Attempt at Cu-catalyzed N-1 arylation of hydantoin

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Thesis submitted for the degree of
Master in Chemistry
60 credits

Department of Chemistry
Faculty of mathematics and natural sciences

UNIVERSITY OF OSLO

14.06.2021

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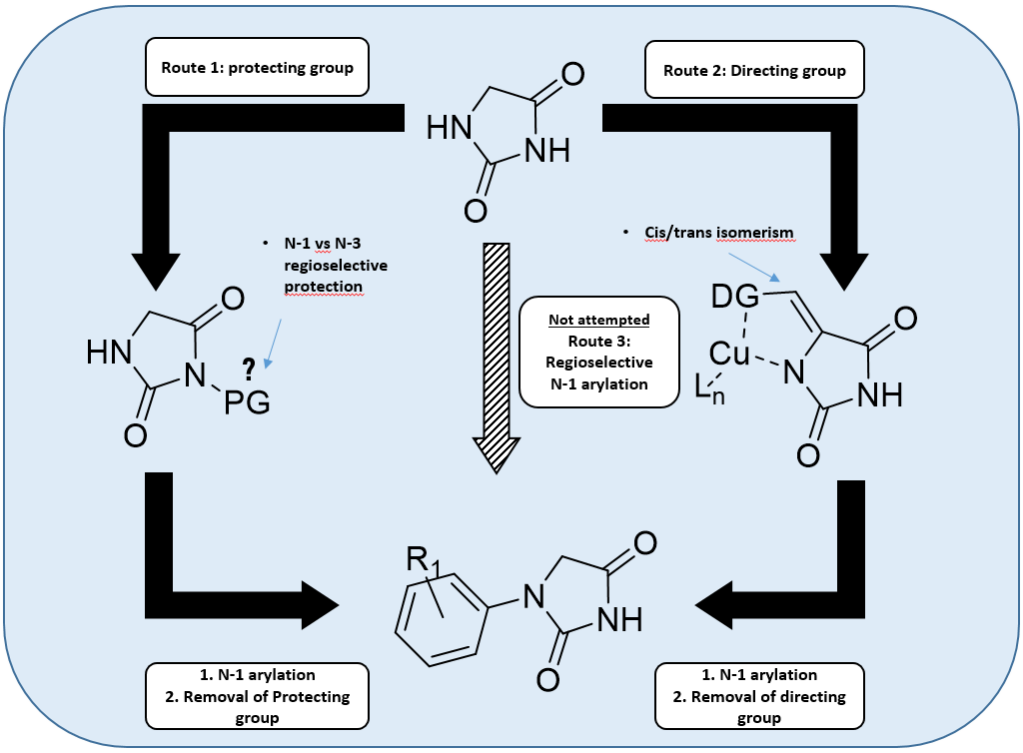
http://www.duo.uio.no/

Printed: Reprosentralen, Universitetet i Oslo

Abstract



Currently, there is no general and regioselective method for the direct N-1-arylation of hydantoin. Previous disclosures report a mixture of both N-1-arylated and 1,3-bis-arylated hydantoins.[1] This project aims to address this issue through the development of a method for direct and general N-1-arylation. A protocol enabling this functionalization will open up new paths for the synthesis of more diversely substituted hydantoins, and complement previous efforts in the Sandtorv group.

Studies done in the Sandtorv group has shown that direct N-3 arylation of hydantoin is possible by a copper catalyzed reaction that is regioselective for the N-3 position on hydantoin.[2] The proposed study will attempt to shift selectivity for the C-N-bond forming event to the N-1-position by working through the different synthesis routes that could lead to N-1 arylhydantoins.

The study's starting point will therefore be to synthesis N-3 protected hydantoins and novel alkylidenehydantoins with the potential of being more selective towards the N-1 position when using the copper catalyzed reaction. [2] The study's end goal is a reaction that utilizes catalytic amounts of the metal catalyst in a one pot reaction, while still allowing the N-3 position of hydantoin to be unsubstituted.

Acknowledgements

The work presented in this master's thesis was carried out in the Department of Chemistry at the University of Oslo under the supervision of Associate Professor Alexander Harald Sandtorv.

I would like to begin with thanking my supervisor Alexander Harald Sandtorv for his support and enthusiasm during these last two years. Your discussions have been invigorating and helped me stay on track, even during the temporary shut downs of the university while working on this thesis. Thank you for teaching me a great deal of chemistry and the ins and outs of research related work in the world of organic chemistry. I would like to especially thank you for the freedom you have given me when developing and working on the master thesis.

I would also like to thank PhD candidate Linn Neerbye Berntsen in particular for her cheerful company and helpful attitude. Thank you for teaching me how to work as an independent chemist and for showing me that lab work can be both fun and exciting. You have been a great influence on my work, and I am grateful for the time you have spent helping me.

I would like to say thanks to all members of the Sandtorv group for their company and help these last two years. You have made it a fun and interesting place to work on my thesis, and I appreciate the time we have spent together.

Thanks go to Frode Rise and Dirk Pedersen for their persistent work on maintaining and enabling all of us in the Sandtorv group to use the NMR facilities. Without their essential work in teaching NMR and maintenance, none of the work in this master's thesis would be possible.

Thank you, Inga Schmidtke, for doing the X-ray analysis of one of my structures and helping me uncover a mystery in my master's thesis.

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1 Introduction

Hydantoin

Hydantoins are a group of heterocyclic compounds all sharing the same skeleton (figure 1). When all the possible substituents of this skeleton consists of hydrogen, we get regular hydantoin. What makes hydantoin interesting is when we look at what we get if we start substituting the hydrogens with different substituents like aryl groups or alkyl groups etc. As shown in figure 2, we find that there is a wide usage area for hydantoins. We find hydantoins in medicine (Nilutamide), agriculture (Iprodione), and in everyday cosmetics (DMDM hydantoin). In addition, we see that some of the hydantoins contain aryl groups, which we call arylhydantoins. More specifically N-3 arylhydantoins when the N-3 position is substituted. As the main goal of this master's thesis is to develop a method for N-1 arylating unsubstituted hydantoin, we need to answer some important questions:

- Why do we want to make N-1 arylhydantoins directly from unsubstituted hydantoin?
- What are the challenges involved with making chemioselective and regioselective reactions on hydantoin?
- How are arylhydantoins synthesized normally? Moreover, what new developments have been made?
- What routes to synthesizing N-1 arylhydantoins will I attempt to follow?
- What goals do we hope to achieve by the end of this project?

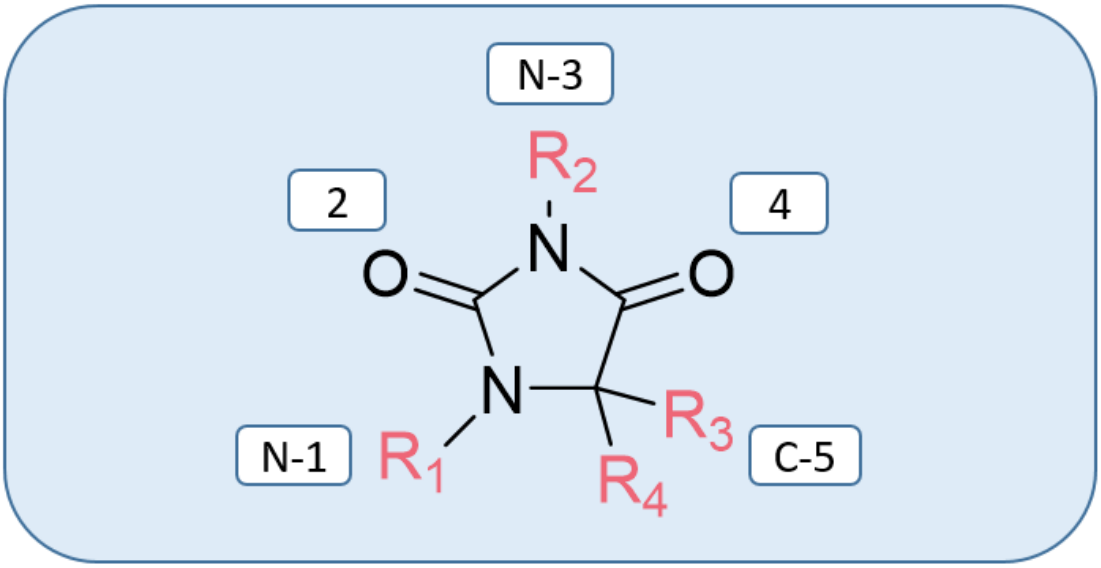


Figure 1: The hydantoin skeleton. R represents all possible substituents. The numbers represent each position of the hydantoin, starting at N-1.

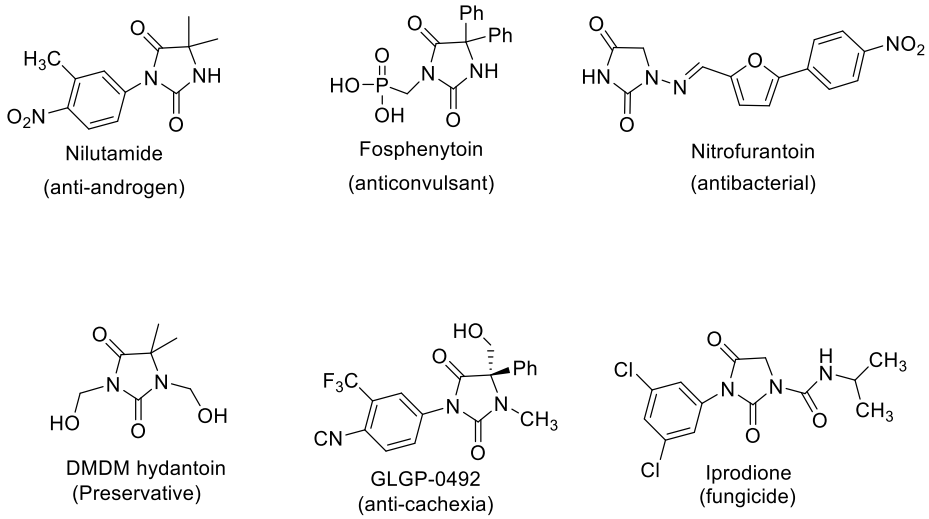


Figure 2: Hydantoins that have shown biological activity for treating different conditions.

Why do we want to make N-1 arylhydantoins from unsubstituted hydantoin? One may come to a different conclusion depending on whom you ask, but from a chemist's point of view, there are some compelling reasons. Firstly, as far as I am aware, no methods for directly N-1 arylating unsubstituted hydantoin in a selective manner has yet to be developed. Simply attempting to do a reaction none has done before can be compelling, but it is even more compelling with the knowledge that many hydantoins previously made has shown biological activity (figure 2). Secondly, unsubstituted hydantoin presents itself as a challenging substrate

because of hydantoin's similar functional groups, e.g. N-1 vs N-3. Lastly, developing new methods for synthesizing hydantoins may increase the knowledge base surrounding hydantoins and lead to a better understanding of previous work on hydantoins.

It would be prudent to get an overview of hydantoin's reactivity before looking at the many ways one could derivatize the hydantoin skeleton. As shown in figure 1, there are 5 positions of interest in regards to regioselectivity. Beginning with the amide like N-1 position, we find that it is more nucleophilic when compared to the imide like N-3 position.[3] On the other hand, the N-3 position is more acidic than the N-1 position, with a pK_a value of around 9.1.[4] This trend can be mostly explained by the carbonyl groups present at the 2 and 4 positions. The N-3 position neighbors not one carbonyl like the N-1 position, but two carbonyl groups. This leads to the N-3 deprotonated hydantoin being stabilized by an additional resonance structure when compared to the N-1 deprotonated hydantoin. The additional stability thus leads to a stronger acidity of the N-3 position, which in turn generally leads to N-3 also being a weaker nucleophile.

The steric hindrance caused by the carbonyl groups and the C-5 position is also a consideration one must make when assessing the relative nucleophilic strength. In unsubstituted hydantoin, you could argue that the C-5 position is less sterically hindering than the carbonyl groups due to the smaller size of the hydrogen atoms. Thus, it becomes apparent that the N-1 position is less sterically hindered and therefore more nucleophilic. Research on the strength of this effect has been published, and it showed that larger C-5 substituents could decrease the N-1 positions relative nucleophilicity to the point that the N-3 becomes favored in nucleophilic substitution reactions.[3]

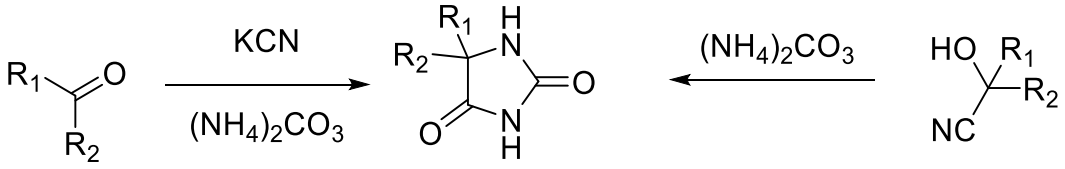
With an overview of hydantoin's reactivity fresh in mind, let us use the anti-androgen Nilutamide as an example of a product that could be made via direct N-arylation of a hydantoin, and see what selectivity issues that might arise. The direct N-arylation would have to take place using the appropriate arylating reagent and 5,5-dimethylhydantoin. Considering that we want the reaction to only take place on the N-3 position, we would need the reaction to be chemioselective for N-H positions and not the carbonyl (2, 4) or methylene position(C-5). Once you have chemoselectivity for N-H positions, you would also need to consider the fact that there is both an N-1 and N-3 position. Since the arylation reaction is

supposed to favor the N-3 position, we would need regioselective control, whereby the reaction proceeds at N-3 while leaving N-1 untouched. Of course, in the real world we might end up with a reaction that proceeds at varying degrees on the other positions while giving the N-3 arylated product as the major product.

Now, how would we obtain the regioselectivity and chemoselectivity required for synthesizing Nilutamide via a direct N-arylation? One way to achieve chemoselectivity would be to, as an example, use a base that only or mainly deprotonates a certain functional group over another. In the Nilutamide synthesis example, you would want the base to deprotonate The N-H moiety and not the CH_2 moiety. In order to gain regioselective control one would then need to adjust reaction conditions or choice of reagents until the N-3 position is favored even where a reaction on N-1 would be plausible.

Cyclization reactions

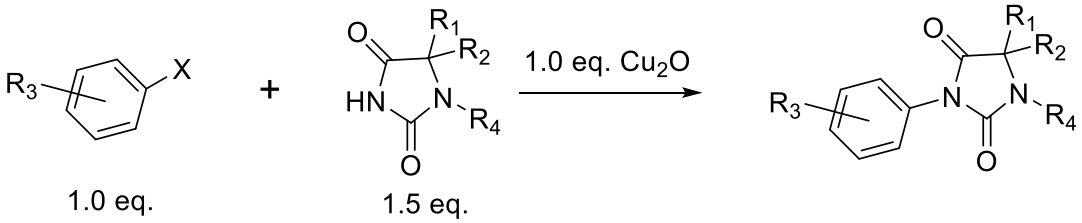
Hydantoins have traditionally been made using cyclization reactions of precursor compounds already containing the desired substituents(scheme 3). Some historical examples are the Urech hydantoin synthesis,[5] Read,[6] and the Bucherer-Bergs synthesis.[7]. A newer approach for creating a wide variety of hydantoins using automated systems with the ugi reaction have also been developed.[8] This does not come without its limitations, as the cyclization reaction often requires harsh conditions, such as the presence of strong base or acid, with potassium hydroxide or hydrochloric acid being some of the reagents utilized.[8] The limited substituents would thus contain base or acid labile functional groups, e.g. nitriles, esters, and amides. Another undesirable aspect of these cyclization reactions is the usage of possibly hazardous chemicals such as potassium cyanide in the Bucherer-Bergs reaction (scheme 1).[7] As a consequence of these limits, finding other ways to synthesize hydantoins using milder reagents would be of great interest to the scientific community.



Scheme 1: The Bucherer-Bergs synthesis of hydantons.

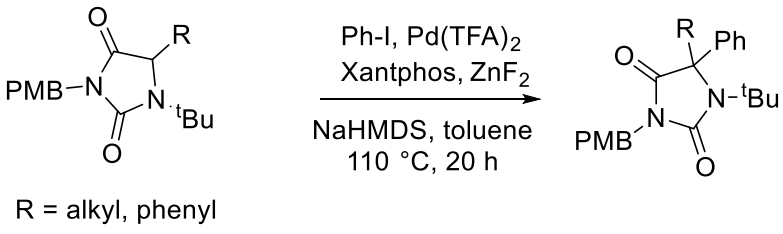
Direct arylation of the hydantoin skeleton

Relatively recently, work on directly arylating hydantoins at N-1, N-3, and both C-5 positions has been done. Scheme 2 shows a copper mediated arylation of the N-3 position with substituents present at the N-1 and C-5 positions.[1] The method utilizes stoichiometric amounts of copper (I) oxide without the addition of base or ligands. The reaction lacks selectivity for N-3 arylation when N-1 or C-5 is unsubstituted, which limits the variety of N-3 hydantoins that can be made using this method.



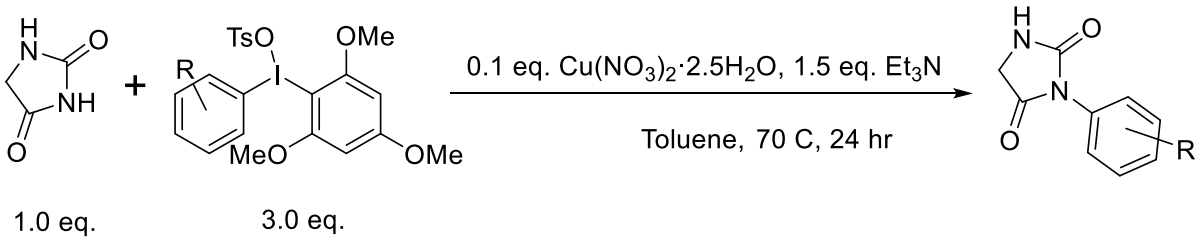
Scheme 2: Copper mediated N-3 arylation of hydantoin.

Palladium catalyzed C-5 arylation of the hydantoin skeleton has been reported in literature Scheme 4).[9] The reported yields of the reaction lies between 50 % and 92 % yield for the phenylation, but arylation using different aryl iodides has also been successful. As this reaction does not lead to N-arylation, it is worth to note how this reaction differs from the other arylation reactions. The usage of protecting groups hints at possible N-arylation without the presence of the protecting groups.



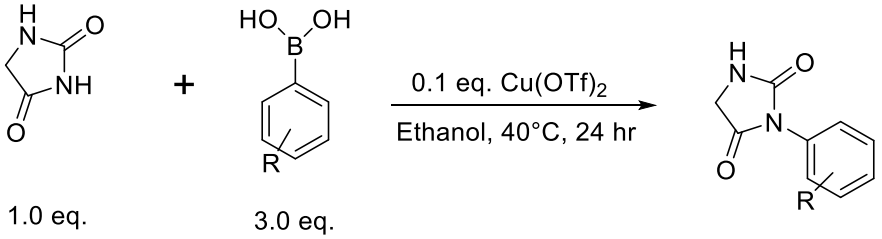
scheme 3: Palladium catalyzed C-5 arylation of N-1, N-3 protected hydantoin.

The Sandtorv group has developed some variations of copper catalyzed arylation of hydantoin.[2] The main target has been the N-3 arylation of hydantoin, as well as arylation of both N-H positions in one pot. The N-3 arylation reaction on hydantoin developed in the group (scheme 4) differs substantially from the reaction shown in scheme 2. Firstly, it is copper catalyzed with the use of base/ligand. Secondly, it utilizes reactive asymmetric diaryliodonium salts that enables the reaction to proceed where aryl halides fail. It has a wide scope, albeit with varying yields.



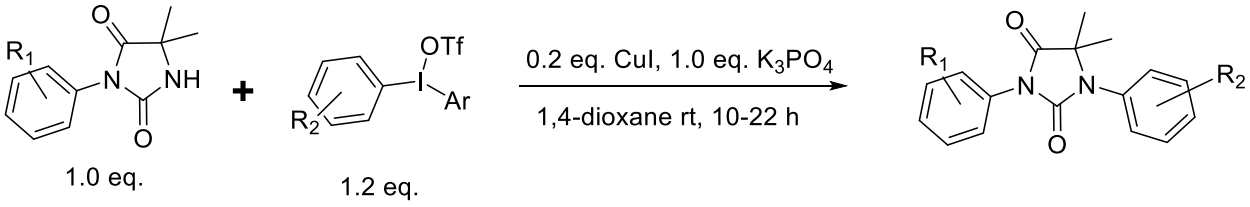
Scheme 4: N-3 arylation of hydantoin developed in the Sandtorv group.[2]

Another Copper catalyzed N-3 arylation reaction developed in the Sandtorv group using arylboronic acid has also been developed (scheme 5).[10] This reaction, inspired by the Chan-Lan coupling, uses copper(II) triflate in catalytic amounts combined with arylboronic acid to efficiently N-3 arylate hydantoin. The lack of added base or ligand is a notable feature, when compared to diaryliodonium salt-based reaction in scheme 4.



scheme 5: N-3 arylation of hydantoin using arylboronic acid

As recently as 2021, N-1 arylation of substituted hydantoins have been reported.[11] As shown in scheme 6, the reaction is copper catalyzed, uses diaryliodonium salts, and base. The overall reaction yields are useful given the scope, and may be a good starting point for exploring the N-1 arylation of unsubstituted hydantoins. The reaction however has zero examples of N-1 arylation on hydantoins without N-3 substitutes.



Scheme 6: N-1 arylation on N-3, C-5, substituted hydantoins.

The goal: N-1 arylation of unsubstituted hydantoin

The goal of this master's thesis was to develop a synthesis route that could lead to N-1 aryl hydantoins both with and without substitutions at the N-3 and C-5 position of hydantoin. Starting with unsubstituted hydantoin, three routes were proposed (figure 1).

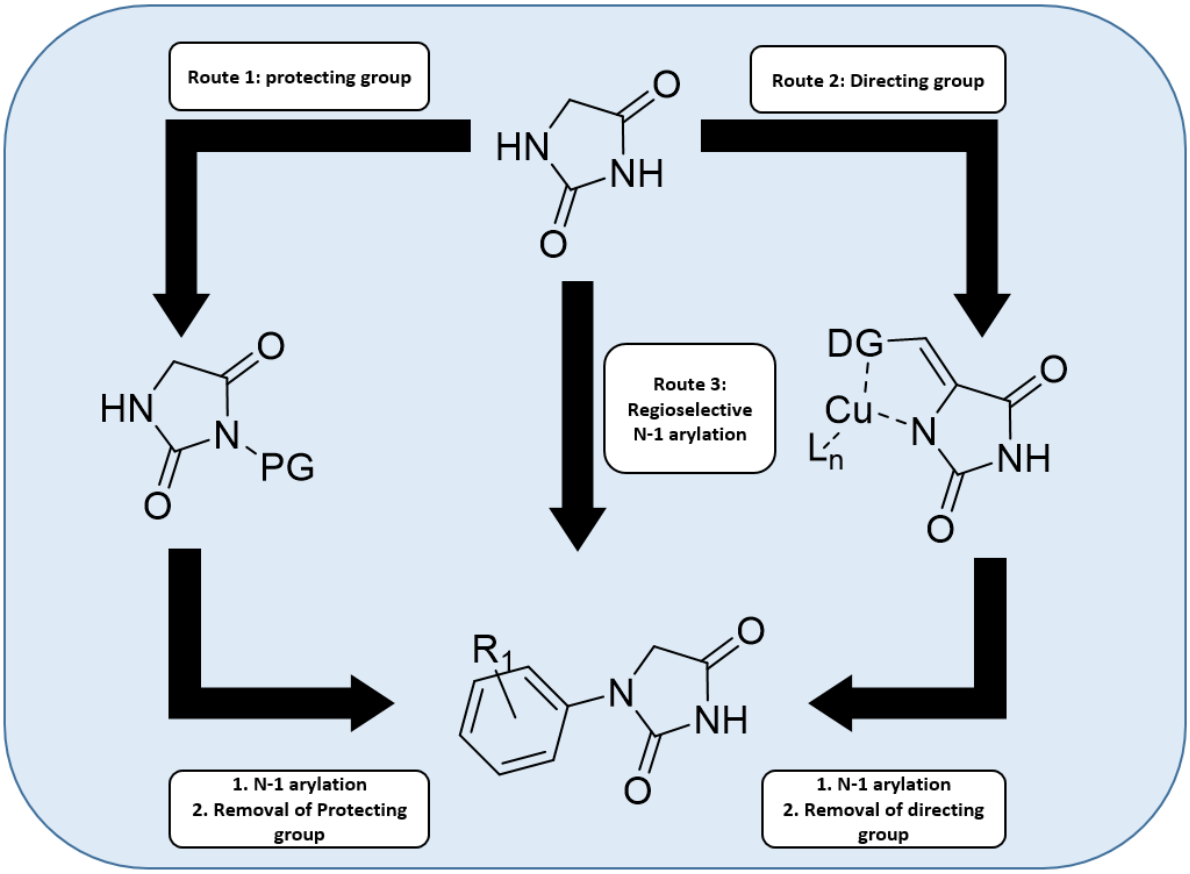


Figure 1: The three proposed routes for synthesizing unsubstituted N-1 arylhydantoins. PG = protecting group. DG = directing group.

The first route, using a protecting group, considers the inherent reactivity of the N-3 position when attempting substitution reactions. As shown above from known arylation reactions, most reaction conditions lead to N-3 arylation, thus interfering with any chance at synthesizing unsubstituted N-1 arylhydantoins. Route 1 therefore uses protecting groups to prevent selectivity issues that may arise when attempting to N-1 arylate.

Selecting a proper protecting group is essential in order for route 1 to work. It is important to choose a protecting group that is stabile under the conditions required to N-1 arylate. As shown in the schemes of the arylation reactions, basic conditions is required during most

arylation reactions. The reliance on base thus limits the choice of protecting groups to base compatible protecting groups. Another consideration is the ease of removal when using a protecting group. If the deprotection requires harsh conditions, you might end up limiting the scope of possible N-1 arylhydantoins synthesizable by this method. Some reported N-3 protected hydantoins used in hydantoin synthesis utilize the tert-butyloxycarbonyl (Boc) and benzyl (Bn) groups.[12] The base lability, choice of solvent, and temperature would therefore be important to test if one decides to use these protecting groups for N-1 arylation.

The second route uses a removable directing group coupled to the C-5 position of the hydantoin skeleton. By using an appropriate directing group, one could change the reactivity of the N-1 position to the point that preferential N-1 arylation occurs. This change in selectivity should originate from the gain in stability caused by the donor group acting as a ligand when bound as a complex with the catalytic copper ion. As shown in figure 3, if the N-1 arylation reaction were to occur via a copper catalyzed cross-coupling mechanism, one would expect the directing group to act as a stabilizing ligand through a free electron pair.[2]

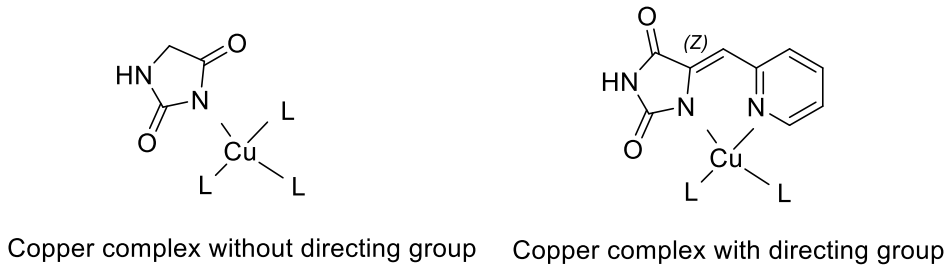


Figure 3: Theoretical copper complexes that illustrates the bidentate ligand effect of the directing group, which in this case is a pyridine ring.

The third route explores the possibility of a regioselective N-1 arylation on unsubstituted hydanton. As previously shown in the reaction shown in scheme 2, selectivity for the N-1 position comes with challenges due to the higher reactivity of the N-3 position. Any method that leads to N-1 arylation would require changing the inherent reactivity of hydantoin. One way to accomplish such a change in selectivity to the N-1 position would be to introduce a chemical that would favor N-1 arylation via steric hindrance or ligand stabilization.

Goals for each route

With these three routes in mind, a summary of the possible goals we wish to achieve for each route based on the above discussion would be in order:

Route 1: protecting group

- Synthesize N-3 protected hydantoins
- Make sure that the N-3 protected hydantoins are stabile under the experimental conditions for N-1 arylation.
- Develop an N-1 selective metal catalyzed arylation reaction that uses the N-3 protected hydantoin as substrate.
- Find an efficient method of removing the protecting group without affecting the functional groups present on the protected arylated hydantoin.
- Explore the N-1 arylation's scope of aryl groups and hydantoins with different C-5 substituents.
- Develop a one pot N-1 arylation reaction.

Route 2: directing group

- Synthesis 5-arylidenehydantoins with directing groups that could lead to N-1 arylation
- Find compatible 5-arylidenehydantoins for metal catalyzed cross-couplings that will not create too stabile complexes.
- Develop an N-1 selective metal catalyzed arylation reaction that uses the 5-arylidenehydantoin as substrate.
- Find an efficient method of removing the directing group without affecting the functional groups present on the arylated 5-arylidenehydantoin.
- Explore the N-1 arylation's scope of aryl groups and hydantoins with different C-5 substituents.
- Develop a one pot N-1 arylation reaction.

Route 3: Direct regioselective N-1 arylation

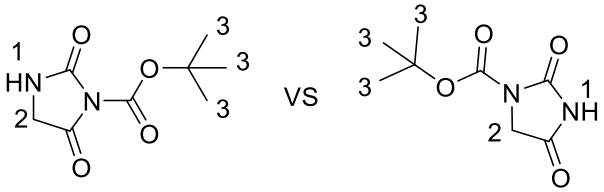
- Find N-arylation reactions that possess some selectivity for the N-1 position.
- Achieve regioselectivity for the N-1 arylation on N-3, C-5 unsubstituted hydantoin.

2 Results and discussions

2.1 Attempt at protection of the N-3 position on hydantoin using a protecting group

The following work under 2.1 based itself on the belief that molecule **2A** was N-3 Bochydantoin and not N-1 Bochydantoin. The Boc protecting group study based itself on a published article released in 2012 that claims to synthesize N-3 Bochydantoin.[12] Another article found after the Boc protecting group study published in 2020 attempted the same reaction and reported, after slight modification of the method, that N-1 Bochydantoin and not N-3 Bochydantoin was the main product of the synthesis.[13] A comparison of spectral data between each study reveals that the reported N-1 Bochydantoin's spectral data matches the mono Boc protected hydantoin made during the master's thesis, as well as the article published in 2012 (table 1).

Table 1: Spectral data comparing the mono Boc protected hydantoin synthesized in this thesis to reported values.



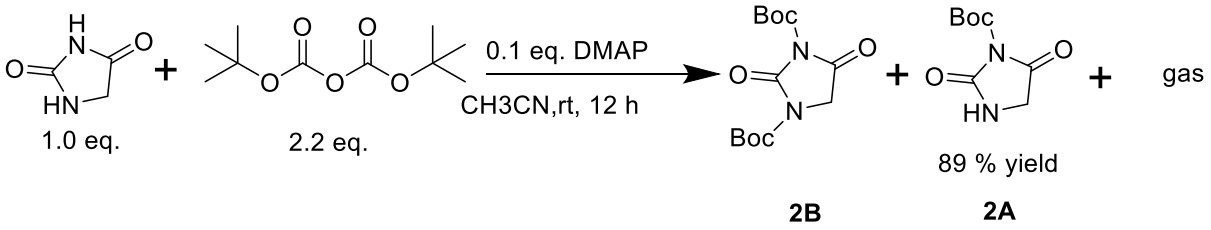
N-3 Bochydantoin N-1 Bochydantoin

Source of ^{1}H-NMR data solvent: CDCl3	N-H (ppm) (1)	C-5 (ppm) (2)	Boc t-butyl (ppm) (3)
This thesis (2021): (400 mHz)	8.46	4.26	1.54
N-3 Bochydantoin (2012): (500 mHz)[12]	8.93	4.24	1.52
N-1 Bochydantoin (2020): (500 mHz)[13]	9.00	4.24	1.52

The Boc group

One of the most common protecting group utilized today for N-H groups is the tert-Butyloxycarbonyl group, also known as the Boc group. The Boc group is stabile towards most bases and can handle relatively high temperatures.[14] Therefore, it is applicable for many different metal catalyzed coupling reactions that work with the addition of base.[14]

Previous work on protecting hydantoin using the Boc group has been published.[12] As shown in the reaction scheme below (scheme 3), the Boc anhydride has the possibility to react at both the N-1 and N-3 position on hydantoin. This leads to regioelectivity issues when trying to protect the N-3 position while leaving the N-1 position bare. Luckily, the N-H of the N-3 position is more acidic than the N-1 position, which could lead to selective product formation given the right conditions.



