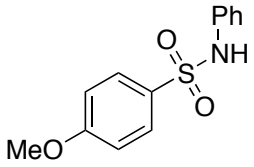
^{13}C NMR (101 MHz, $CDCl_3$)





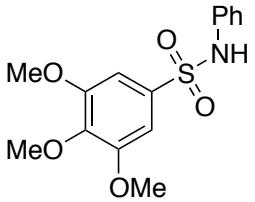
5c

^{1}H NMR (300 MHz, $CDCl_3$)



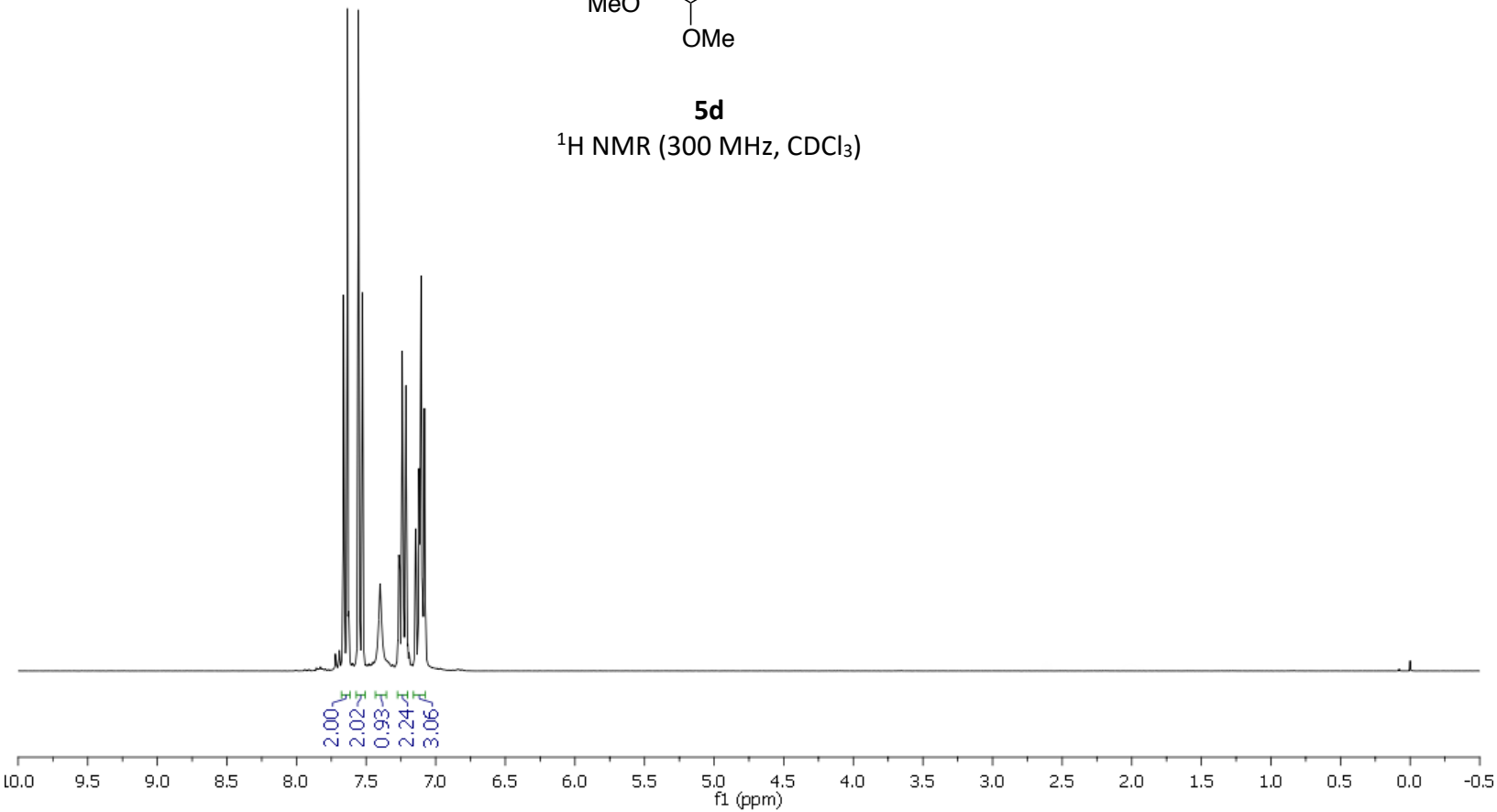
5c

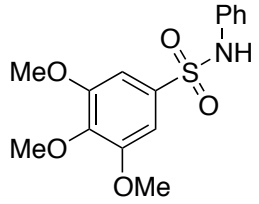
^{13}C NMR (101 MHz, $CDCl_3$)



