Modified Conditions for Acyl Azide and Carbamate Synthesis

by

Christopher N. Copeland II

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Modified Conditions for Acyl Azide and Carbamate Synthesis

Christopher N. Copeland II

Signature:

Christopher N. Copeland II, Student Date

Approvals:

Dr. Peter Norris, Thesis Advisor Date

Dr. John A. Jackson, Committee Member Date

Dr. Sherri Lovelace-Cameron, Committee Member Date

Dr. Salvatore A. Sanders, Dean of Graduate Studies Date

Thesis Abstract:

Carbamate chemistry has a wide variety of applications both in synthetic chemistry as well as in biology. This carbon-nitrogen containing functional group is used as a linker in many potential pharmaceutical agents and in numerous biological systems. These linkages are not only found in naturally occurring substances, however, but can be synthesized in the lab under quite facile conditions via different routes. Organic acyl azides are excellent precursors for these types of linkers and in this thesis we have developed an alternative one-pot synthesis to yield the carbamate product.

Acknowledgements:

First and foremost, I would like to thank Dr. Peter Norris, my graduate advisor. Since coming under your guidance, I have become a better student, professional and scientist. I have thoroughly enjoyed the last three years under your wing, and cannot wait to put my skills to the test in the next phase of life. Thank you for all of your time since bringing me into your research group.

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Background

Organic azides are one of the most versatile and useful functional groups and are important intermediates in organic and bio-organic synthesis. They are compounds that contain an azide group (N_3^-) bonded to carbon atoms in an organic molecule. These compounds were first discovered by Peter Grieβ in 1864, when he first synthesized phenyl azide. Over the years, organic azides have been shown to produce other very important functionalities, such as amines and heterocycles, that can be used en route to larger and more complex biological molecules. [1]

Metallic azides have very interesting properties. In an industrial setting, the azide source that is most commonly used is sodium azide (NaN_3). This ionic relationship can be troublesome from a synthetic standpoint, in which these azide salts can be rendered explosive. This is due to the decomposition, with loss of nitrogen gas, by external means such as impact, heat and reduced pressure. Ionically bound azides are used as detonators, with sodium azide being used in vehicle airbags.[1]

Azides are classified as high energy materials (HEM's). The π bonds are polarizable, and the azide decomposes into molecular nitrogen and a nitrene.[2] The loss of molecular nitrogen explains the high reactivity of the azide functional group, especially its detonation potential. The general structure of ionic azide is described in **Figure 1**.

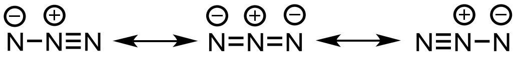


Figure 1: Resonance structures of azide anion.

Although azides can be dangerous to use in the laboratory, they are very important to synthetic chemists and process engineers. Pharmaceutical companies use azides as intermediates in syntheses en route to their medicinal products, for example in the production of AZT (**Figure 2**). The easy conversion of azides to amines makes azide chemistry invaluable in the medicinal chemistry field due to the presence of the amine functionality in amino acids and other biologically derivatives. Polymer chemists also have uses for azides, as they can be co heterocycles such as triazoles, with such heterocycles being used as linkers between biologically active monomers.[3]

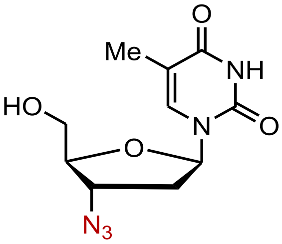
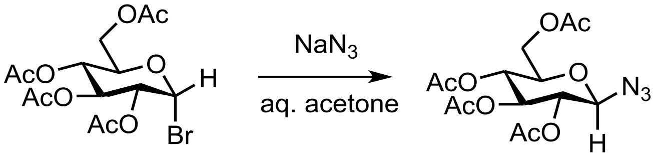


Figure 2: 3'-Azido-3'-deoxythymidine, an anti-HIV medication.

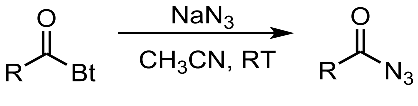
Interest has also grown in the general organic field with regards to azide chemistry. Synthetic chemists can generate azides through a variety of different reactions with one of the more common methods being insertion of the N_3 group via substitution or addition chemistry (e.g. **Equation 1**). A versatile application of the azido group is in the Staudinger reaction, in which alkyl azides are reacted with aryl phosphines resulting in amine formation.[4] In the initial substitution reactions, azides typically are attached by reaction of the azide anion with a substrate bearing a good leaving group. With respect to the work presented here, azides bearing sulfonate leaving groups will be reacted with a nucleophilic base to displace the azide group from the sulfonate leaving group. Subsequently, the free azide in solution can react with acyl chlorides, forming acyl azides. These will be the precursors for the second type of reaction used, which is the Curtius Rearrangement to produce carbamate products.



Equation 1: Formation of azide via S_N2 reaction.

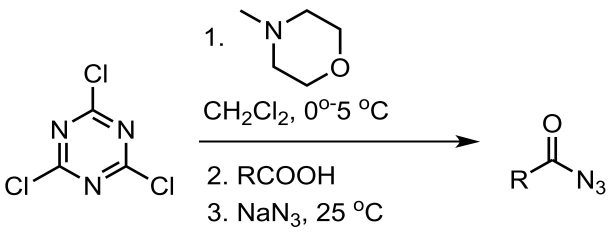
The first part of this research involves the formation of acyl azides. These are highly reactive compounds that are used further as reagents in organic research. They are typically prepared by reacting NaN_3 with either acid chlorides or mixed anhydrides. Other methods that have been employed to synthesize acyl azides include the use of carboxylic acids.[5] Reagents such as diphenyl phosphoryl azide (DPPA) in the presence of base are used, as well as acid activators such as $SOCl_2$ and DMF,[5] cyanuric chloride and *N*-methylmorpholine,[6] and triphosgene with triethylamine.[7]

The formation of acyl azides has been reported by Katritzky and coworkers, where NaN_3 was reacted with acyl benzotriazoles rather than utilizing the more traditional acid chloride method (**Equation 2**). This is a two-step synthesis that avoids the use of NO^+ acid activators which are typically used in these reactions. Although yields were good, the use of NaN_3 in synthesis does not represent the safest protocol that can be utilized.[8]



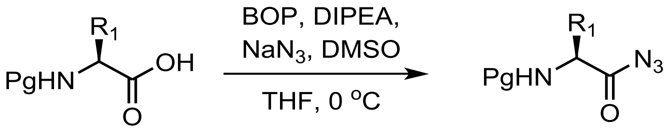
Equation 2: Synthesis of acyl azide by Katritzky and coworkers.

B.P. Bandgar and colleagues were also able to successfully synthesize acyl azides. In their research, they converted carboxylic acids to azides with the use of cyanuric chloride. This took the place of other more dangerous acid activators that have been used, such as triphosgene, which is a very toxic reagent due to its decomposition to poisonous phosgene in the presence of moisture. Cyanuric chloride is commercially available and inexpensive. (**Equation 3**).[6]



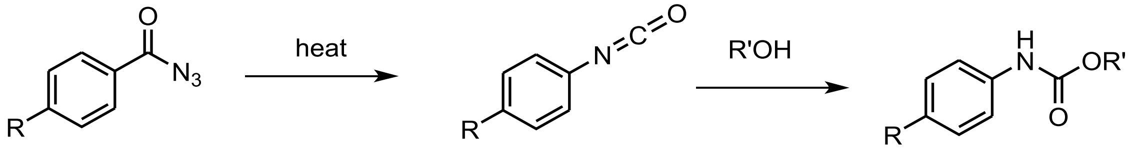
Equation 3: Acyl azide conversion using cyanuric chloride and a carboxylic acid.

Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) has been used for the synthesis for acyl azides and protected amino acid azides also (**Equation 4**). A carboxylic acid reacts with base, then BOP coordinates the carboxylate, thus forming an acyl phosphonium salt in the second step. After the benzotriazole group reattaches to the acyl group, NaN_3 is added to completely form the acyl azide in good yield. This procedure is not only inexpensive but it takes place within 20 minutes, which is very fast for a two-step protocol.[8]



Equation 4: Two-step protocol for acyl azide synthesis using BOP reagent.

The second interest of this research is generating the acyl azide *in situ* so that it may undergo the Curtius rearrangement to synthesize organic carbamates (**Scheme 1**). This would be accomplished through heating the acyl azide, which will decompose to give an isocyanate. This is a highly reactive intermediate electrophile that can be trapped by a host of nucleophiles. In this case, we will use alcohols as the nucleophiles to intercept these intermediates.



Scheme 1: Formation of carbamates via the Curtius rearrangement.

Organic carbamates are very versatile compounds that have an interesting functionality for synthetic chemists. They are important as useful intermediates,[9] and play a role in drug design and medicinal chemistry.[10] The structure of a carbamate mimics that of an amide, which serves as the peptide linker in proteins. The hydrogen bound to the nitrogen of the carbamate can also play a key role in proton donation. These molecules are also used for the design for enzyme inhibitors. Additionally, they are used in agrochemistry,[11] being found as components of many pesticides[12] (**Figure 3**).

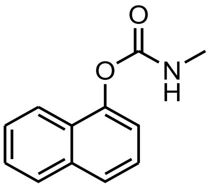
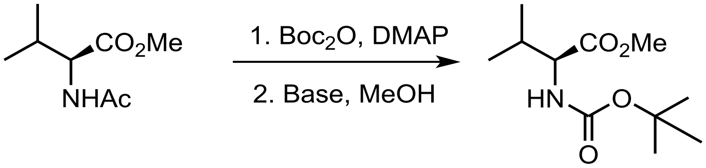


Figure 3: Carbaryl, an insecticide carbamate.

The Curtius rearrangement is the thermal excitation of an acyl azide in forming an intermediate isocyanate. This intermediate can be trapped with water, amines or alcohols to form carbamates and ureas.[13] Normally, the process for the formation of carbamates via the Curtius rearrangement is done by azidation of an acyl chloride using sodium azide.[12] This will result in the acyl azide, in which the reaction mixture is subjected to a reflux and the addition of an alcohol or amine as the nucleophile. Upon formation of the isocyanate, the alcohol will trap the isocyanate, forming the desired carbamate product.

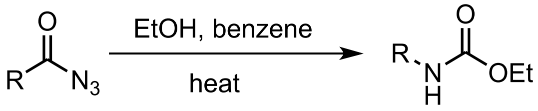
One problem with the way Curtius rearrangements have been performed in the past is with the use and subsequent heating of NaN_3. The use of excess NaN_3 is common due to its low solubility in many organic solvents, with the issue being proper disposal after the reaction is completed. This also makes heating an issue, as adding direct heat to any azide source could cause it to explode, as well as allowing for the formation of HN_3, which is poisonous.[2]

One modified approach to carbamate formation was reported by Burk and coworkers (**Equation 5**). In this two-step procedure, a secondary amine was reacted in DMAP and di-*tert*-butyl dicarbonate. The Boc-protected amine was then subjected to a hydrolysis with a base in methanol.[14]



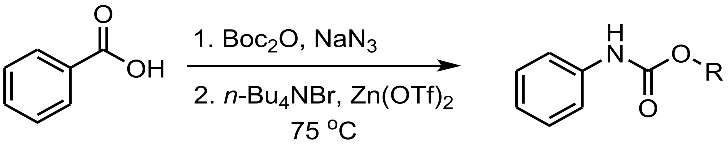
Equation 5: Acetamide conversion to carbamate by Burk and coworkers.

A Curtius rearrangement was also reported by Dussault and coworkers, in which they converted peroxide-containing azides (shown as "R" groups here) to carbamates (**Equation 6**). The acyl azides that were formed from carboxylic acids were quenched, and an aqueous workup was performed before the crude concentrate was treated with ethanol in dry benzene, and the mixture allowed to reflux for 1.5 hours. [15]



Equation 6: Carbamate conversion from acyl azide by Dussault and coworkers.

Another synthesis of aromatic carbamates reported via the Curtius rearrangement has been reported by Lebel and coworkers. In this one-pot protocol, a carboxylic acid was subjected to di-*tert*-butyldicarbonate and sodium azide to generate the acyl azide as an intermediate. Treatment with tetrabutylammonium bromide and zinc(II) triflate at 75 °C then afforded the corresponding carbamate product in high yields (**Equation 7**).[16]



Equation 7: Curtius rearrangement from carboxylic acid derivatives by Lebel and coworkers.

Proposed Research Topics

The above methods described for acyl azide formations are not ideal. They demonstrate disadvantages such as prolonged reaction times, expensive reagents and the use of hazardous materials. There has yet to be seen a fast, inexpensive and completely safe synthesis for the formation of these acyl azides. That is where this research will begin.

Part one of this research topic will be to synthesize acyl azides in a manner that is safe, inexpensive, and less time-consuming than current methods. One issue is the constant use of NaN_3 in synthesis, which has detonation potential upon heating, reduced pressure, and impact; the first two mentioned will have a direct impact upon this research. In our research lab, we have synthesized a safer azide source, *para*-nitrobenzenesulfonyl azide (*p*-NBSA), rather than using NaN_3 exclusively (**Figure 4**). This azide source is covalently bound, and will act as the same anionic azide source in solution as sodium azide does. This material is also readily soluble in many organic solvents and is quite stable.