Scheme 7: The method used from published work involving hydantoin and the Boc group.

In figure 3, we find the proposed reaction mechanism for the N-3 Boc protection of hydantoin. The reaction is catalyzed by 4-dimethylaminopyridine, also known as DMAP. As shown in step a, the first step is the formation of the 1-acylpyridinium ion. This is a key step, as the 1-acylpyridinum ion formed tends to be more reactive than the anhydride. In step b, DMAP should favor the deprotonation of the N-3 position over the N-1 position due to the N-3 position being more acidic.[4] The deprotonated Hydantoin then reacts with the 1-acylpyridinum ion and forms N-3 Bochydantoin (**2A**) (step c). During the reaction, tert-butyl carbonate left over from the 1-acylpyridinium formation is unstable and decomposes into carbon dioxide gas and tert-butoxide (step d). The tert-butoxide then deprotonates the protonated DMAP, which completes the catalytic cycle (step e). The tert-butoxide could in theory deprotonate hydantoin as well as DMAP, but DMAP was chosen in this proposed reaction mechanism, as it is present from the beginning of the reaction.

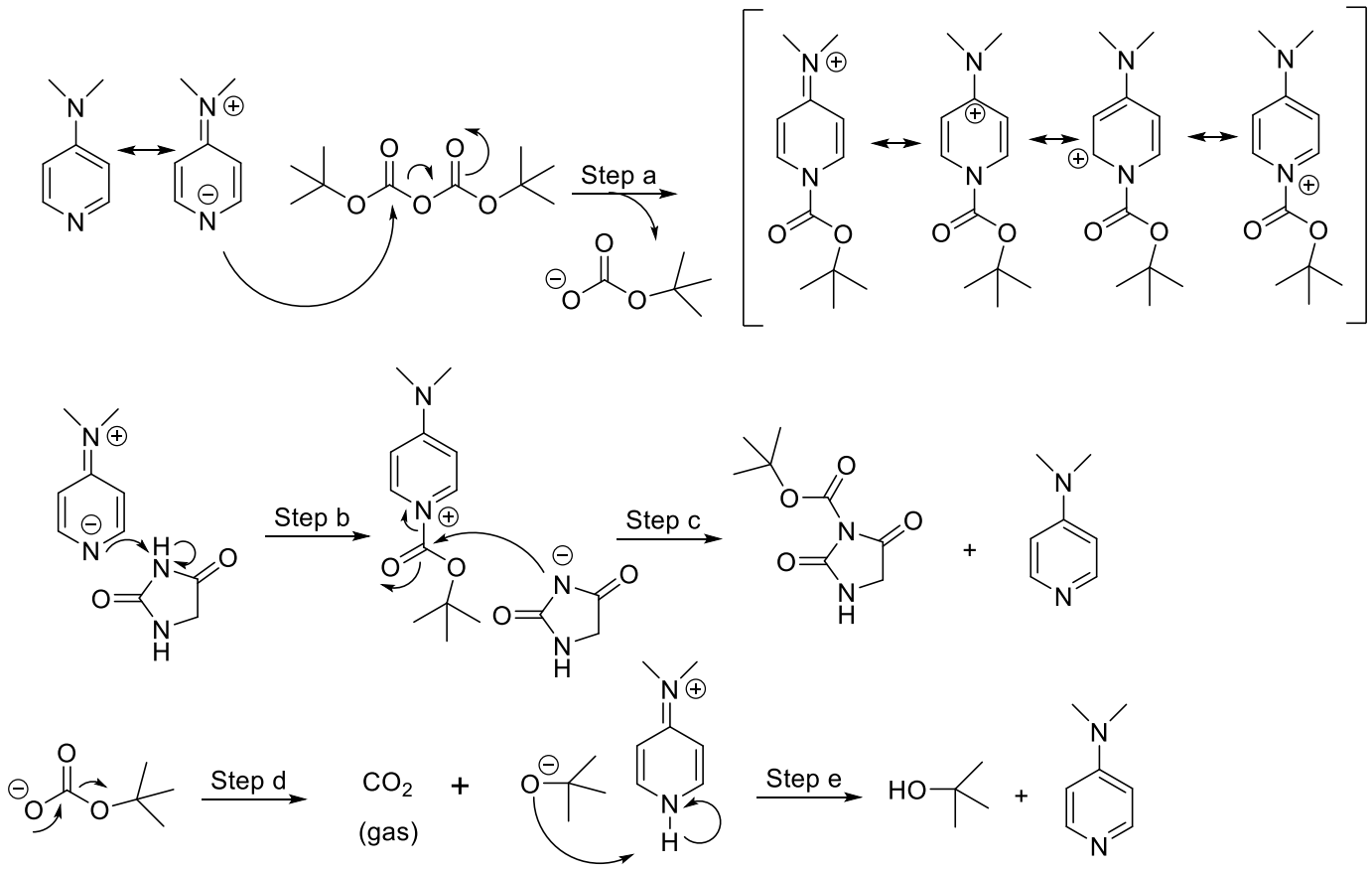
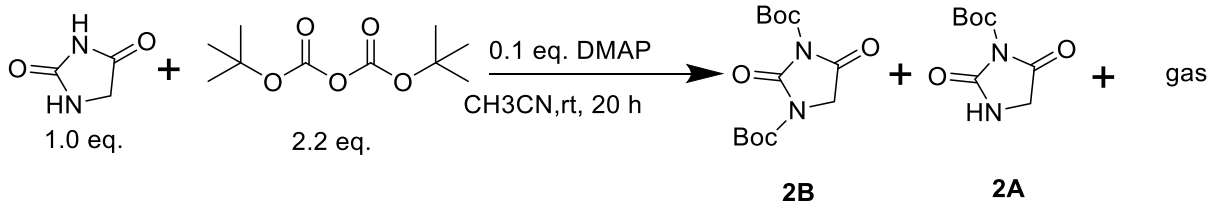


Figure 2: the proposed reaction mechanism for the Boc protection of hydantoin. Step a: formation of the reactive 1-acyl pyridinium ion from Boc anhydride and DMAP. Step b:deprotonation of hydantoin by. Step d: decomposition of tert-butyl carbonate into carbon dioxide and tert butoxide.

The first method of Boc protection attempted, shown in the reaction scheme below (scheme 3), was based on the previously reported N-3 protection of hydantoin using Boc anhydride (scheme 7).[12] The reaction yield of N-3 Bochydantoin based on crude ^{1}H-NMR (**2A**) ended up being 0 %, a stark difference from the 89 % reported from literature. Upon isolating the other products found in the mixture, N-1 N-3 diBochydantoin (**2B**) was discovered to be the main product. This unexpected result initiated a series of experiments for reaction conditions that would lead to N-3 Bochydantoin.



scheme 8: the reaction condition

As the reaction conditions between the literature method and the attempted method (table 2, entry 1) differed slightly, 12 hours vs 20 hours, another experiment was deemed necessary. The new experiment (table 2, entry 2) was monitored using thin-layer chromatography (TLC), and with the newly isolated **2B**, one would be able to spot the formation of the double protected product and differentiate it from the other chemical species present in the mixture.

Table 2: Reaction conditions attempted in order to make N-3 Bochydantoin (2A)

Entry	Hydantoin (eq.)	Boc_2O (eq.)	DMAP (eq.)	Temp. (℃)	Reaction time (h)	2B yield (%)	2A Yield (%)
1	1.0	2.2	0.1	25	20	48 %[a]	0 %[a]
2	1.0	2.2	0.1	25	2.5	99 %[b]	0 %[b]
3	1.1	1.0	0.1	25	72	99 %[b]	0 %[b]
4	1.2	1.0	0.1	25[c]	5.0	49 %[a]	7 %[a]
5	1.2	1.0	0.05	≈ -10[b]	24	Not isolated	14 %[a]
6	1.2	1.0	0.1	≈ -10[b]	24	Not isolated	33 %[a]
7	1.0	2.2	0.0	25	20	0 %[e]	0 %[e]

[a] Isolated yield.
[b] Estimated yield base on TLC.
[c] Ice/salt bath left to warm up to room temperature during the reaction.
[d] The mixture of hydanton in MeCN was warmed to 50 °C before cooling to 25 °C.
[e] Yield based on ^{1}H-NMR analysis.

The result of the monitoring was surprising. Only **2B** was forming from the first minute of the TLC monitoring. The reaction was monitored for an additional 30 minutes, and it was found that the reaction went to completion rather within these 30 minutes, and that no side products was present when checked with TLC after 2.5 hours. The conclusion of this experiment (table 2, entry 2) was that the excess Boc anhydride was the cause of only **2B** forming.

The next experiment (table 2, entry 3) reasoned that reducing the equivalents of Boc anhydride to 1.0 equivalent would favor the formation of the mono Boc protected hydantoin. Even with the reduced amount of Boc anhydride, the reaction ended up only forming **2B**. A notable observation was made during this experiment however. The amount of hydantoin actually dissolved in the acetonitrile was observed to be particularly low. Thus, the Boc anhydride would actually be in excess during this reaction, and any mono Boc protected hydantoin would quickly react with the excess Boc anhydride.

The next experiment (table 2, entry 4) was an attempt to increase the relative concentration of hydantoin during the reaction. The first difference was that 1.2 equivalents of hydantoin was used, from 1.1 equivalents. The hydantoin was finely ground using a pestle and mortar in order to help with the solubility, and the hydantoin was allowed to stir in acetonitrile at 50 °C before cooling down to 25 °C. The Boc anhydride was then added dropwise while also being dissolved in acetonitrile to lower the concentration. The experimental conditions paid off, and what was presumed to be N-3 Bochydantoin, based on a ^{1}H-NMR comparison with reported spectral values, was isolated in 7 % yield.[12] The 7 % yield was however a far cry from the reported 89 %. Additional experiments where therefore done to obtain synthetically useful quantities.

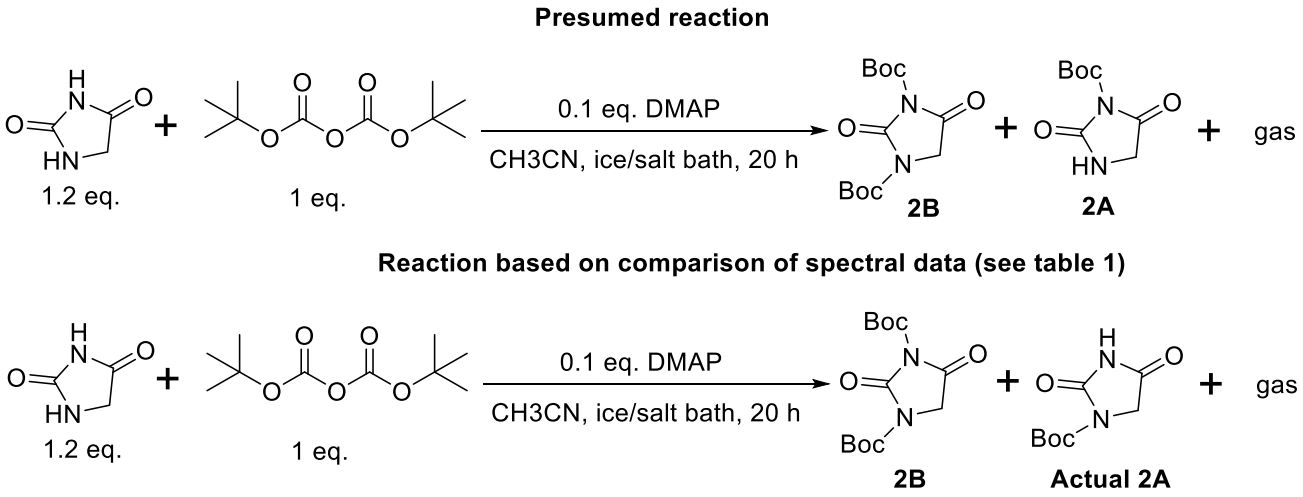
As the acylating species based on the proposed reaction mechanism requires DMAP, the next experiment used half the amount of DMAP normally used (table 2, entry 5). The reasoning behind this is that a lower amount of DMAP available would decrease the reaction rate. This would cause the reaction to favor the N-3 position, as it is more acidic and therefore more reactive at the deprotonation step. The lowering of the reaction temperature using an ice/salt bath also based itself on decreasing the reaction rate. This reaction used the finely powdered hydantoin, as well as adding the Boc anhydride dissolved in acetonitrile dropwise. The resulting yield of the presumed N-3 Bochydantoin ended up being 14 %, which was a welcome increase in yield.

Another experiment was also done where the normal 0.1 equivalent of DMAP was used with an ice/salt bath (table 2, entry 6). The reaction used finely powdered hydantoin and the Boc anhydride was added dropwise this time too. The reaction yield of presumed N-3 Bochydantoin ended up being 33 %. This increase in yield was unexpected given the assumed theory that the deprotonation on the N-1 position would increase with a larger amount of DMAP. One theory for why the yield increased at the time of doing the experiment was that

an increase in DMAP would decrease the total reaction time. By decreasing the reaction time while still having conditions presumed to favor the N-3 position, one might expect that the side reaction of forming the double protected **2B** to be reduced.

An experiment to make sure that DMAP was necessary for the protection to proceed on hydantoin was also done (table 2, entry 7). The crude was assessed using ^{1}H-NMR and no product peaks were found. This result meant that DMAP was necessary for the reaction to proceed at any reasonable rate.

As time was of the essence, the work on increasing the yield for N-3 Bochydantoin was put on hold, and the result of this series of experiments was the reaction shown below (scheme 9). As previously discussed in the beginning, spectral data (table 1) shows that N-1 Bochydantoin is more likely to be the mono protected product.

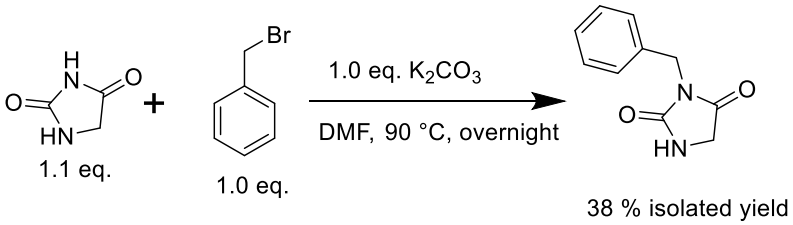


Scheme 9: Method for protecting the N-H positions on hydantoin.

The Benzyl group

An alternative for the Boc group, is the particularly stabile benzyl group (often abbreviated as Bn). The synthesis of N-3 benzylhydantoin (**2C**) has been reported in literature.[15] The obvious advantages to this protecting group is the ease of application combined with being compatible with many functional groups. Removal of the benzyl group is however not always successful due to the relatively high stability, which might explain why other protecting groups are more common.

The benzyl protection of hydantoin (scheme 10) is assumed to proceed via a S_N2 reaction not unlike the Williamson ether synthesis. The isolated yield of 38 % was somewhat lower than the reported 65 %.[12] The difference in yield could be caused by many factors, but the most apparent factor is the smaller quantity of benzyl bromide used per equivalent of hydantoin.

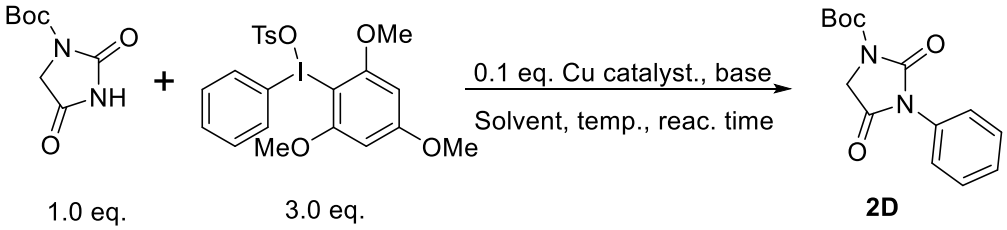


Scheme 10: Benzyl protection of hydantoin´s N-3 position.

2.2 Attempt at N-arylation of protected hydantoins

N-arylation of N-1 Bochydantoin (2A)

In the Sandtorv group, two methods for arylation of hydantoin has led to a substantial amount of N-3 arylated product (scheme 4 and 5). The first method (scheme 4) is the arylation of hydantoin using diaryliodonium salts with Copper (II) salts and Triethylamine. The diaryliodonium salt method showed N-1, N-3 arylated hydantoin as a byproduct, which meant that it was able to N-1 arylate hydantoins to a certain degree. This led to the decision to test versions of this reaction for the N-arylation of Boc protected hydantoin first (scheme 11). Using the method in scheme 4 as a basis, different combinations of catalyst, solvent, and base was tested (table 2). It was also decided that the benzyl protected hydantoin **2C** would be tested on the same reactions that successfully arylated **2A**.



Scheme 11: general scheme for the N-arylation of N-1 Bochydantoin.

*Table 3: reaction conditions based on scheme 11 for the N-arylation of **2A**.*

Entry	catalyst	Arylating agent	solvent	Base/ligand	Temp.℃	Yield[a]
1	$Cu(OTf)_2$	Ph(TMP)IOTs	Toluene	TEA	70	≈ 0
2	CuI	Ph(TMP)IOTs	Toluene	TEA	70	≈ 0
3	$Cu(NO_3)_2 \cdot 2.5H2O$	Ph(TMP)IOTs	Toluene	TEA	70	≈ 0
4	CuI	Ph(TMP)IOTs	1,4 dioxane	K_3PO_4	Room temp.	≈ 0

[a] Yields obtained utilizing crude ^{1}H-NMR analysis.

The reactions were checked with crude ^{1}H-NMR peaks corresponding to an arylated protected hydantoin. No arylated Boc protected hydantoins was found, however an observation was made. The first observation made was that the Boc group peak was missing for the reaction in entry 1 in table 3. Considering that the Boc group was supposed to not be affected by the given conditions, a small stability study was done (table 4).

*Table 4: Stability study of **2A** and **2C** under the N-arylation conditions given in scheme 4 and 5.*

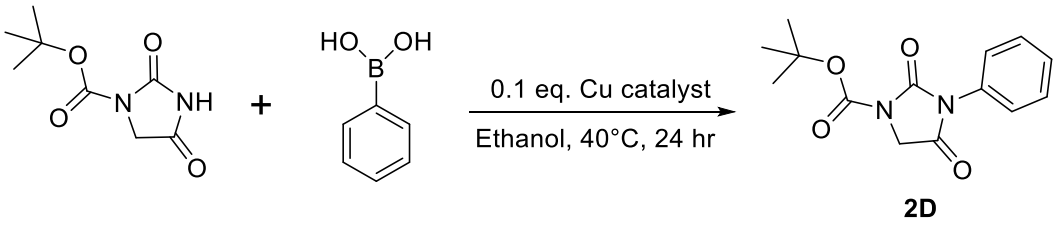
Entry	catalyst	Protected hyd.	solvent	Temp.℃	Result[a]
1	$Cu(OTf)_2$	2A	Toluene	70	Not Stabile
2	$Cu(OTf)_2$	2C	Toluene	70	Stabile
3	$Cu(OTf)_2$	2A	Ethanol	40	Not stabile
4	$Cu(OTf)_2$	2C	Ethanol	40	stabile
5	No cat.	2A	Ethanol	40	stabile

[a] Stability checked by looking for decomposition of Boc group via ^{1}H-NMR.

The result of the stability study pin pointed that copper(II) triflate could be the culprit. A quick literature check confirmed copper(II) triflate's ability to remove Boc groups catalytically.[16] The article reported deprotection of Boc protected amides using only 0.05 equivalents of catalyst in room temperature.

Further attempts on N-arylation of 2A was conducted using a general method based on scheme 4, (scheme 12). The reaction in scheme 4 differs from the reaction in scheme 5 by the

fact that the arylating reagent is an arylboronic acid, in addition to choice of solvent, lack of base, and lower reaction temperature.



Scheme 12: General scheme for N-arylation using arylboronic acid as arylating reagent.

Entry 1-3 in table 5 explored if the N-arylation would take place with any of the Copper catalysts previously used in table 3.

Table 5: reaction conditions used based on scheme 12.

Entry	catalyst	Arylating agent (eq.)	Base/ligand (eq.)	Temp. (℃)	Yield[a] (%)
1	$Cu(OTf)_2$	1.0 eq. PhB(OH)2	Nothing	40	0
2	CuI	1.0 eq. PhB(OH)2	nothing	40	0
3	$Cu(NO_3)2 \cdot 2.5H2O$	1.0 eq. PhB(OH)2	Nothing	40	0
4	CuI	1.0 eq. PhB(OH)2	1.0 eq. Pyridine	40	40[b]
5	Cu(NO3)2 · 2.5H2O	1.0 eq. PhB(OH)2	1.0 eq. Pyridine	40	43[b]
6	Cu(NO3)2 · 2.5H2O	3 eq. PhB(OH)2	3 eq. pyridine	40	69[b]

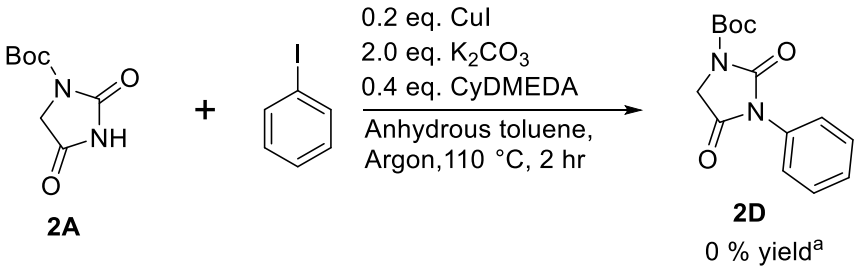
[a] Yields obtained via crude ^{1}H-NMR analysis.

[b] Isolated yield.

Experiments done previously in the group had shown that some N-arylation reactions required the addition of pyridine in order to proceed. Thus, the same general reaction conditions, but

with the addition of pyridine, was used for N-arylation. Successful N-arylation of **2A** was observed after adding pyridine, and N-arylated Boc protected hydantoin was isolated. Both copper(I) iodide (table 5, entry 4) and Copper nitrate(II) hemipentahydrate (table 5, entry 5) successfully catalyzed the N-arylation reaction with similar yields, that is 40 % for copper(I) iodide and 43 % for Copper nitrate(II) hemipentahydrate. An attempt at increasing the yield of the reaction was done by tripling the amount of arylating reagent and base/ligand (table 5, entry 6). The reasoning being that a higher excess of reagents would promote the N-arylation. An increase in in isolated yield from 43 % to 69 % was observed. The nonlinear increase in yield suggests that other parameters than amount of arylating reagent should be addressed if one would wish to further increase the yield.

A reaction reporting N-1 arylation from literature was also tested on **2A** with a shorter reaction time of 2 hours vs 64 hours (scheme 13).[1] The reaction gave no indications of product being formed after 2 hours on neither the TLC nor the crude ^{1}H-NMR spectrum.



Scheme 13: N-1 arylation of hydantoin using iodobenzene as arylating agent.
[a] Yields obtained via crude ^{1}H-NMR analysis

The crystal structure of **2D** was elucidated using x-ray crystallography, revealing an N-1 Boc protected N-3 arylated hydantoin (figure 4). The crystal structure was obtained after all N-arylation experiments were finished. The true nature of **2D** was an unexpected discovery

as all experiments were based on the presumed structure of **2A** being N-3 Bochydantoin.[12] As far as I am aware, **2D** not been reported in literature, although similar molecules may exist.

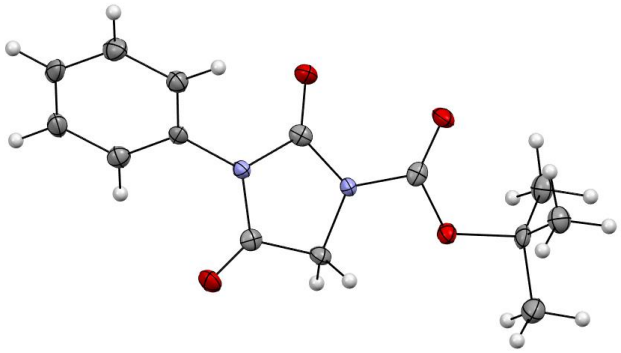
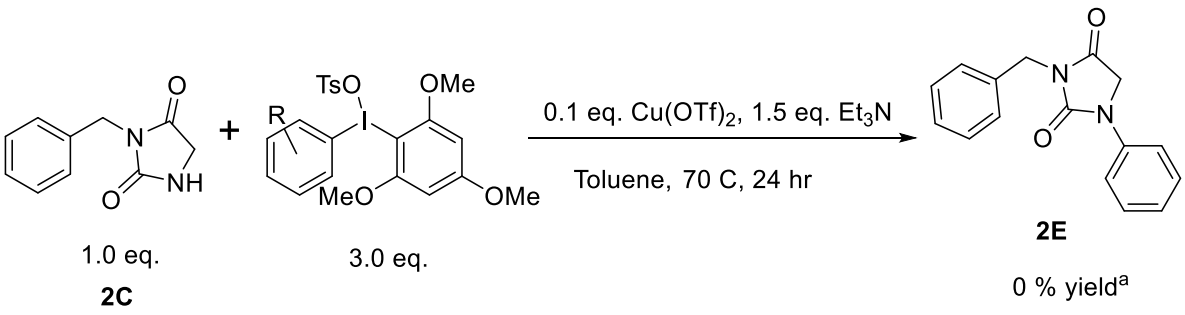


*Figure 4: Crystal structure of N-1, N-3 Bocphenylhydantoin (**2D**).*

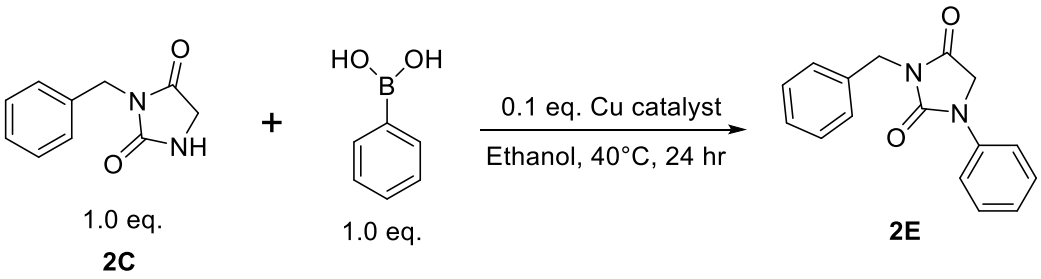
N-arylation of N-3 benzylhydantoin (2C)

The first reaction attempted for **2C** (scheme14) was based on the reaction in scheme 4, that is the reaction utilizing diaryliodonium salts as an arylating agent. The attempt was made with the belief that **2C** would be stable under these conditions. No N-1 arylated product was found however, which might not be as unexpected as the reaction conditions are optimized for N-3 arylation.



*Scheme 14: attempted N-1 arylation of N-3 benzylhydantoin **2C**. [a] = Yields obtained via crude [1]H-NMR analysis.*

As shown in table 6, three more experiments on N-1 arylation of **2C** was attempted using a general arylboronic acid method (scheme 15).



*Scheme 15: General method used for N-1 arylation of **2C** using an arylboronic acid as arylating reagent.*

*Table 6: Reaction conditions used in scheme 15 for the N-1 arylation of **2C**.*

Entry	catalyst	Arylating agent	Base/ligand (eq.)	Temp. (℃)	Yield[a] (%)
1	$Cu(OTf)_2$	PhB(OH)2	nothing	40	0
2	CuI	PhB(OH)2	pyridine	40	18
3	Cu(NO3)2 · 2.5H2O	PhB(OH)2	pyridine	40	28

[a] Isolated yield. yield of entry 1 obtained via crude [1]H-NMR analysis.

From the stability study, we know that **2C** is stabile under the reaction conditions attempted in entry 1, found in table 6. Thus, when we compare the results between the entries in table 6, we may assume that another experiment where the combination of $Cu(OTf)_2$ and pyridine might lead to product formation. The difference in yield between entry 2 and 3 comes from the incomplete column chromatography of entry. Additional replicates would be necessary to ascertain any certainty of possible yield from these reactions.

The successful synthesis of **2E** begs the same question as for **2D**: which isomer of **2E** have we obtained?

In figure 5, we find the two suggested synthesized isomers of **2E**. The difference in connectivity between the phenyl and benzyl group gives rise to a difference in the experienced chemical environment for each atom. Finding a unique correlation that can only exist in one isomer would be a strong indicator of which isomer that has been synthesized.

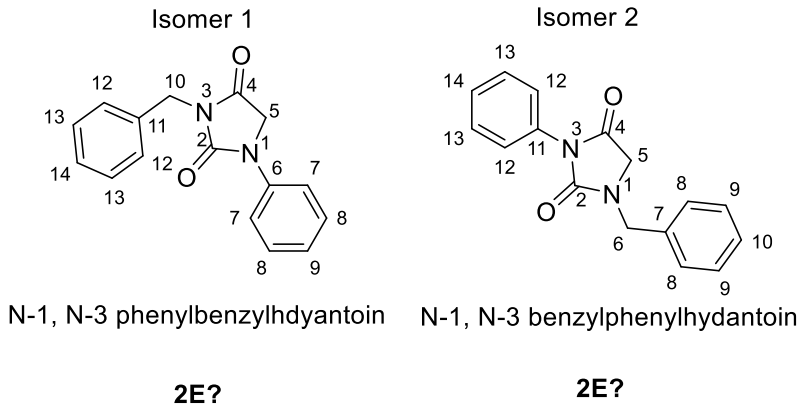


*Figure 5: the two suggested synthesized isomers of **2E**.*

From observing the two possible isomers, a correlation in a 1H-13C HMBC between the CH2 protons found in the benzyl group and both of the carbonyl groups would only be possible given that the identity of **2E** was isomer 1. This correlation is shown in figure 6, where we can see six clear correlations. In regular 1H-13C HMBC, correlations between atoms 2-3 bounds away are strongest, with correlations up to 4 bonds away sometimes being possible in aromatic systems. The correlations for H-10 and H-5 is found directly below their respective peaks in a straight line. If you were to draw a line horizontally from the correlation, you would find that it intersects with the corresponding 13C atom that gives rise to the correlation.

