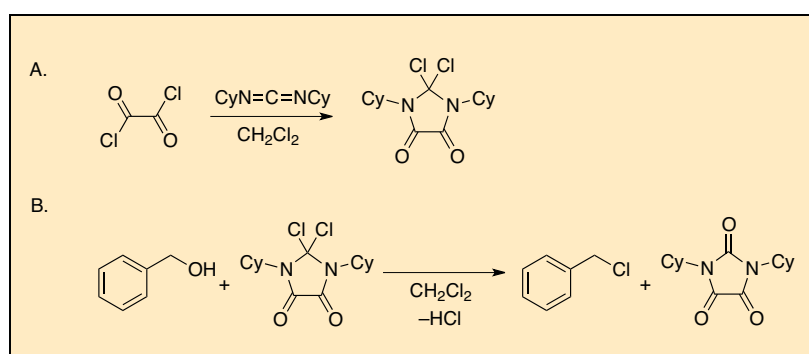


## Synthesis of a 2,2-Dichloroimidazolidine-4,5-dione and its Application in a Chlorodehydroxylation

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### Procedure

A. *2,2-Dichloro-1,3-dicyclohexylimidazolidine-4,5-dione (1Cl<sub>2</sub>)*. An oven-dried 250 mL 24/40 round-bottomed flask (Note 1), equipped with a 3 cm Teflon-coated magnetic stir bar, is sealed with a rubber septum. A Teflon-coated thermocouple is inserted through the septum and the flask is cooled under a stream of N<sub>2</sub> delivered via a Schlenk line through a needle inserted into the septum. The septum is briefly removed, *N,N'*-dicyclohexylcarbodiimide (12 g, 58 mmol) (Note 2) is added to the flask, and the septum with the thermocouple is reattached to the flask. Dichloromethane (125 mL) (Note 3) is added via cannula and the resulting

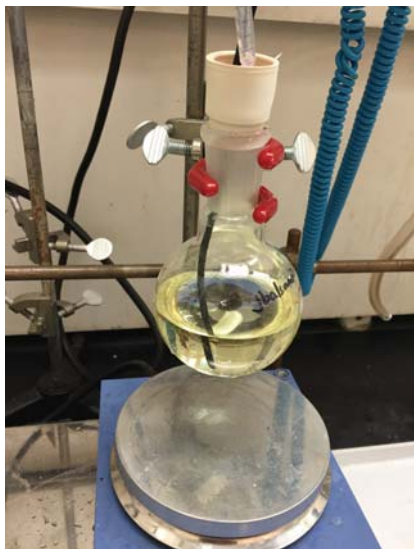


Figure 1. Reaction mixture obtained using Step A after stirring for 2 h



Figure 2. Cannula filtration setup used in Step A

mixture is stirred to effect dissolution. The mixture is cooled to *ca.*  $-5\text{ }^{\circ}\text{C}$  in an ice/NaCl bath, after which oxalyl chloride (7.9 g, 5.4 mL, 61 mmol, 1.05 equiv) (Note 4) is added dropwise over 10 min using a 5 mL gastight syringe (Note 5). The solution is allowed to stir for 2 h, during which most of the ice melts and the reaction mixture develops a pale yellow color (Note 6) (Figure 1). The septum is removed, the flask is quickly attached to a rotary evaporator, and the solution is evaporated to dryness. Upon completion of the evaporation, the flask is blanketed with nitrogen while still on the rotary evaporator. The flask is then quickly removed and capped with a septum. A septum is attached to the flask and the remaining off-white powder is washed with hexane ( $4 \times 50\text{ mL}$ ) that is added via syringe (Note 7). The source flask is kept under nitrogen and house vacuum (*ca.* 25–40 mmHg) is used as needed to remove the solvent through the filter cannula (Figure 2). The washings sequentially become less yellow in color. The resulting solids are dried under vacuum ( $<2\text{ mmHg}$ ) to give product **1Cl<sub>2</sub>** as a white powder (16.5 g, 49.3 mmol, 85%) (Notes 8, 9, and 10) of 99% purity (Note 11).