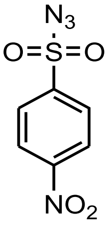
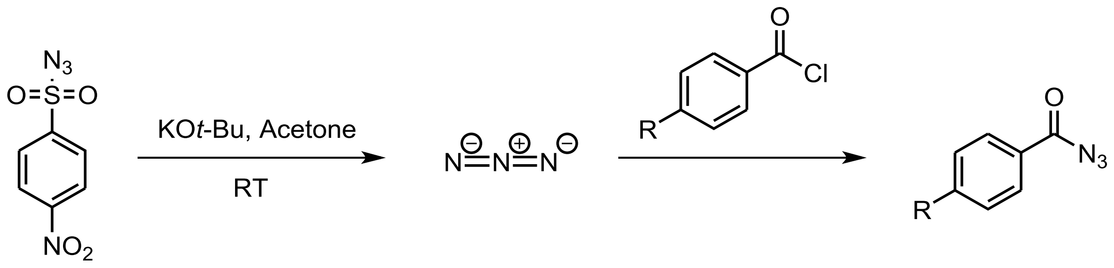


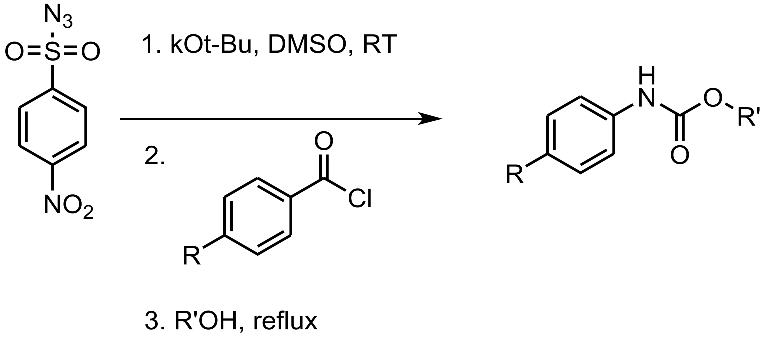
Figure 4: Structure of *para*-nitrobenzenesulfonyl azide (*p*-NBSA).

In our procedure, we chose acetone as the solvent due to it being low boiling, readily available, and it dissolves up the starting material readily. Potassium *tert*-butoxide was used as our nucleophilic base, which will displace the azide from the sulfonate group, generating an anionic azide *in situ*. The progression of this reaction will be monitored by TLC, showing if the azide is still bound to the sulfonate group. Once displaced, we can add a variety of acid chlorides to react with our free azide in solution to form acyl azides (**Scheme 2**).



Scheme 2: Use of our safe azide source, *p*-NBSA to generate an acyl azide.

During this research, we wanted to focus on less traditional methods. The use of sodium azide in synthesis could be harmful. Therefore, we would like to omit it and use another azide source. Many procedures call for the isolation of the azide via aqueous work-up, rather than using it as an intermediate in a one-pot procedure. Here, we will use a one-pot method to synthesize our carbamates, using acyl azides as our intermediates, while modifying the reaction conditions (**Equation 8**).

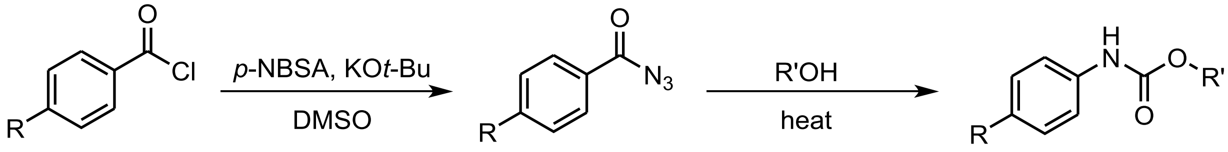


Equation 8: Proposed method for carbamate conversions via the Curtius rearrangement.

Statement of Problem

Organic carbamates are important to synthetic chemists due to their biological significance. Typically, these compounds are synthesized in a multi-step fashion, in which intermediates are isolated. There are also one-pot procedures used that are time-consuming, expensive, and involve the use of dangerous reagents.

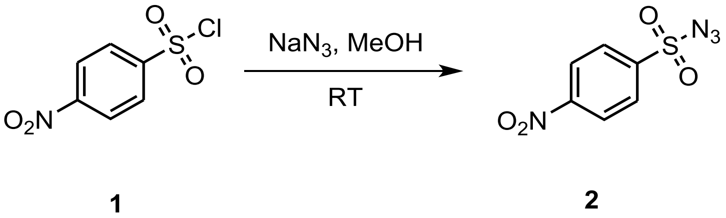
Here we report a one-pot method for the safe, efficient, and inexpensive production of acyl azides. In doing that, we will then explore the synthesis of organic carbamates via the Curtius Rearrangement, using a safe, efficient and inexpensive protocol (**Scheme 3)**.



Scheme 3: Scheme for carbamate formation using our safe azide source, *p*-NBSA.

Results and Discussion

This research began by studying a safer organic azide source that would avoid using sodium azide in individual azidation reactions. We synthesized *para*-nitrobenzenesulfonyl azide (**2**), *p*-NBSA, from *para*-nitrobenzene-sulfonyl chloride (**1**) and NaN_3, using methanol as the solvent (**Equation 9**). The reaction was left to stir overnight at room temperature, and was monitored by TLC until the presence of a new spot ($R_f = 0.31$) appeared; this was yellow in color after staining in *p*-anisaldehyde and heating the plate. After aqueous workup, the crude product was recrystallized from hot 2-propanol. An IR spectrum of the solid showed a peak at 2140 cm^{-1} which corresponds to the azide functionality. Successful conversion to *p*-NBSA was supported by ^1H and ^{13}C NMR spectra.



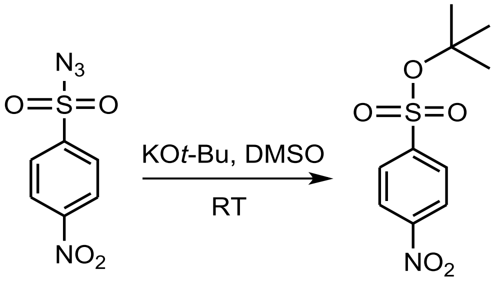
Equation 9: Synthesis of *p*-nitrobenzenesulfonyl azide (**2**) from *p*-nitrobenzenesulfonyl chloride (**1**).

The first part of this research was focused on acyl azide conversions from our safe azide source, *p*-NBSA. First and foremost, an optimization of solvent was done to determine the best solvent for the reaction. The correct solvent had to be able to dissolve *p*-NBSA readily, be low boiling, be easily accessible in terms of price and availability, and potentially decrease the number of side products formed.

The three solvents initially tested were DMF (dimethylformamide), THF (tetrahydrofuran), and acetone. DMF dissolved *p*-NBSA readily, however it was too high boiling (153 °C), which would cause issues when evaporating the solvent in the presence of azide functional groups. THF also dissolved the azide source easily; however upon addition of the nucleophile potassium *tert*-butoxide, stirring became difficult due to it not fully dissolving. Excess solvent was needed in this case, which was not ideal. The third solvent tested, acetone, both dissolved up *p*-NBSA readily, allowed for the addition of minimal solvent upon the addition of the nucleophile, and was low boiling (56 °C). Also, the anionic azide formed faster in acetone than in the other two solvents.

To minimize reaction time, the addition of different amounts of potassium *tert*-butoxide was also optimized. This was done to find the shortest time taken to form the anionic azide in solution. To begin, we added 1.0 equivalent of *p*-NBSA and 1.0 equivalent of nucleophile dissolved in acetone and left the mixture to stir until completion was verified by TLC and IR. After 1 hour, the IR spectrum of the reaction showed both a covalent azide at 2139 cm^{-1} (*p*-NBSA) and that of the anionic azide in solution, shown at 2009 cm^{-1}. Allowing the reaction to stir overnight before being monitored via IR revealed the same results. Next, we added 1.0 equivalent of the azide source, with 2.0 equivalents of the nucleophile, and allowed it to stir for approximately 1 hour. The results via TLC and IR showed consumption of the starting material, with the IR showing one single azide signal at 2008 cm^{-1}. This was the optimization that proved to be useful.

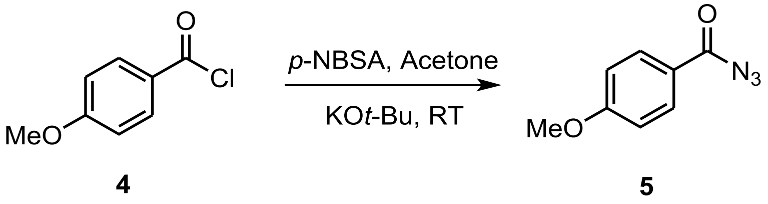
Addition of the base to the arylsulfonyl azide yielded anionic azide *in situ*, as well as an arylsulfonyl by-product (**3**, **Equation 10**) which was seen through monitoring via TLC (R_f = 0.05). A small aliquot was removed for NMR studies, which revealed **3** was present. The ^{1}H NMR spectrum showed a large *t*-butyl signal at 1.09 ppm, with two doublets in the aromatic region at 8.20 and 7.89, respectively. This is evidence that the alkoxide base has displaced the azide group and attached itself to the arylsulfonyl ring, as shown in **Equation 10**.



2 **3**

Equation 10: Arylsulfonyl byproduct (**3**) produced in step 1 of one-pot synthesis.

After base was added to the reaction mixture, the reaction went from a light yellow in color to a dark brown, in which it looked as if a precipitate formed. It was left to stir while being monitored by TLC until all of the starting material was consumed. IR was also used to monitor the reaction, showing a shift in the spectrum from 2140 cm^{-1}, to 2009 cm^{-1}, which was confirmation of an ionic azide being present in solution. The next step was to add the acid chloride to the mixture. The first acid chloride that was tested was 4-methoxybenzoyl chloride (**4**, **Equation 11**). After consumption of the *p*-NBSA starting material, noted by TLC and IR, **4** was dissolved in acetone, added to the reaction mixture dropwise and left to stir overnight. Upon TLC, a new spot was shown (R_f = 0.88) and burned yellow upon staining with *p*-anisaldehyde and heat. An IR spectrum of the solution also showed a peak at 2136 cm^{-1}, which was evident of a covalently bound azide. After the solvent was removed under reduced pressure, the dark orange mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were concentrated under reduced pressure where a dark yellow solid was formed. The proton NMR spectrum of the crude mixture showed an impure acyl azide **5**, which was subjected to purification by flash column chromatography (5:1 hexane : ethyl acetate). Compound **5** was isolated as a white solid in 33% yield. This was most notably confirmed via NMR from the ^{13}C spectrum of the pure solid, with the carbonyl group shifting downfield to 171 ppm from **4** at 167 ppm. However, the yield was compromised, and further studies of the reaction needed to be sought out.

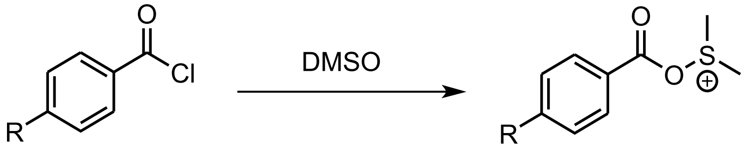


Equation 11: Conversion of 4-methoxybenzoyl chloride (**4**) to 4-methoxybenzoyl azide (**5**).

The crude TLC sample showed many spots, indicative of many by-products being formed. This could have been contributed to by a number of things; most notably the non-homogenous mixture formed when the base was added. Acetone as the solvent did not fully dissolve potassium *tert*-butoxide, which could have not allowed all of the starting material to react with the base. Now, another solvent had to be optimized. Dimethylsulfoxide (DMSO) was then optimized, which allowed for the sulfonyl azide **1** to be fully dissolved. Upon addition of base, the solution turned a dark brown in color but was homogenous, rather than being extremely cloudy as it was with acetone. Although DMSO is considered a health hazard and is high boiling (189 °C), safety precautions can be taken to ensure safety when in use.

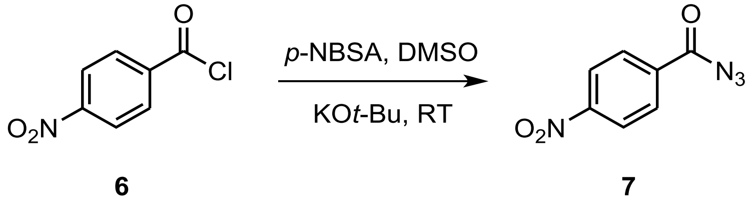
Upon addition of acid chloride **4** in DMSO, the reaction went from a dark brown to a light yellow-orange color, and was left to stir overnight. After monitoring via TLC, a new spot formed (R_f = 0.88), as well as a peak of 2134 cm^{-1} in the IR, both of which are consistent with the presence of **5**. After aqueous workup, the solid formed was of a dark yellow color. NMR analysis of the crude mixture showed an impure acyl azide, which needed purification via flash column (5:1 hexane : ethyl acetate). Azide **5** was then isolated in 51% yield. This yield was much better than that of the reactions when acetone was used as the solvent. NMR analysis of the pure solid was that of **5**, indicated by the ^{13}C NMR spectrum, which showed the carbonyl carbon shifting downfield from its original position in **4** from 167 ppm to 170 ppm. Also, the melting point matched with that of the literature at 68-70 °C [17]. Therefore, DMSO was shown to be the solvent of choice.