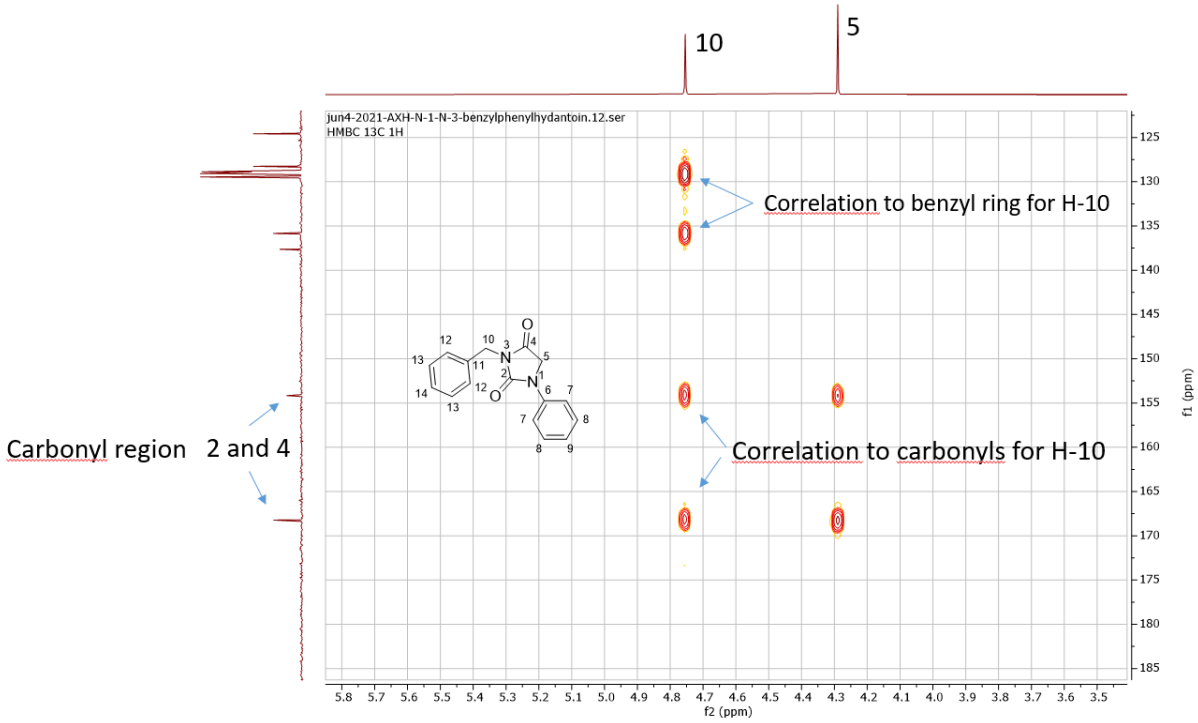


*Figure 6: 1H-13C HMBC of **2E**. The horizontal-axis shows the ^{1}H-NMR peaks, while the vertical-axis shows ^{13}C-NMR peaks.*

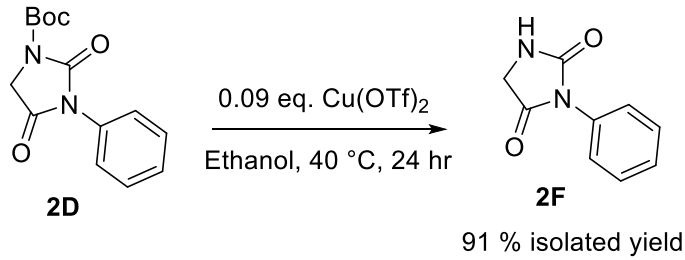
If we now were to predict the 1H-13C HMBC for isomer 2, would we find the same correlations shown in figure 6?

We begin with the correlations for H-5 in isomer 2. We see that the protons in the C-5 position is 3 bonds away from the carbonyl carbon found at the 2 position. We also see that the protons are only 2 bonds away from the carbonyl carbon found at the 4 position. These correlations are in accordance with figure 6. If we now check the correlations for H-6 we find that something else is the case. The protons from H-6 would be 3 bonds away from the carbonyl carbon found at position 2, which does not yet exclude isomer 2. We find however that the number of bonds between the protons at H-6 and the carbonyl carbon at position 4 is 4 bonds away from each other. As atoms 4 bonds away from each other does not lead to visible correlations in regular 1H-13C HMBC, we can presume that isomer 1 is true identity of **2E**.

2.3 Removal of the protecting group

The Boc group

One attempt at removing the Boc group from **2D** was done (scheme 16). The yield of **2F** was a gratifying 91 %. The catalytic removal of the Boc group using $Cu(OTf)_2$ is thought to happen via the slow release of triflic acid during the reaction.[16] The reaction is then driven to completion by the release of isobutylene gas. The successful deprotection of **2D** using $Cu(OTf)_2$ indicates that N-1, N-3 phenylBochydantoin could be deprotected via the same method because of the similarity to **2D**.



Scheme 16: the catalytic deprotection of a Boc protected arylhydantoin using $Cu(OTf)_2$ catalyst in relatively mild conditions.

Attempts at verifying the N-3 substitution of **2F** was done using ^{1}H-NMR (figure 7). Comparison of the chemical shifts between **2F** and N-3 phenylhydantoin revealed almost identical shift values. In addition, the chemical shift range of the remaining N-H proton in **2F** was found to lie closer to the N-1 amide like proton of hydantoin. With these comparisons in hand, one might say with large certainty that **2F** is N-3 phenylhydantoin.

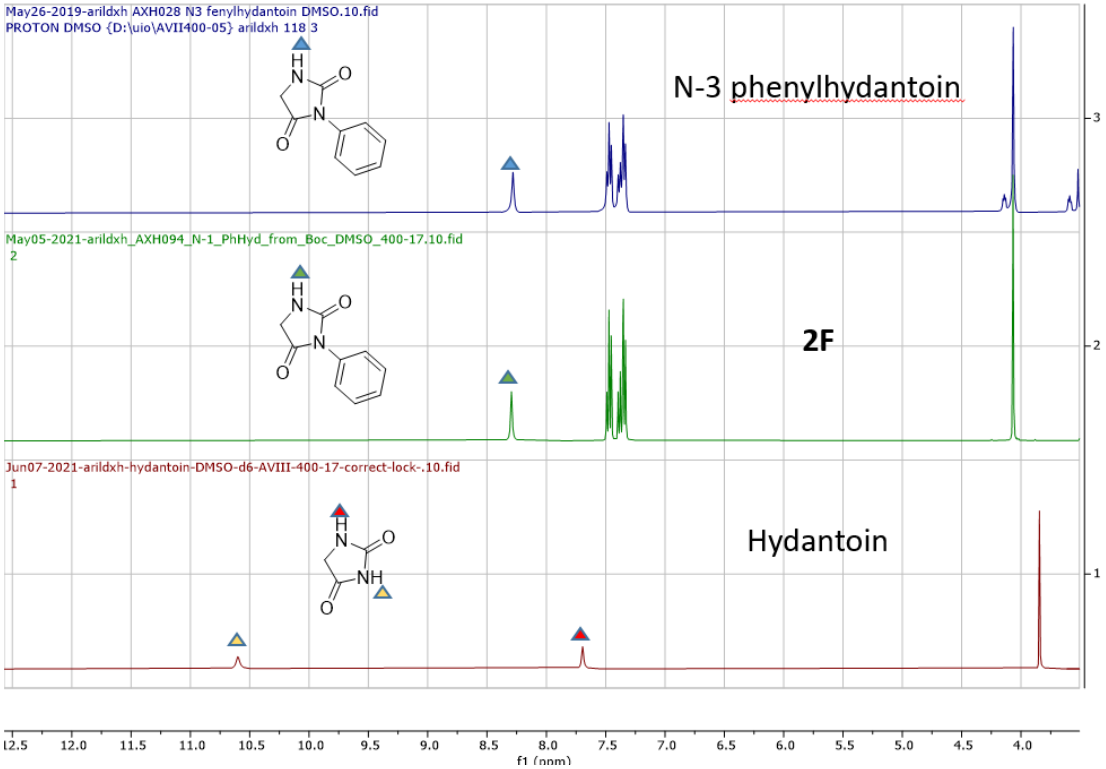
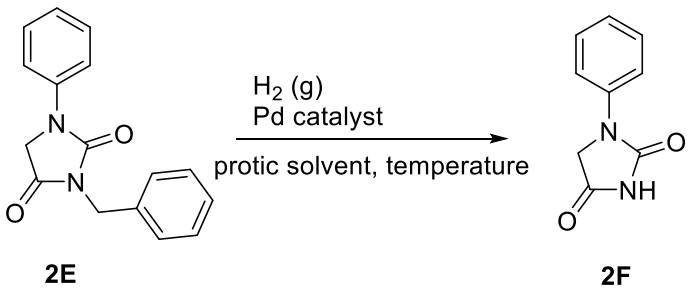


*Figure 7: The comparison of N-H protons between **2F,** Hydantoin, and N-3 phenylhydantoin.*

The benzyl group

One of the most commonly used methods for debenzylation is by reduction using a hydrogen gas/ palladium on carbon system (scheme 9).[17] This could afford a mild and selective method for the benzyl group, while leaving the desired aryl group as is.



Scheme 9: An general scheme for the debenzylation reaction.

As shown in in entry 1 (table 7), the first attempted reaction setup used rather mild conditions, which in theory should leave the phenyl moiety of **2E** unreduced, while hopefully reducing the benzyl group into toluene. With a result of 0 % yield, another attempt at debenzylation using a different catalyst was made. In entry 2, palladium hydroxide on carbon, also known as Pearlman`s catalyst, was used instead of palladium on carbon. Palladium hydroxide on carbon has been reported as a catalyst in benzyl deprotection where normal palladium on carbon proved insufficient.[17] The reaction yield using palladium hydroxide on carbon ended with the same 0 % yield as in entry 1. One last attempt (entry 3, table 7) was made using a combination of palladium on carbon and palladium hydroxide on carbon. Based on literature reports, the combination of both catalysts showed superior reactivity when compared to only using one catalyst. [17] The combination of both catalysts proved unsuccessful however, with 0 % yield. The results was not unexpected given the renown of the benzyl group for its stability, and other methods for removing the benzyl group could be tested.

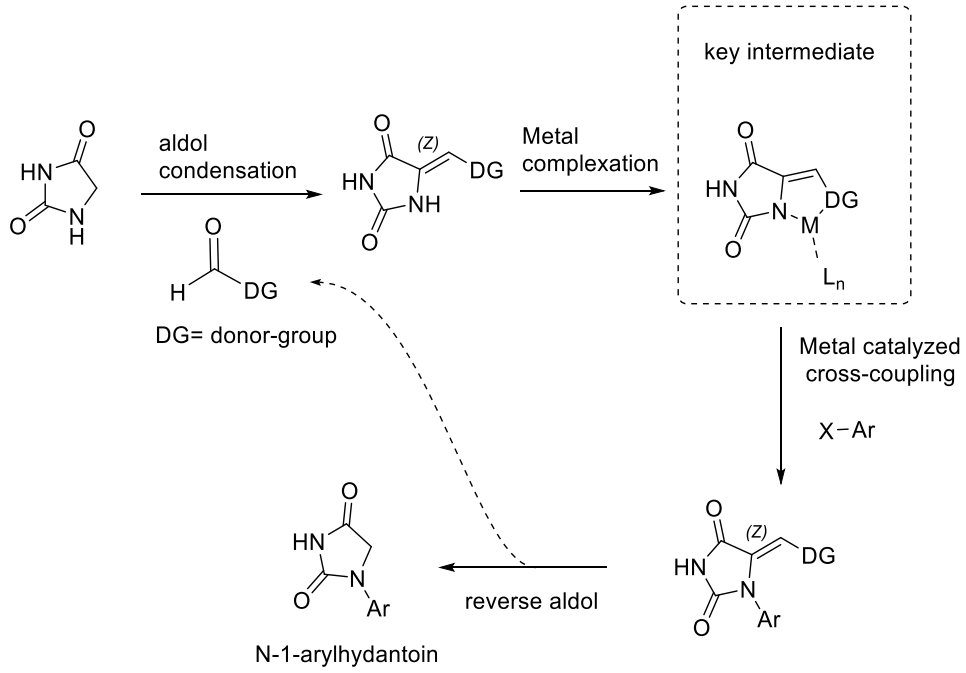
Table 7: Reaction variables tested for the removal of benzyl from N-1,N-3 phenylbenzylhydantoin.

Entry	Catalyst[a]	Solvent	Reducing agent[b]	Temp.℃	React. time	% yield[c]
1	Pd/C	Ethanol	H_2 (g)	rt	20 hr	**0**
2	$Pd(OH)_2/C$	Ethanol	H_2 (g)	40 ℃	20 hr	**0**
3	Pd/C + $Pd(OH)_2/C$	Methanol	H_2 (g)	rt	20 hr	**0**

[a] Entry 1 used 0,2 eq. of 5 % Pd/C 53,9 % water content. Entry 2 used 0.2 eq. 20 % $Pd(OH)_2/C$ 50% water content. Entry 3 used 0.1 eq. each of 5 % Pd/C 53,9 % water content and 20 % $Pd(OH)_2/C$ 50% water content.
[b] Hydrogen gas supplied using a hydrogen filled balloon.
[c] No product formation was observed via TLC.

2.4 Directing group assisted N-1 arylation using 5-alkylidenehydantoins

As discussed in the introduction, route 2 attempts to use a directing group in order to achieve the desired N-1 arylation regioselectivity. The theory is that the directing group would bond to the metal complex in a bidentate fashion, leading to higher stability of the metal complex where the N-1 position is posed for arylation. In addition, the stability of the complex would have to be not so high that it hinders product formation. The proposed reaction sequence for route 2 is drawn out in scheme 17.

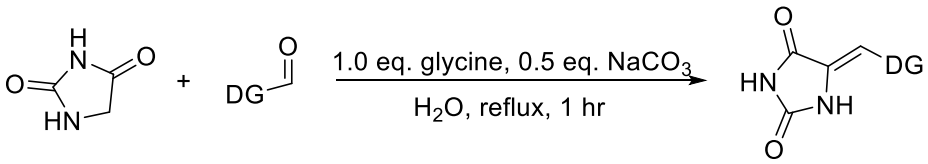


Scheme 17. The proposed reaction sequence for the formation of N1-arylhydantoin

The reaction sequence can be divided into four parts. The first step is the formation of the hydantoin with a directing group attached via an aldol condensation to the C-5 position. The next step would be the metal complexation of the 5-alkylidenehydantoin to a metal ion in such a way that N-1 arylation would be favored. The third step is the direct N-1 arylation of the hydantoin via metal catalysis, followed by the last step, which would be a reverse aldol reaction leading us to the final N-1 arylhydantoin.

In this work, experiments on the synthesis of hydantoins with plausible directing groups and metal complexes was done. The first step, the aldol condensation, was tested using different

methods, which were all based on previously reported methods.[18, 19] The general reaction successfully applied to synthesize each alkylidenehydantoin is shown in scheme 18.[19]



Scheme 18: Aldol condensation reaction conditions for the synthesis of 5-alkylidenehydantoins.

In figure 8, we find the 5-alkylidenehydantoins synthesized during this thesis. The 5-alkylidenehydantoins were synthesized based on their theoretical ability to make metal complexes. The ability to bind and create metal complexes is essential for the metal catalyzed cross-coupling step shown in scheme 17. Therefore, synthesizing different variants of the 5-alkylidenehydantoins will enable us to explore the required ligand strength necessary for the arylation to take place selectively at the N-1 position.

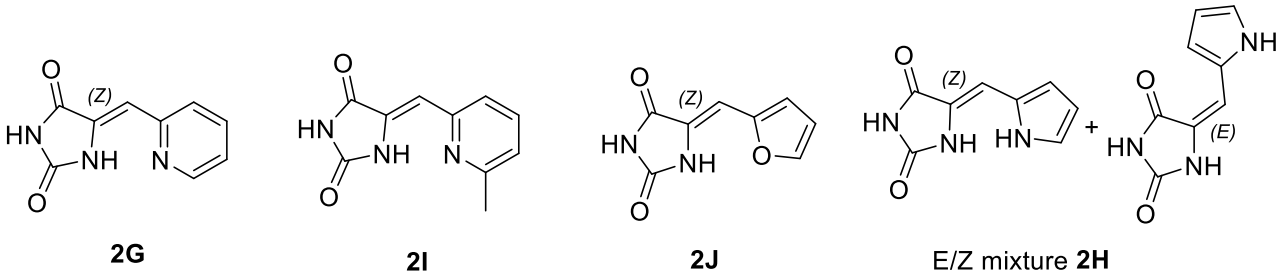
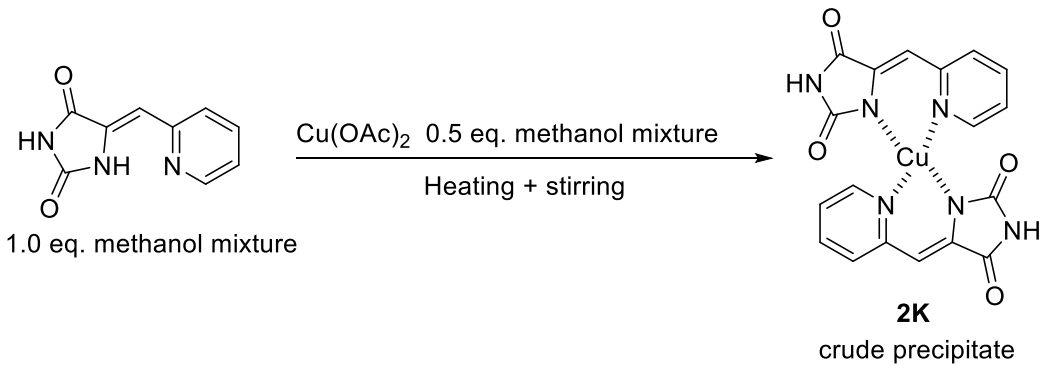
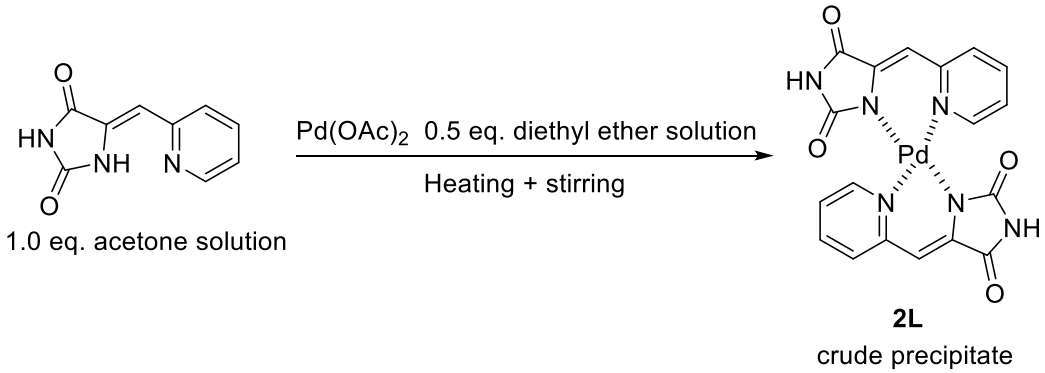


Figure 8: 5-alkylidenehydantoins synthesized with the method shown in scheme 18.

The first and only 5-alkyidenehydantoin tested for its ligand strength to different metals was PyHy (**2G**). The metal ions used were copper(II) and Palladium(II), two metal ions commonly used for N-arylation. The resulting complexes and the method of their formation is shown in scheme 19 and 20.



Scheme 19: The method used to form the PyHy Cu(II) complex



Scheme 20: The method used to form the PyHy Pd(II) complex.

An attempt at elucidating the presumed structures of metal complexes **2K** and **2L** using ^{1}H-NMR was unsuccessful. The paramagnetic nature of copper(II) and Palladium(II) was suspected to be the cause. Instead, HRMS analysis showed peaks that corresponded to the expected mass of each metal complex.

The first test necessary for the metal complexes **2K** and **2L**, was to find a suitable solvent for N-1 arylation. The first criteria was the solubility of each complex. In order to find a suitable solvent, most common laboratory solvents were tested. This included water, acetone, diethyl ether, hexane, ethyl acetate, dimethyl sulfoxide, N, N dimethyl formamide, toluene, and methanol. None of these solvents managed to fully dissolve the metal complexes. The only solvent found to slightly dissolve the metal complexes was found to be boiling acetic acid, which in the interest of N-arylation made **2G** seem like an unfavorable choice for further work. Work on making metal complexes with the other 5-alkylidenehydantoins would be a natural next step, but alas, the work had to be put on hold due to work constraints.

2.5 Conclusion and further work

Conclusion

The goal of this master's thesis was to explore two of three proposed routes for direct N-1 arylation of hydantoin. The first route, route 1, attempted to shift the selectivity of the arylation reaction to N-1 from N-3 by blocking the N-3 position with protecting groups.

The work done under route 1 has shown that protecting hydantoins on the N-3 position does not come without its challenges. The use of the Boc group led to a long search for the correct regioisomer of **2D** and **2A**, in which **2A** showed unexpected regioselectivity given previous reports of the structure.[12, 13] The application of the Benzyl group was considerably more straightforward, and led to **2C.** Attempts at N-1 arylation of **2C** has been successful, giving **2E**. The N-1 arylation did however giver meager yields when compared to the N-3 arylation shown in scheme 4. Attempts at removing the benzyl group from **2E** has so far been unsuccessful. The attempted removal of the relatively stabile benzyl group by using hydrogen gas and palladium on carbon reductive systems was not enough, hinting that more reductive conditions has to be tested.

The work done in route 2, that attempts to use directing groups to shift N-arylation selectivity to N-1, has led to the synthesis of 5-alkylidenehydantoins (figure 8) and two metal complexes(scheme 19 and 20). The synthesized 5-alkylidenehydantoins were synthesized with their ability to form metal complexes in mind, particularly to Copper(II). The metal complexes **2G** and **2L** were formed in order to test the corresponding 5-alkylidenehydantoins ligand strength, giving a rough pointer towards whether or not the 5-alkylidenehydantoin is suitable for metal catalyzed arylation. The resulting solubility problems led to the conclusion that **2G** most likely would be unsuitable due to lack of solubility when complexed with copper(II) and palladium(II).

Route 3, the direct regioselective N-1 arylation of N-3, C-5 unsubstituted hydantoin, was not attempted.

Further work

An overview of the further work required to achieve the goals set for each route at the end of the introduction chapter is in order.

Route 1

Further attempts at synthesizing different N-3 protected hydantoins should be attempted. A natural choice would be the benzyloxycarbonyl (Cbz), which is structurally not that different from the Boc group. Improvements to the synthetic yield of **2E** would make the reaction more desirable for synthesis of different hydantoins. Further work on removing the benzyl protecting group from **2E** remains, and any attempt should consider the harshness of the conditions required. Exploring the scope of the N-1 arylation reaction on **2E** also remains. This scope should find out how the reaction is affected by steric hindrance from the C-5 position, and how electron poor/rich aryl groups affects the resulting yield. Lastly, a one pot reaction that applies the protecting group, N-1 arylates, and removes the protecting group, could be developed. Such a reaction would reduce the necessary steps for the synthesis of N-1 arylhydantoins using this method and make it on par with already developed N-3 arylation reactions.

- Synthesize N-3 protected hydantoins
- Make sure that the N-3 protected hydantoins are stabile under the experimental conditions for N-1 arylation.
- Develop an N-1 selective metal catalyzed arylation reaction that uses the N-3 protected hydantoin as substrate.
- Find an efficient method of removing the protecting group without affecting the functional groups present on the protected arylated hydantoin.
- Explore the N-1 arylation's scope of aryl groups and hydantoins with different C-5 substituents.
- Develop a one pot N-1 arylation reaction.

Route 2

All of the goals presented for route 2 should continue to be worked on in order achieve N-1 arylation with the help of a directing group. Synthesizing additional 5-alkylidenehydantoins and testing their ability to form metal complexes would be a natural starting point. Attempting to N-1 arylate the 5-alkylidenehydantoins and working on removing the directing group would be the next steps to explore. After successfully doing each step in route 2, a one pot synthesis should be attempted.

- Synthesis 5-arylidenehydantoins with directing groups that could lead to N-1 arylation
- Find compatible 5-arylidenehydantoins for metal catalyzed cross-couplings that will not create too stabile complexes.
- Develop an N-1 selective metal catalyzed arylation reaction that uses the 5-arylidenehydantoin as substrate.
- Find an efficient method of removing the directing group without affecting the functional groups present on the arylated 5-arylidenehydantoin.
- Explore the N-1 arylation's scope of aryl groups and hydantoins with different C-5 substituents.
- Develop a one pot N-1 arylation reaction.

Route 3

As route 3 was not attempted in this thesis, work on both goals still remain in order to create direct N-1 regioselective arylation of N-3, C-5 unsubstituted hydantoin.

- Find N-arylation reactions that possess some selectivity for the N-1 position.
- Achieve regioselectivity for the N-1 arylation on N-3, C-5 unsubstituted hydantoin.

3 Experimental section

General

Chemicals were used as delivered from Sigma Aldrich, and fluorochem. NMR-solvents were used as delivered from Cambridge Isotope Laboratories, with molecular sieves of size 3-4 Å in order to prevent water contamination in larger bottles. Hexane and sometimes ethyl acetate was distilled prior to use. Other solvents were used as delivered

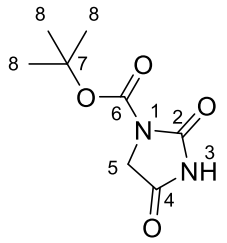
Thin layer chromatography was performed on 60 F_{254} silica coated aluminium plates from Merck. Flash chromatography was performed on silica gel from Merck (Silicagel 60, 0.040-0.063 mm) manually.

^{1}H and ^{13}C experiments were recorded in $CDCl_3$ or DMSO-d_6 using Bruker AVII400 or AVIII400 operating at 400MH_z (^{1}H) and 101 MH_z (^{13}C), or AVII600 operating at 600MH_z (^{1}H) and 151 MH_z (^{13}C). All spectra were recorded at 25 °C.

FTIR spectra were recorded in ATR (Bruker ATR A225/Q) on a Vertex 80 Bruker infrared spectrophotometer, equipped with a DTGS detector; 64 interferograms (recorded at 4 cm^{-1} resolution) were typically averaged for each spectrum.

3.1 Synthesized products

N-1 Bochydantoin
(1-Imidazolidinecarboxylic acid, 2,5-dioxo-, 1,1-dimethylethyl ester) (2A) [CAS: 1398413-16-5]



2A was obtained using the following method: To a 250 mL round bottomed flask hydantoin (1.20 g, 12.0 mmol 1.2 eq.) was added followed by acetonitrile (60 mL). DMAP (0.12 g, 1.0 mmol, 0.1 eq.) was then added to the flask while stirring. Boc anhydride (2.22 g, 10.2 mmol, 1.0 eq.) was dissolved in acetonitrile (140 mL), and placed in an addition funnel fitted to the top of the 250 mL round bottomed flask. The flask was submerged in a 50/50 ice/salt bath, showing a temperature below -10 °C. The Boc anhydride solution was added dropwise for 1 hour and the reaction was left to run overnight. The crude mixture was concentrated under reduced pressure, then purified using column chromatography (SiO_2, DCM:EtOAc 60:40) which afforded 679 mg of **2A** as a colorless powder in 33 % yield

^{1}H-NMR (600 MHz, DMSO-d_6): δ 11.29 (s, 1H, H-1), 4.16 (s, 2H, H-5), 1.45 (s, 9H, H-8).

^{13}C-NMR (151 MHz, DMSO-d_6): δ 169.6, 152.7, 148.2, 82.3, 49.9(C-5), 27.7 (C-8).

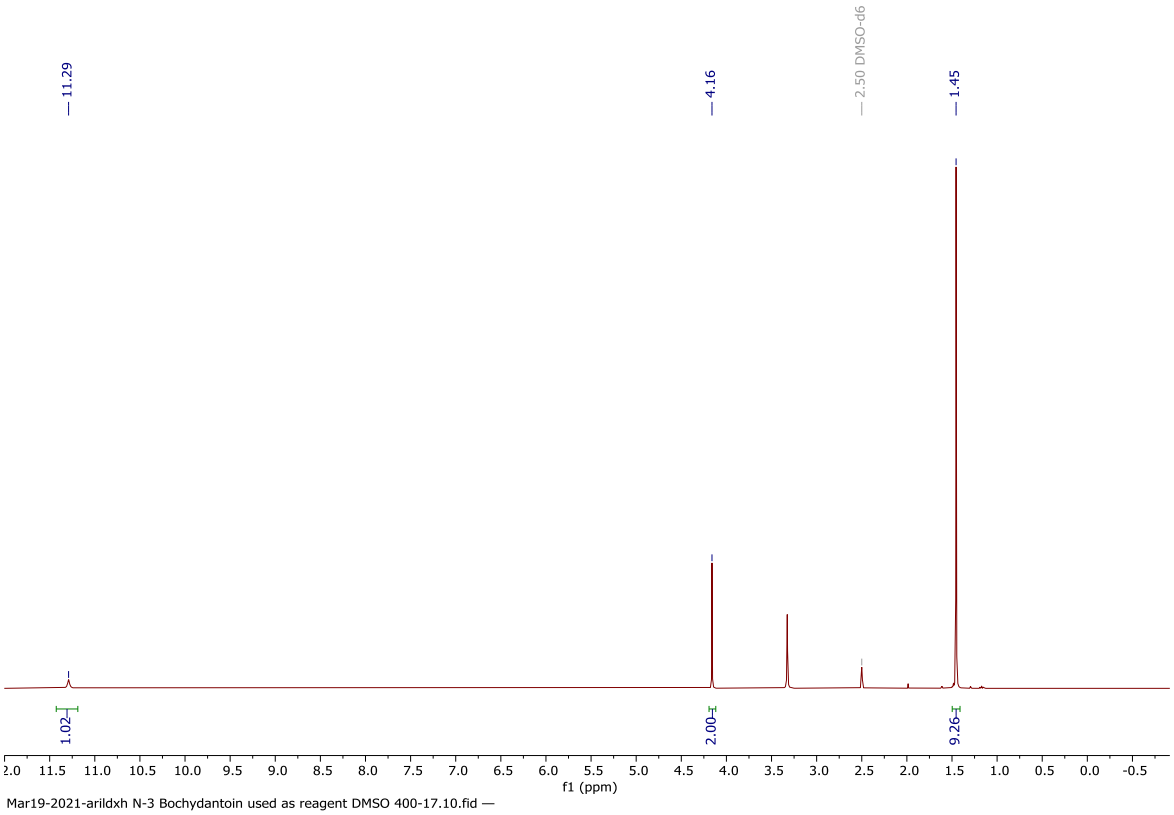
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_8H_{12}N_2NaO_4^+$: 223.0689, found: 223.0689

TLC: R_f [hexane:EtOAc (80:20 %): 0.15

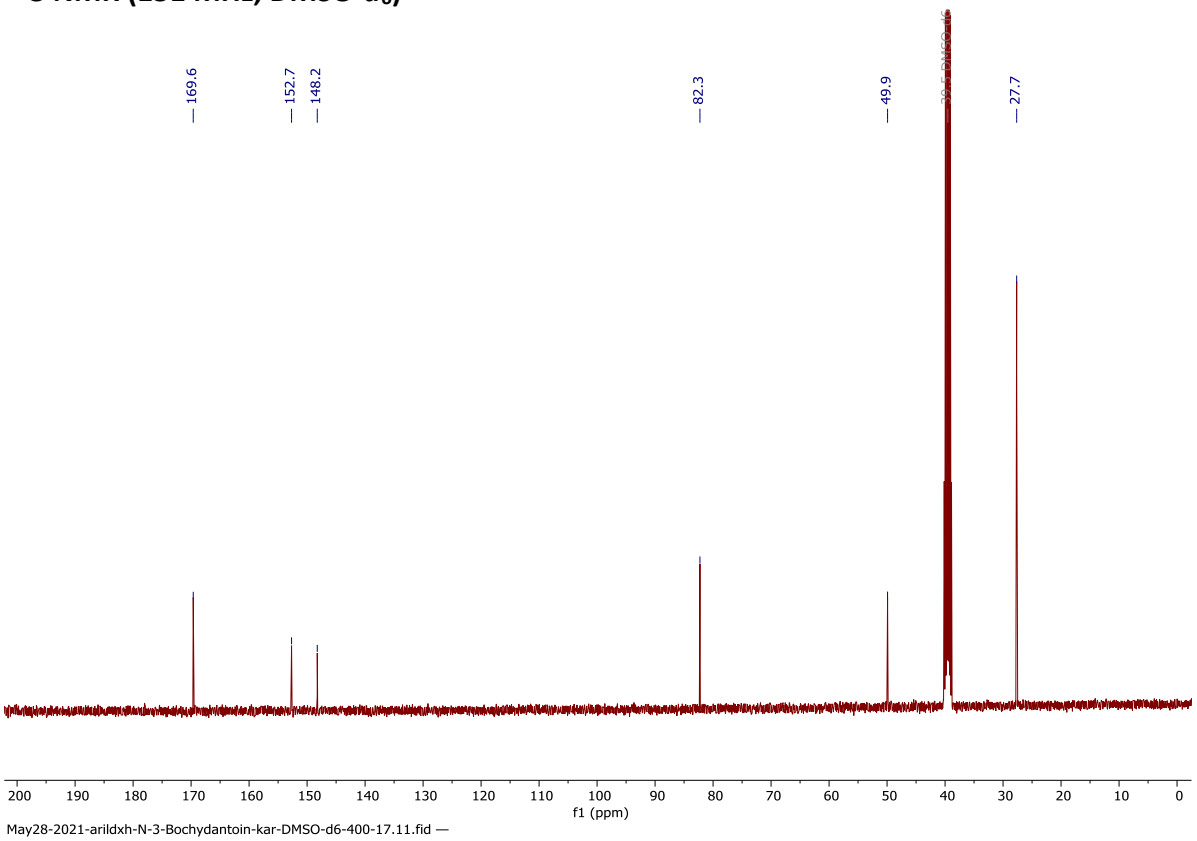
Melting point: 121-122 °C.