B. *Benzyl chloride*. A 500 mL 24/40 round-bottomed flask equipped with a 3 cm Teflon-coated magnetic stir bar (Note 1) is sealed with a rubber septum and cooled under a stream of  $\text{N}_2$  at a Schlenk line. Dichloromethane (250 mL) (Note 2) is added via cannula and benzyl alcohol (5.0 g, 4.8 mL, 46 mmol) (Note 12) is added, with stirring, using a 5 mL gastight syringe. 2,2-Dichloro-1,3-dicyclohexylimidazolidine-4,5-dione (**1Cl<sub>2</sub>**) (16.4 g, 49.3 mmol, 1.1 equiv) is quickly weighed out (Note 13) and then promptly added using a powder funnel, which is then replaced with a septum immediately after the addition. The resulting solution is stirred for an additional 3 h (Note 14), after which it is transferred to a 500 mL 24/40 round-bottomed flask and the volatiles are removed on a rotary evaporator (Notes 15 and 16). The crude material is purified using column chromatography on  $\text{SiO}_2$  (column dimensions: 8 cm high  $\times$  3.5 cm diameter) (Note 17) packed in pentane (Note 18). While eluting with pentane, the first UV-active band is collected and the volatiles are removed on a rotary evaporator (Note 15) to give benzyl chloride as a colorless oil (5.1 g, 40 mmol, 86% yield, 99% purity as determined by quantitative NMR spectroscopy) (Notes 19 and 20).

## Notes

1. Due to the sensitivity of the reagents, the Submitters recommend the use of a Schlenk flask equipped with a vacuum pump to facilitate evaporation through the Schlenk line. Higher yields (94-96%) were reported by the Submitters when using a Schlenk flask and vacuum line for solvent removal.
2. *N,N'*-Dicyclohexylcarbodiimide (Alfa Aesar, 99%), as received, may be rather clumpy in nature. Large crystals can be broken up with a metal spatula under a cone of N<sub>2</sub>.
3. New bottles of anhydrous HPLC-grade CH<sub>2</sub>Cl<sub>2</sub> (Sigma-Aldrich) were sparged with N<sub>2</sub> prior to use. Karl-Fischer titration determined that the water content in the solvent was <0.001%. The Submitters used CH<sub>2</sub>Cl<sub>2</sub> that was dried over alumina in a solvent purification system, such that the final moisture content is 1.1 ppm according to Karl-Fischer titration.
4. Oxalyl chloride (Alfa Aesar, 98%) is used as received. Exposure to air should be limited and the liquid should be taken up in the syringe as quickly as is safe and practical.
5. The Submitters oven-dried (110 °C) the syringe and the 20 gauge Luer-lock needle for an hour and then cooled the instruments under N<sub>2</sub> before use. The Checkers did not perform this step.
6. The punctured septum is replaced with a new septum and secured with a copper wire. The same is done after the cannula filtration. After 2 h, an aliquot of the reaction mixture is subjected to LC-MS analysis, which confirms formation of 2,2-dichloro-1,3-dicyclohexylimidazolidine-4,5-dione.
7. Hexane (Sigma-Aldrich, HPLC grade) was sparged with N<sub>2</sub> prior to use. Karl-Fischer titration indicated that the water content in the solvent was <0.01%. The fourth wash was almost colorless.
8. The solids are dispersed by stirring, after which they are allowed to settle. The filter cannula barrel is then immersed in the supernatant and the pale yellow solution is removed under a positive pressure of N<sub>2</sub>.
9. A separate reaction performed on a similar scale yielded 18.05 g (88%) of the same product.
10. Analytical data for 1Cl<sub>2</sub>: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.33 (m, 6H), 1.69 (m, 2H), 1.93 (m, 8H), 2.25 (m, 4H), 3.74 (tt, *J* = 12.3, 3.8 Hz, 2H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ: 24.7, 25.9, 28.8, 57.0, 103.2, 154.4. <sup>1</sup>H and <sup>13</sup>C NMR data referenced to residual solvent signals at 7.26 and