One potential problem with the use of DMSO in this reaction is its own reactivity with acid chlorides. Upon the addition of an acid chloride to DMSO, the electrophilic carbon of the acid chloride undergoes an attack from the DMSO oxygen, thus releasing the chloride from the molecule. This is present in all reactions where DMSO was used with the acid chlorides, in which yield is compromised due to the formation of another byproduct.



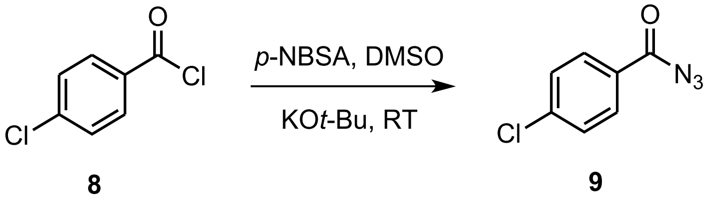
Equation 12: Acid chloride reaction with DMSO solvent yielding a by-product.

Next, 4-nitrobenzoyl chloride (**6**) was used, being added to the anionic azide *in situ*, in which the reaction went from dark brown to light orange in color. The reaction was monitored by TLC, where a new spot was revealed (R_f = 0.78), and by IR, as a new peak was shown at 2132 cm^{-1}. This was consistent with the formation of **7** (**Equation 13**). Workup of the crude mixture yielded an orange colored solid. NMR of the solid showed that of **7**, although impure. The solid was subjected to flash column chromatography (5:1 hexanes : ethyl acetate) and azide **7** was isolated in 63% yield. The ^{13}C NMR of the pure solid showed the carbonyl peak at 164.04 ppm, with the IR spectrum showing a 2125 cm^{-1} peak, which is evident of a covalently bound azide. Also, the melting point agreed with that of the literature, at 68-69 °C. [18]



Equation 13: Conversion of 4-nitrobenzoyl chloride (**6**) to 4-nitrobenzoyl azide (**7**).

Another azide that was formed was 4-chlorobenzoyl azide (**9**) from 4-chlorobenzoyl chloride (**8**) (**Equation 14**). After addition of the base to the reaction, it was monitored by IR until disappearance of the azide peak at 2142 cm^{-1} and appearance of the anionic azide peak at 2008 cm^{-1}. Chloride **8** was then added dropwise, turning the reaction a light orange color, and allowing to stir overnight. Monitoring the reaction by TLC, a new spot was revealed (R_f =0.71), suggesting the formation of azide **9**. After aqueous workup, the crude product was subject to purification via flash column chromatography (5:1 hexane : ethyl acetate). Pure **9** was isolated in 29% yield as a light yellow solid. The ^{13}C NMR of the pure solid showed the carbonyl peak downfield at 171 ppm from that of the acid chloride, with the melting point also matching with the literature value of 39-40 °C. [19]

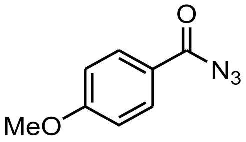
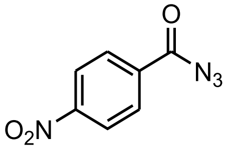
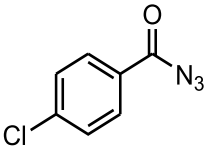


8

9

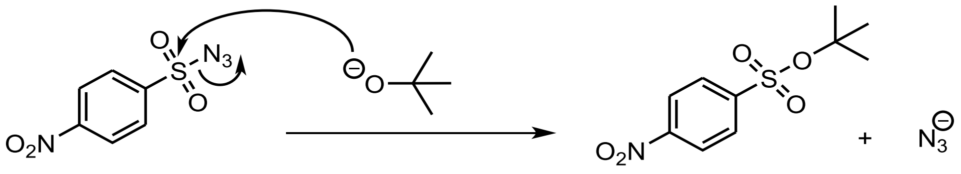
Equation 14: Conversion of 4-chlorobenzoyl azide (**9**) from 4-chlorobenzoyl chloride (**8**).

Table 1: Respective colors and yields for acyl azides.

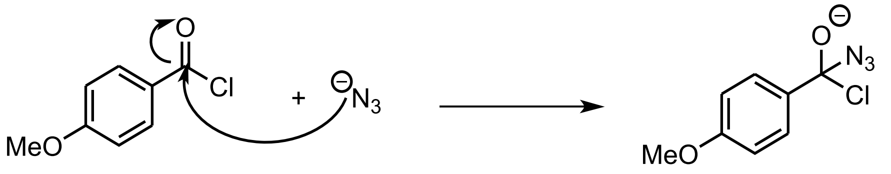
Product	**Color**	**Yield**
 4	White solid	51%
 7	Light yellow solid	63%
 9	Light yellow solid	29%

Mechanism for Acyl Azide Formation

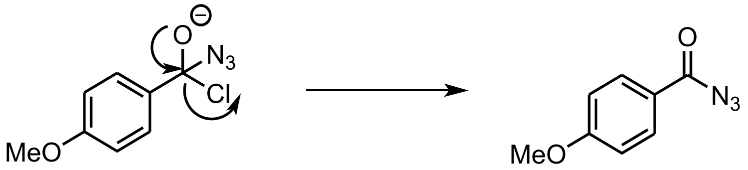
1. Formation of anionic azide



2. Nucleophilic acyl substitution of free azide to carbonyl of acyl chloride

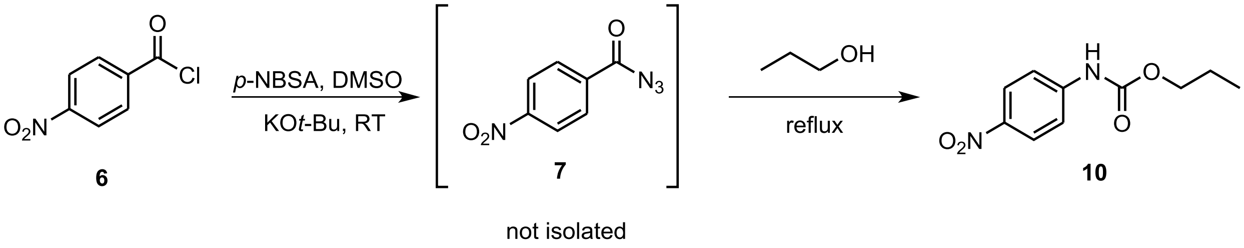


3. Collapsing of tetrahedral intermediate to form acyl azide



The next focus of this research is based on the formation of organic carbamates via the Curtius Rearrangement. This will be done through the formation of the acyl azide using the same procedure as above, in a one-pot manner.

After preparing acyl azide **7**, propanol was added and a reflux condenser was attached. The reaction mixture was then heated at 92 °C, while being monitored by TLC and IR (**Equation 15**). On the third day, TLC revealed the yellow spot for the acyl azide had disappeared, as well as a new spot that had formed (R_f = 0.76). Also, the IR spectrum showed the disappearance of the azide signal at 2132 cm^{-1}. The crude reaction mixture was then subjected to aqueous work-up, and concentrated under reduced pressure. NMR studies of the crude sample showed an impure organic carbamate **12**, which needed to be purified. Flash column chromatography was the method of choice (5:1 hexane: ethyl acetate). Pure **12** was isolated in 25% yield as a colorless solid. This was evident by the ^{1}H NMR spectrum of the pure compound showing the NH proton as a singlet at 10.34 ppm. The aromatic ring protons are more shielded, being found as doublets at 8.20 ppm and 7.70 ppm, respectively. The alkyl protons for the alkoxy chain are found at 4.09 ppm, 1.66 ppm and 0.94 ppm.

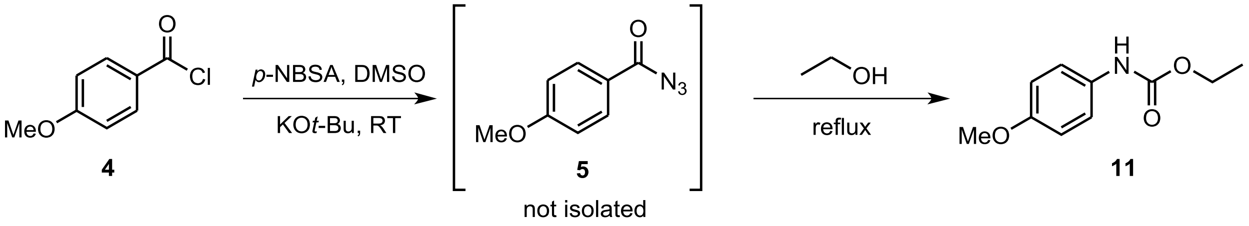


Equation 15: Formation of propyl (4-nitrophenyl) carbamate (**12**) from 4-nitrobenzoyl azide (**7**).

The aromatic ring carbons in the ^{13}C spectrum show at 145.74 ppm, 141.60 ppm, 125.01 ppm and 117.60 ppm, respectively. The carbonyl signal was found at 153.32 ppm, upfield from 171 ppm, with the alkyl chain carbon signals showing at 66.34 ppm, 21.71 ppm, and 10.16 ppm, respectively.

Following the same protocol for the formation of acyl azide **5** as an intermediate, ethanol was added and a reflux condenser was attached, with the reaction mixture being heated to 78 °C (**Equation 16**). After three days, IR showed the peak of 2136 cm^{-1} to have disappeared, along with the yellow spot via TLC after staining in *p*-anisaldehyde and burning. Instead, a new spot formed ($R_f = 0.75$). After aqueous work-up, solvent was removed under reduced pressure, and the concentrated crude sample was characterized by NMR. Crude proton NMR spectra showed impure **13**, which was subjected to purification by flash column chromatography (5:1 hexane : ethyl acetate). Pure carbamate **13** was isolated in 55% yield as colorless crystals. This was shown to be the product by ^{1}H NMR, with the amide proton being found at 9.35 ppm. Aromatic ring protons are shown at 7.35 ppm and 6.85 ppm, with the methylene and methyl protons of the alkyl chain shown at 4.10 ppm and 1.23 ppm, respectively.

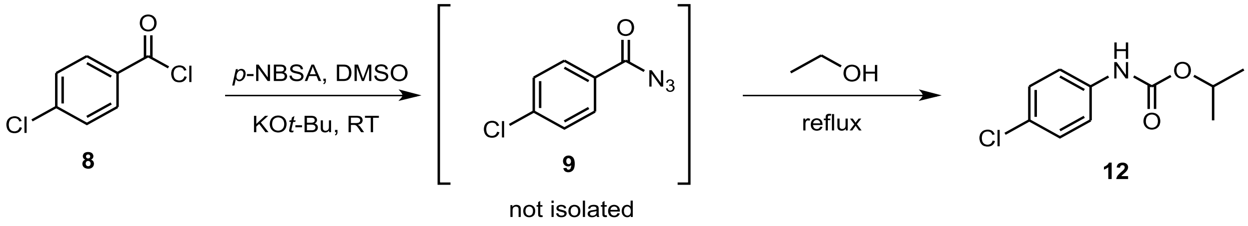
^{13}C NMR of the pure solid showed the carbonyl carbon signal shifted upfield from 171 ppm to 153 ppm. Aromatic ring carbons are found at 132 ppm, 119 ppm, 113 ppm, with the methylene and methyl carbons being found at 29 ppm and 14 ppm, respectively.



Equation 16: Synthesis of Ethyl (4-methoxyphenyl) carbamate **(13)** from 4-methoxybenzoyl azide (**5**).

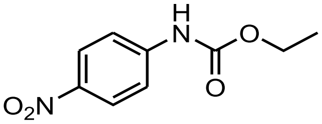
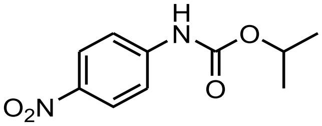
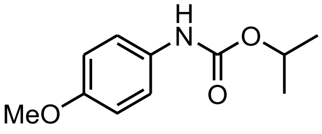
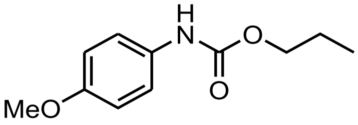
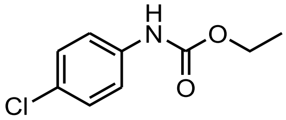
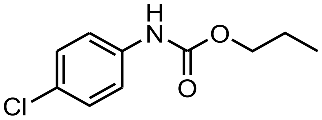
After acyl azide **9** was formed using the above procedure, 2-propanol was added and a reflux condenser was attached. The reaction mixture was then heated to 88 °C (**Equation 17**). The covalent azide peak for the acyl azide found at 2142 cm^{-1} disappeared via IR, in addition to a new spot forming via TLC ($R_f = 0.74$). Aqueous work-up was then performed, and solvents were removed under reduced pressure. The crude sample was then characterized by NMR, in which an impure carbamate **14** was observed, and subjected to purification via flash column chromatography (5:1 hexane : ethyl acetate). Pure **14** was isolated in 42% yield. After analysis of the pure ^{1}H NMR, it was noted that the amide proton was found at 9.67 ppm, which was evidence of the carbamate. The aromatic ring protons are found at 7.48 ppm and 7.31 ppm respectively, with the alkyl chain protons found at 4.89 ppm and 1.25 ppm.