FTIR (neat, $V_{max}cm^{-1}$): 3186, 3107, 2991, 1717, 1311, 1107, 840, 766.

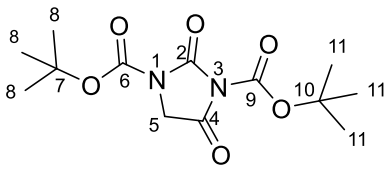
^{1}H-NMR (400 MHz, DMSO-d_6)



^{13}C-NMR (151 MHz, DMSO-d_6)



N-1, N-3, diBochydantoin
(1,3-Imidazolidinedicarboxylic acid, 2,4-dioxo-, 1,3-bis(1,1-dimethylethyl) ester)
(2B) [CAS: 404009-03-6]



10 mmol scale

2B was obtained using the following method: To a 250 mL round bottomed flask hydantoin (1.20 g, 12.0 mmol 1.2 eq.) was added followed by acetonitrile (60 mL). DMAP (0.12 g, 1.0 mmol, 0.1 eq.) was then added to the flask while stirring. Boc anhydride (2.22 g, 10.2 mmol, 1.0 eq.) was dissolved in acetonitrile (140 mL), and placed in an addition funnel fitted to the top of the 250 mL round bottomed flask. The flask was submerged in a 50/50 ice/salt bath, showing a temperature below -10 °C. The Boc anhydride solution was added dropwise for 1 hour and the reaction was left to run overnight. The crude mixture was concentrated under reduced pressure, then purified using column chromatography (SiO_2, DCM:EtOAc 60:40) which afforded 1,668 g of **2B** as a colorless powder in 48 % yield.

^{1}H-NMR (400 MHz, CDCl3): δ 4.22 (s, 2H, H-5), 1.58 (s, 9H), 1.55 (s, 9H)

^{13}C-NMR (101 MHz, CDCl3): δ 164.0, 148.4, 147.5, 145.2, 86.9, 85.2, 48.4, 28.1, 27.9

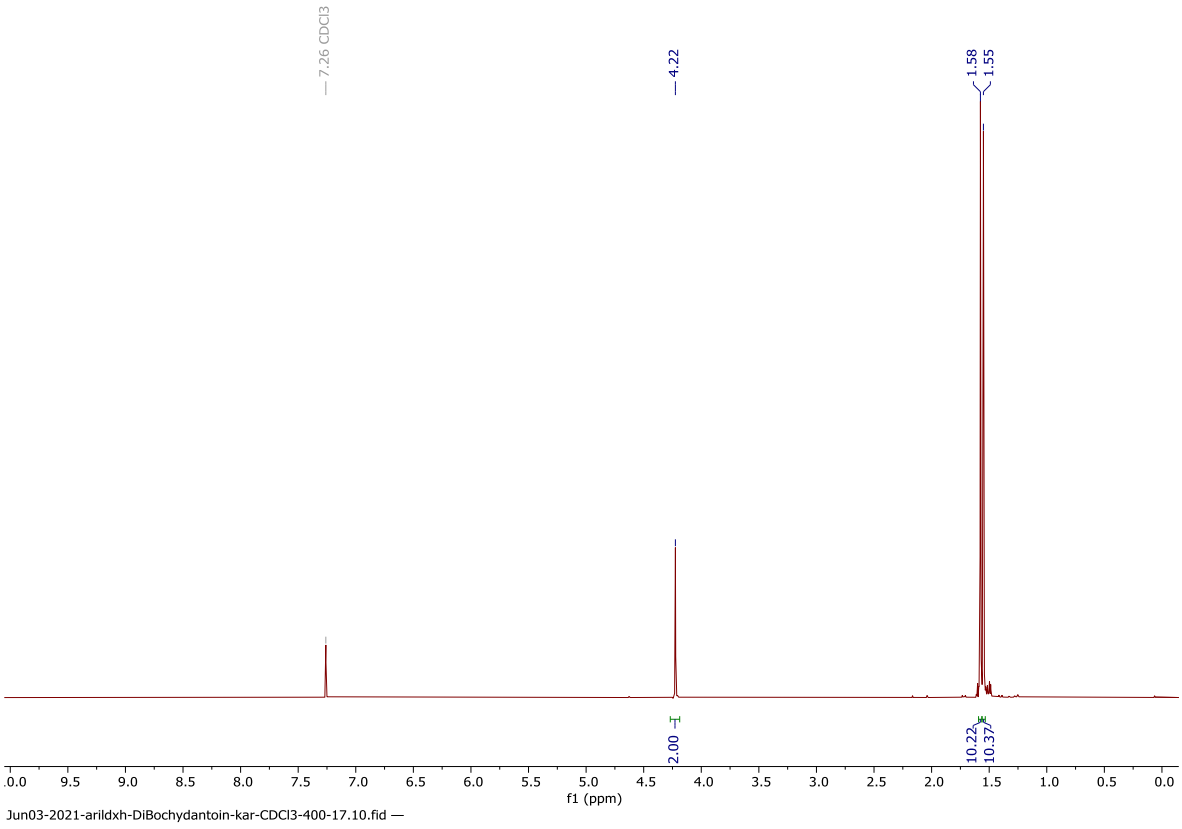
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{13}H_{20}N_2NaO_6^+$: 323.1214, found: 323.1214

TLC: R_f [hexane: EtOAc (80:20 %): 0.7

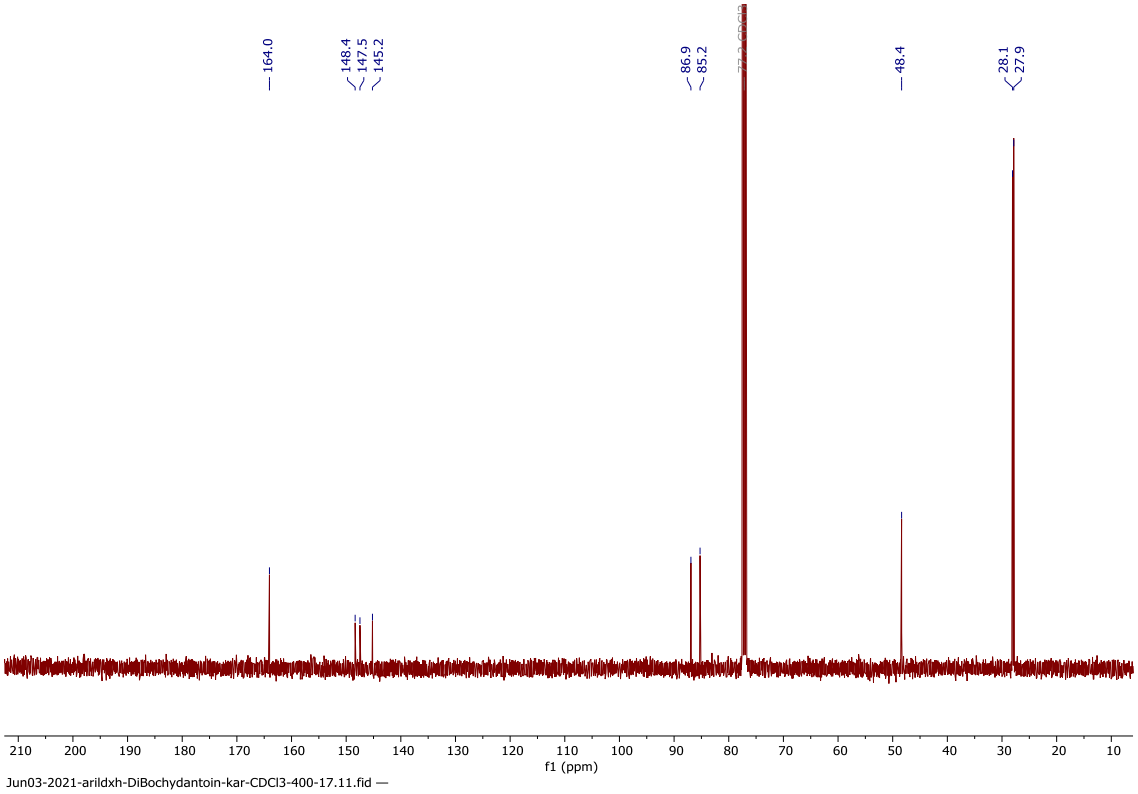
Melting point: 131-132 ^{o}C.

FTIR (neat, $V_{max}cm^{-1}$): 2981, 1820, 1769, 1720, 1361, 1256, 1136, 947, 842, 781, 640.

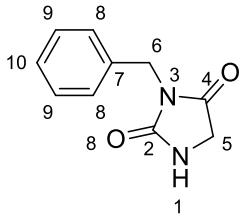
^{1}H-NMR (400 MHz, CDCl3)



^{13}C-NMR (101 MHz, CDCl3)



N-3 benzylhydantoin (3-benzylimidazolidine-2,4-dione) (2C) [CAS: 2301-40-8]



10 mmol scale

2C was obtained using the following method: To a 50 mL round bottomed flask hydantoin (1.09 g, 10.9 mmol, 1.1 eq.) was added, followed by a magnetic stirring bar. Potassium carbonate (1.39 g, 10.0 mmol, 1.0 eq.) was then added to the flask while stirring. DMF (10 mL) was added to the round bottomed flask and stirring was turned on. Benzyl bromide (1.2 mL, 10.1 mmol, 1.0 eq.) was added to the round bottomed flask. The flask was set to stir at 90 °C and a condenser was fitted to the flask. The reaction was allowed to stir overnight before being concentrated under reduced pressure. The crude mixture was purified using column chromatography (SiO_2, Hex:EtOAc 8:2) which afforded 735 mg off white powder in 38 % yield.

^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.12 (s, 1H, H-1), 7.35-7.22(m, 5H, H-8, H-9. H-10), 1.45 (s, 9H) placeholder

^{13}C-NMR (151 MHz, DMSO-d_6): δ 170.7, needs to be done

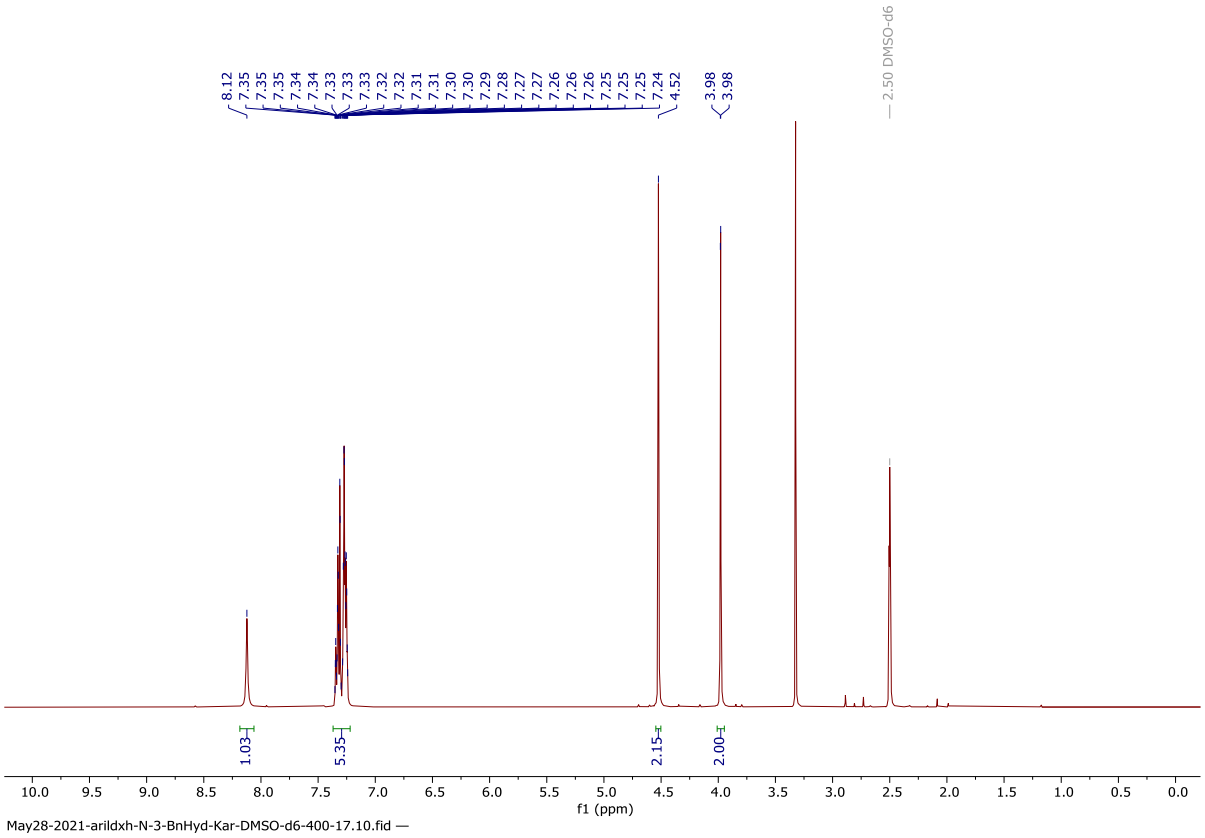
HRMS (ESI) m/z [M + Na]$^+$: Calcd. for $C_{10}H_{10}N_2NaO_2^+$: 213.0634, found: 213.0634

TLC: R_f [EtOAc (100 %): 0.4.

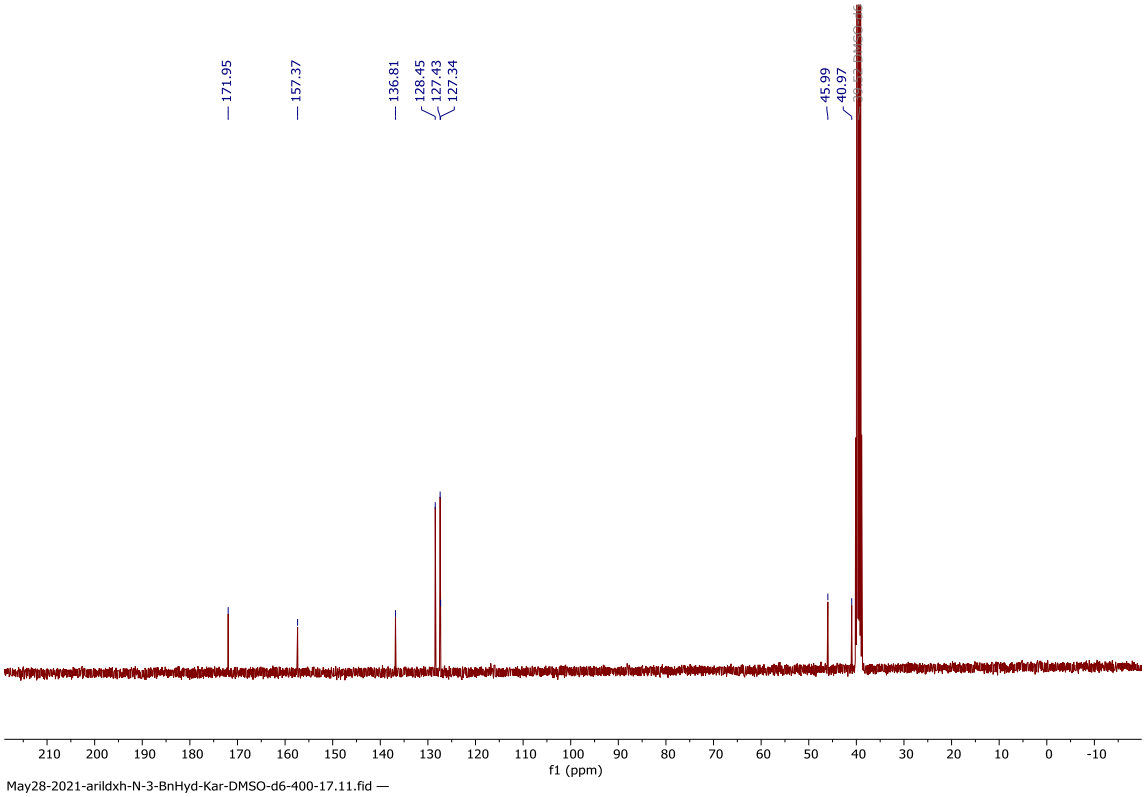
Melting point: 139-140 °C.

FTIR (neat, $V_{max}cm^{-1}$): 3440, 1769, 1703, 1450, 1340, 1303, 1142, 721, 694, 635.

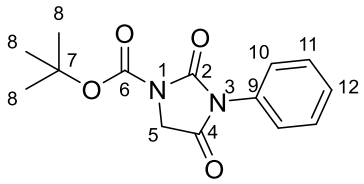
^{1}H-NMR (400 MHz, DMSO-d_6)



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



N-1, N-3 phenylBochydantoin (tert-butyl 2,4-dioxo-3-phenylimidazolidine-1-carboxylate) (2D) [No CAS number]



2D was obtained using the following method: To a 10 mL round bottomed flask **2A** (82.3 mg, 0.41 mmol, 1.0 eq.), Copper nitrate hemipentahydrate (11.2 mg, 0,05 mmol, 0,1 eq.), and phenylboronic acid (144.1 mg, 1.18 mmol, 3.0 eq.) was added, followed by a magnetic stirring bar. Ethanol (2 ml) was added to the flask followed by pyridine (96 µl). A condenser was fit to the flask and the mixture was set to stir at 40 °C for 24 hours. The product was purified using column chromatography (SiO_2, Hex:EtOAc 8:2) which afforded 79 mg of colorless powder in 69 % yield.

^{1}H-NMR (400 MHz, CDCl3): δ 7.40-7.13 (m, 5H, H-7, H-8, H-9, CDCl3 overlap), 4.28 (s, 2H, H-5), 1.47 (s, 9H, H-12)

^{13}C-NMR (101 MHz, CDCl3): δ 166.8, 151.2, 148.6, 130.8, 129.4, 129.0, 126.5, 84.9, 48.8, 28.1.

HRMS (ESI) *m/z* [M + Na]$^+$: Calcd. for $C_{14}H_{16}N_2NaO_4^+$: 299,1002, found: 299.1002

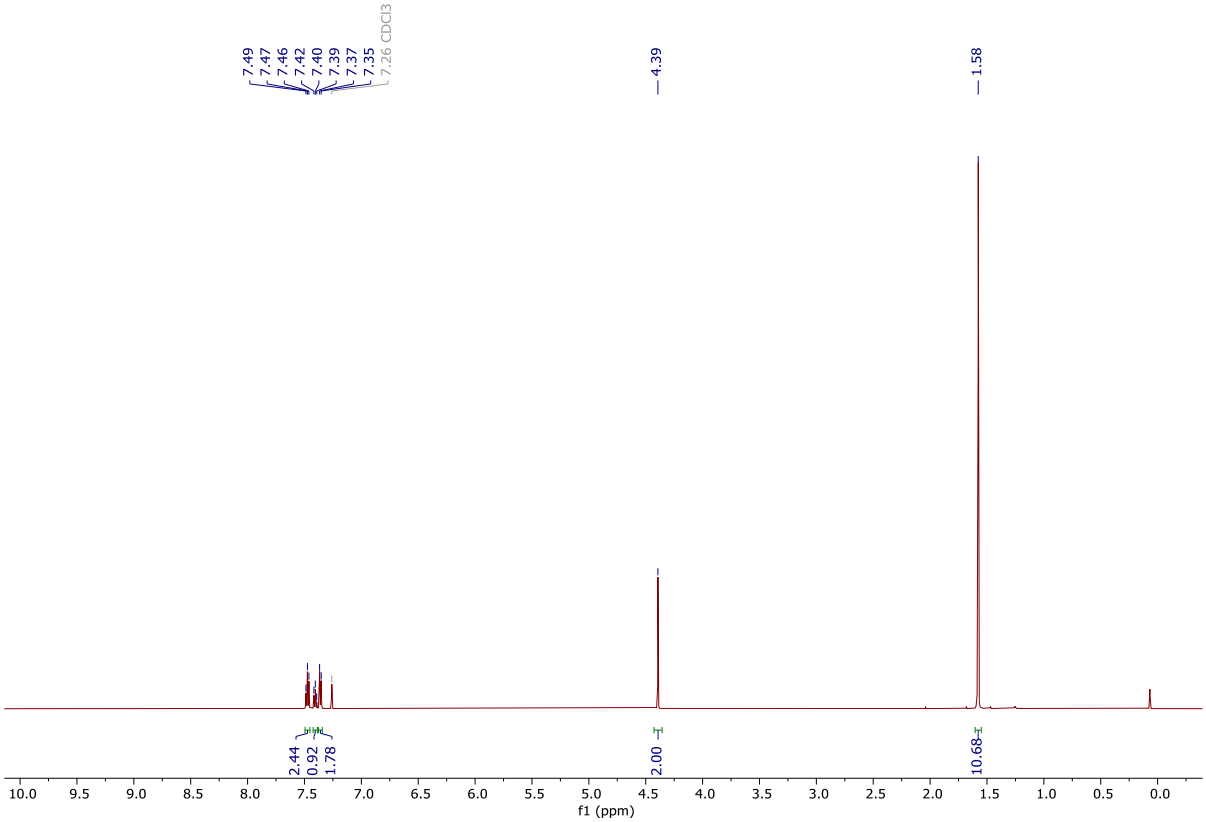
TLC: R_f [EtOAc (100 %): 0.7.

Melting point: 160-161 ^{o}C.

FTIR (neat, $V_{max}cm^{-1}$): 2920, 2358, 1812, 1743, 1500, 1444, 1359, 1288, 1153, 1109.

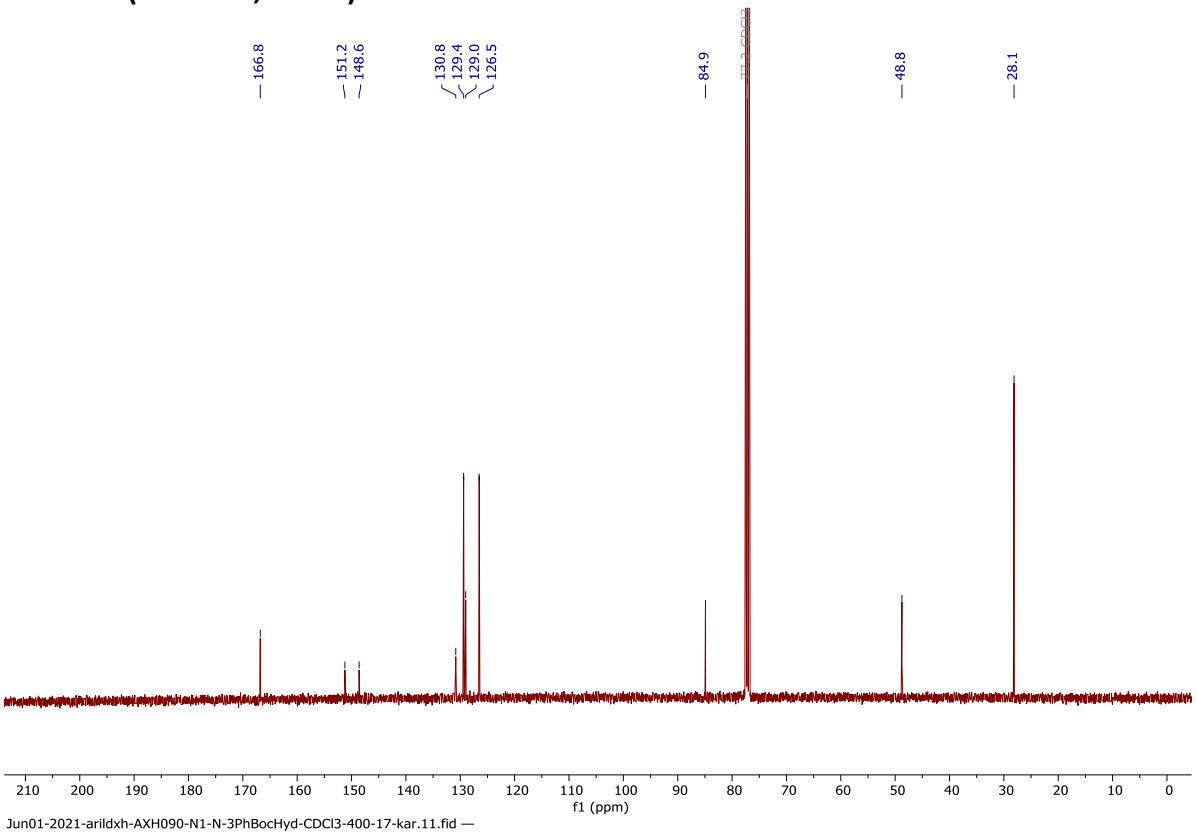
Crystal Data for $C_{14}H_{16}N_2aO_4$ (M =276.29 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 5.7770(4) Å, *b* = 14.0323(11) Å, *c* = 16.7410(13) Å, *V* = 1357.10(18) Å^3, *Z* = 4, *T* = 100.0 K, µ(MoKα) = 0.100 mm^{-1}, *Dcalc* = 1.352 g/cm^3, 5378 reflections measured (4.866° ≤ 2Θ ≤ 46.468°), 1948 unique (R_{int} = 0.0348, R_{sigma} = 0.0472) which were used in all calculations. The final R*1* was 0.0337 ($I > 2\sigma(I)$) and wR_2 was 0.0683 (all data).

^{1}H-NMR (400 MHz, CDCl3)



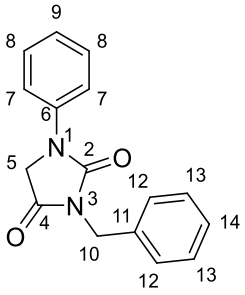
jun4-2021-AXH-N-1-N-3-Bocphenylhydantoin.10.fid — 1H NMR 600 MHz 45 degree pulse

^{13}C-NMR (101 MHz, CDCl3)



Jun01-2021-arildxh-AXH090-N1-N-3PhBocHyd-CDCl3-400-17-kar.11.fid —

N-1, N-3 phenylbenzylhydantoin (3-benzyl-1-phenylimidazolidine-2,4-dione) (2E) [CAS: 34658-62-3]



2E was obtained using the following method: To a 50 ml round bottomed flask **2C** (77.4 mg, 0.41 mmol, 1.0 eq.), Copper nitrate hemipentahydrate (9.3 mg, 0,04 mmol, 0,1 eq.), and phenylboronic acid (49.8 mg, 0.41 mmol, 1.0 eq.) was added, followed by a magnetic stirring bar. Ethanol (2 ml) was added to the flask followed by pyridine (32 µl). A condenser was fit to the flask and the mixture was set to stir at 40 °C for 24 hours. The product was purified using column chromatography (SiO_2, Hex:EtOAc 8:2) which afforded 30.6 mg of off white powder in 28 % yield.

^{1}H-NMR (400 MHz, CDCl3): δ 7.49-7.00 (m, 10H, H-7, H-8, H-9, H-12, H-13, H-14), 4.66 (s, 2H, H-10), 4.16 (s, 2H, H-5)

^{13}C-NMR (101 MHz, CDCl3): δ 168.2, 154.2, 137.6, 135.8, 129.5, 128.9, 128.3, 124.6, 118.4, 50.0, 42.8.

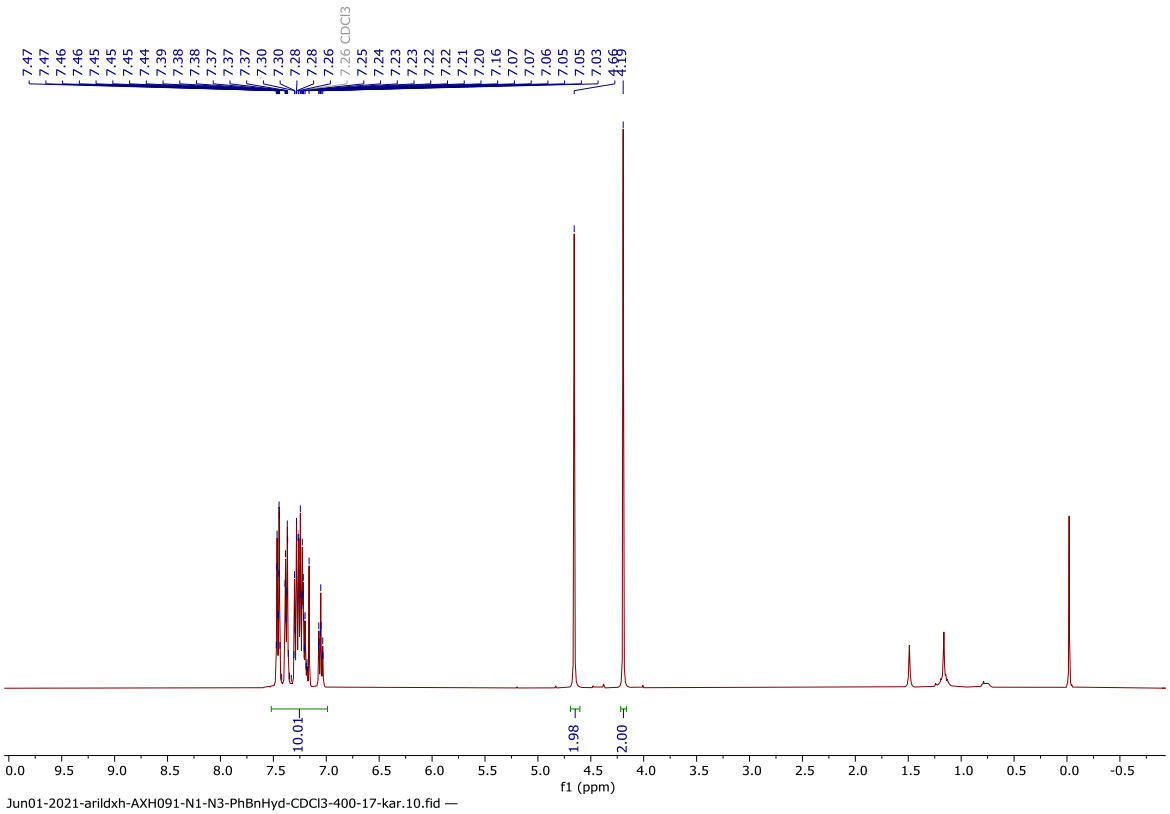
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{16}H_{14}N_2NaO_2^+$: 289.0947, found: 289.0947

TLC: R_f [EtOAc (100 %): 0.7.

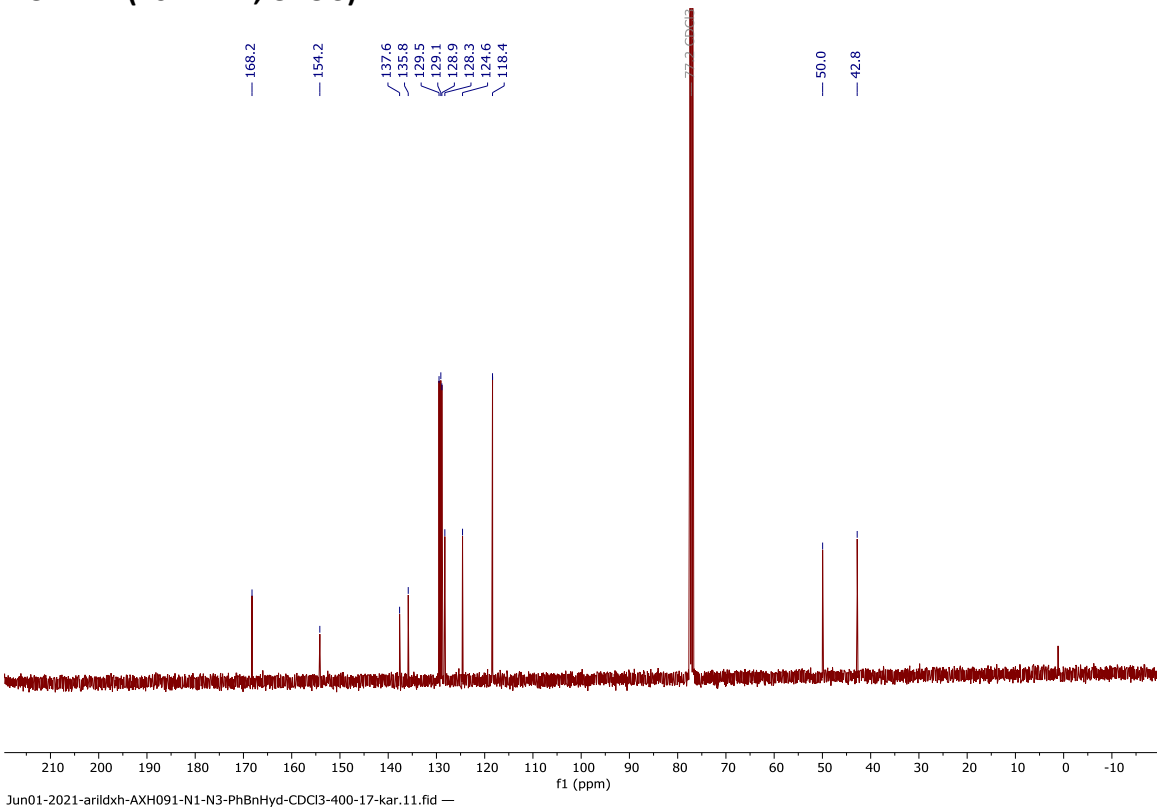
Melting point: 193-195 ^oC . decomposes.