5d

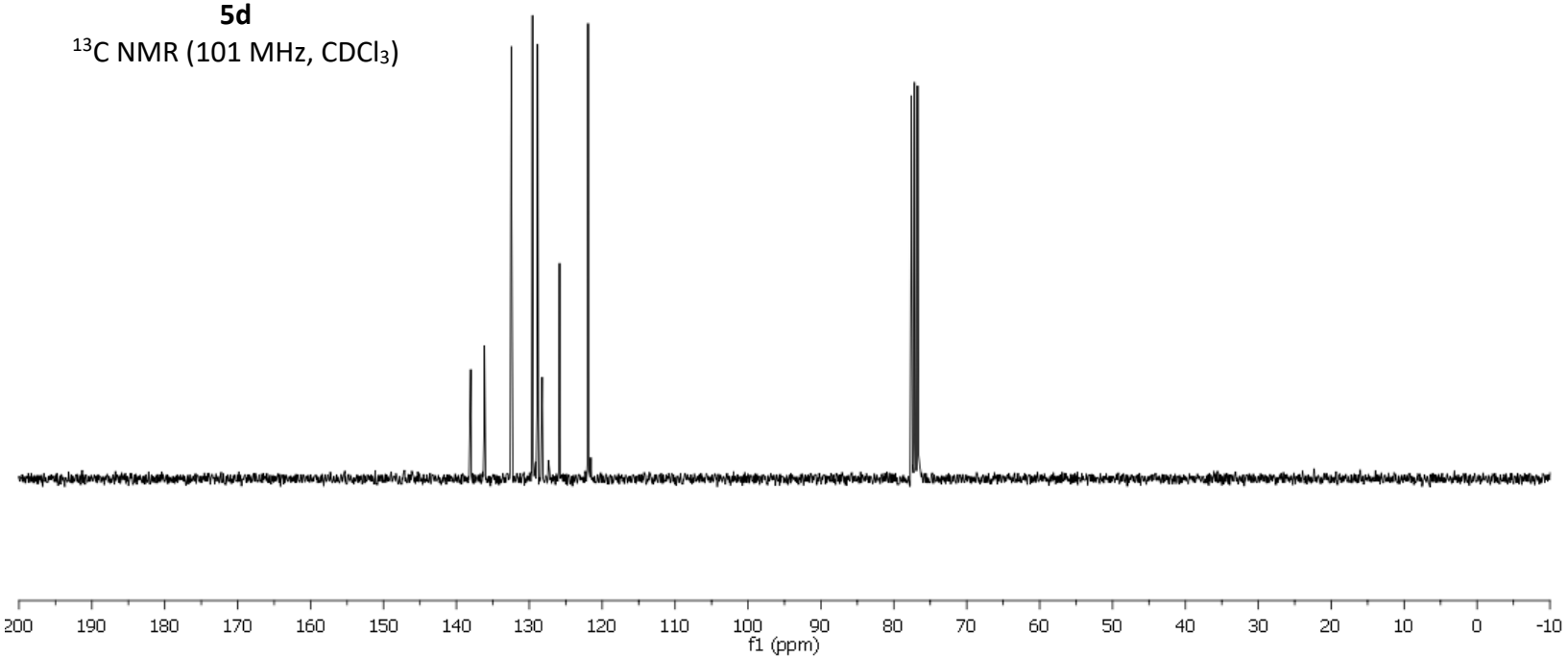
^{1}H NMR (300 MHz, $CDCl_3$)

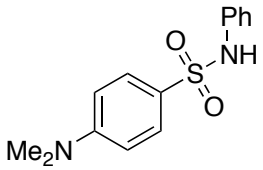




5d

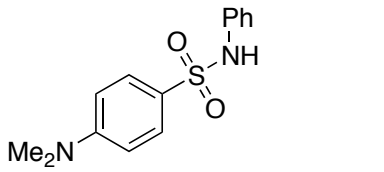
^{13}C NMR (101 MHz, $CDCl_3$)