The ^{13}C NMR spectrum of the pure white solid showed the carbonyl carbon signal to be further upfield at 153.03 ppm, with the aromatic ring carbons found at 138.29 ppm, 128.53 ppm, 125.79 ppm and 119.55 ppm. Also, the alkyl chain carbons are shown at 67.62 ppm and 21.89 ppm. This method was used for a variety of different alcohol nucleophiles, using the same procedure, with results shown in **Table 2**.



Equation 17: Synthesis of Isopropyl (4-chlorophenyl) carbamate (**14**) from 4-chlorobenzoyl azide (**9**).

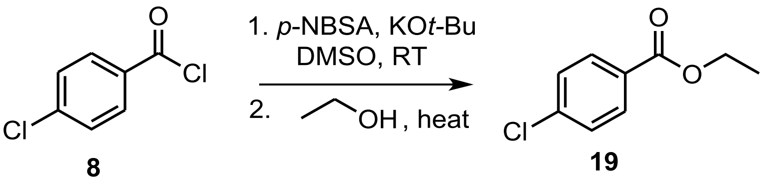
Table 2: Color and yields reported for remaining organic carbamates formed.

Product	Color	Yield
 13	Pale yellow	21%
 14	Pale yellow	40%
 15	White solid	60%
 16	Pale yellow	43%
 17	White solid	43%
 18	Pale yellow	30%

While monitoring the Curtius rearrangements by TLC, it was observed that a by-product had formed in each case. This says that another reaction took place in competition with the Curtius rearrangement. After these by-products were isolated, they were characterized by NMR, and were found to be alkyl esters. These were presumably formed from unreacted acid chloride left over, which the added alcohol nucleophile then reacted with. These compounds were synthesized independently for confirmation.

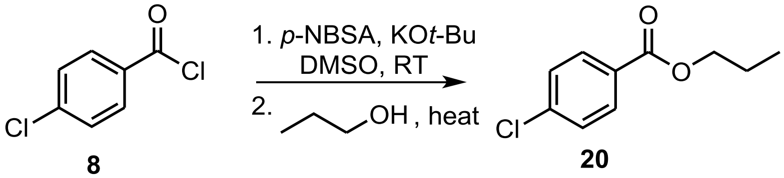
After the addition of **8** to the anionic azide in solution, ethanol was added and a reflux condenser was attached, with the reaction being heated to 75 °C for three days while being monitored by TLC. On the third day, there was a disappearance of the azide spot, with the appearance of a new spot (R_f = 0.85). With unreacted **8** still present in solution, it reacted with the ethanol to form ethyl 4-chlorobenzoate (**21**). After analyzing product **21** (22% yield) via NMR, it was seen that the methylene protons and methyl proton signals are found as a quartet at 4.32 and a triplet at 1.32, respectively. It was also noted that there was no evidence of a carbamate, due to the amide proton not being present in the spectrum.

Analyzing the ^{13}C NMR spectrum, the carbonyl signal shifted further upfield from 167 ppm to 164 ppm, which is in the range for a carbonyl of an ester. The aromatic ring carbon signals are found at 138.13 ppm, 130.89 ppm, 128.85 ppm and 128.69 ppm, with the carbons of the alkyl chain being found at 60.96 ppm and 14.04 ppm, respectively.



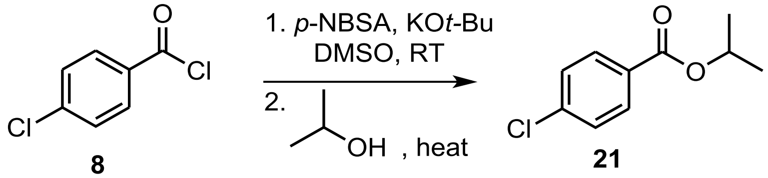
Equation 18: Formation of Ethyl 4-chlorobenzoate (**21**) from 4-chlorobenzoyl chloride (**8**).

After adding propanol as the nucleophile to acid chloride **8**, propyl 4-chloro-benzoate (**22**) was formed in 25% yield (**Equation 19)**. While analyzing the ^{1}H NMR spectrum, there was no evidence of an amide proton, with the methylene protons having a signal at 4.24 ppm and 1.73 as a triplet and a sextet, and the methyl group at 0.97 ppm observed as a triplet. The ^{13}C NMR spectrum showed the carbonyl carbon of the ester at 164.91 ppm and the aromatic ring carbons were shown at 138.16 ppm, 130.90 ppm, 128.90 ppm and 128.69 ppm. The aliphatic carbon signals were found at 66.35 ppm, 21.52 ppm and 10.26 ppm.



Equation 19: Conversion from 4-chlorobenzoyl chloride (**8**) to propyl 4-chlorobenzoate (**22**).

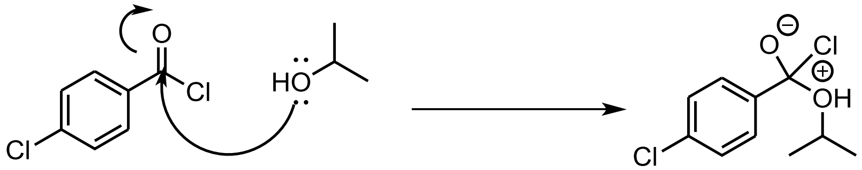
The use of 4-chlorobenzoyl chloride **8** also led to the formation of isopropyl 4-chlorobenzoate (**23**), when 2-propanol was used as the nucleophile, reacting with unreacted **8** (**Equation 20**). Here, the two different types of proton signals in the ^{1}H NMR spectrum were that of a septet and a doublet at 5.14 ppm and 1.33 ppm, respectively. The ^{13}C NMR spectrum gave the carbonyl signal of the ester at 164.35 ppm, with the aromatic ring carbons giving signals at 138.06 ppm, 130.88 ppm, 129.03 ppm and 128.85 ppm. The alkyl group carbon signals were then found at 68.51 ppm and 21.57 ppm.



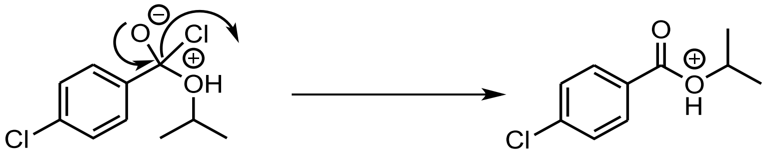
Equation 20: Conversion from 4-chlorobenzoyl azide (**8**) to isopropyl 4-chlorobenzoate (**23**).

Mechanism for alkyl ester formation

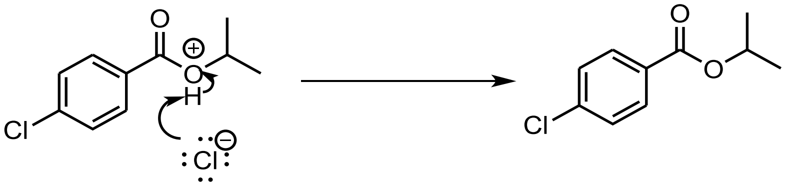
1. Nucleophilic attack on the carbonyl carbon from the alcohol nucleophile.



2. Displacement of the chlorine atom, reforming the carbonyl.



3. Removal of the proton by the chlorine atom to form the ester product.



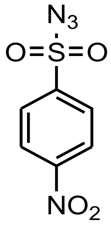
This procedure has shown that various acyl azides can be converted to carbamates via the Curtius rearrangement from their corresponding acid chlorides. This was also carried out in a one-pot process. The formation of these carbamates competed with the generation of a by-product, which after isolation and characterization were found to be alkyl esters. The esters were thought to be formed by leftover acid chloride reacting with the alcohol nucleophile.

Experimental

General Experimental Procedures for Synthesis

All reactions where monitored via thin layer chromatography on Whatman aluminum-backed plates, with the usage of an ultraviolet light and staining with *p*-anisaldehyde for detection of compounds. Characterization of compounds was done using a Thermo Electron Corporation IR 200 Infrared Spectrometer and analyzed using the EZ-Omnic software. Purification was completed through flash column chromatography using 32-60 Å silica gel with various eluting solvents, as well as crystallization with various solvents. Bruker Avance II and III Nuclear Magnetic Resonance (NMR) instruments were used for ^{1}H and ^{13}C spectroscopy, at 400 and 100 MHz respectively, with $CDCl_3$ or D^6-DMSO as the solvent. Both proton and carbon chemical shifts are reported in parts per million (ppm). Splitting patterns are labeled as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet).

Conversion of *para*-nitrobenzenesulfonyl chloride to *para*-nitrobenzenesulfonyl azide (2)



2

To a 500 mL oven-dried round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzenesulfonyl chloride (10.004 g, 45.14 mmol) was dissolved in methanol (100 mL). Sodium azide (10.002 g, 153.9 mmol) was then added and left to stir overnight. The methanol was removed via rotary evaporation at 40 °C. The resulting solid was dissolved in water (50 mL) and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried using $MgSO_4$, filtered, and solvent was removed under reduced pressure. The crude solid was then crystallized using hot 2-propanol, yielding 8.62 g for 83.69% yield of *p*-NBSA (**2**).

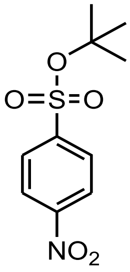
^{1}H NMR (400 MHz, D^6-DMSO): δ 8.31 (d, 2H, J = 9.04 Hz), 8.50 (d, 2H, J = 9.04 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 151.1, 142.5, 129.1 (double intensity), 125.3 (double intensity).

IR absorption: 2139 cm^{-1} for azide functionality.

Melting Point: 96-98° C.

Conversion of *para*-nitrobenzenesulfonyl azide to *tert*-butyl 4-nitrobenzenesulfonate (3)



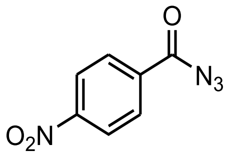
3

To a 50 mL oven dried flask fitted with a septum and magnetic stir bar, *para*-nitrobenzene-sulfonyl azide (0.458 g, 2.00 mmol) was dissolved in DMSO (5 mL) at room temperature. Potassium *tert*-butoxide (0.459 g, 4.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material, and that of an arylsulfonyl by-product (R_f = 0.05). The crude reaction was then monitored by ^{1}H and ^{13}C NMR.

^{1}H NMR (400 MHz, D^6-DMSO): *δ* 8.20 (d, 2H, *J* = 8.64 Hz), 7.89 (d, 2H, *J* = 8.60 Hz), 1.09 (s, 9H).

^{13}C NMR (100 MHz, D^6-DMSO): δ 153.45, 147.39, 127.00, 123.34, 66.97, 31.15.

Conversion of 4-nitrobenzoyl chloride to 4-nitrobenzoyl azide (7)



7

To a 50 mL oven dried flask fitted with a septum and magnetic stir bar, *para*-nitrobenzene-sulfonyl azide (0.687g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.673 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-nitrobenzoyl chloride (0.597 g, 3.2 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of **7** by showing a yellow spot after staining with *p*-anisaldehyde and heating. At this point, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using a 5:1 hexane : ethyl acetate solvent system. Pure 4-nitrobenzoyl azide (**7**) was collected as a pale yellow solid, yielding 0.254 g for a 44% overall yield.

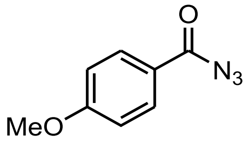
^{1}H NMR (400 MHz, D^6-DMSO): δ 8.23 (d, 2H, J = 9.00 Hz), 8.37 (d, 2H, J = 8.96 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 165.75, 150.02, 136.37, 130.65 (double intensity), 123.68 (double intensity).

IR absorption: 2123 cm^{-1} for azide functionality.

Melting Point: 68-69 °C.

Conversion of 4-methoxybenzoyl chloride to 4-methoxybenzoyl azide (5)



5

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.687 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.678 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane : ethyl acetate) showed consumption of the starting material. 4-methoxybenzoyl chloride (0.55 mL, 3.2 mmol) was then added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane : ethyl acetate) confirmed the appearance of **5** by showing a yellow spot after staining with *p*-anisaldehyde and heating. At this point, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate solvent system. Pure 4-methoxybenzoyl azide (**5**) was collected as a pale yellow solid in 51% yield.

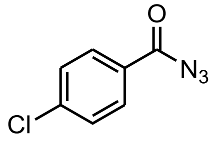
^{1}H NMR (400 MHz, D^{6}-DMSO): δ 7.93 (d, 2H, J = 9.00 Hz), 7.09 (d, 2H, J = 9.00 Hz), 3.86 (s, 1H).

^{13}C NMR (100 MHz, D^{6}-DMSO): δ 170.90, 164.46, 131.39 (double intensity), 122.39, 114.41 (double intensity), 55.69.

IR absorption: 2136 cm^{-1} for azide functionality.

Melting Point: 69-70 °C.

Conversion of 4-chlorobenzoyl chloride to 4-chlorobenzoyl azide (9)



9

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.685 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.673 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-Chlorobenzoyl chloride (0.41 mL, 3.2 mmol) was then added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. At this point, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with water (5 x 20 mL), and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate solvent system. Pure 4-chlorobenzoyl azide (**9**) was collected as a pale yellow solid at 0.174 g, in 32% yield.