FTIR (neat, $V_{max}cm^{-1}$): 2956, 2923, 2854, 2360, 2337, 1762, 1701, 1600, 1504, 1444.

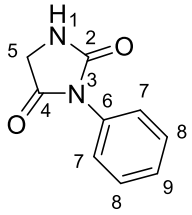
^{1}H-NMR (400 MHz, CDCl3)



^{13}C-NMR (101 MHz, CDCl3)



N-3 phenylhydantoin (3-phenylimidazolidine-2,4-dione) (2F) [CAS: 2221-13-8]



2F was obtained using the following method: **2D** (8.1 mg, 0.03 mmol, 1.0 eq.) was added to a 10 mL round bottomed flask followed by a magnetic stir bar, copper(II) triflate (1.0 mg, 0.003 mmol, 0.09 eq.) and ethanol (1 mL). The mixture was set to stir at 40 ^{o}C for 24 hours. The reaction mixture was then concentrated under reduced pressure, then dissolved in Ethyl acetate and eluted through a silica-packed pipette using ethyl acetate as eluent. The filtered liquid was then concentrated under pressure and afforded 4.7 mg of white powder in 91 % yield.

^{1}H-NMR (400 MHz, CDCl3): δ 7.52-7.36 (m, 5H, H-7, H-8, H-9), 6.20 (s, 1H, H-1), 4.13 (d, J = 1.2 Hz, 2H, H-5).

^{13}C-NMR (101 MHz, CDCl3): δ 170.2, 157.5, 131.4 (C-6), 129.4, 128.6 (C-9), 126.3, 46.6 (C-5).

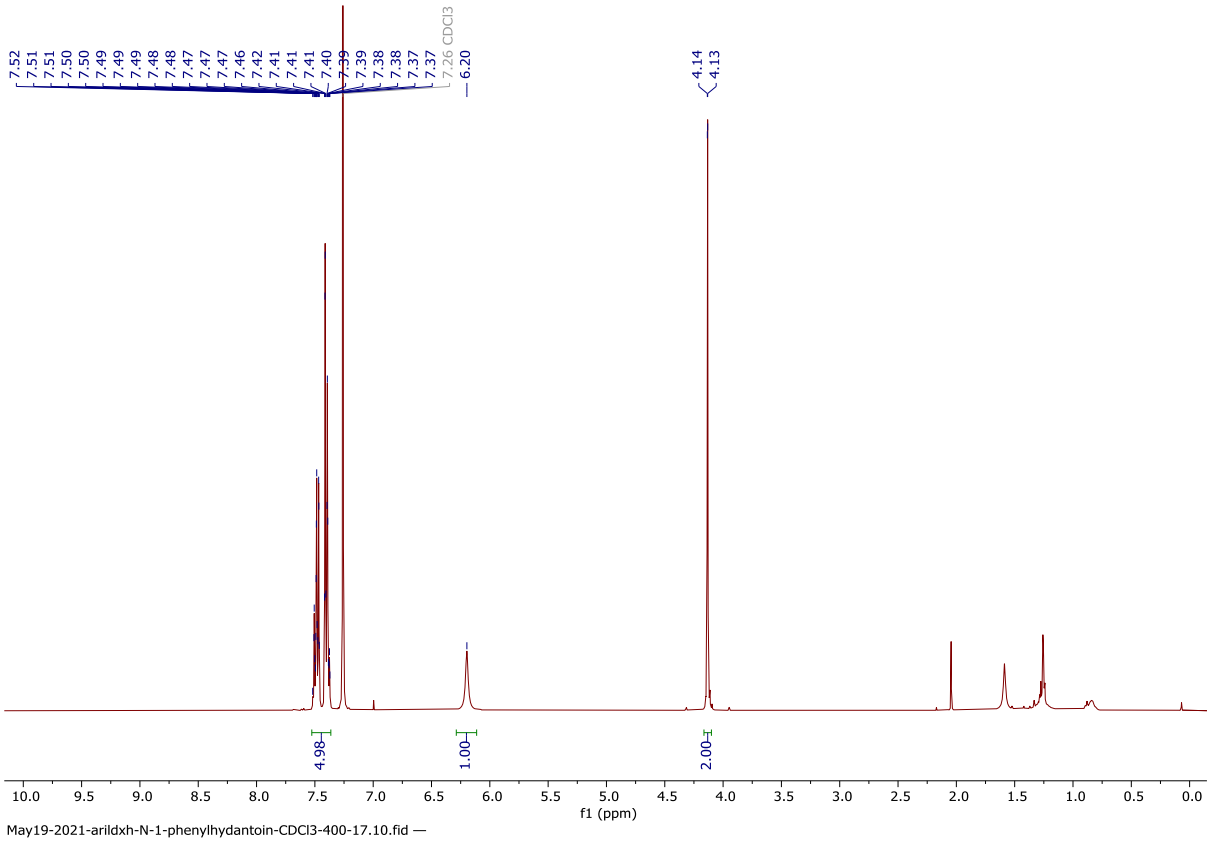
HRMS (ESI) *m/z* $[M + Na]^{+}$: Calcd. for $C_9H_8N_2NaO_2^{+}$: 199.0478, found: 199.0478

TLC: R_f [Ethyl acetate (100 %): 0.4.

Melting point: 144-145 ^{o}C. (Literature reports 191-192 ^{o}C)[11]

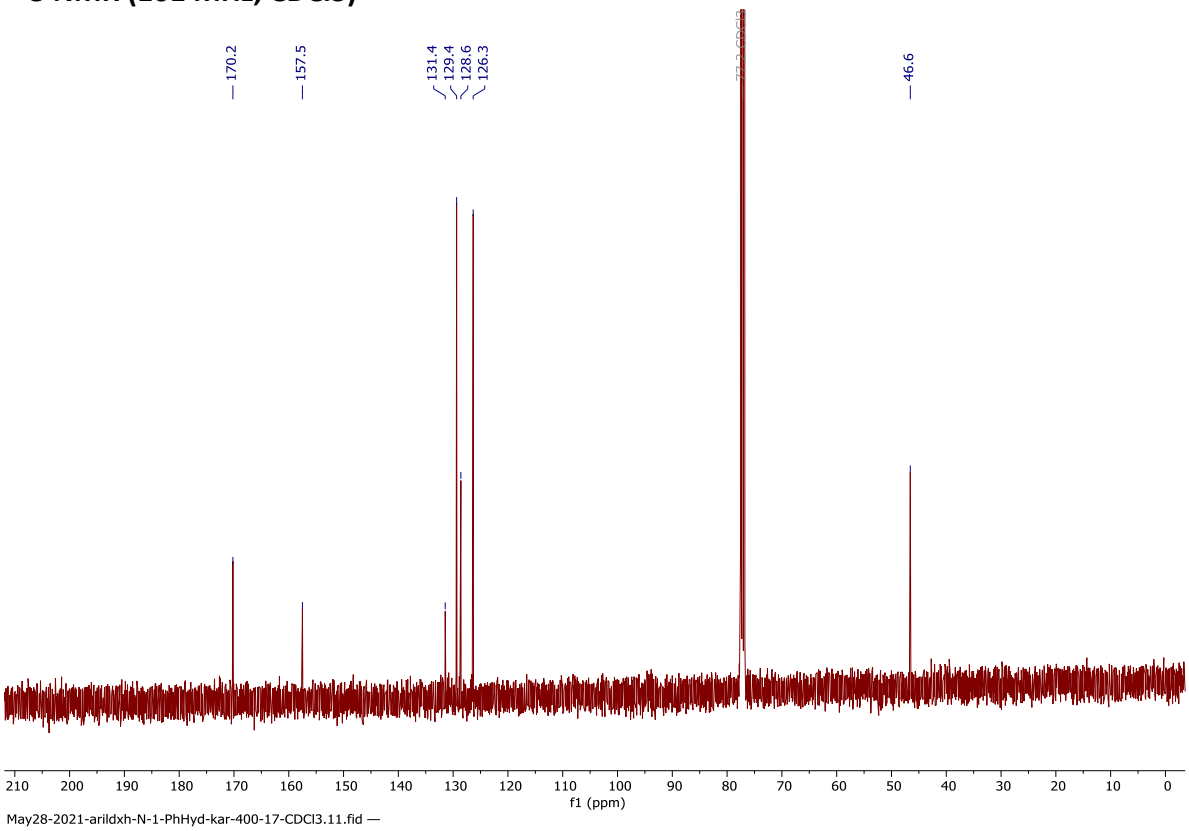
FTIR (neat, $V_{max}cm^{-1}$): 3068, 2954, 2358, 2335, 1774, 1693, 1596, 1500, 1427, 1321, 1176, 1093, 1031.

^{1}H-NMR (400 MHz, CDCl3)



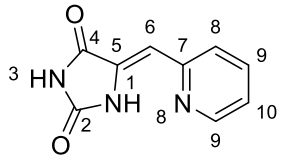
May19-2021-arildxh-N-1-phenylhydantoin-CDCl3-400-17.10.fid —

^{13}C-NMR (101 MHz, CDCl3)



May28-2021-arildxh-N-1-PhHyd-kar-400-17-CDCl3.11.fid —

PyHy ((Z)-5-(pyridin-2-ylmethylene)imidazolidine-2,4-dione) (2G) [CAS: 132478-12-7]

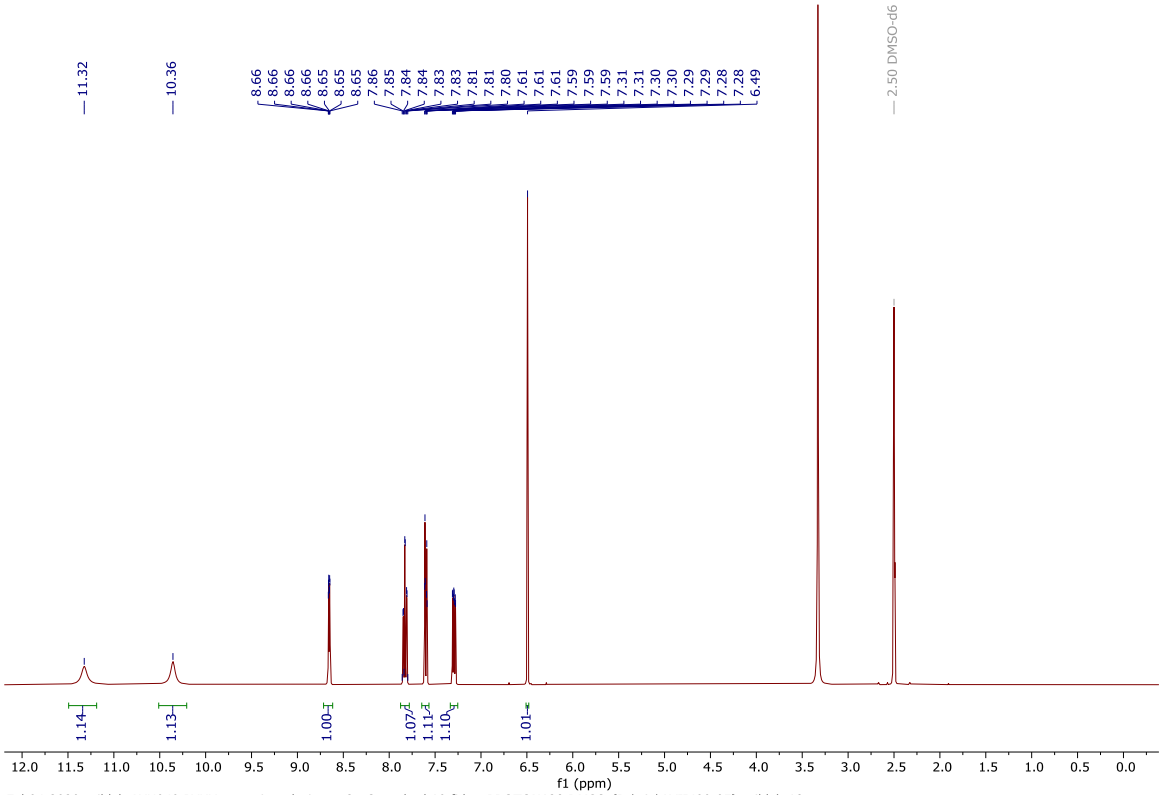


2G was obtained using the following method: hydantoin (501.3 mg, 5.01 mmol, 1.0 eq.), glycine (374.9 mg, 4.99 mmol, 1.0 eq.), Na_2CO_3 (263.4 mg, 2.50 mmol, 0.5 eq.) was added to a 10 mL round bottomed flask containing a magnetic stir bar. Pyridine-2-carboxaldehyde (475 µL, 5.0 mmol, 1.0 eq.) was added dropwise into the flask followed by water (3.5 mL). A condenser was fitted to the flask and the mixture was refluxed for 1 hour. A yellow precipitate formed and the flask was set to cool down to room temperature. The precipitate was then filtered off and washed generously with water before being dried under reduced pressure. This afforded 257.2 mg of yellow powder in 27 % yield.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H), 10.36 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 7.83 (dt, J = 7.7, 1.8 Hz, 1H), 7.60 (dt, J = 7.9, 1.1 Hz, 1H) 7.29 (ddd, J = 7.7, 4.8, 1.1 Hz, 1H), 6.49 (s, 1H)

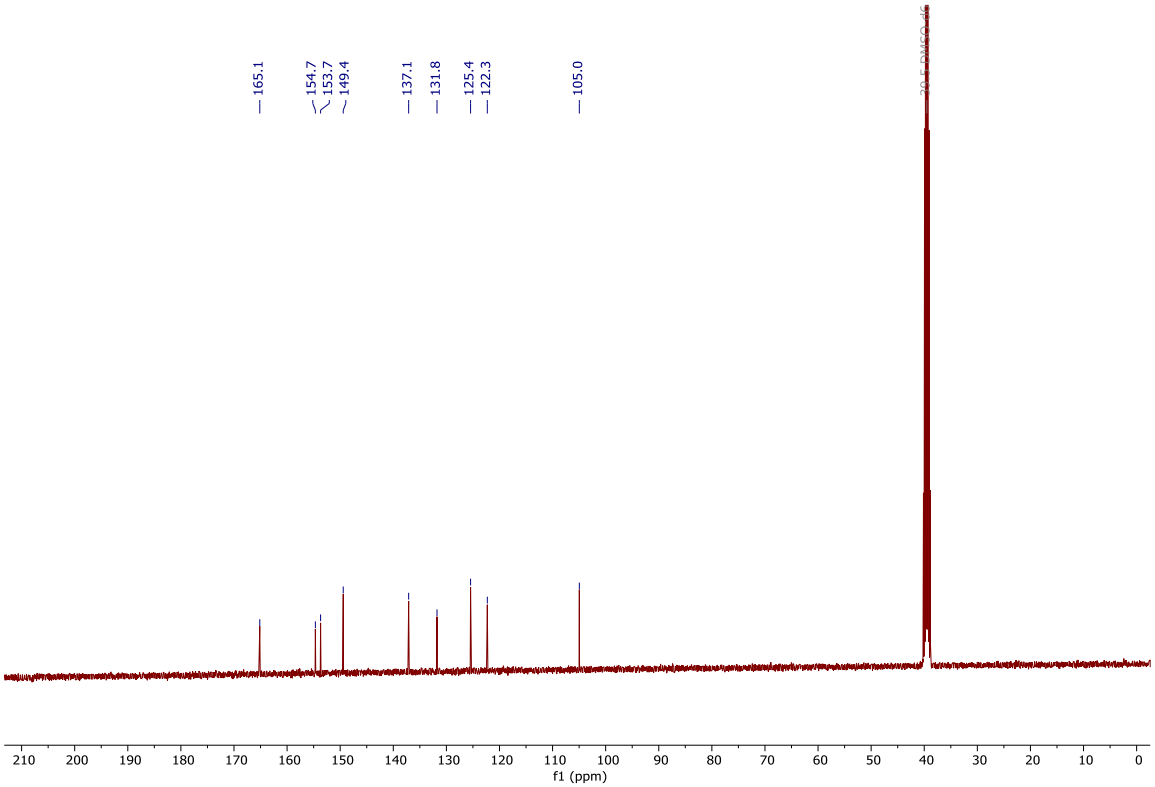
^{13}C-NMR (101 MHz, DMSO-d_6): δ 165.1, 154.7, 153.7, 149.4, 137.1, 131.8, 125.4, 122.3, 105.0.

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



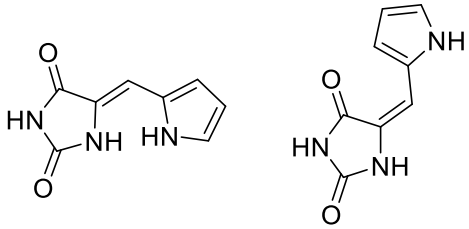
Feb04-2020-arildxh AXH049 PYHY syn using glycine na2co3 method.10.fid — PROTON128 DMSO {D:\uio\AVII400-05} arildxh 18

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



Feb04-2020-arildxh AXH049 PYHY syn using glycine na2co3 method.11.fid — C13CPD DMSO {D:\uio\AVII400-05} arildxh 18

(Z/E)-5-((1H-pyrrol-2-yl)methylene)imidazolidine-2,4-dione (2H) [CAS: 136949-32-1]

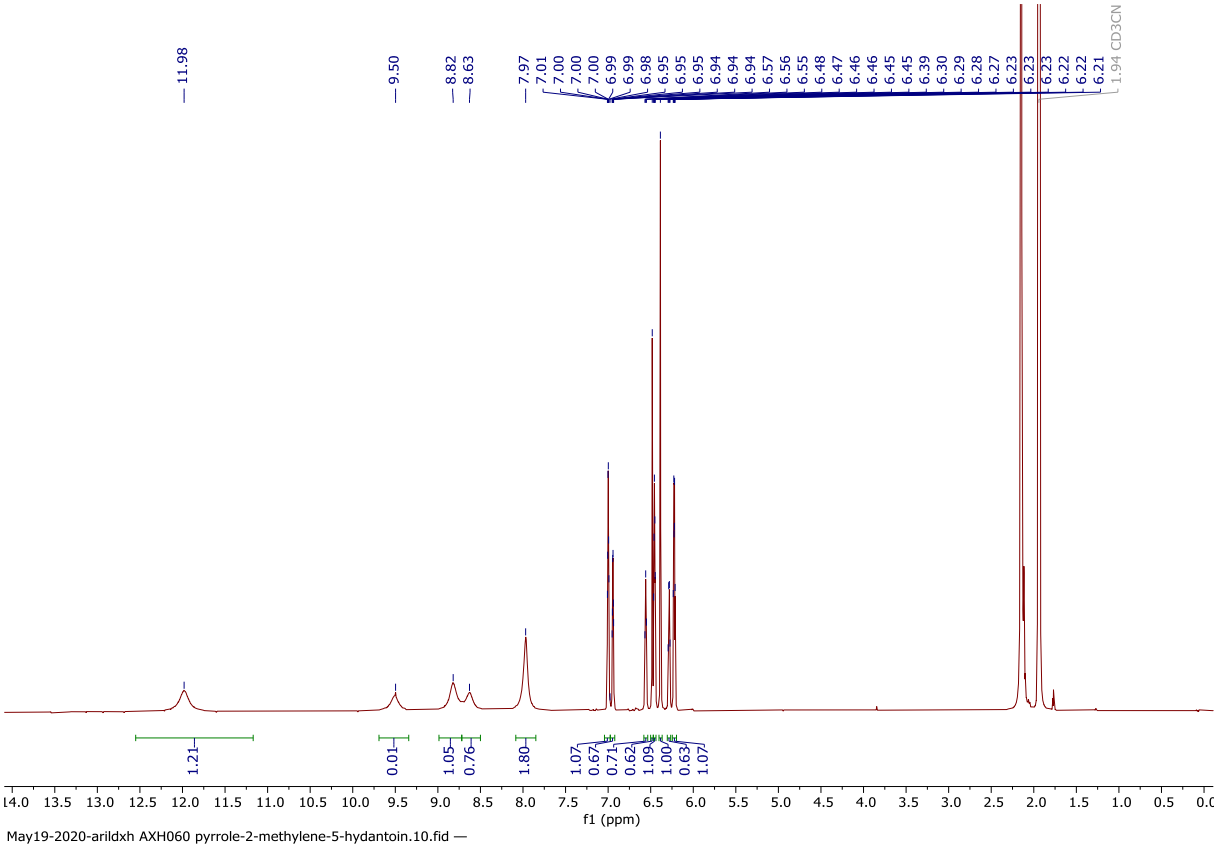


2H was obtained using the following method: hydantoin (502.7 mg, 5.02 mmol, 1.0 eq.), glycine (379.1 mg, 5.01 mmol, 1.0 eq.), Na_2CO_3 (264.4 mg, 2.49 mmol, 0.5 eq.) was added to a 10 mL round bottomed flask containing a magnetic stir bar. Pyrrole-2-carboxaldehyde (476.8 mg, 5.01 mmol, 1.0 eq.) was added dropwise into the flask followed by water (3.0 mL). A condenser was fitted to the flask and the mixture was refluxed for 1 hour. A brownish precipitate formed and the flask was set to cool down to room temperature. The precipitate was then filtered off and washed generously with water before being dried under reduced pressure. This afforded 439.5 mg of brown powder in 49 % yield.

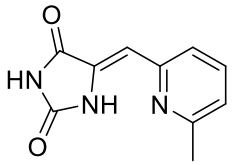
^{1}H-NMR (400 MHz, CD3CN): δ 11.98 (s, 1H), 9.50 (s, 0.65H), 8.68 (overlapping singlets, 1.6 H) 7.96 (overlapping singlets, 1.8H), 6.56(s, 0.65H), 6.48(s, 0.62H), 6.46 (quint, J = 1.8 Hz, 1H), 6.39 (s, 1H), 6.29-6.28 (m, 0.63H), 6.22 (q, J = 2.5 Hz, 0.93H.

TLC: R_f [Ethyl acetate (100 %): 0.5

^{1}H-NMR (400 MHz, CD3CN)



MePyHy ((Z)-5-((6-methylpyridin-2-yl)methylene)imidazolidine-2,4-dione) (2I) [No CAS number]

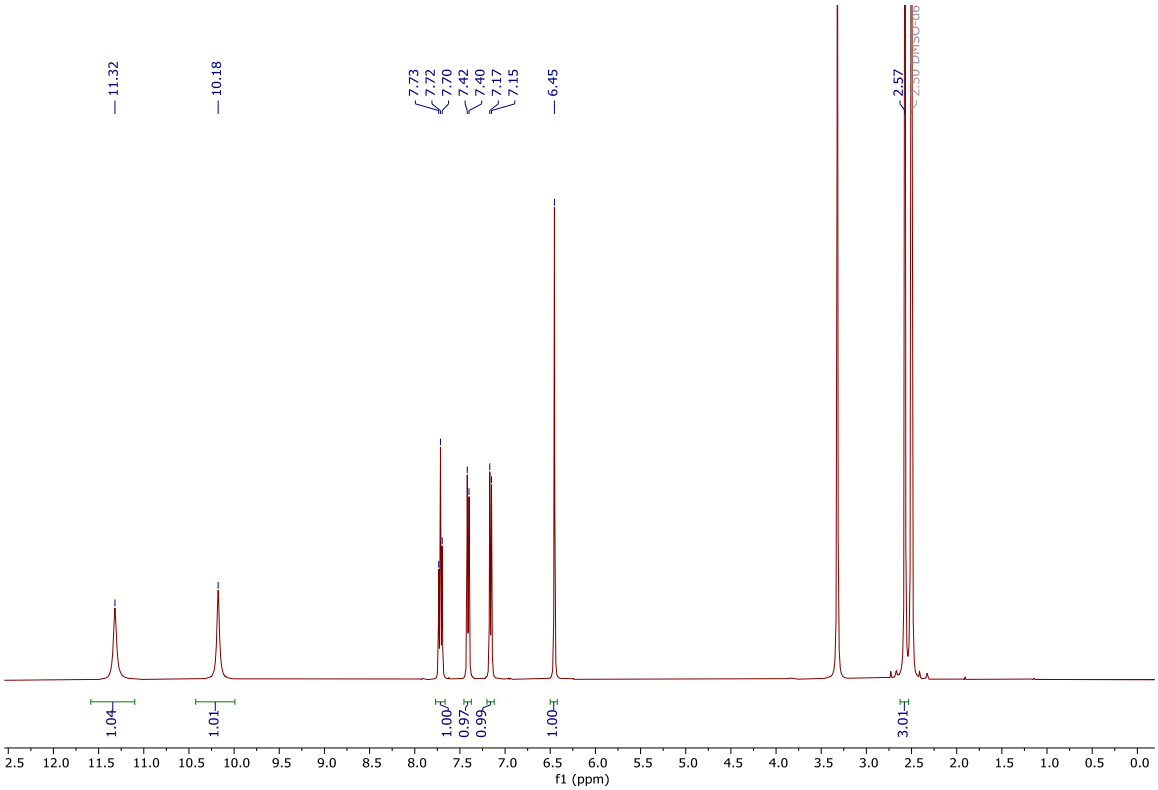


2I was obtained using the following method: hydantoin (200.8 mg, 2.01 mmol, 1.0 eq.), glycine (159.2 mg, 2.12 mmol, 1.1 eq.), Na_2CO_3 (106.8 mg, 1.01 mmol, 0.5 eq.) was added to a 10 mL round bottomed flask containing a magnetic stir bar. 6-methylpyridine-2-carboxaldehyde (253.6 mg, 2.09 mmol, 1.1 eq.) was added dropwise into the flask followed by water (1.4 mL). A condenser was fitted to the flask and the mixture was refluxed for 1 hour. A yellow precipitate formed and the flask was set to cool down to room temperature. The precipitate was then filtered off and washed with a 1:5 ethanol:water mixture (25 mL) before being dried under reduced pressure. This afforded 109.8 mg of bright yellow powder in 27 % yield.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H), 10.18 (s, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 7,7 Hz, 1H) 7.16 (d, J = 7.7 Hz, 1H), 6.45 (s, 1H), 2.57 (s, 3H).

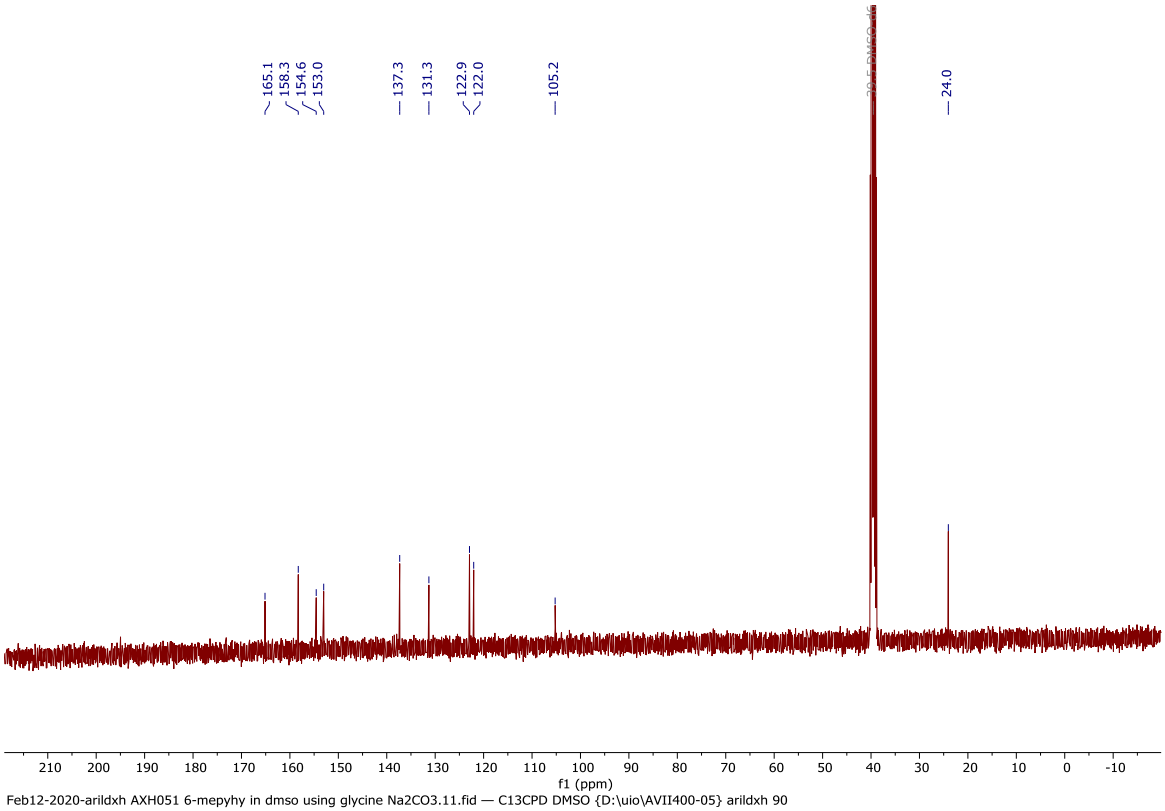
^{13}C-NMR (101 MHz, DMSO-d_6): δ 165.1, 158.3, 154.6, 153.0, 137.3, 131.3, 122.9, 122.0, 105.2, 24.0.