- 77.2 ppm, respectively. IR (film): 2936, 2858, 1732, 1412, 1372, 1319, 1260, 1186, 1117, 894, 871  $\text{cm}^{-1}$ . mp 176–178 °C (dec.).
- The product was determined by quantitative NMR spectroscopy to be 98.7% pure when benzyl benzoate was used as an internal standard.
  - Benzyl alcohol (Alfa Aesar, 99%) is used as received.
  - Solid  $\text{1Cl}_2$  can be briefly handled in air (e.g., for weighing), but is best stored in a Schlenk flask under dry  $\text{N}_2$  or in a vial inside a desiccator. Moisture induces the formation of its colorless hydrolysis product according to the reaction:  $\text{1Cl}_2 + \text{H}_2\text{O} \rightarrow$  1,3-dicyclohexylimidazolidine-1,4,5-trione (10) + 2 HCl. Analytical data for 10:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 1.27 (m, 6H), 1.68 (m, 2H), 1.74 (m, 4H), 1.86 (dt,  $J = 13.4$ , 3.0 Hz, 4H), 2.07 (m, 4H), 4.01 (tt,  $J = 12.4$ , 3.9 Hz, 2H).
  - LC-MS was used to monitor the reaction until its completion.
  - If the reaction has gone to completion, any losses in yield may be due to evaporation of the product during workup.
  - $P = 75$  mmHg and an ice/water bath is used. Extended application can result in excessive evaporation of benzyl chloride. In the Checker's experimental run, residual solids, presumably of the chlorinating reagent, remained in the round-bottomed flask (Figure 2). These were removed using a syringe filter after mixing benzyl chloride with pentane.
  - $\text{SiO}_2$  (Merck, Silica Gel 60, 60 – 200  $\mu\text{m}$ ) is used as received. Although the authors used silica gel chromatographs, the Checkers performed the purification using a Biotage chromatography system equipped with a Biotage 50 g Snap Ultra KP-Sil flash chromatography cartridge.
  - Pentane (Sigma-Aldrich, HPLC grade) is used as received. The crude product consists of an oil and solids. Rather than directly pipetting the oil onto the column, it is best taken up in pentane, transferred to the column, and then washed with additional pentane to ensure that all of the benzyl chloride is loaded.
  - Analytical data for benzyl chloride:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.61 (s, 2H) 7.30–7.42 (m, 5H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 45.9, 128.6, 137.5. IR (film): 676  $\text{cm}^{-1}$ .  $R_f$  ( $\text{SiO}_2/\text{pentane}$ ) = 0.7. Quantitative NMR spectroscopy was used to determine the purity by mass of the isolated material against benzyl benzoate (Sigma-Aldrich) as a standard.
  - A separate reaction on the same scale afforded 5.84 g (86%) of benzyl chloride.

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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](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

While dihaloimidazolidinediones have been known for more than a half a century,<sup>2</sup> their utility has only recently been demonstrated. Simple to prepare in almost quantitative yield,<sup>3</sup> the dihaloimidazolidinediones exhibit electrophilic characteristics applicable to the synthesis of, *inter alia*, dioxoguanides<sup>4</sup> or imidazolidinetriones upon treatment with primary amines or water, respectively. Additionally, such reagents can facilitate

efficient and mild chlorodehydroxylations of alcohols. While the conversion of benzyl alcohol to benzyl chloride is demonstrated here, dihaloimidazolidinediones may also be used to chlorodehydroxylate secondary and some tertiary alcohols.

The utility of dihaloimidazolidinediones is, however, not limited to chlorodehydroxylations. Such species can be viewed as  $\text{Cl}_2$  adducts of diamidocarbenes (DACs), to which they can be converted by reduction with elemental K,<sup>5</sup> or NaI.<sup>6</sup> The resulting *N,N'*-disubstituted imidazolylidenediones, isolable when <sup>t</sup>Bu or 1-adamantyl *N*-substituents are present, offer less crowded steric profiles than their 6-membered analogues.<sup>7</sup> The 5-membered DACs also distinguish themselves from imidazolylidenes in view of their enhanced  $\pi$ -basicity. The dihaloimidazolidinediones and their carbene derivatives thus may be considered as privileged reagents envisioned for use in a range of transition metal-mediated and organocatalyzed transformations.

## References

1. Center for Multidimensional Carbon Materials (CMCM), Institute for Basic Science (IBS), Ulsan 44919, Republic of Korea; Department of Chemistry, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919, Republic of Korea; \*E-mail: d.schilter@gmail.com or bielawski@unist.ac.kr; Financial support from the Institute for Basic Science (IBS-R019-D1) is gratefully acknowledged.
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

Oxalyl chloride: Ethanedioyl chloride; (79-37-8)

*N,N'*-Dicyclohexylcarbodiimide: *N,N'*-Methanetetraylbiscyclohexanamine  
(538-75-0)

2,2-Dichloro-1,3-dicyclohexylimidazolidine-4,5-  
Imidazolidinedione, 2,2-dichloro-1,3-dicyclohexyl (3621-77-0)

Benzyl alcohol: Benzene methanol; (100-51-6)

Benzyl chloride: Benzene, (chloromethyl)-; (100-44-7)



David Schilter was educated at The University of Sydney, from which he received B.Sc. (Hons.) and Ph.D. degrees in 2005 and 2009, respectively, the latter under the auspices of Louis M. Rendina. These studies were followed by postdoctoral research at the University of Illinois at Urbana-Champaign (Thomas B. Rauchfuss) and at the IBS Center for Multidimensional Carbon Materials at UNIST (Christopher W. Bielawski), where he has served as a research scientist since 2014. His interests include coordination, organometallic and materials chemistry.