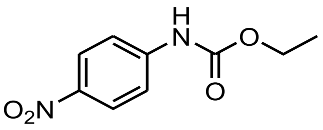
^{1}H NMR (400 MHz, D^6-DMSO): δ 7.97 (d, 2H, J = 8.72 Hz), 7.64 (d, 2H, J = 8.76 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 171.07, 139.73, 130.83 (double intensity), 129.27 (double intensity), 128.94.

IR absorption: 2125 cm^{-1} for azide functionality.

Melting Point: 39-40 ^{o}C.

Conversion of 4-nitrobenzoyl chloride to ethyl (4-nitrophenyl) carbamate (13)



13

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.685 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.673 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-nitrobenzoyl chloride (0.597 g, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **7** by showing a yellow spot after staining with *p*-anisaldehyde and heating. Ethanol (10 mL) was added and left to stir for three days while heating at 82 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate solvent system. Pure ethyl (4-nitrophenyl) carbamate (**13**) was collected as a pale yellow solid at 0.172 g, in 25% yield.

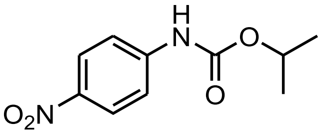
^{1}H NMR (400 MHz, D^6-DMSO): δ 10.35 (s, 1H), 8.20 (d, 2H, J = 9.32 Hz), 7.70 (d, 2H, J = 9.32 Hz), 4.19 (q, 2H, J = 7.10 Hz), 1.27 (t, 3H, J = 7.08 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 153.22, 145.74, 141.60, 125.01, 117.58, 60.87, 14.31.

IR absorption: 3497 cm^{-1}, 1620 cm^{-1}.

Melting point: 126-128 °C.

Conversion of 4-nitrobenzoyl chloride to isopropyl (4-nitrophenyl) carbamate (14)



14

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.678 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-nitrobenzoyl chloride (0.599 g, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **7** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 2-Propanol (10 mL) was added and left to stir for three days at 85 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, followed by saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. The crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as the solvent system. Pure isopropyl (4-nitrophenyl) carbamate (**14**) was collected as a pale yellow solid (0.183 g, 27% yield).

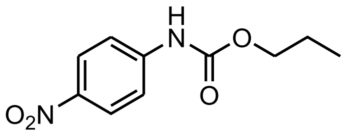
^{1}H NMR (400 MHz, D^6-DMSO): δ 10.28 (s, 1H), 8.18 (d, 2H, J = 9.28 Hz), 7.69 (d, 2H, J = 9.36 Hz), 4.94 (septet, 1H, J = 6.26 Hz), 1.28 (d, 6H, J = 6.24 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 153.22, 145.74, 141.60, 125.01, 117.58, 60.87, 14.31.

IR absorption: 3435 cm^{-1}, 1664 cm^{-1}.

Melting point: 110-112 ^{o}C.

Conversion of 4-nitrobenzoyl chloride to propyl (4-nitrophenyl) carbamate (10)



10

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.685 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.673 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-nitrobenzoyl chloride (0.599 g, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **7** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 1-Propanol (10 mL) was added and the mixture left to stir for three days at 90^{o} C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). At this point, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was added to the combined organic layers, and then saturated NaCl (20 mL). Organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as solvent system. Pure propyl (4-nitrophenyl) carbamate (**10**) was collected as a pale yellow solid (0.17 g, 25% yield).

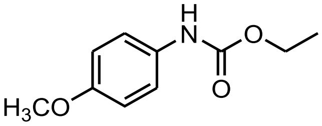
^{1}H NMR (400 MHz, D^{6}-DMSO): δ 10.35 (s, 1H), 8.20 (d, 2H, *J* = 9.28 Hz), 7.70 (d, 2H, *J* = 9.32 Hz), 4.09 (t, 2H, *J* = 6.66 Hz), 1.67 (sextet, 2H, *J* = 7.12 Hz), 0.95 (t, 3H, *J* = 7.42 Hz).

^{13}C NMR (100 MHz, D^{6}-DMSO): δ 153.32, 145.74, 141.60, 125.01, 117.59, 66.34, 21.71, 10.62.

IR absorption: 3467 cm^{-1} 1662 cm^{-1}.

Melting point: 115-117 ^{o}C.

Conversion of 4-methoxybenzoyl chloride to ethyl (4-methoxyphenyl) carbamate (11)



11

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.672 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-nitrobenzoyl chloride (0.43 mL, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **5** by showing a yellow spot after staining with *p*-anisaldehyde and heating. Ethanol (10 mL) was added and the mixture left to stir for three days at 78 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water

(5 x 20 mL) was used to wash the combined organic layers, and then a portion of saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using a 5:1 hexane : ethyl acetate solvent system. Pure ethyl (4-methoxyphenyl) carbamate (**11**) was collected as a pale yellow solid (0.32 g, 55% yield).

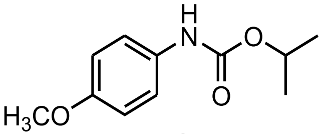
^{1}H NMR (400 MHz, D^{6}-DMSO): δ 9.35 (s, 1H), 7.34 (d, 2H, J = 8.96 Hz), 6.85 (d, 2H, J = 8.88 Hz), 4.10 (q, 2H, J = 7.10 Hz), 3.71 (s, 3H), 1.23 (t, 3H, J = 7.08 Hz).

^{13}C NMR (100 MHz, D^{6}-DMSO): δ 153.67, 132.24, 119.60, 113.89, 55.87, 55.13, 29.22, 14.52.

IR absorption: 3435 cm^{-1}, 1661 cm^{-1}.

Melting point: 61-63 ^{o}C.

Conversion of 4-methoxybenzoyl chloride to isopropyl (4-methoxyphenyl) carbamate (15)



15

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.673 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-methoxybenzoyl chloride (0.43 mL, 3.2 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **5** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 2-Propanol (10 mL) was added and the mixture was left to stir for three days at 82 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, and then a portion of saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as the solvent system. Pure isopropyl (4-methoxyphenyl) carbamate (**15**) was collected as a pale yellow solid (0.38 g, 60% yield).

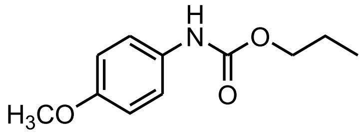
^{1}H NMR (400 MHz, D^6-DMSO): δ 9.29 (s, 1H), 7.35 (d, 2H, *J* = 8.88 Hz), 6.84 (d, 2H, *J* = 9.04 Hz), 4.86 (septet, 1H, *J* = 6.26 Hz), 1.24 (d, 6H, *J* = 6.24 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 154.60, 153.24, 132.36, 119.67, 113.83, 67.06, 55.10, 21.96.

IR absorption: 3437 cm^{-1}, 1654 cm^{-1}.

Melting point: 62-64 °C.

Conversion of 4-methoxybenzoyl chloride to propyl (4-methoxyphenyl) carbamate (16)



16

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.674 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-Methoxybenzoyl chloride (0.44 mL, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **5** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 1-Propanol (10 mL) was added and left to heat for three days at 90 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, followed by a portion of saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as the solvent system. Pure propyl (4-methoxyphenyl) carbamate (**16**) was collected as a pale yellow solid (0.27 g, 43% yield).

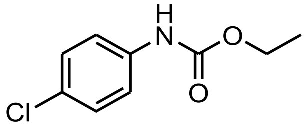
^{1}H NMR (400 MHz, D^6-DMSO): δ 9.35 (s, 1H), 7.35 (d, 2H, J = 8.80 Hz), 6.85 (d, 2H, J = 9.08 Hz), 4.01 (t, 2H, J = 6.68 Hz), 3.71 (s, 3H), 1.63 (sextet, 2H, J = 7.13 Hz), 0.93 (t, 3H, J = 7.42 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 154.68, 153.81, 132.17, 122.13, 119.76, 65.48, 55.10, 30.64, 21.89.

IR absorption: 3436 cm^{-1}, 1662 cm^{-1}.

Melting point: 68-70 °C.

Conversion of 4-chlorobenzoyl chloride to ethyl (4-chlorophenyl) carbamate (17)



17

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.685 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.675 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-chlorobenzoyl chloride (0.41 mL, 3.2 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. Ethanol (10 mL) was added and left to reflux for three days at 78 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was added to the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate solvent system. Pure ethyl (4-chlorophenyl) carbamate (**17**) was collected as a pale yellow solid (0.26 g, 43% yield).

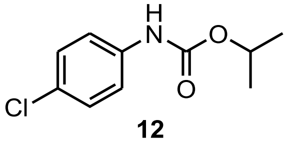
^{1}H NMR (400 MHz, D^6- DMSO): δ 9.73 (s, 1H), 7.48 (d, 2H, *J* = 8.96 Hz), 7.32 (d, 2H, *J* = 8.88 Hz), 4.13 (q, 2H, *J* = 7.10 Hz), 3.71 (s, 3H), 1.25 (t, 3H, *J* = 7.08 Hz).

^{13}C NMR (100 MHz, D6- DMSO): δ 153.44, 138.22, 128.57, 125.87, 119.60, 60.29, 14.43.

IR absorption: 3441 cm^{-1}, 1661 cm^{-1}.

Melting point: 184-186 ^{o}C.

Conversion of 4-chlorobenzoyl chloride to isopropyl (4-chlorophenyl) carbamate (12)



12

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.675 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-chlorobenzoyl chloride (0.41 mL, 3.2 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 2-Propanol (10 mL) was added and left to reflux for three days at 82 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as the solvent system. Pure isopropyl (4-chlorophenyl) carbamate (**12**) was collected as a pale yellow solid (0.27 g, 42% yield).

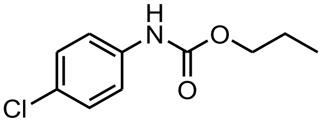
^{1}H NMR (400 MHz, D^6-DMSO): δ 9.67 (s, 1H), 7.48 (d, 2H, J = 8.92 Hz), 7.31 (d, 2H, J = 8.92 Hz), 4.89 (septet, 1H, J = 6.25 Hz), 1.25 (d, 6H, J = 6.27 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 153.03, 138.30, 128.53, 125.79, 119.55, 67.62, 21.89.

IR absorption: 3436 cm^{-1}, 1662 cm^{-1}.

Melting point: 102 ^{o}C.

Conversion of 4-chlorobenzoyl chloride to propyl (4-chlorophenyl) carbamate (18)



18

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.688 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.673 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-chlorobenzoyl chloride (0.41 mL, 3.2 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 1-Propanol (10 mL) was added and left to reflux for three days at 90 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was used to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as the solvent system. Pure propyl (4-chlorophenyl) carbamate (**18**) was collected as a pale yellow solid (0.27 g, 42% yield).

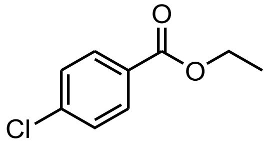
^{1}H NMR (400 MHz, D^6-DMSO): δ 9.78 (s, 1H), 7.48 (d, 2H, *J* = 8.84 Hz), 7.32 (d, 2H, *J* = 8.92 Hz), 4.03 (t, 2H, *J* = 6.68 Hz), 1.63 (sextet, 2H, *J* = 7.13 Hz), 0.93 (t, 3H, *J* = 7.42 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 153.52, 138.22, 128.57, 125.84, 119.54, 65.78, 30.93, 10.20.

IR absorption: 3441 cm^{-1}, 1661 cm^{-1}.

Melting Point: 124-126 ^{o}C.

Conversion of 4-chlorobenzoyl chloride to ethyl 4-chlorobenzoate (19)



19

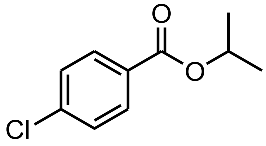
To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.675 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-chlorobenzoyl chloride (0.41 mL, 3.2 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of azide **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. Ethanol (10 mL) was added and the mixture was left to reflux for three days at 78 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was added to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate as solvent system. Pure ethyl 4-chlorobenzoate (**19**) was collected as a pale yellow solid (0.12 g, 22% yield).

^{1}H NMR (400 MHz, D^6-DMSO): *δ* 7.95 (d, 2H, *J* = 8.72 Hz), 7.58 (d, 2H, *J* = 8.72 Hz), 4.32 (q, 2H, *J* = 7.11 Hz), 1.32 (t, 3H, *J* = 7.15 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): *δ* 164.84, 138.13, 130.89, 128.85, 128.70, 60.96, 14.04.

Melting Point: 70-72 °C.

Conversion of 4-chlorobenzoyl chloride to isopropyl 4-chlorobenzoate (21)



21

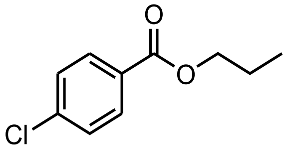
To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.686 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.675 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-chlorobenzoyl chloride (0.41 mL, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 2-Propanol (10 mL) was added and the mixture was left to reflux for three days at 82 °C At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was added to wash the combined organic layers, and then saturated NaCl (20 mL). Organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then purified by flash column chromatography using 5:1 hexane : ethyl acetate solvent system. Pure isopropyl 4-chlorobenzoate (**21**) was collected as a pale yellow solid (0.09 g, 15% yield).