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



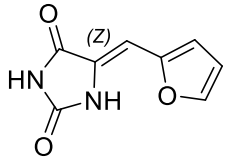
Feb12-2020-arildxh AXH051 6-mepyhy in dmso using glycine Na2CO3.10.fid — PROTON128 DMSO {D:\uio\AVII400-05} arildxh 90

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



Feb12-2020-arildxh AXH051 6-mepyhy in dmso using glycine Na2CO3.11.fid — C13CPD DMSO {D:\uio\AVII400-05} arildxh 90

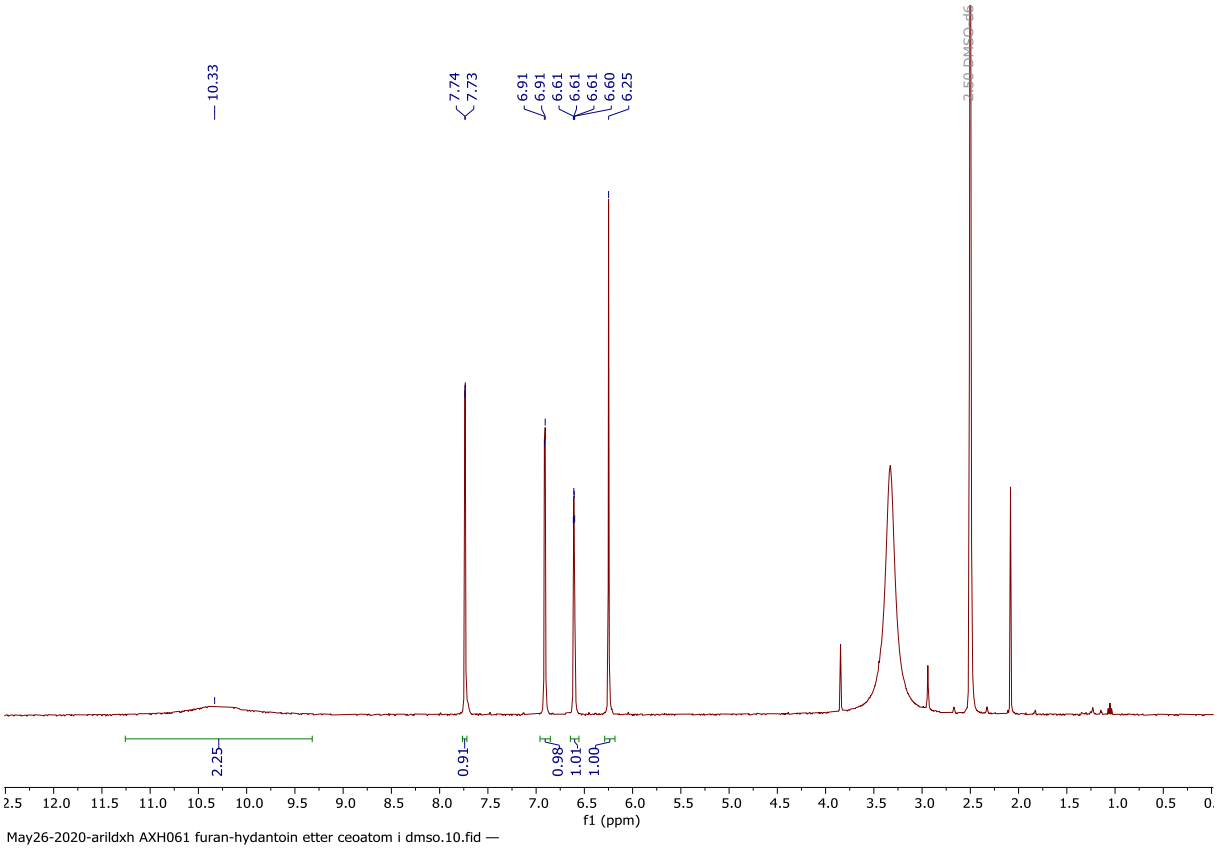
(Z)-5-(furan-2-ylmethylene)imidazolidine-2,4-dione (2J) [CAS: 136949-32-1]



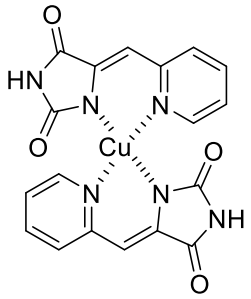
2J was obtained using the following method: hydantoin (504.4 mg, 5.04 mmol, 1.0 eq.), glycine (376.1 mg, 5.01 mmol, 1.0 eq.), Na_2CO_3 (264.3 mg, 2.49 mmol, 0.5 eq.) was added to a 10 mL round bottomed flask containing a magnetic stir bar. 6-methylpyridine-2-carboxaldehyde (253.6 mg, 2.09 mmol, 1.1 eq.) was added dropwise into the flask followed by water (1.4 mL). A condenser was fitted to the flask and the mixture was refluxed for 1 hour. A yellow precipitate formed and the flask was set to cool down to room temperature. The precipitate was then filtered off and washed with a 1:5 ethanol:water mixture (25 mL) before being dried under reduced pressure. This afforded 109.8 mg of bright yellow powder in 27 % yield.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 2H), 7.73 (d, J = 1.5 Hz, 1H), 6.91 (d, J = 3.4 Hz, 1H), 6.61 (dd, J = 3.4, 1.8 Hz, 1H), 6.25 (s, 1H). Shift values may be inaccurate due to large water top.[20]

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



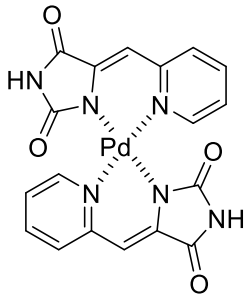
PyHy Cu(II) complex (Copper, bis[5-(2-pyridinylmethylene)-2,4-imidazolidinedionato-N^{1},N^{5}]-, (T-4)-(9CI)) (2K) [CAS: 177840-43-6]



2K was obtained using the following method:

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{18}H_{12}CuN_6NaO_4^+$: 462.0108, found: 462.0108

PyHy Pd(II) complex (Palladium, bis[5-(2-pyridinylmethylene)-2,4-imidazolidinedionato-N^{1},N^{5}]-, (T-4)- (9CI)) (2L) [CAS: 136949-32-1]



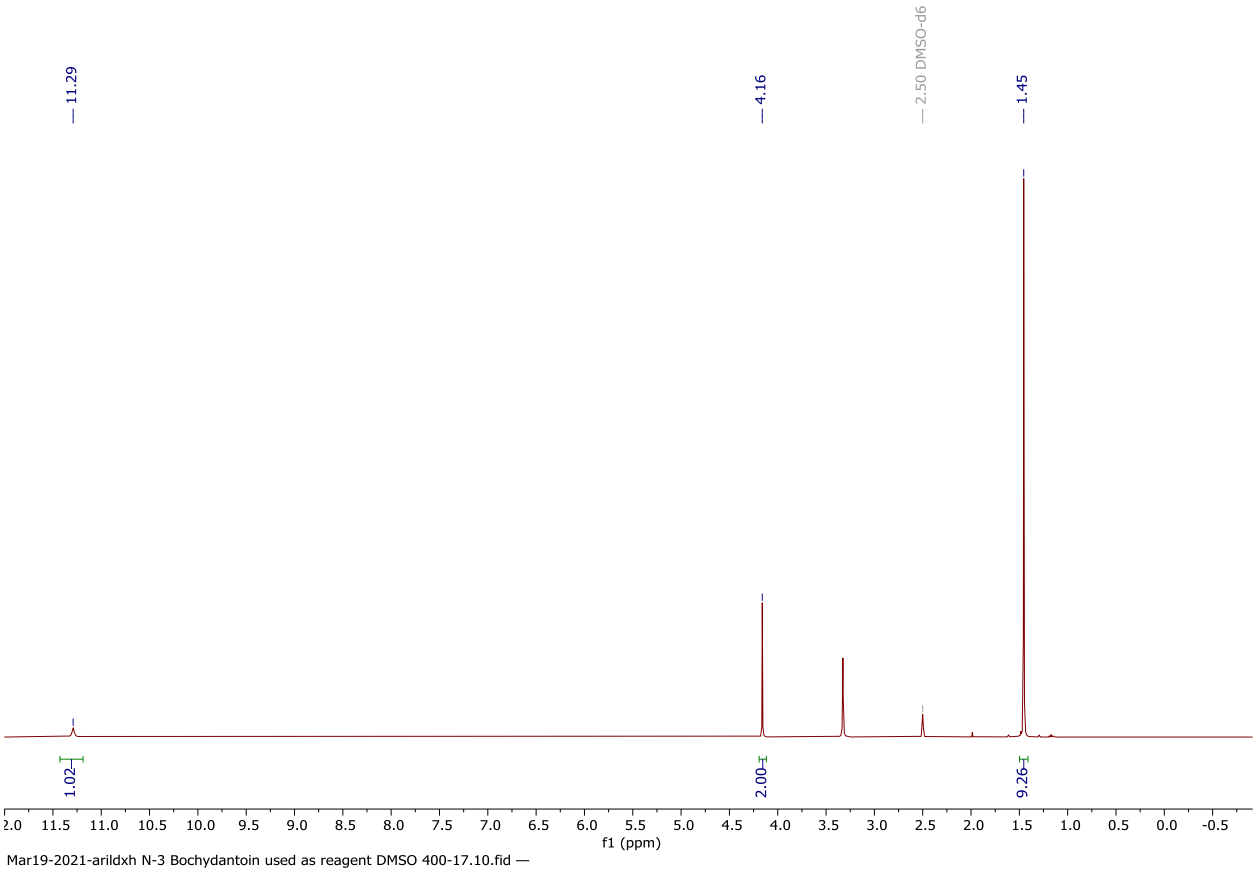
2L was obtained using the following method:

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{18}H_{12}N_6NaO_4{}^{104}Pd^+$: 502.9853, found: 502.9853