Christopher W. Bielawski received a B.S. degree in chemistry from the University of Illinois, Urbana-Champaign and a Ph.D. degree in chemistry from the California Institute of Technology (Caltech). After a postdoctoral appointment (also at Caltech), he assumed an independent position at the University of Texas at Austin where he directed efforts in a broad range of synthetic projects. Recently, he moved his research program to the Ulsan National Institute of Science and Technology (UNIST) and is currently participating in a new initiative focused on the synthesis and study of novel macromolecular materials.





Joanna Balsamo earned a B.S. in chemistry from Florida State University in 2003 and conducted undergraduate research in Dr. Michael Blaber's laboratory. In 2006 she joined Amgen in the Small Molecule Preformulation group, specializing in formulation development and solid state characterization. In 2015 she joined the Synthetic Technologies and Engineering group within Pivotal Drug Substance Technology department, where she currently works on the development of small molecule continuous manufacturing processes.



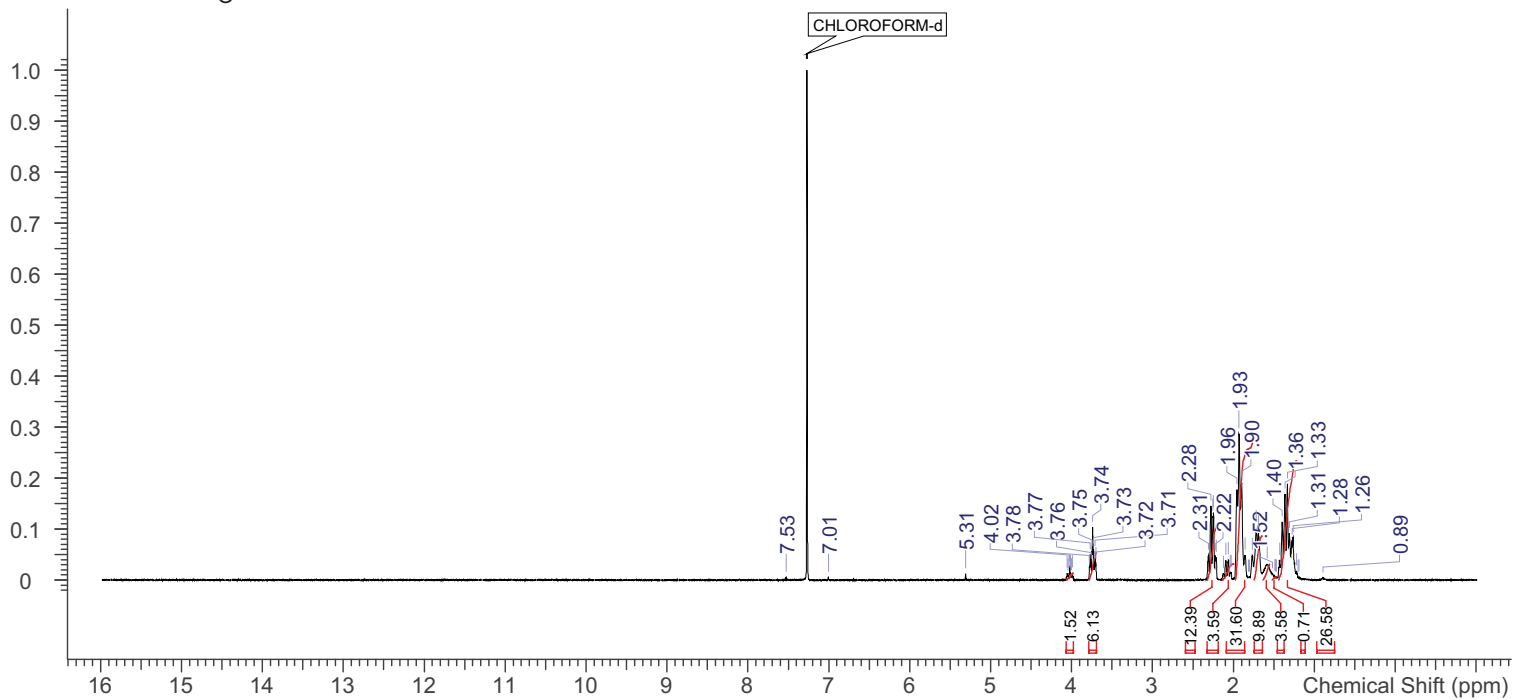
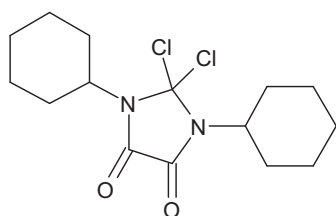
Christopher J. Borths earned a Ph.D. in synthetic organic chemistry from the California Institute of Technology in 2004 for developing novel organocatalytic methods with Prof. David MacMillan. After completing his graduate studies, he joined the Chemical Process Research and Development Group at Amgen where he is currently a Principal Scientist. He is a group leader in the Synthetic and Hybrid Technologies group within Pivotal Drug Substance Technology department, where he currently works on the development of robust and safe manufacturing processes for the production of active pharmaceutical ingredients, including traditional synthetic small molecule drugs, antibody-drug conjugates, and bioconjugation technologies.