^{1}H NMR (400 MHz, D^6-DMSO): δ 7.95 (d, 2H, *J* = 8.72 Hz), 7.60 (d, 2H, *J* = 8.72 Hz), 5.14 (septet, 1H, *J* = 6.23 Hz), 1.32 (d, 6H, *J* = 6.27 Hz).

^{13}C NMR (100 MHz, D^6-DMSO): δ 164.35, 138.06, 130.88, 129.03, 128.85, 68.51, 21.57.

Melting Point: 69-70 °C.

Conversion of 4-chlorobenzoyl chloride to propyl 4-chlorobenzoate (20)



20

To a 50 mL round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzene-sulfonyl azide (0.685 g, 3.00 mmol) was dissolved in DMSO (3 mL) at room temperature. Potassium *tert*-butoxide (0.671 g, 6.00 mmol) was then added. After 1 hour, TLC (2:1 hexane, ethyl acetate) showed consumption of the starting material. 4-chlorobenzoyl chloride (0.41 mL, 3.00 mmol) was then dissolved in DMSO (5 mL) and added to the reaction dropwise and left to stir overnight. TLC (2:1 hexane, ethyl acetate) confirmed the appearance of **9** by showing a yellow spot after staining with *p*-anisaldehyde and heating. 1-Propanol (10 mL) was added and the reaction was left to reflux for three days at 90 °C. At this point, the reaction was allowed to cool to room temperature, and then diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). Water (5 x 20 mL) was added to wash the combined organic layers, and then saturated NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure at 45 °C. Crude product was then recrystallized in hot absolute ethanol and allowed to cool to induce crystallization. Pure propyl 4-chlorobenzoate (**20**) was collected as a pale yellow solid (0.15 g, 25% yield).

^{1}H NMR (400 MHz, D^{6}-DMSO): δ 7.96 (d, 2H, J = 8.72 Hz), 7.60 (d, 2H, J = 8.76 Hz), 4.24 (t, 2H, J = 6.58 Hz), 1.73 (sextet, 2H, J = 7.08 Hz), 0.97 (t, 3H, J = 7.40 Hz).

^{13}C NMR (100 MHz, D^{6}-DMSO): δ 164.91, 138.16, 130.90, 128.90, 128.69, 66.35, 21.52, 10.26.

Melting point: 74-75 ^{o}C.

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Appendix A

NMR and IR Spectra

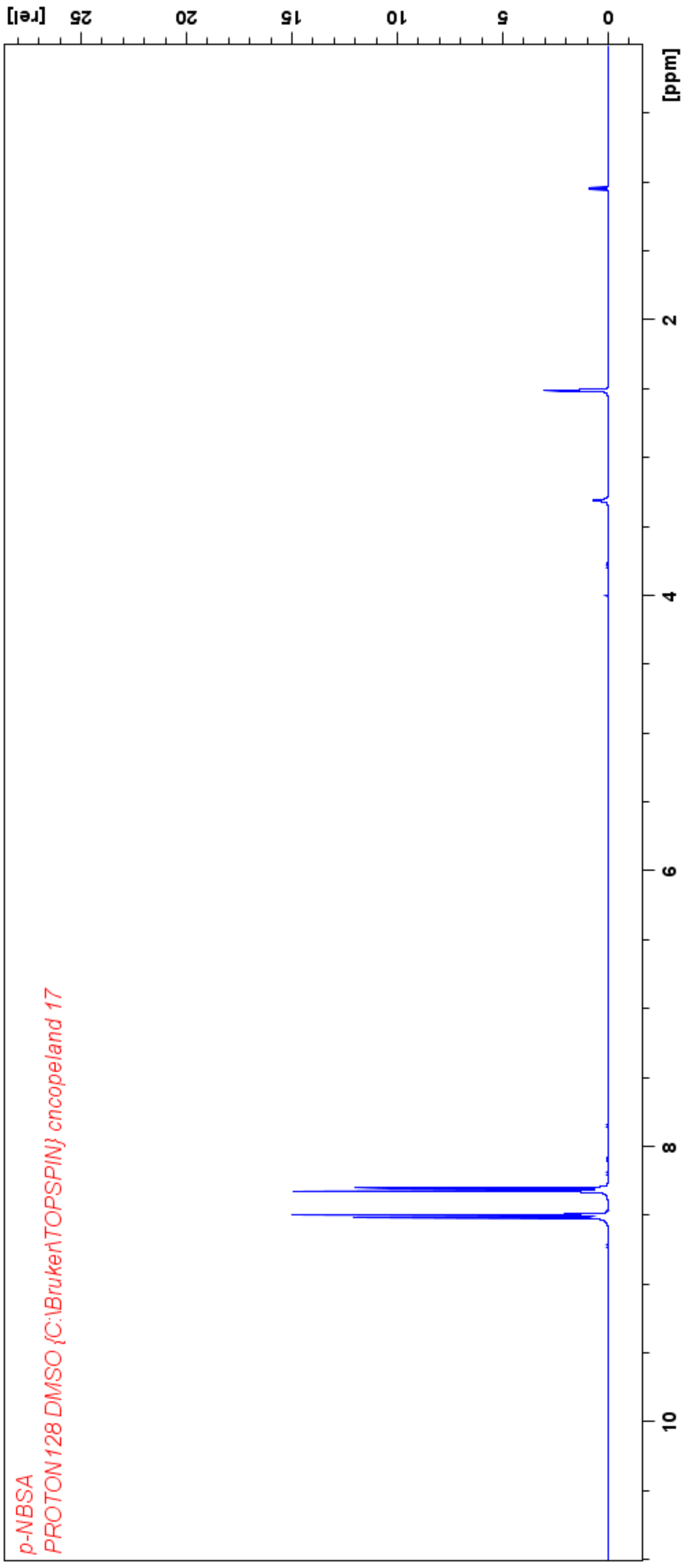

Figure 5: 400 MHz ^{1}H NMR spectrum of *para*-nitrobenzenesulfonyl azide (**2**).

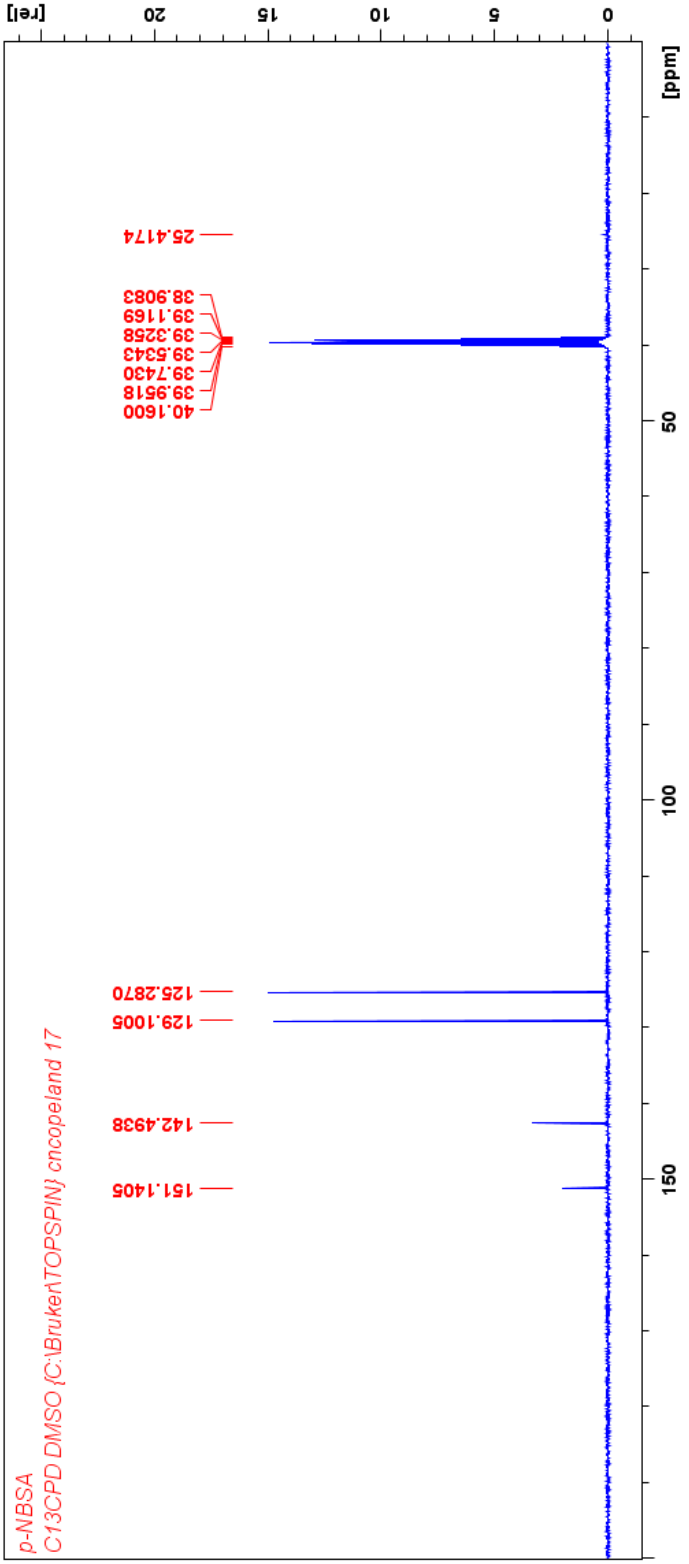

Figure 6: ^{13}C NMR of *para*-nitrobenzenesulfonyl azide (**2**)

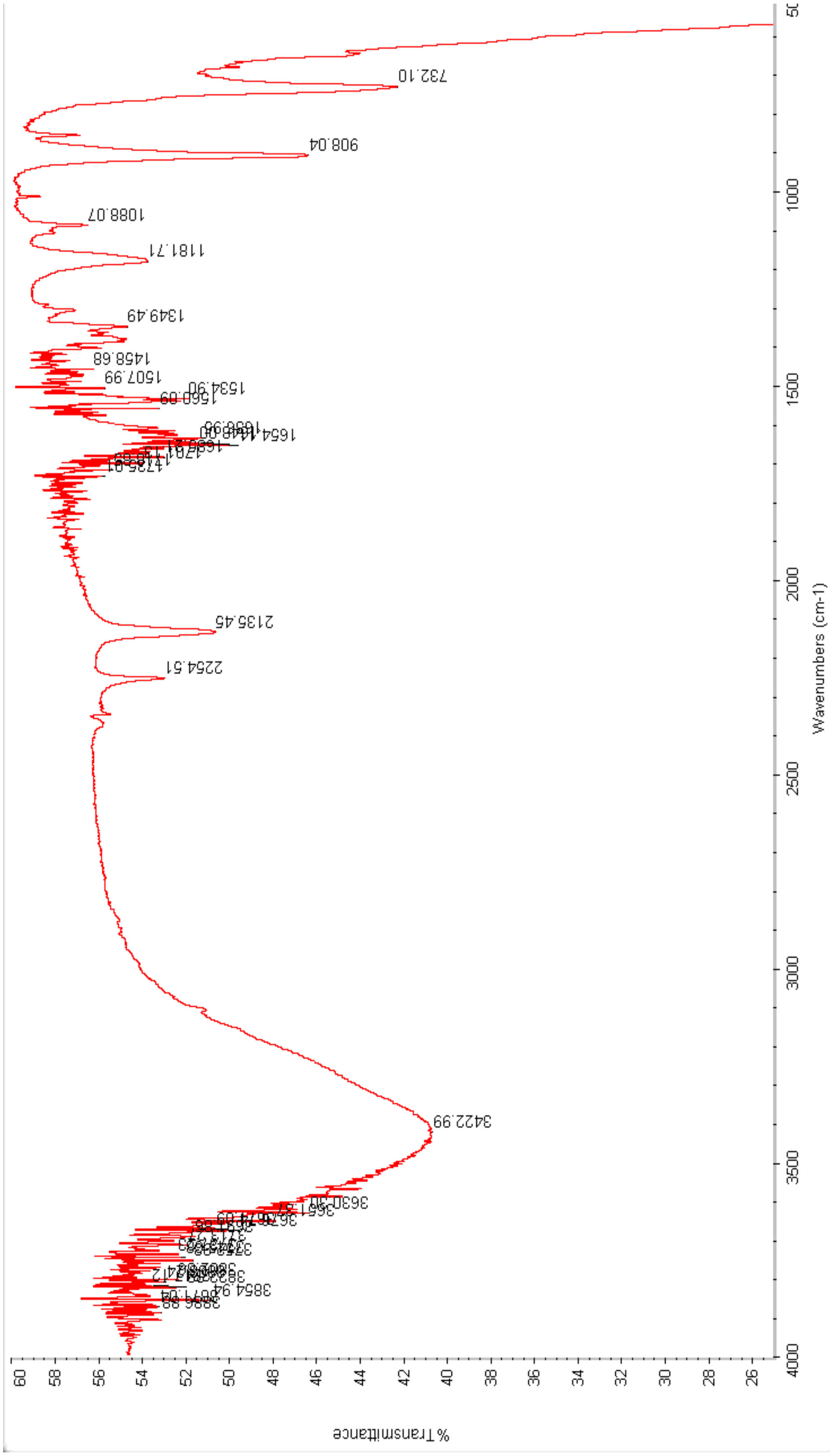

Figure 7: IR of *para*-nitrobenzenesulfonyl azide (**2**)