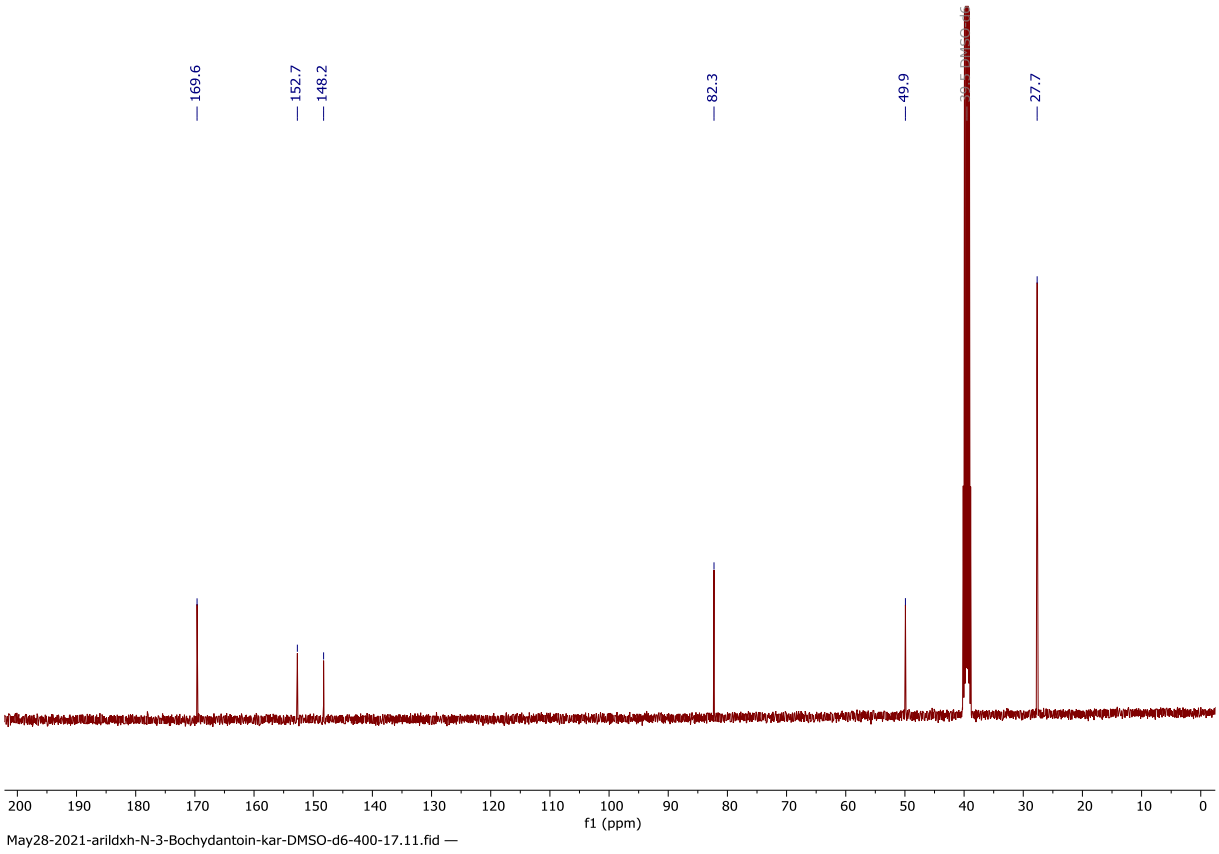
4 Appendix

4.1 N-1 Bochydantoin (2A)

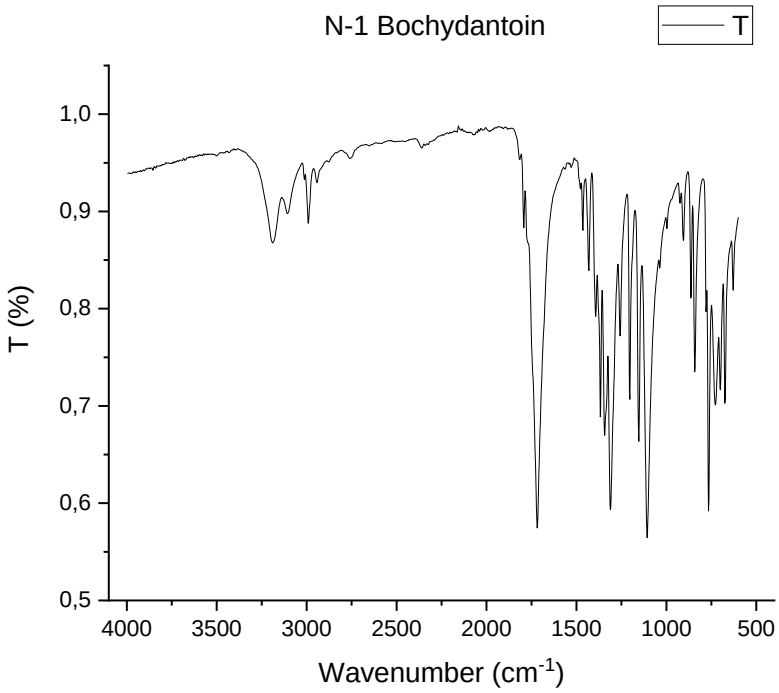
4.1.1 H-NMR spectrum 2A



4.1.2 C- NMR spectrum 2A

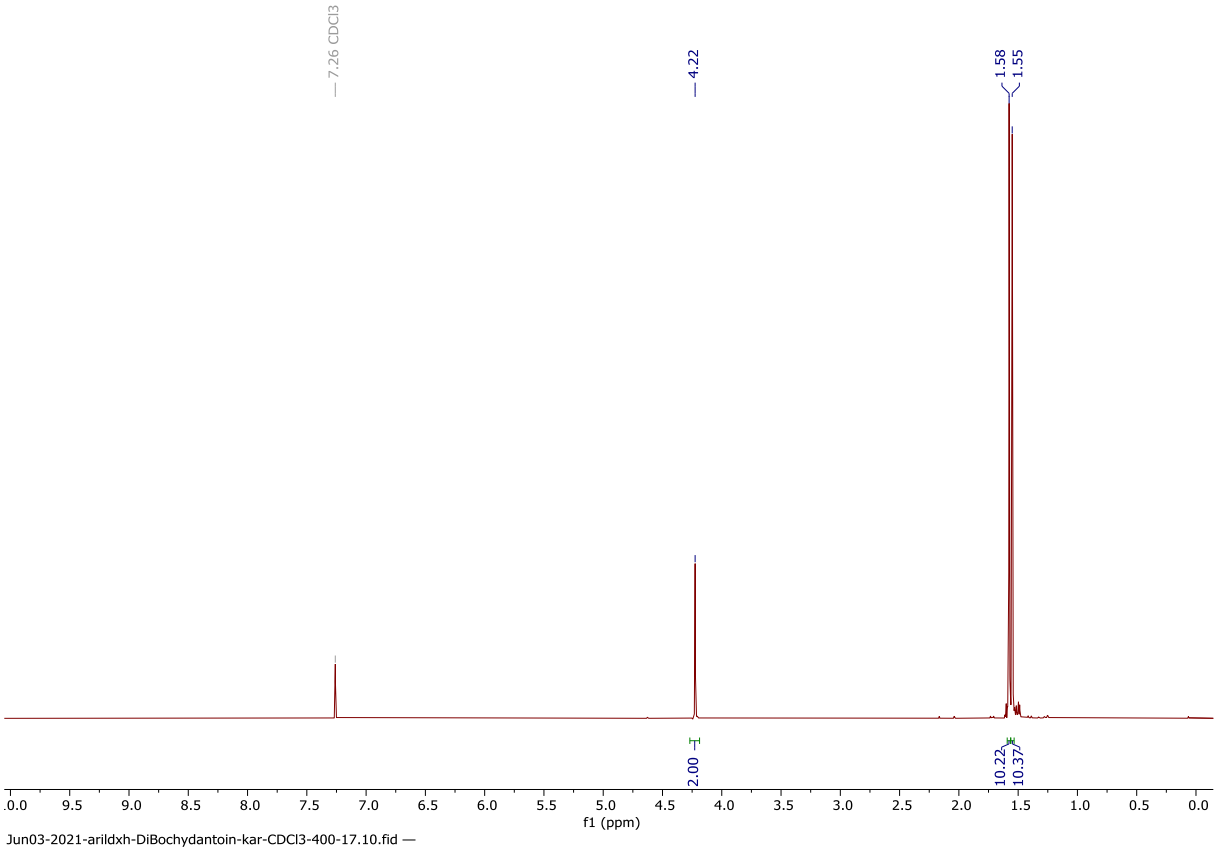


4.1.3 FTIR Absorption spectrum 2A

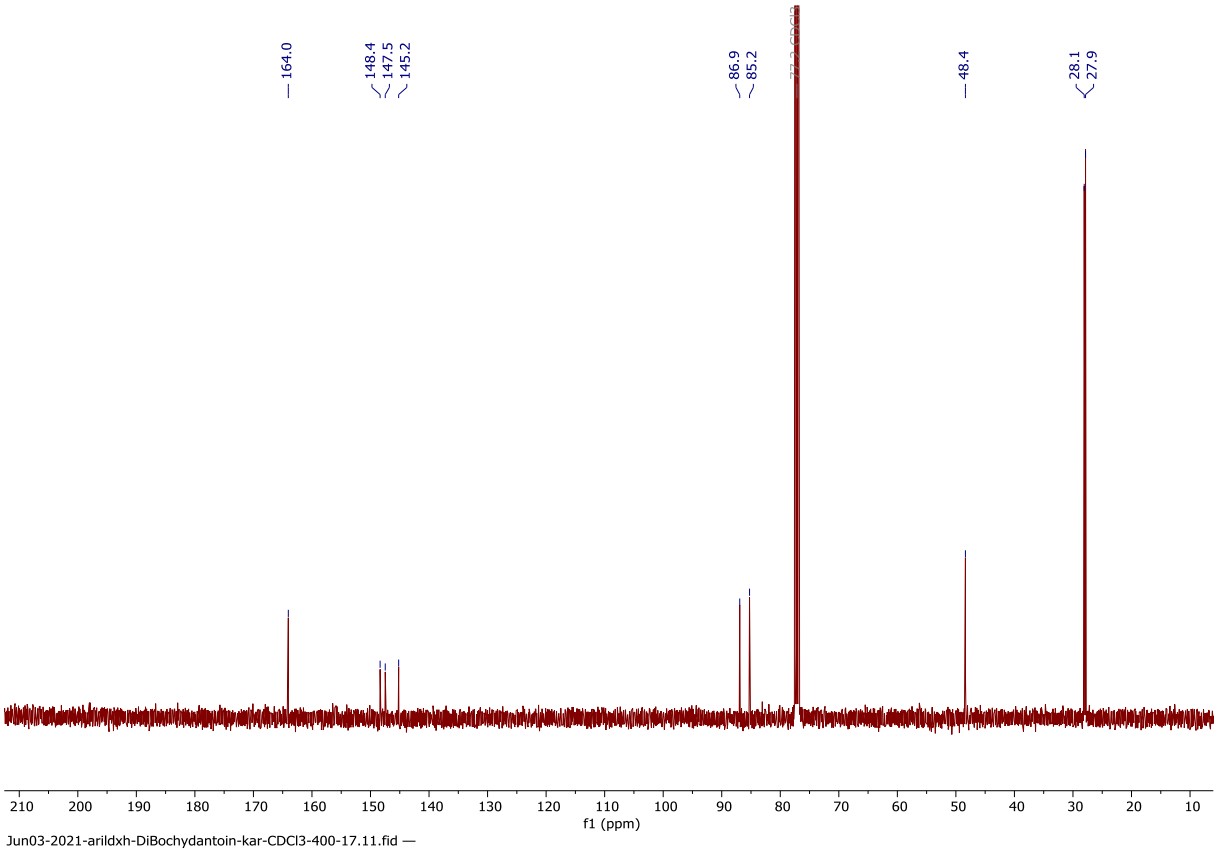


4.2 N-1, N-3 diBochydantoin (2B)

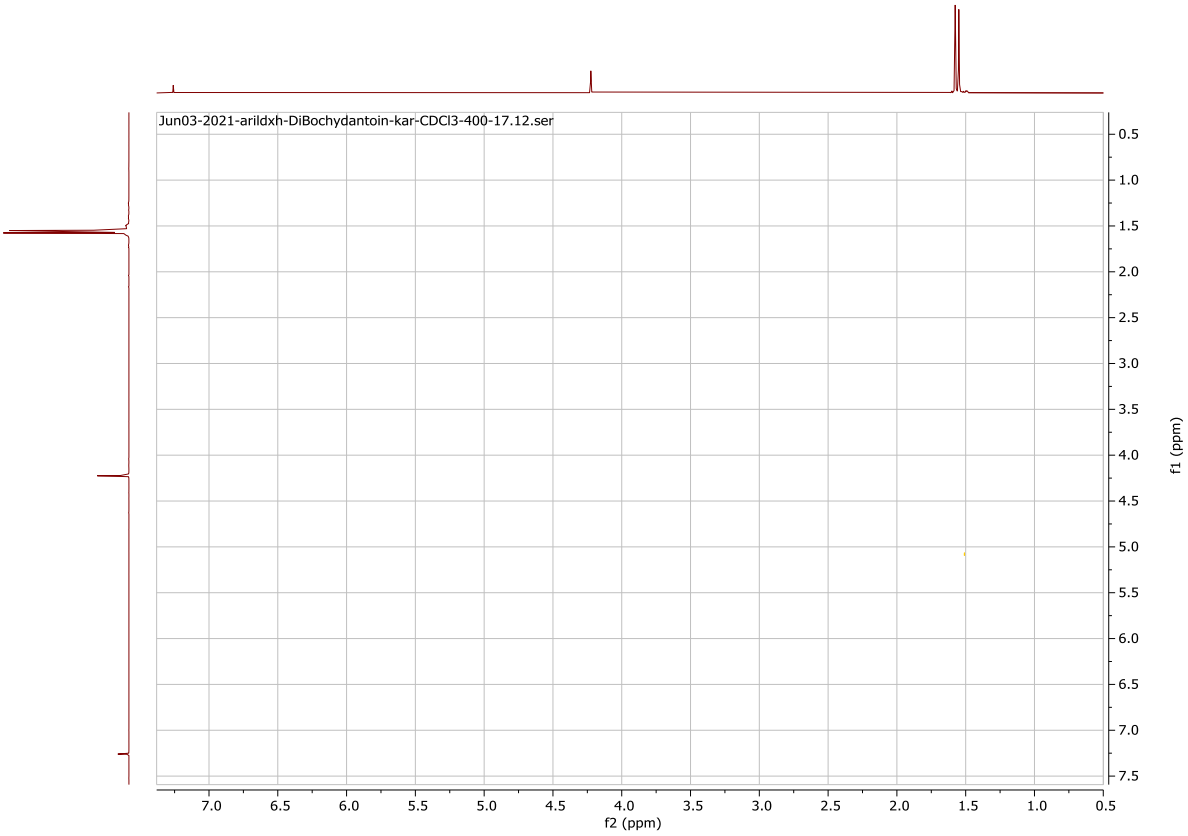
4.2.1 H-NMR spectrum 2B



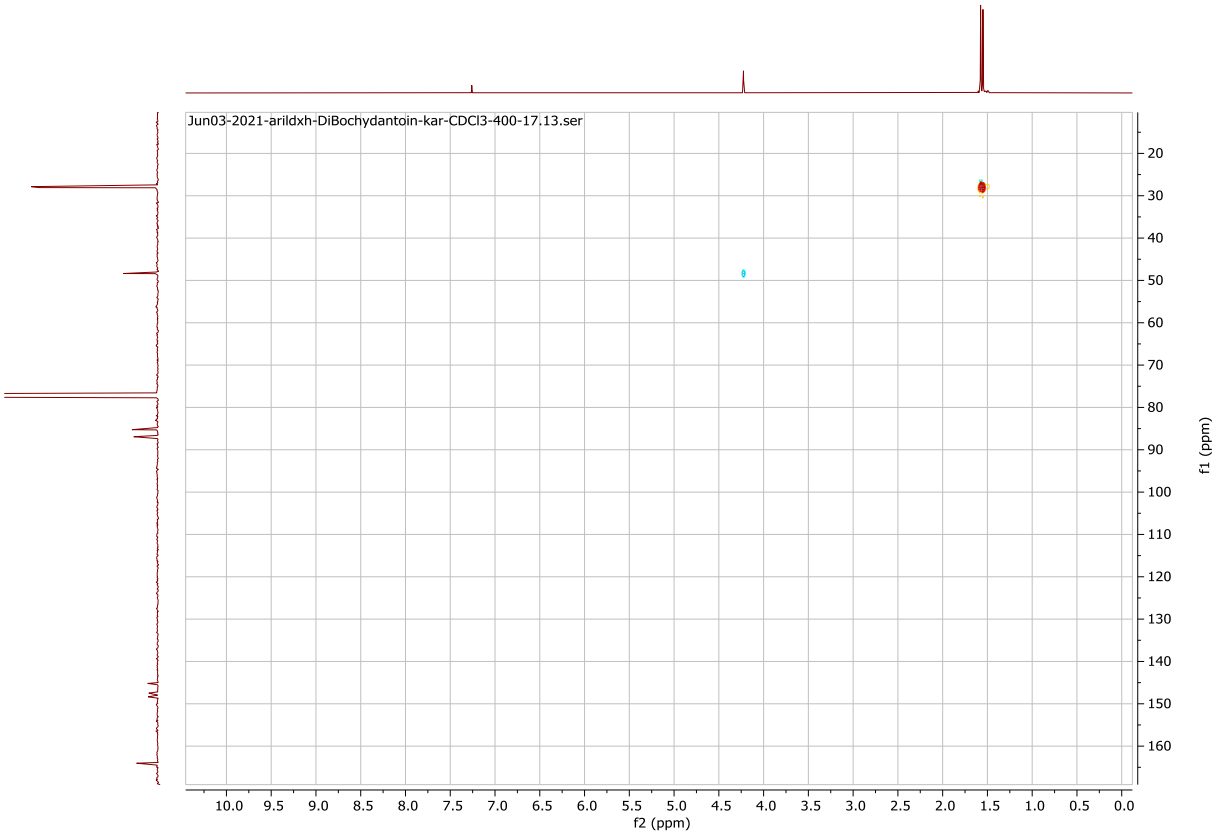
4.2.2 C- NMR spectrum 2B



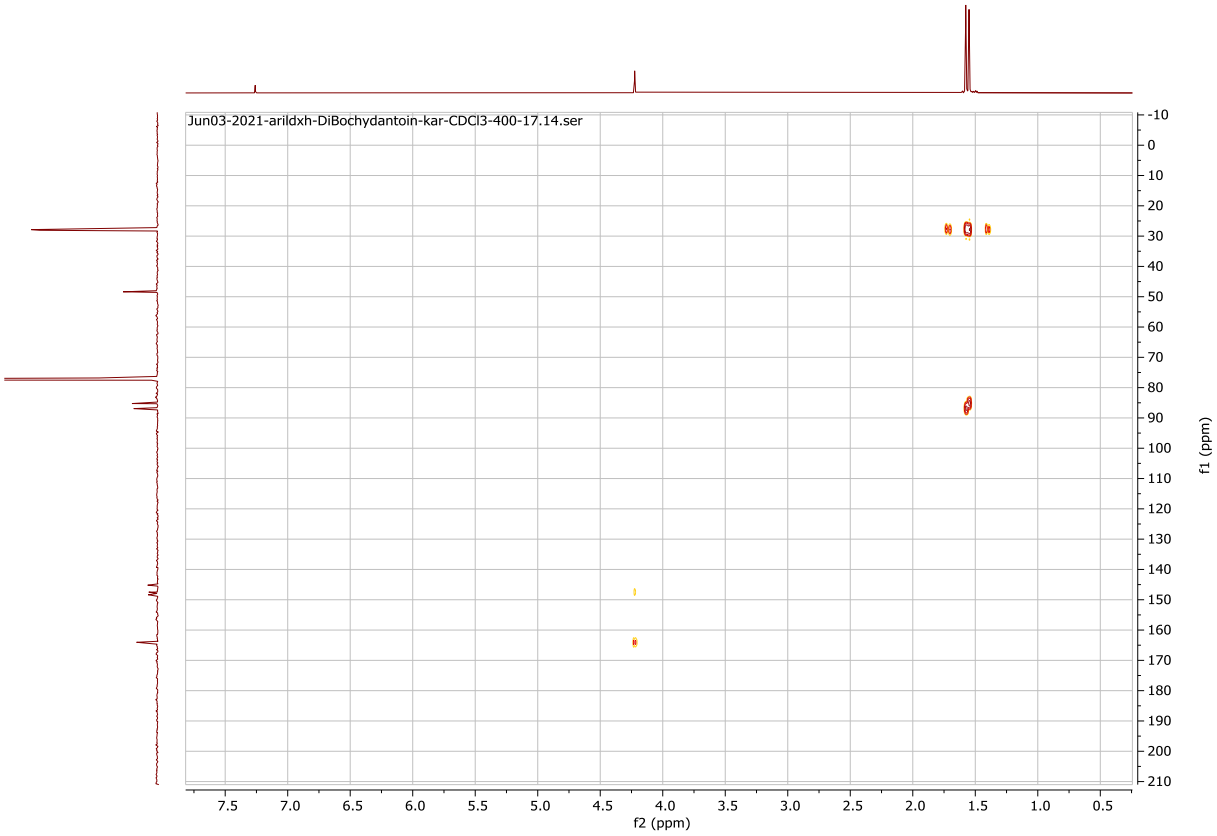
4.2.3 1H-1H COSY spectrum 2B



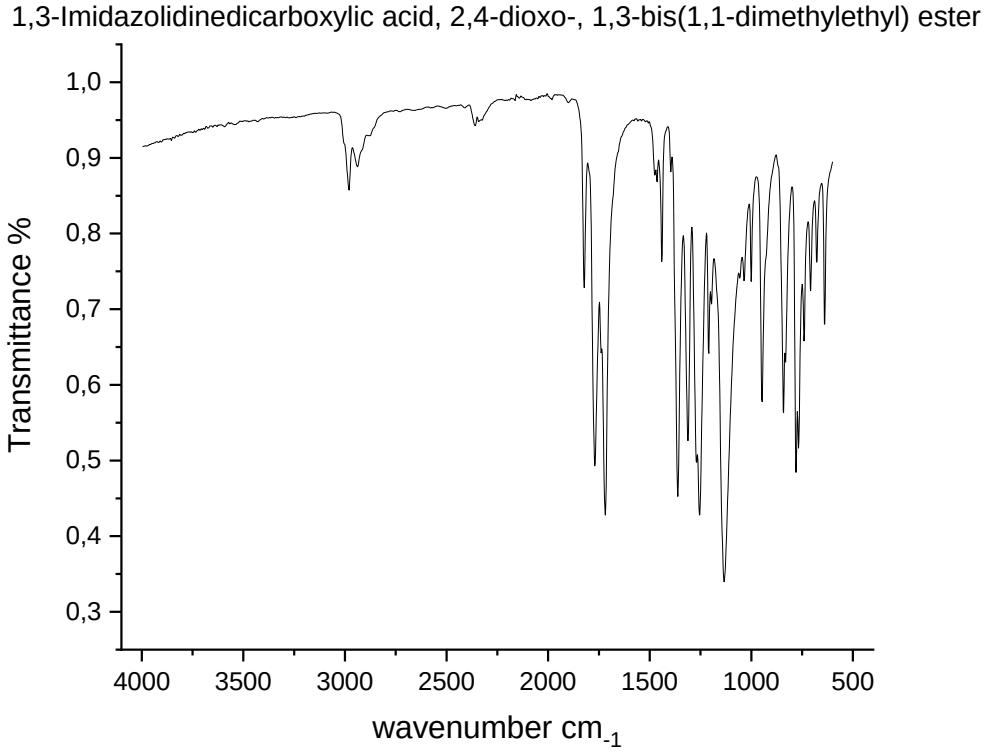
4.2.4 1H-13C HSQC spectrum 2B



4.2.5 1H-13C HMBC spectrum 2B

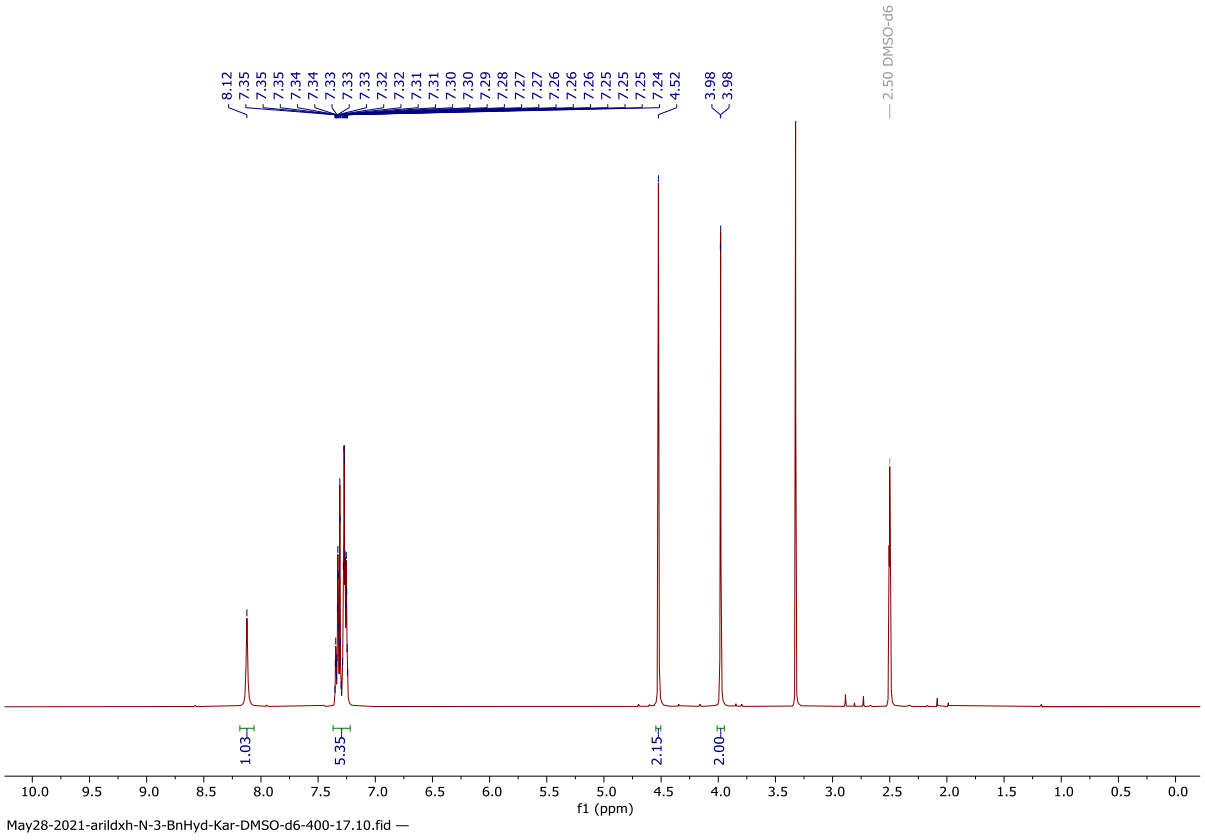


4.2.6 FTIR Absorption spectrum 2B

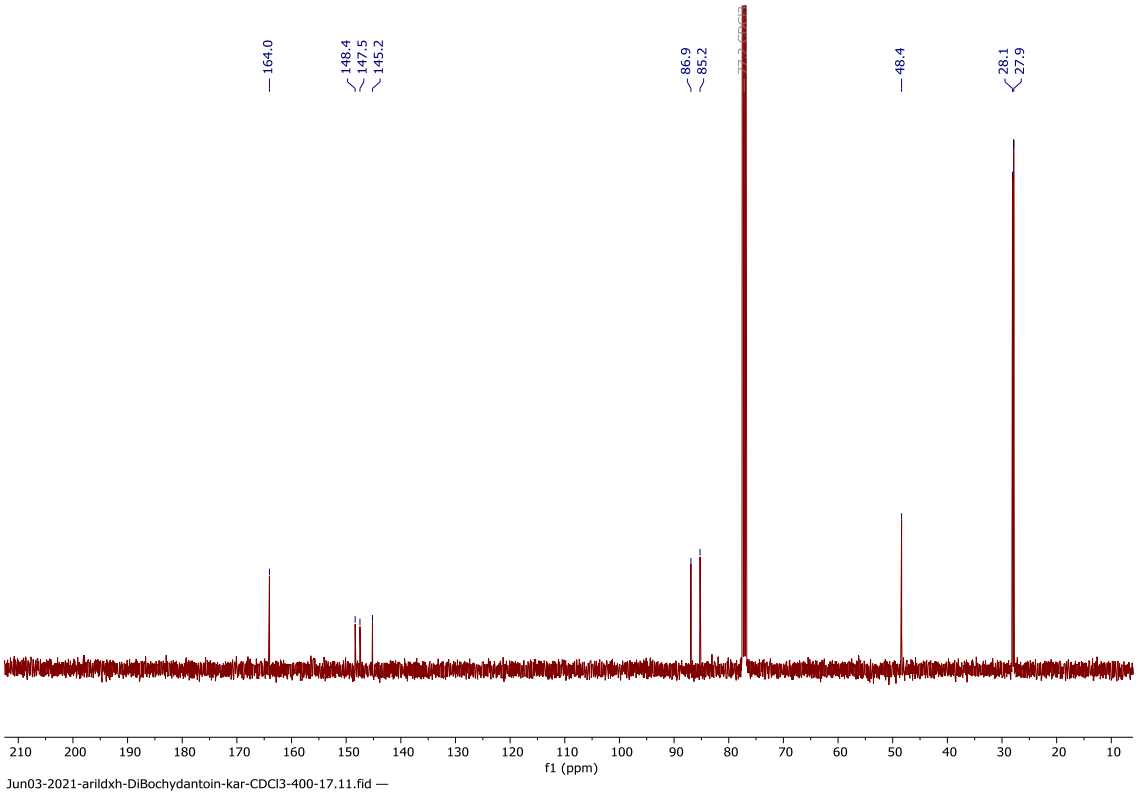


4.3 N-3 benzylhydantoin (2C)

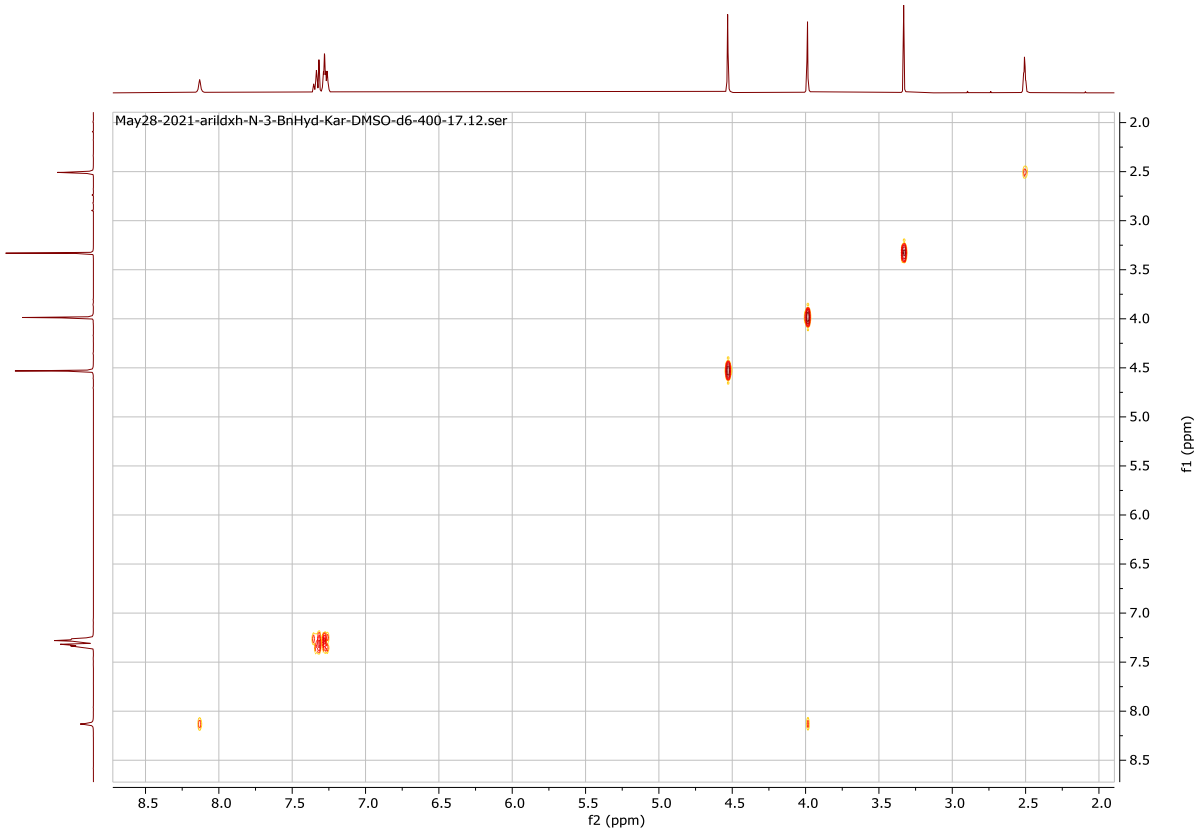
4.3.1 H-NMR spectrum 2C



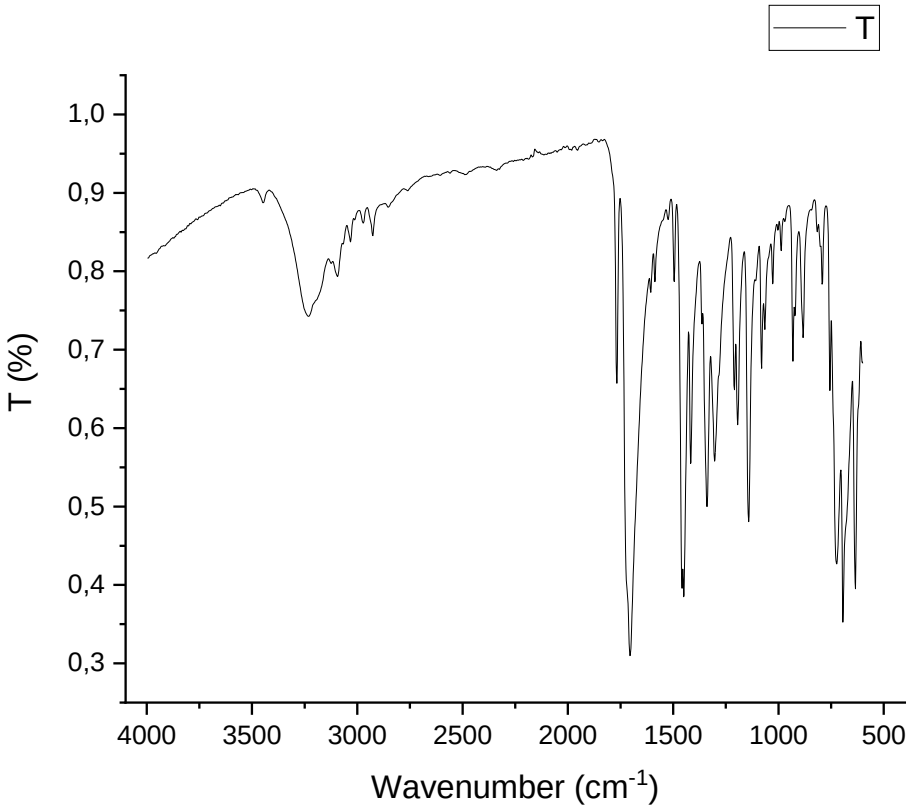
4.3.2 C- NMR spectrum 2C



4.3.3 COSY spectrum 2C

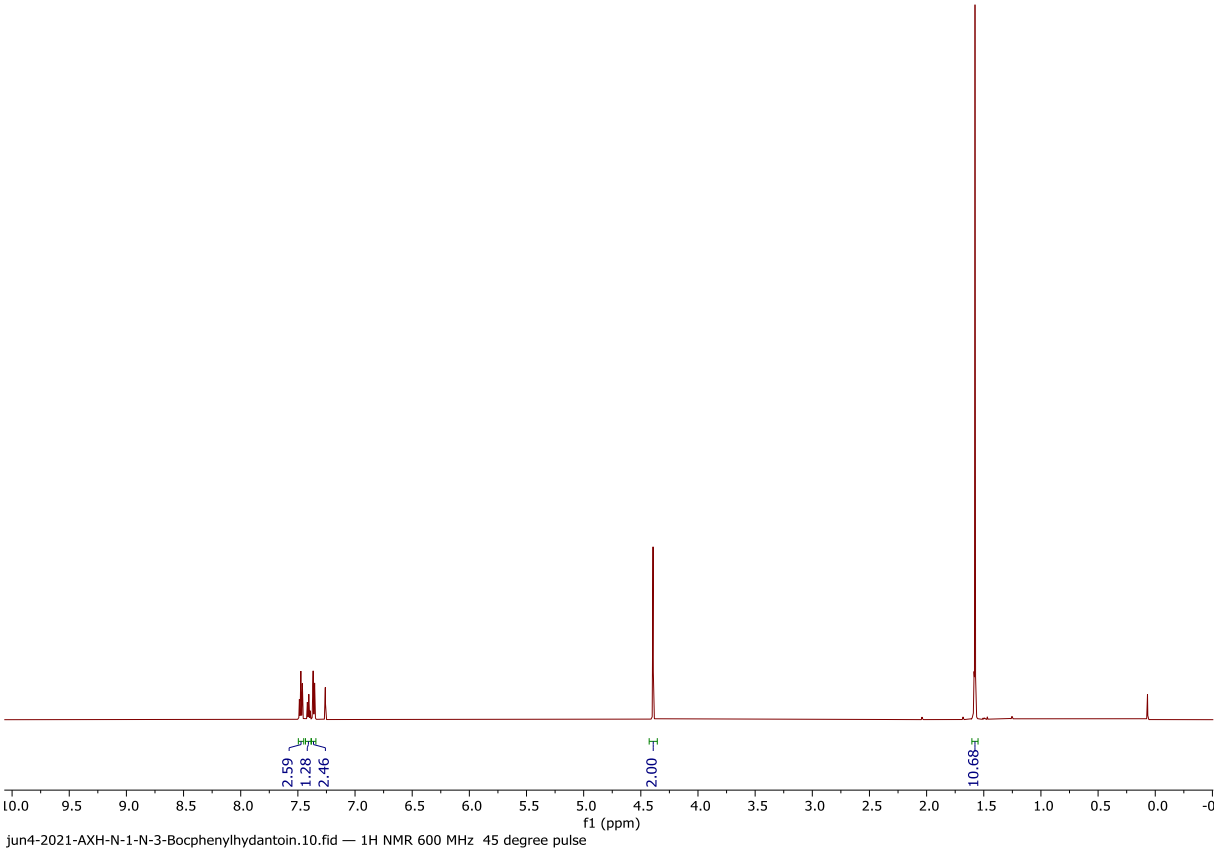


4.3.4 FTIR spectrum 2C

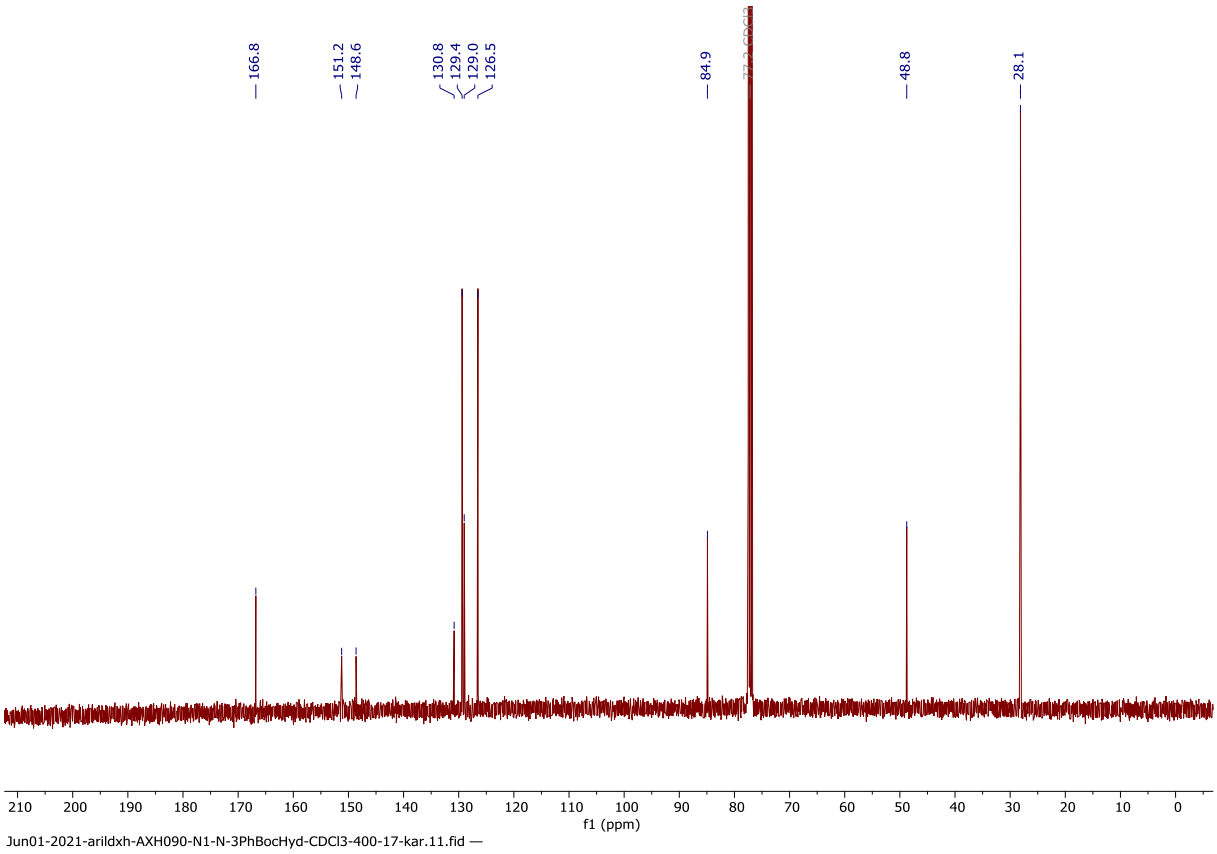


4.4 N-1, N3, Bocphenylhydantoin (2D)

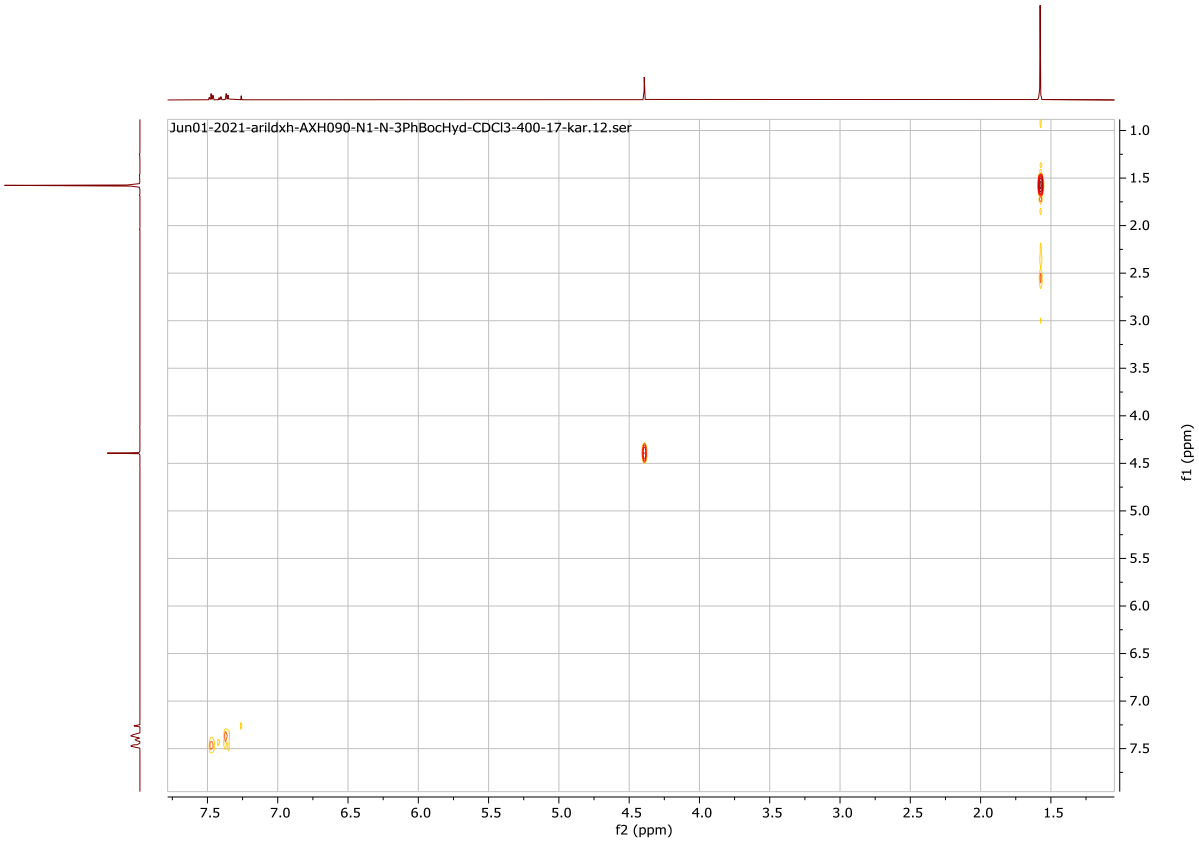
4.4.1 1H-NMR spectrum 2D



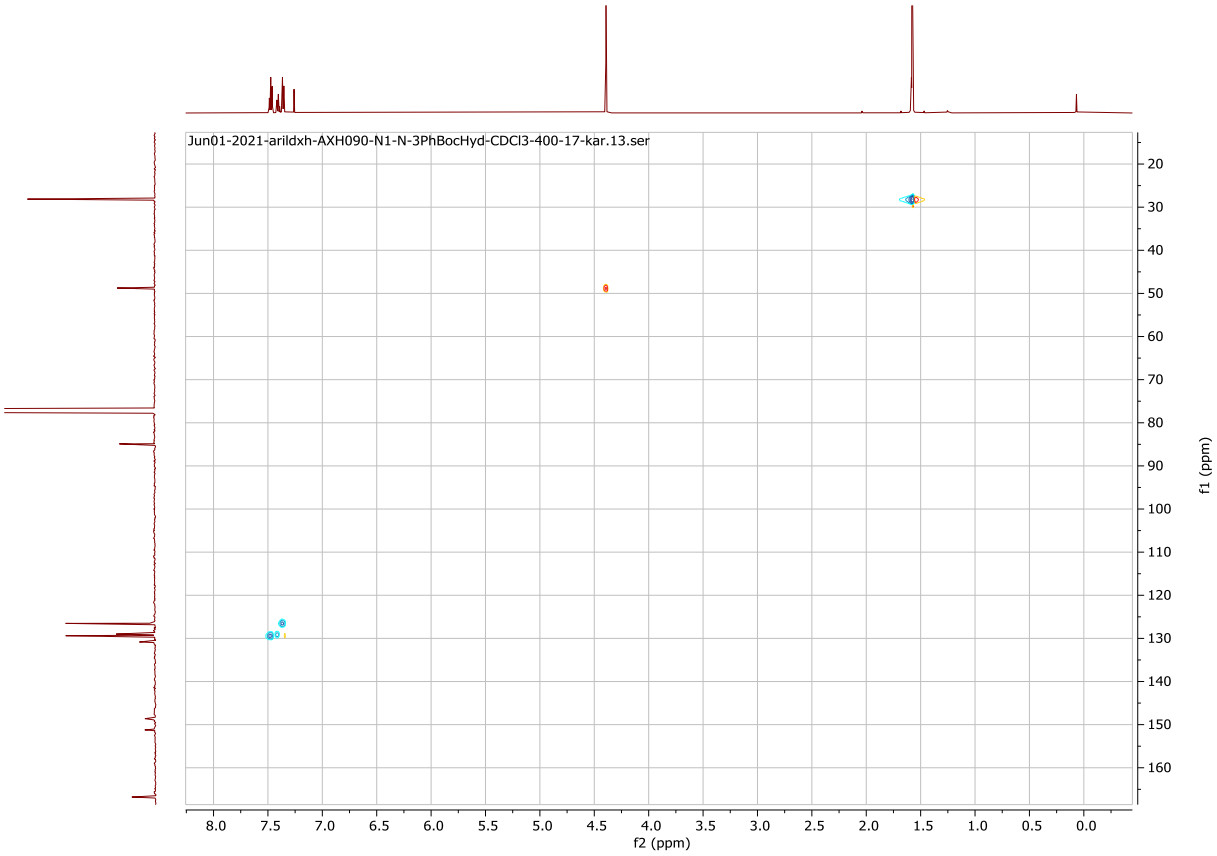
4.4.2 13C- NMR spectrum 2D



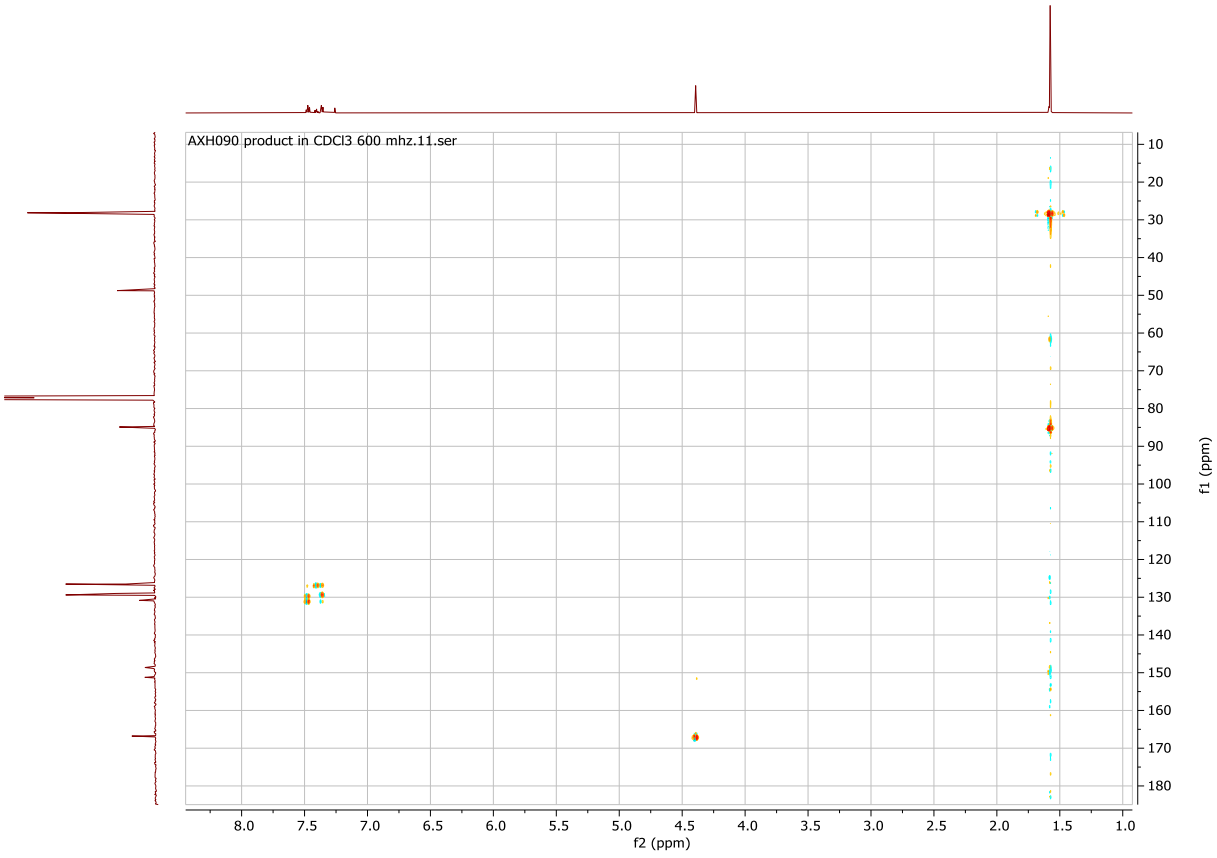
4.4.3 1H-1H COSY spectrum 2D



4.4.4 1H-13C HSQC spectrum 2D

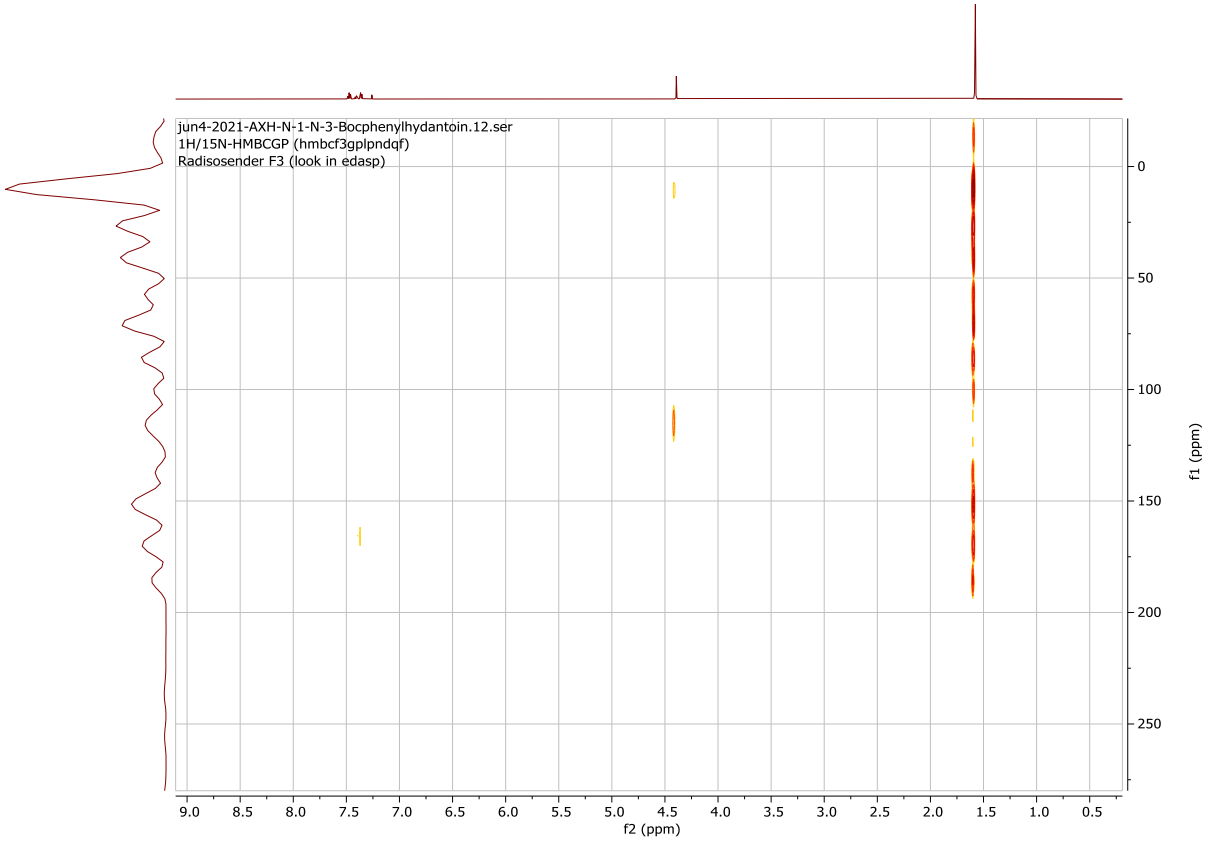


4.4.5 1H-13C HMBC spectrum 2D

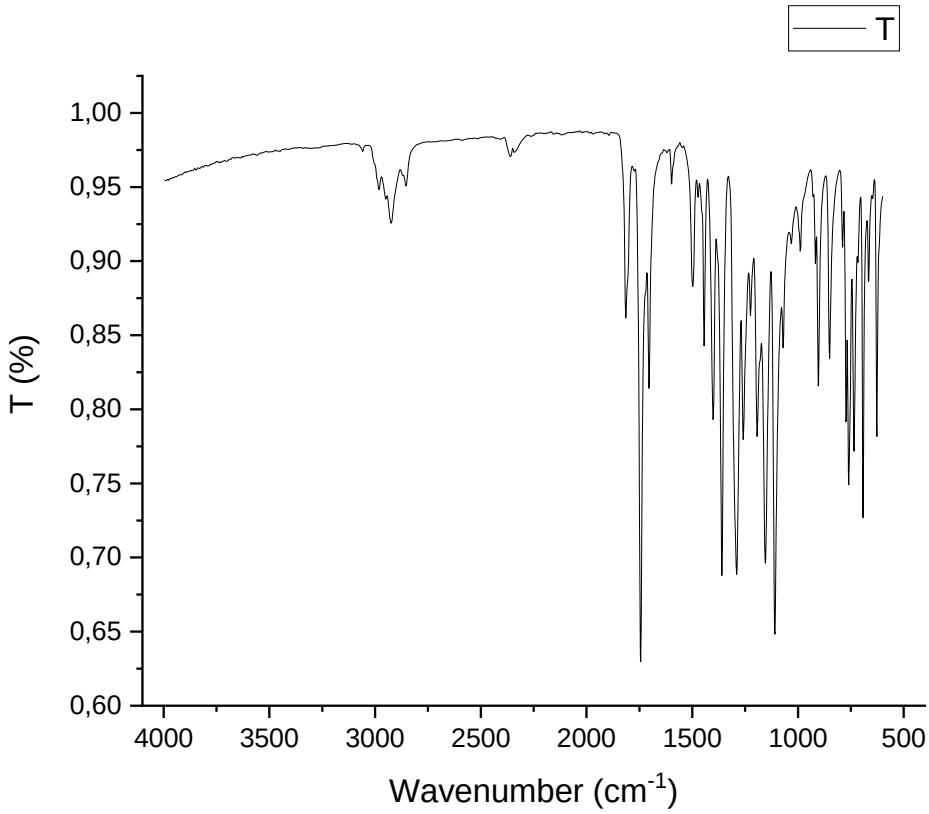


4.4.6 1H-15N HMBC 2D

The Boc tert butyl group at around 1.5 gives mostly noise and not real correlations.