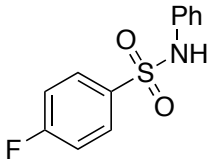
5e

^{1}H NMR (300 MHz, $CDCl_3$)



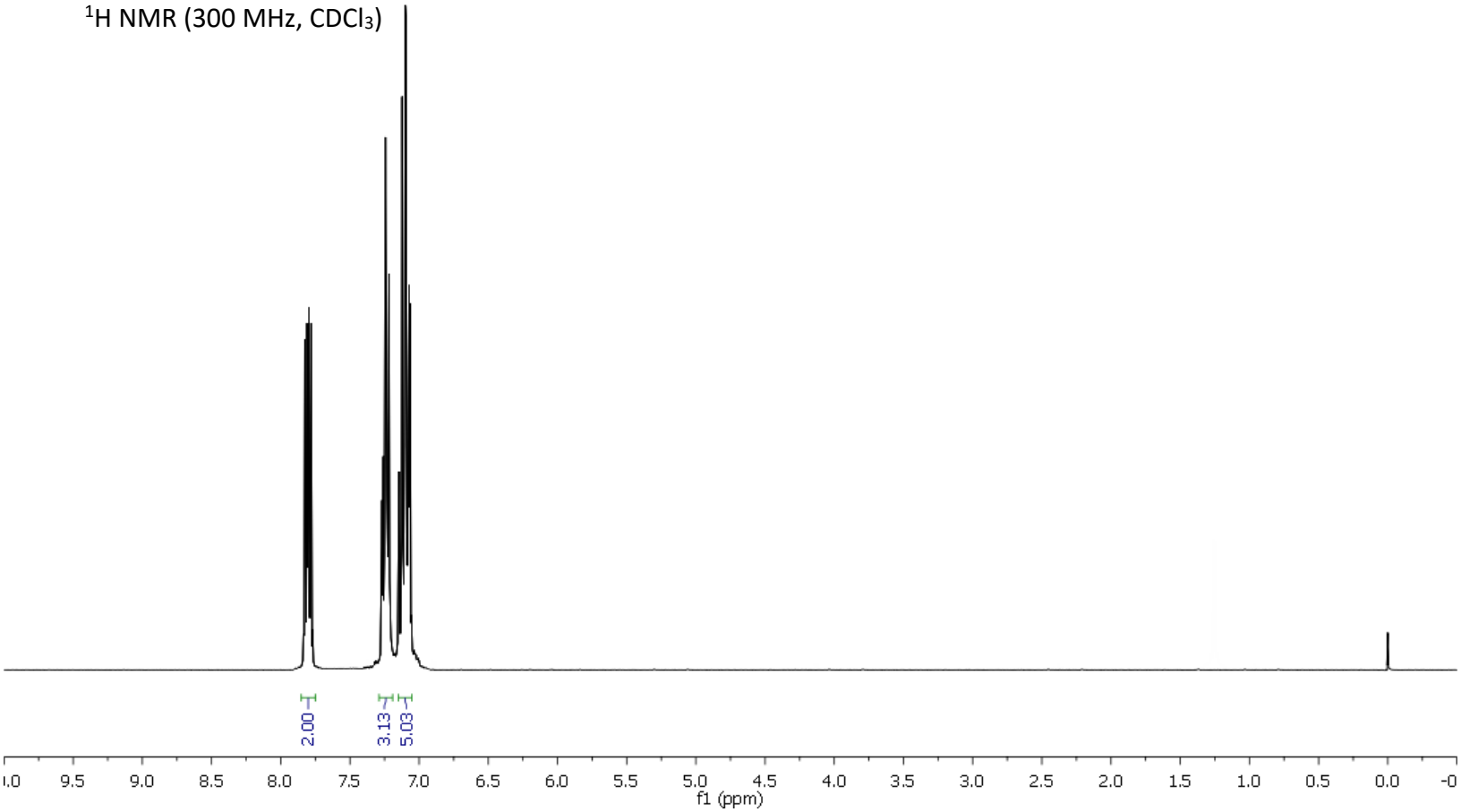
5e

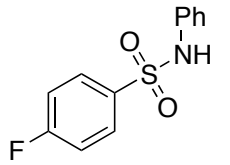
^{13}C NMR (101 MHz, $CDCl_3$)



5f

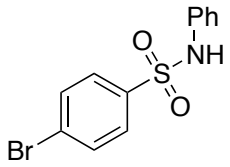
^{1}H NMR (300 MHz, $CDCl_3$)