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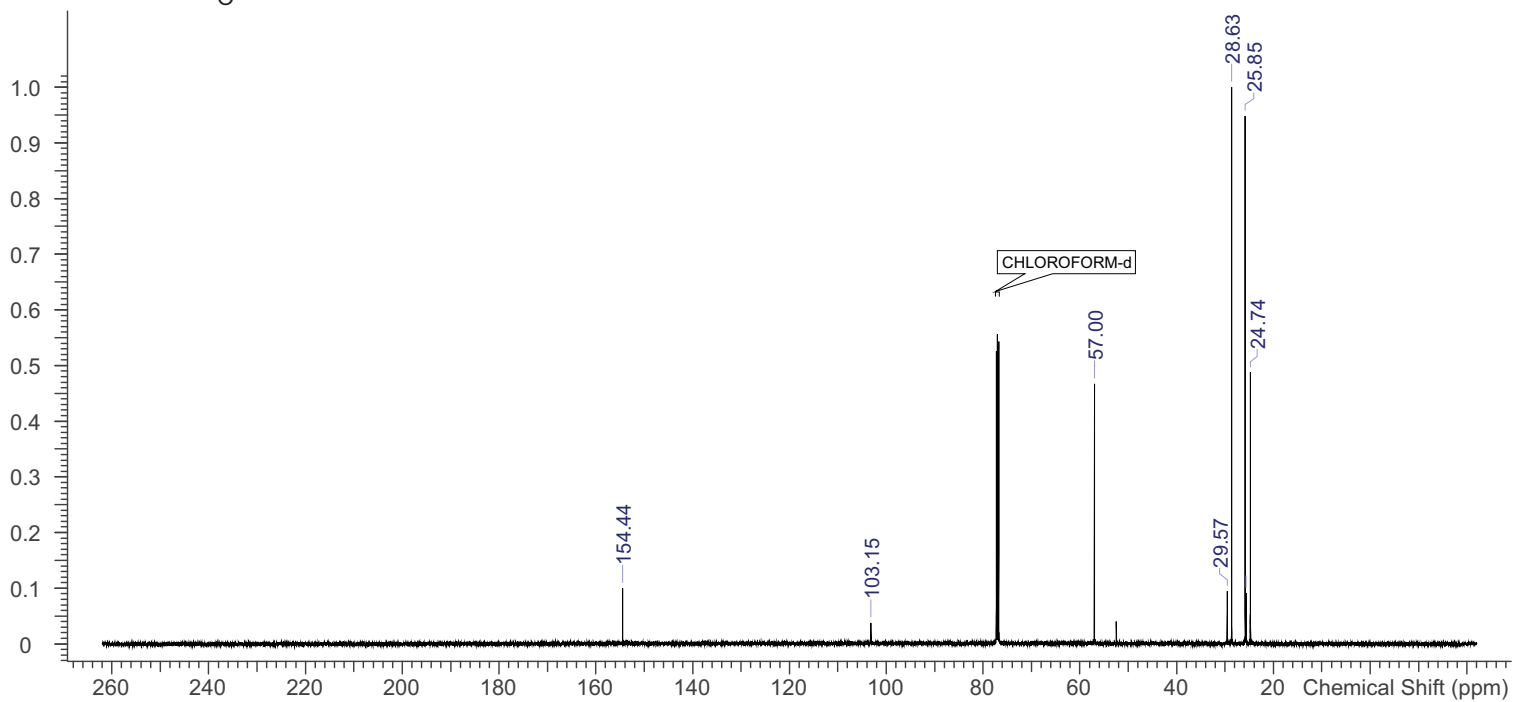
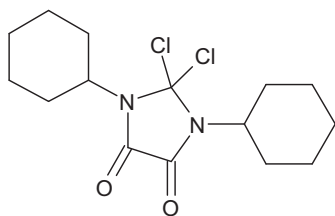