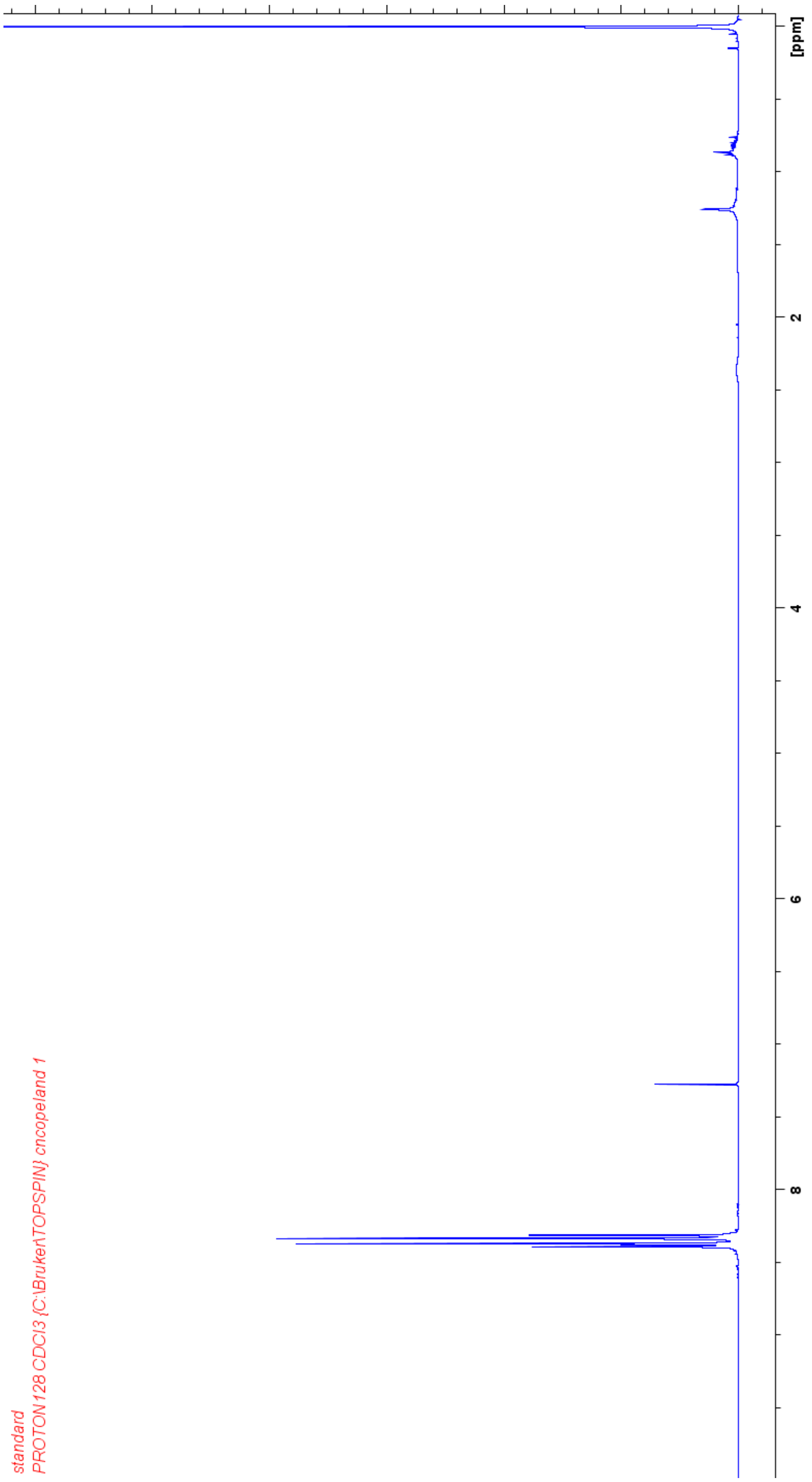

Figure 8: ^{1}H NMR of 4-nitrobenzoyl chloride (**6**)

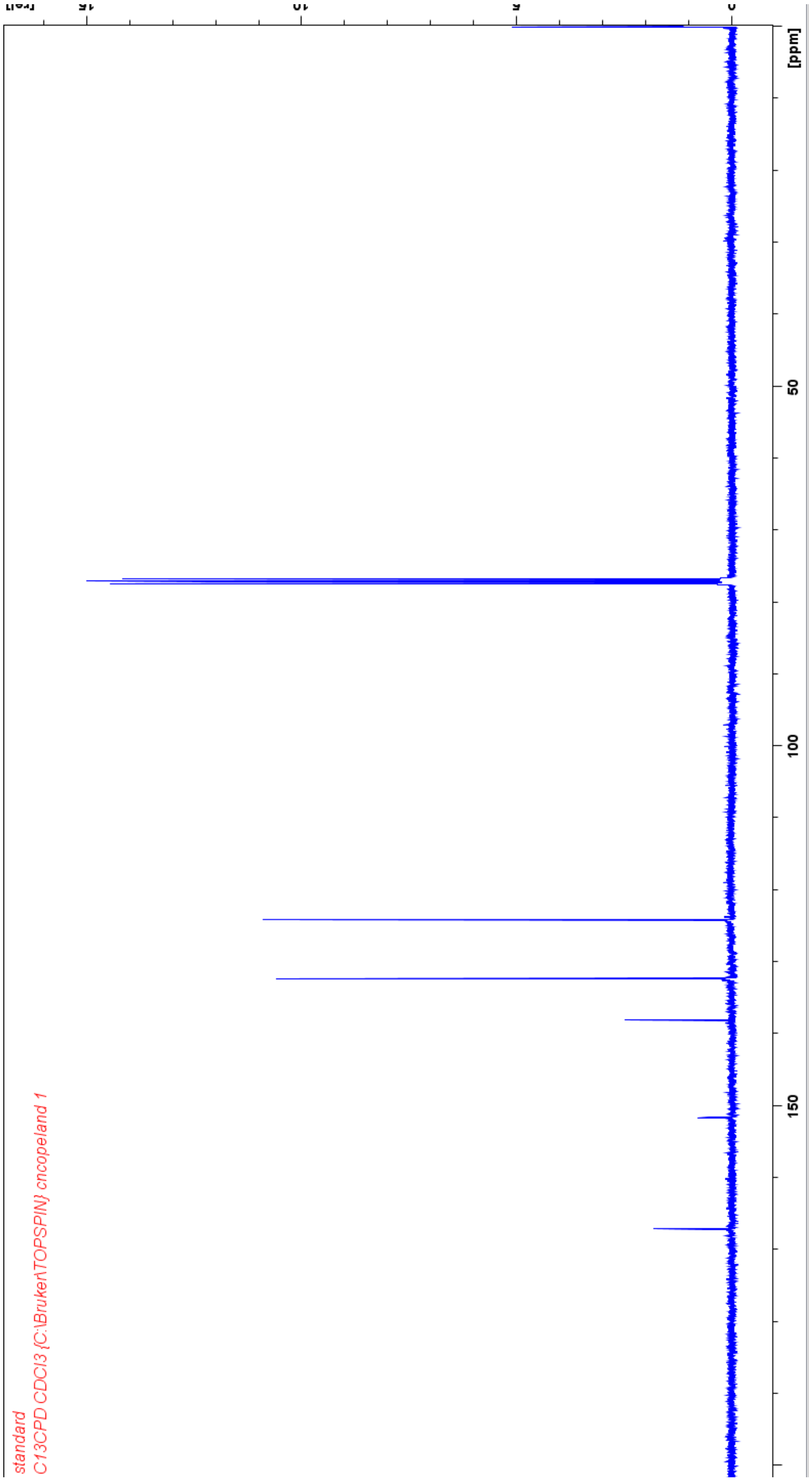

Figure 9: ^{13}C NMR of 4-nitrobenzoyl chloride (**6**)

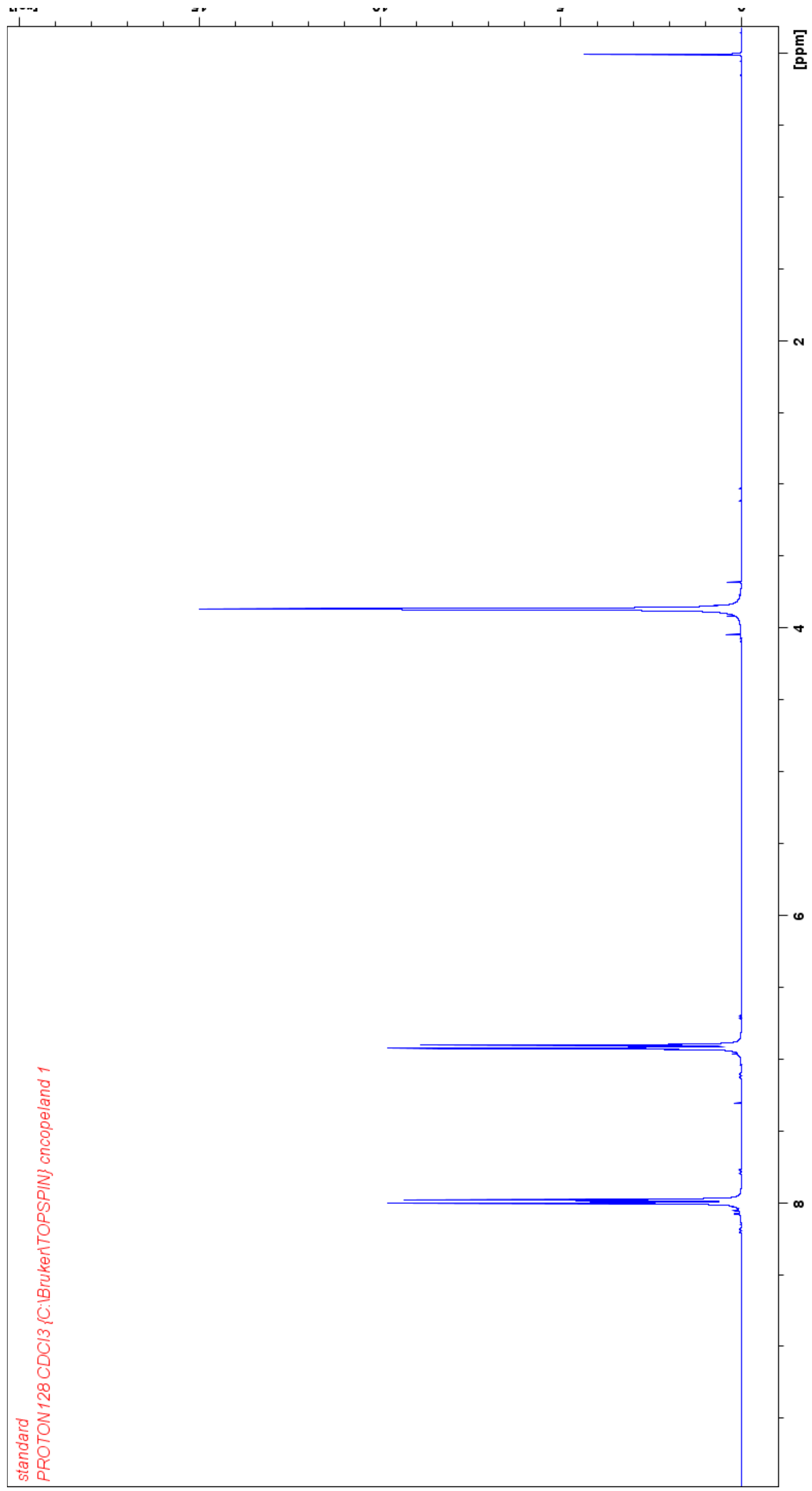

Figure 10: ^{1}H NMR of 4-methoxybenzoyl chloride (**4**)