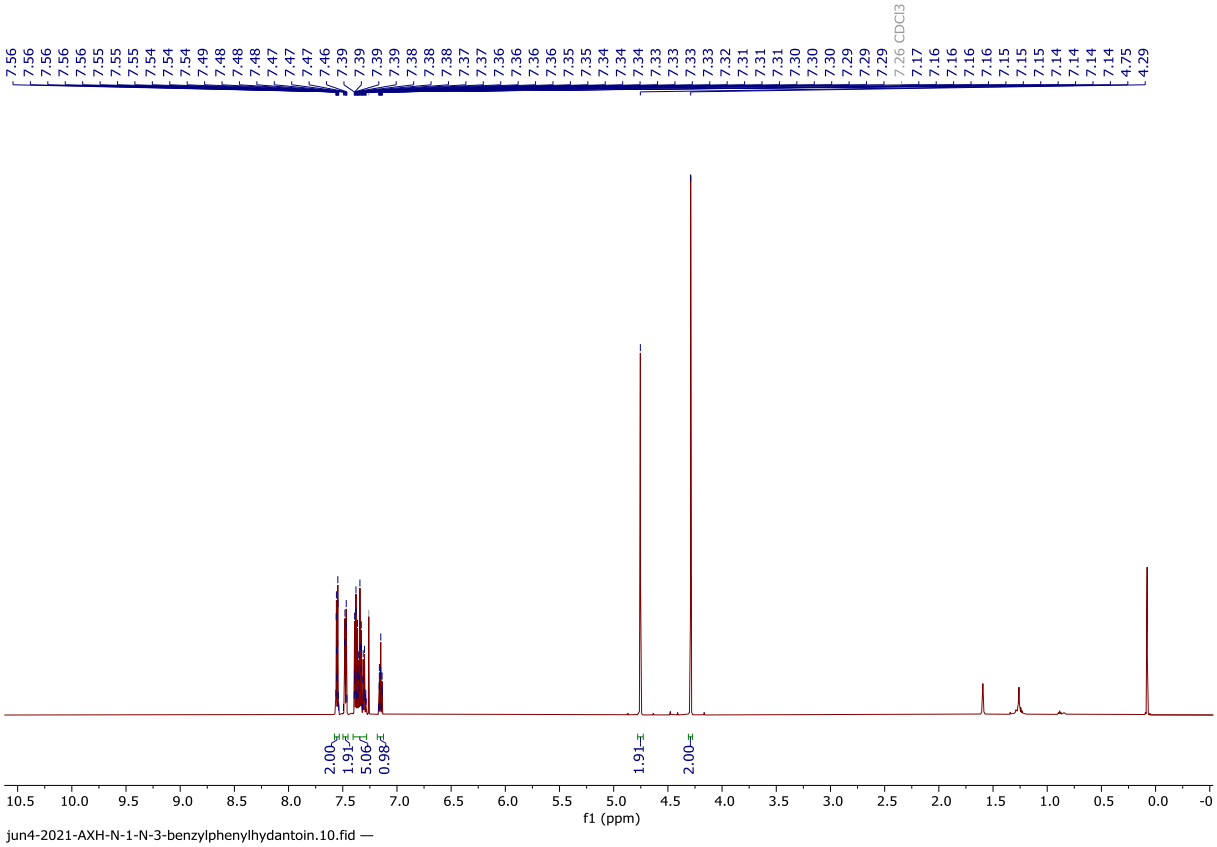


4.4.7 FTIR spectrum 2D

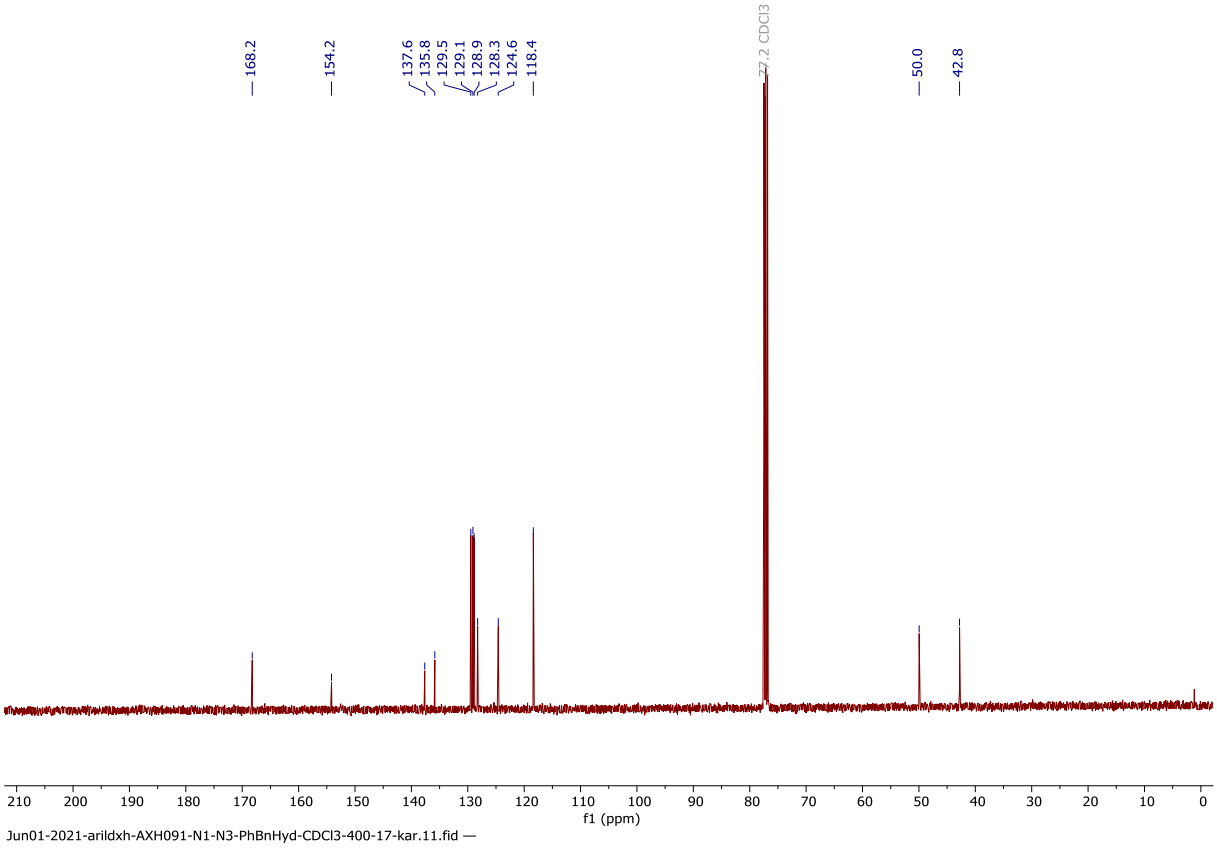


4.5 N-1, N-3 phenylbenzylhydantoin (2E)

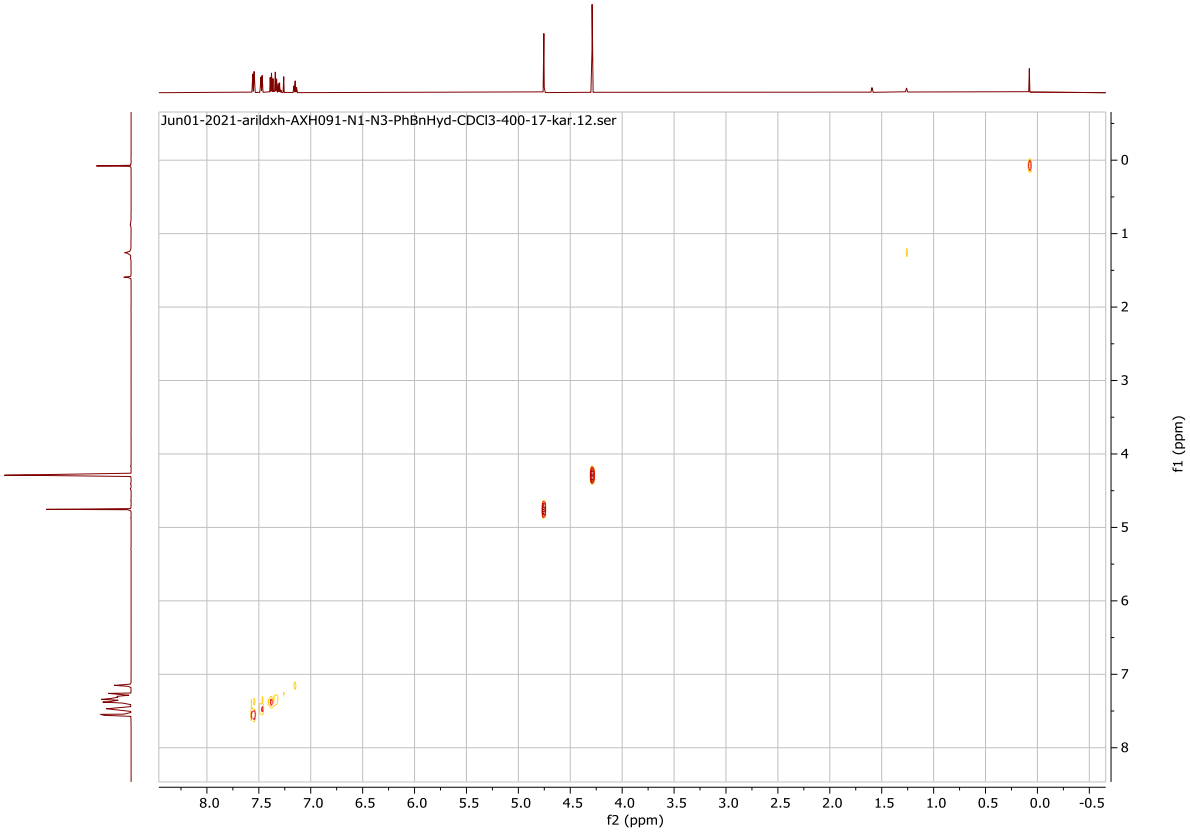
4.5.1 1H-NMR spectrum 2E



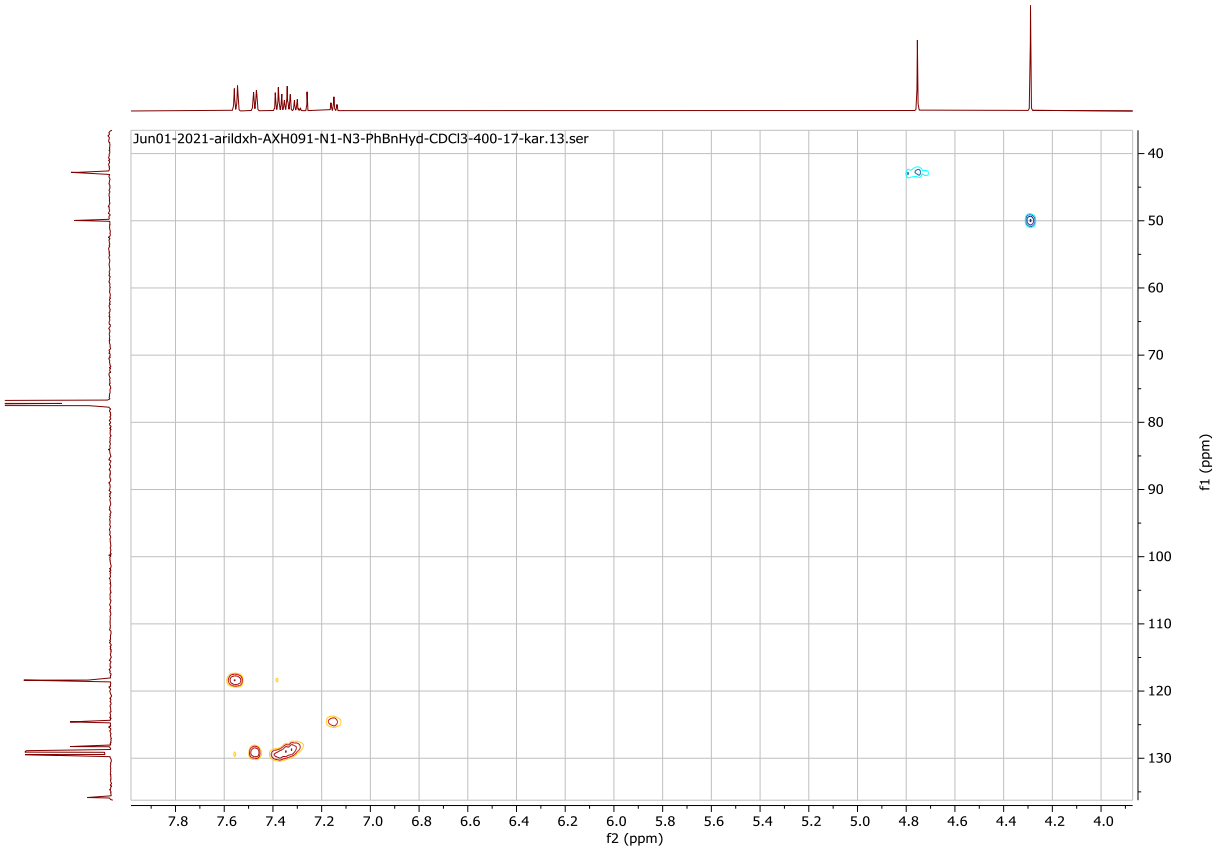
4.5.2 13C- NMR spectrum 2E



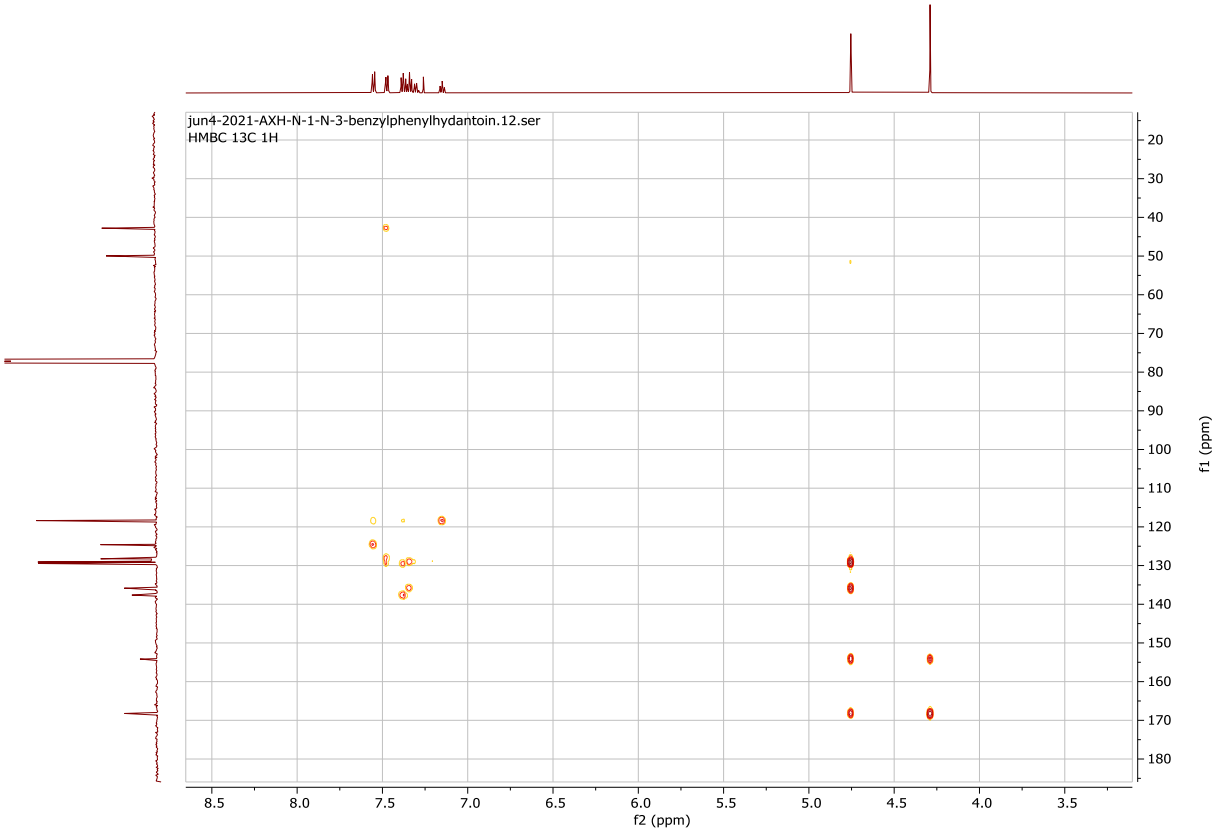
4.5.3 1H-1H COSY spectrum 2E



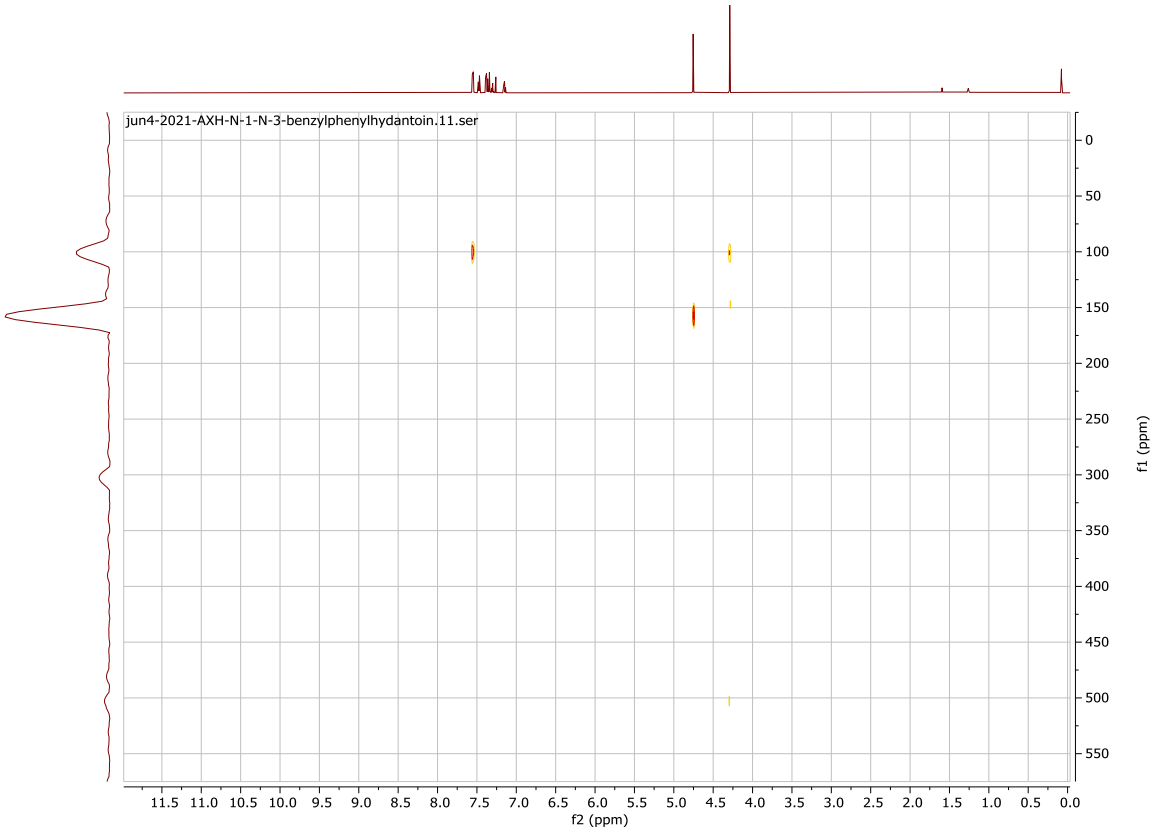
4.5.4 1H-13C HSQC spectrum 2E



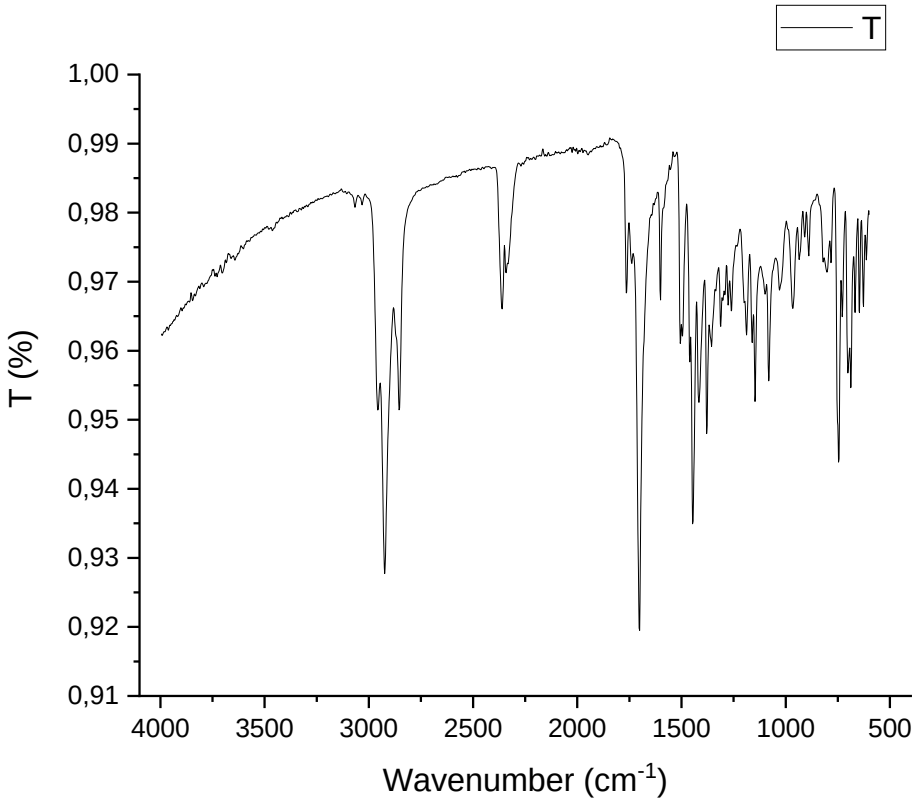
4.5.5 1H-13C HMBC spectrum 2E



4.5.6 1H-15N HMBC 2E

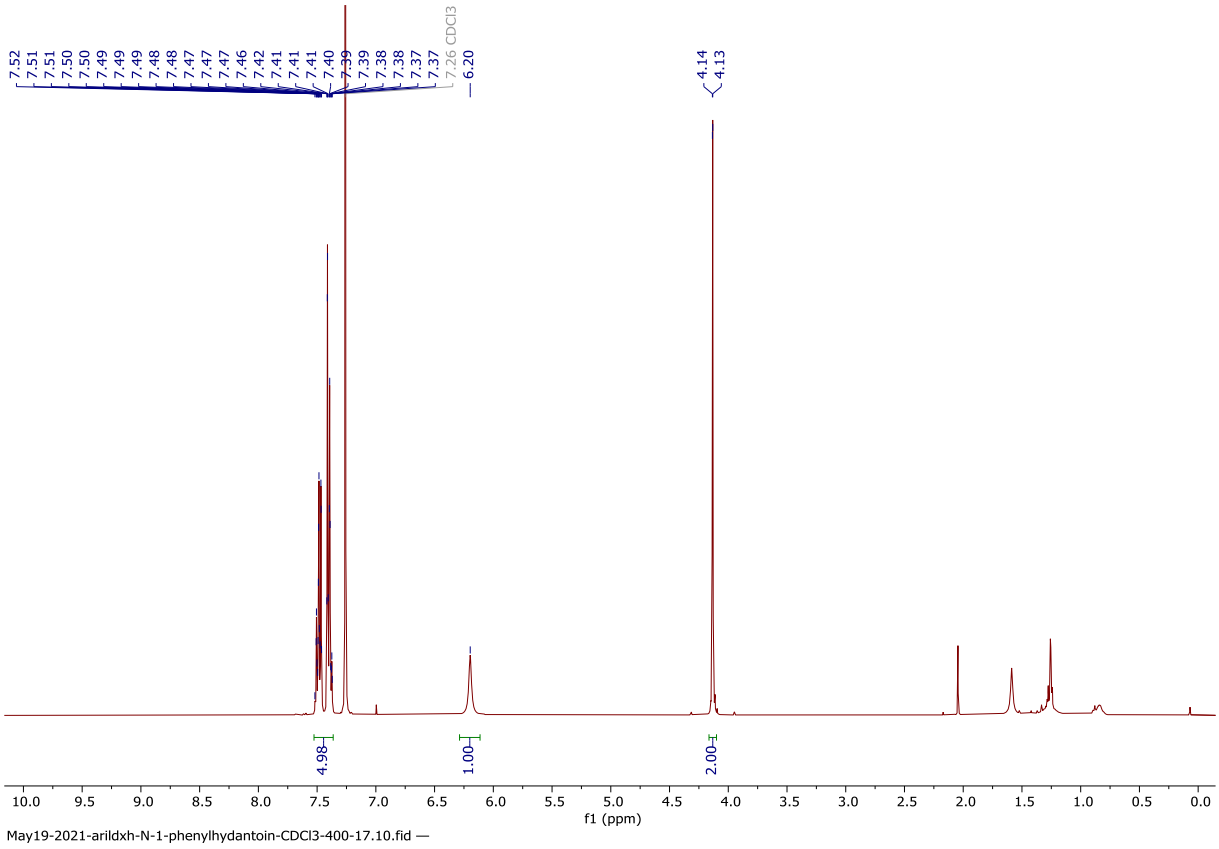


4.5.7 FTIR spectrum 2E

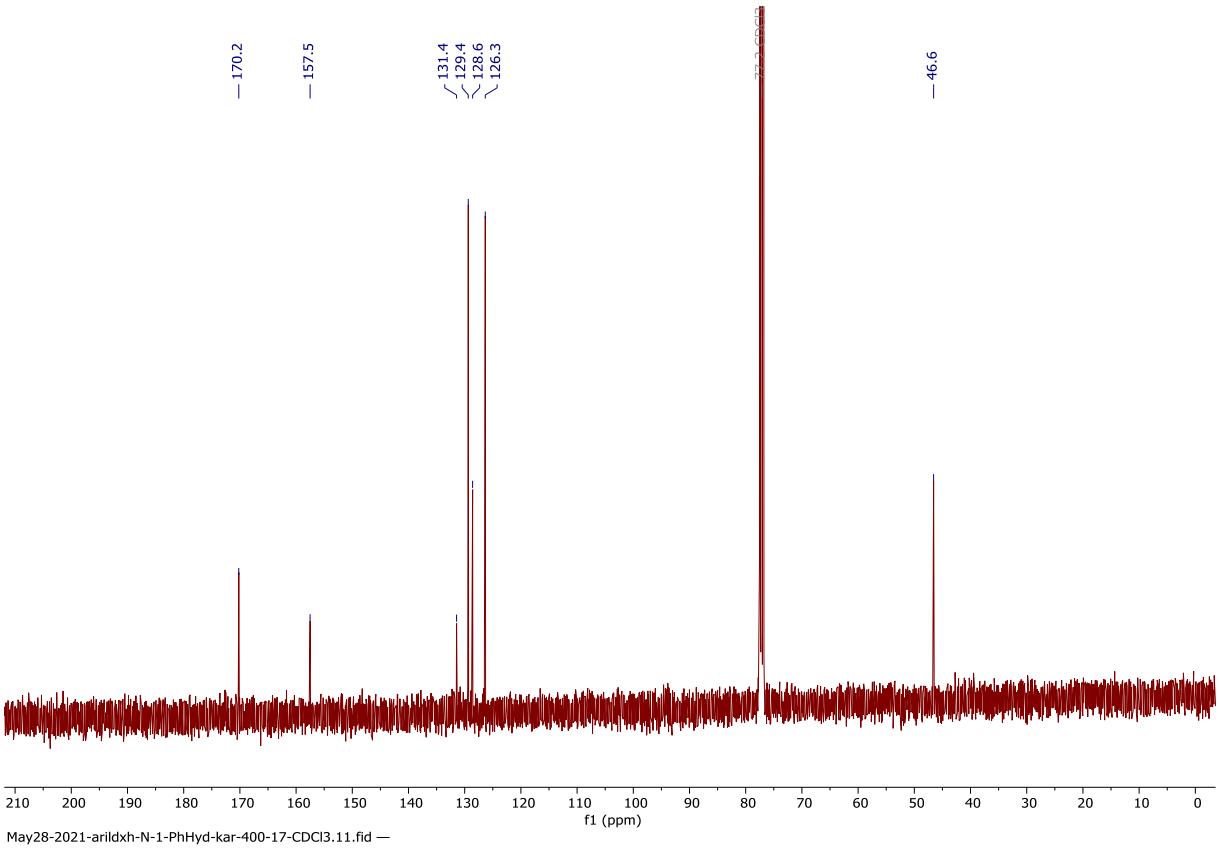


4.6 N-3 phenylhydantoin (2F)

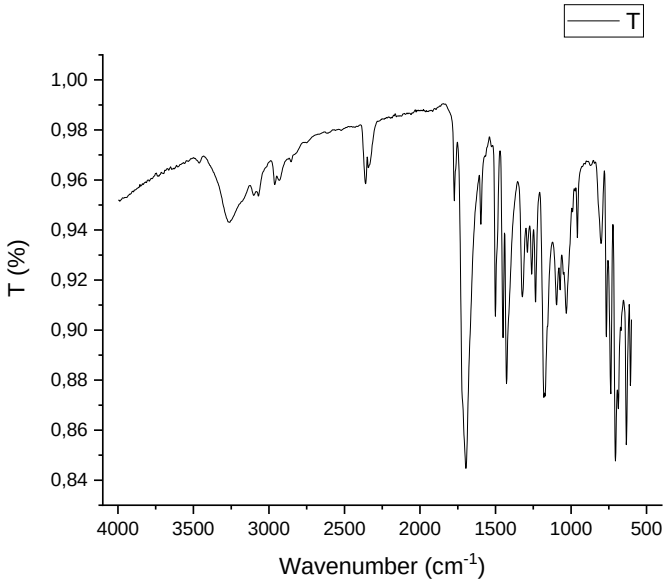
4.6.1 1H-NMR spectrum 2F



4.6.2 C- NMR spectrum 2F



4.6.3 FTIR spectrum 2F



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3. Kruger, H. G.; Mdluli, P. S. Regioselective protection of hydantoins – essential for hydantoin based anti-epileptic drugs. *J. Struct. Chem.* **2006**, 17 (1), 121-125.

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