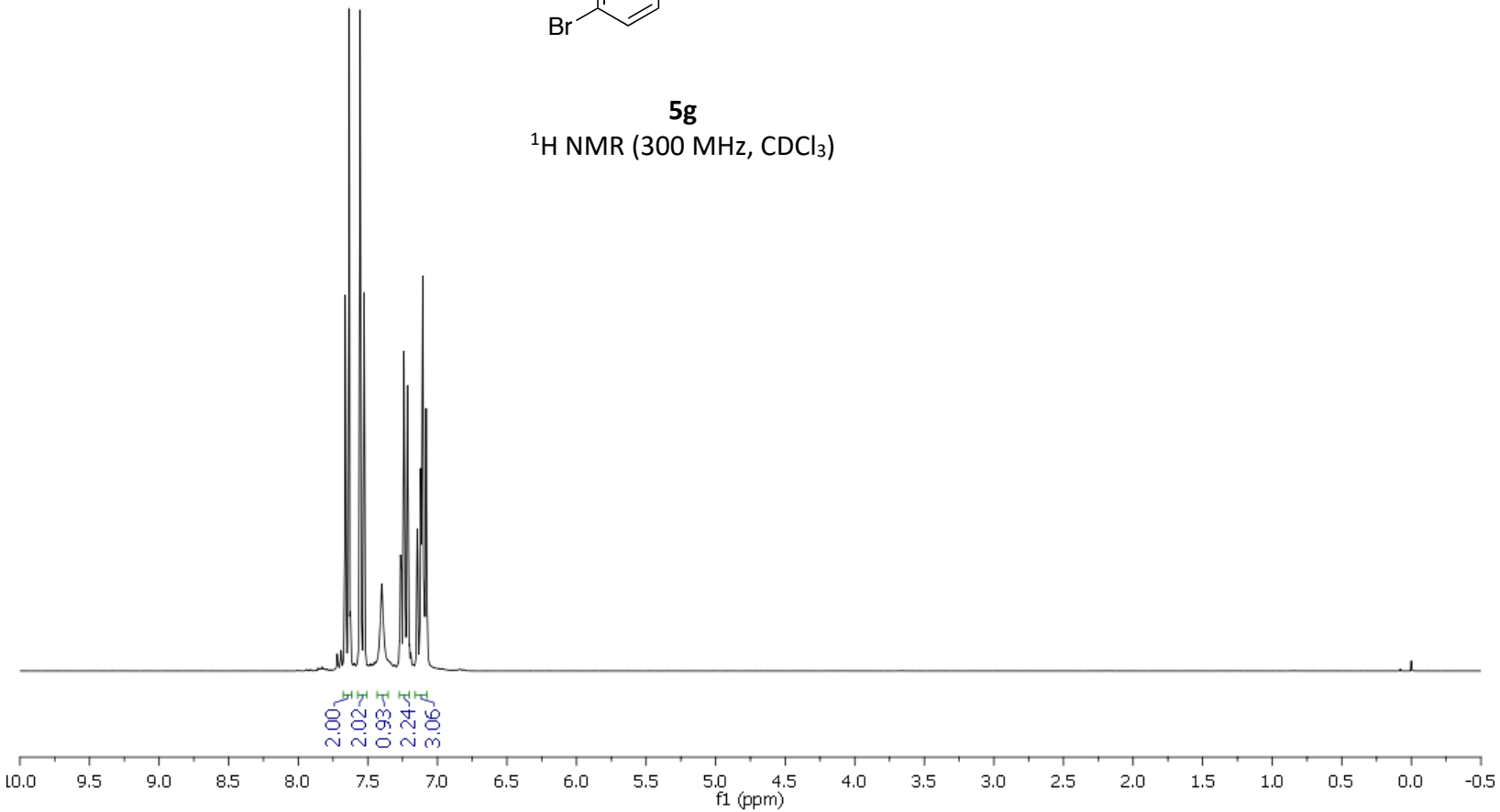
5f

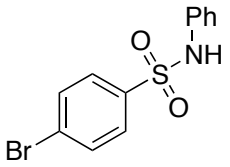
^{13}C NMR (101 MHz, $CDCl_3$)