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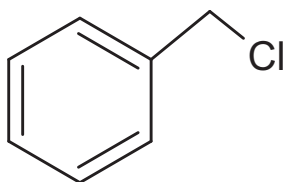




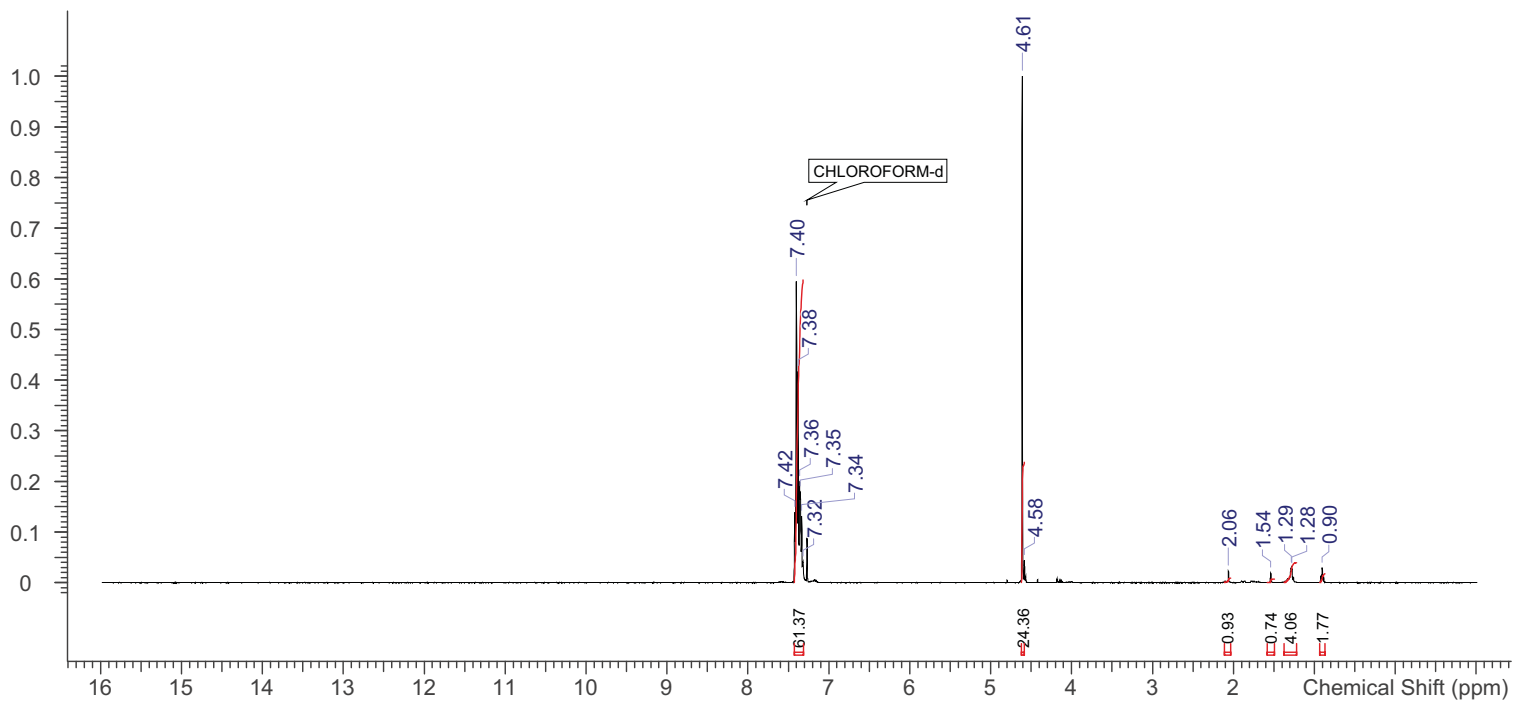
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$^1\text{H}$  NMR (400 MHz, CHLOROFORM-d)  $\delta$  7.32-7.43 (m, 5H), 4.61 (s, 2H)





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