5g

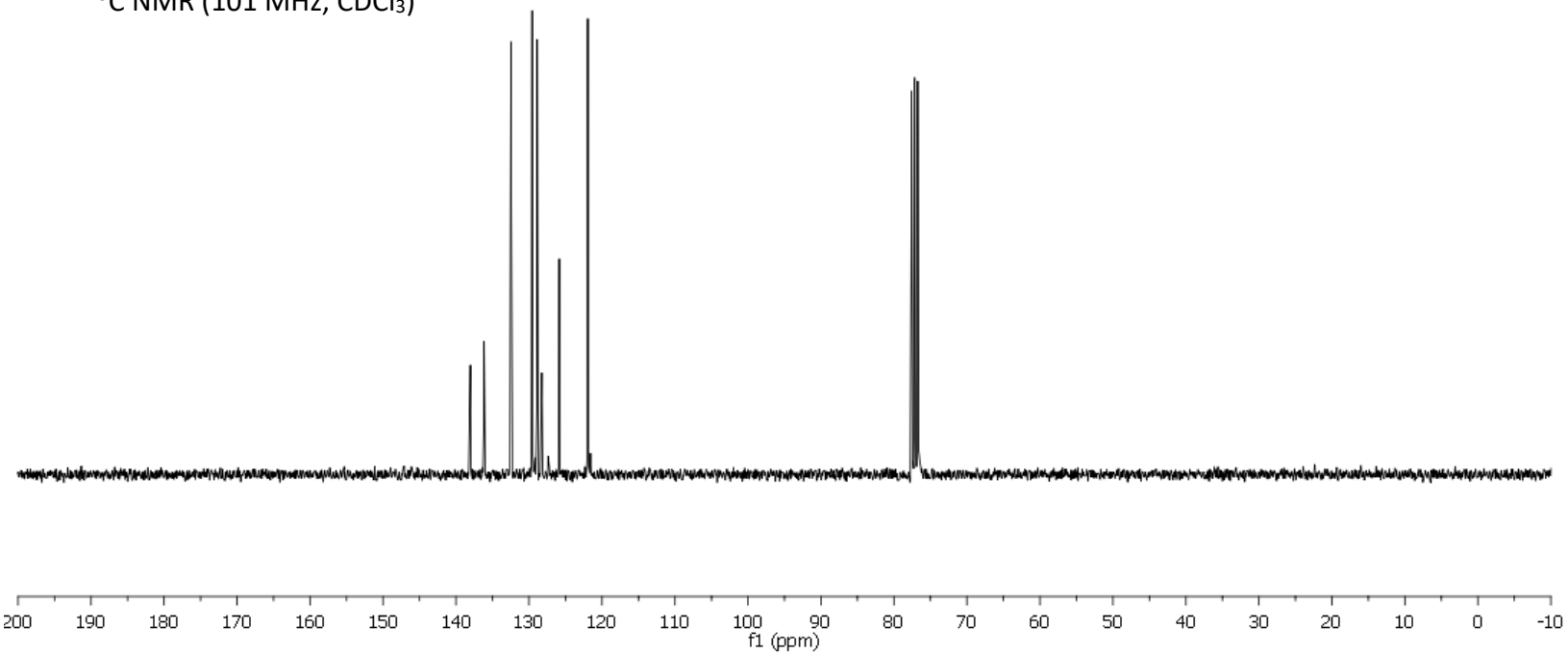
^{1}H NMR (300 MHz, $CDCl_3$)

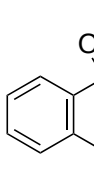




5g

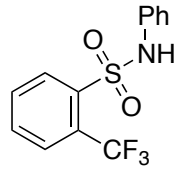
^{13}C NMR (101 MHz, $CDCl_3$)





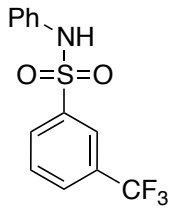
5h

^{1}H NMR (400 MHz, $CDCl_3$)



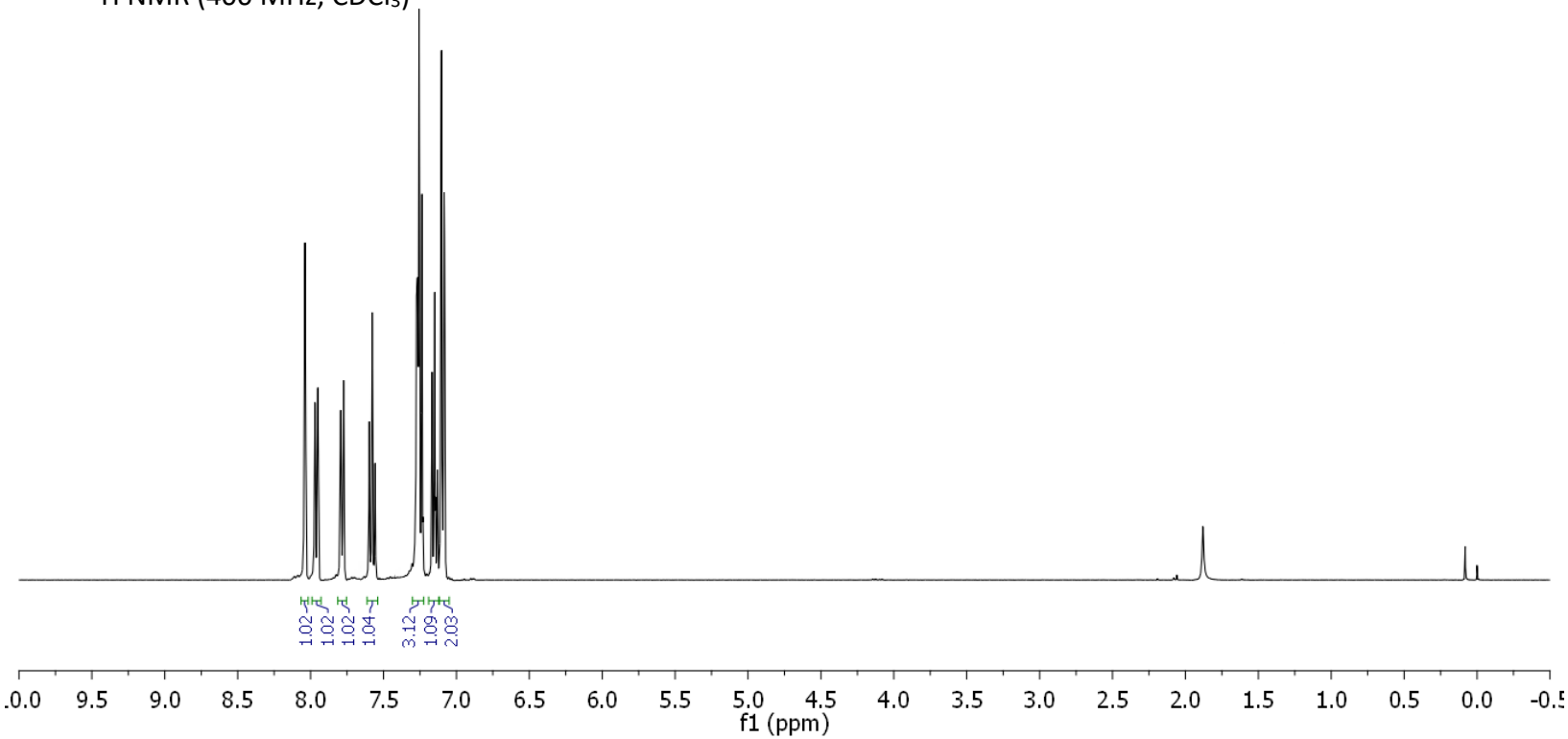
5h

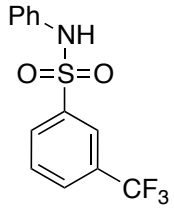
^{13}C NMR (101 MHz, $CDCl_3$)



5i

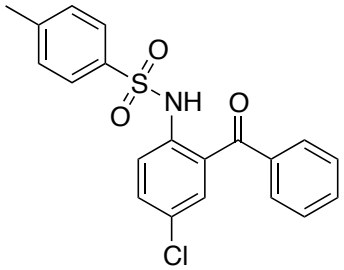
^{1}H NMR (400 MHz, $CDCl_3$)





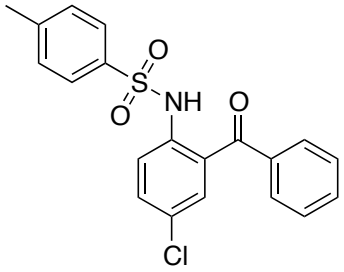
5i

^{13}C NMR (101 MHz, $CDCl_3$)



5j

^{1}H NMR (400 MHz, $CDCl_3$)



5j

^{13}C NMR (101 MHz, $CDCl_3$)