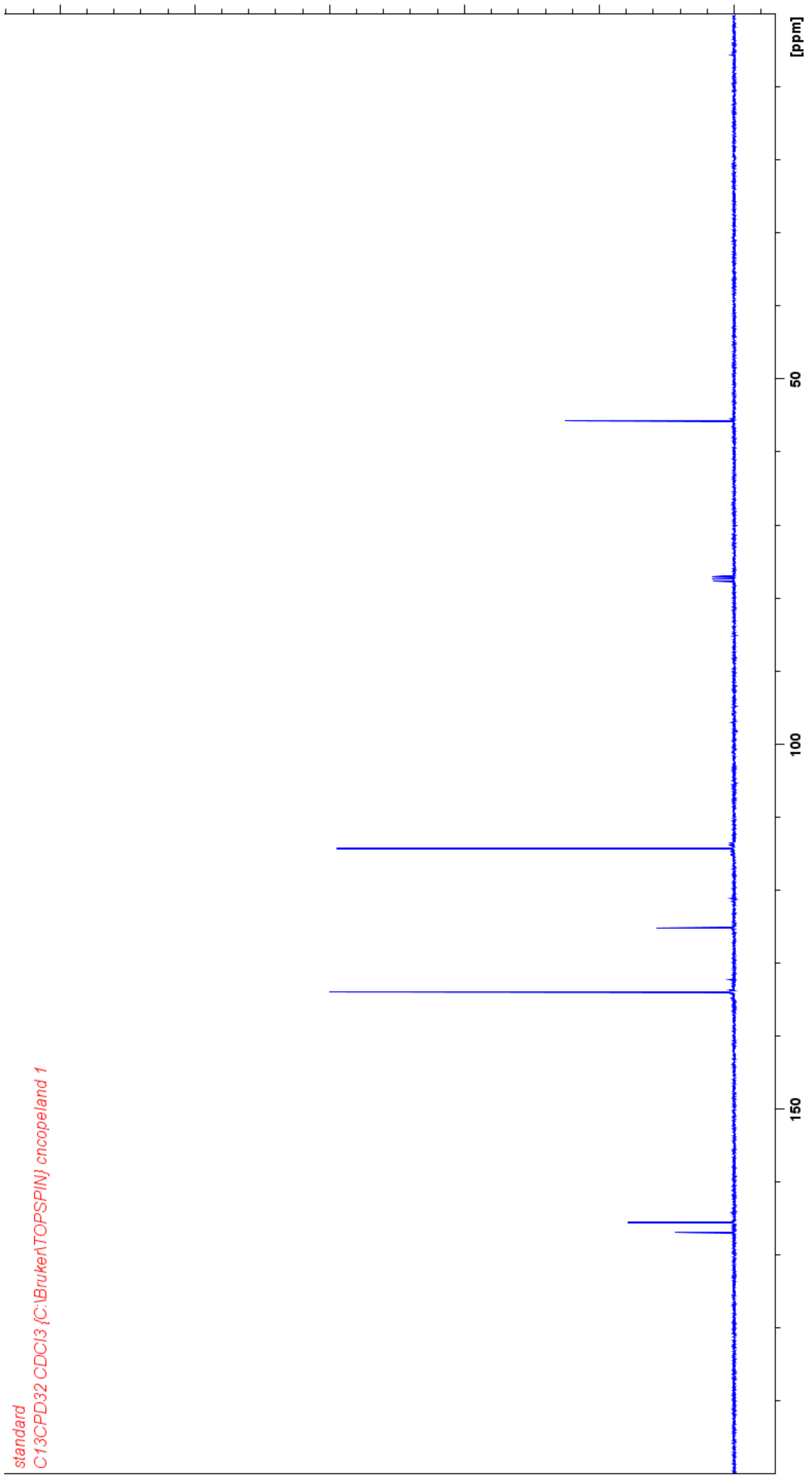

Figure 11: ^{13}C NMR of 4-methoxybenzoyl chloride (**4**)

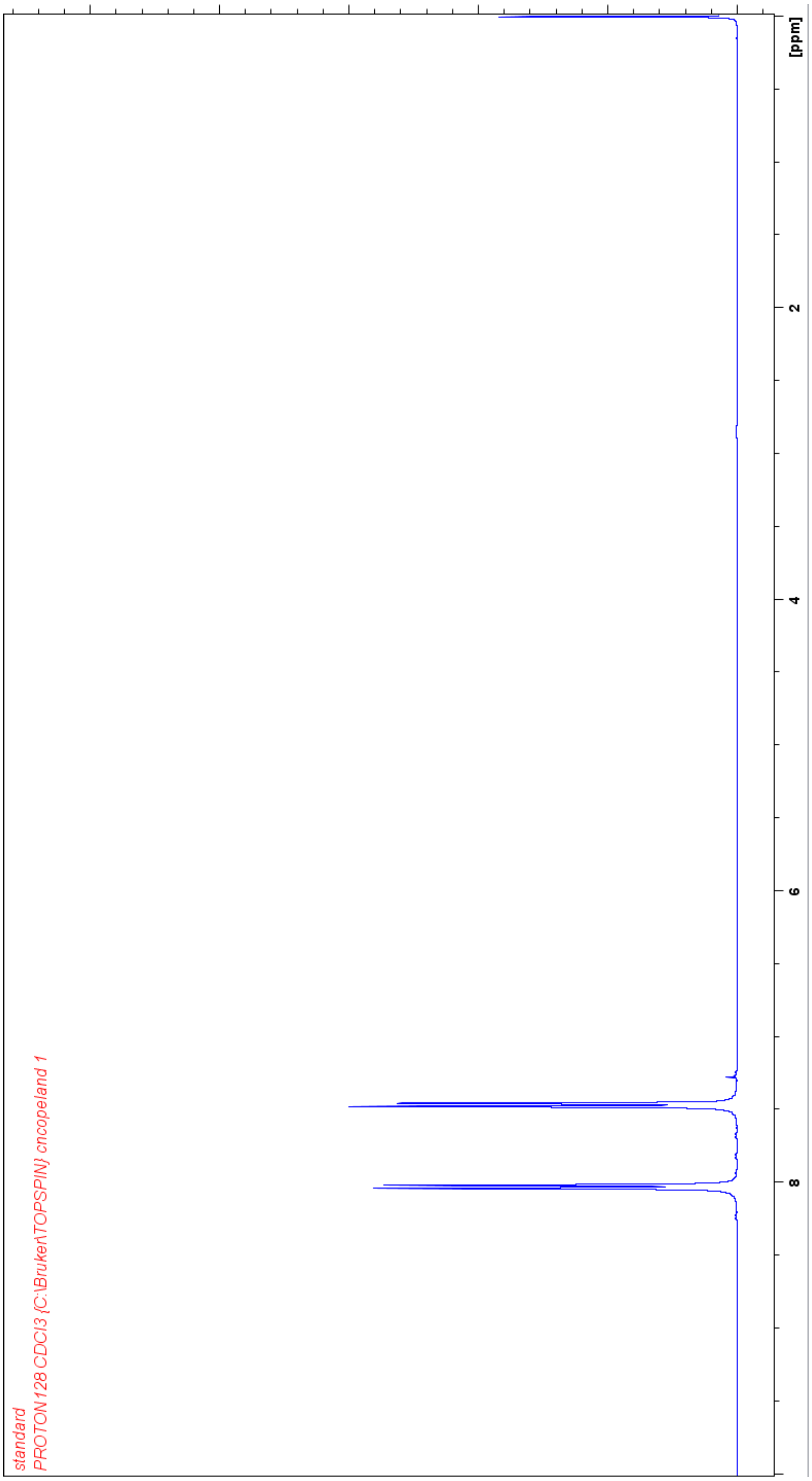

Figure 12: ^{1}H NMR of 4-chlorobenzoyl chloride (**8**)

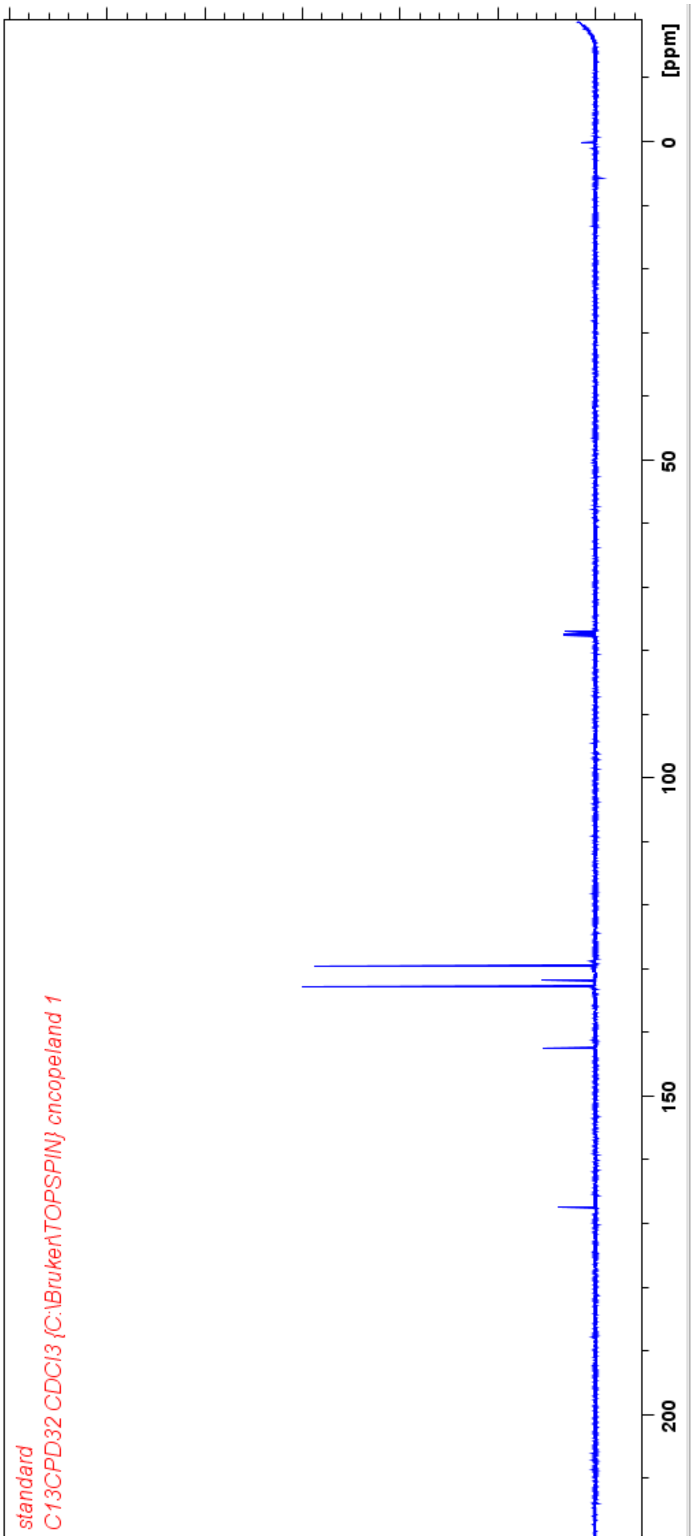

Figure 13: ^{13}C NMR of 4-chlorobenzoyl chloride (**8**)

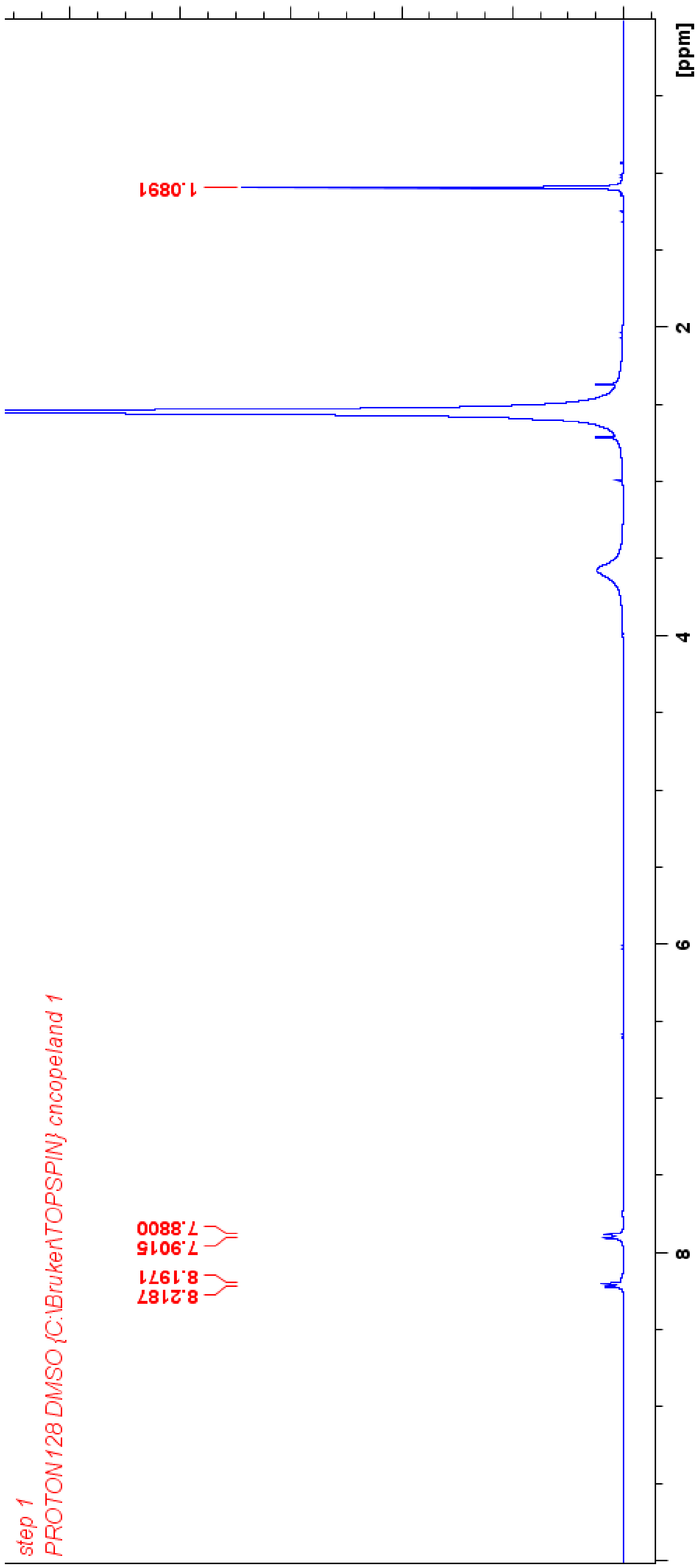

Figure 14: ^{1}H NMR of *tert*-butyl 4-nitrobenzenesulfonate (**3**)

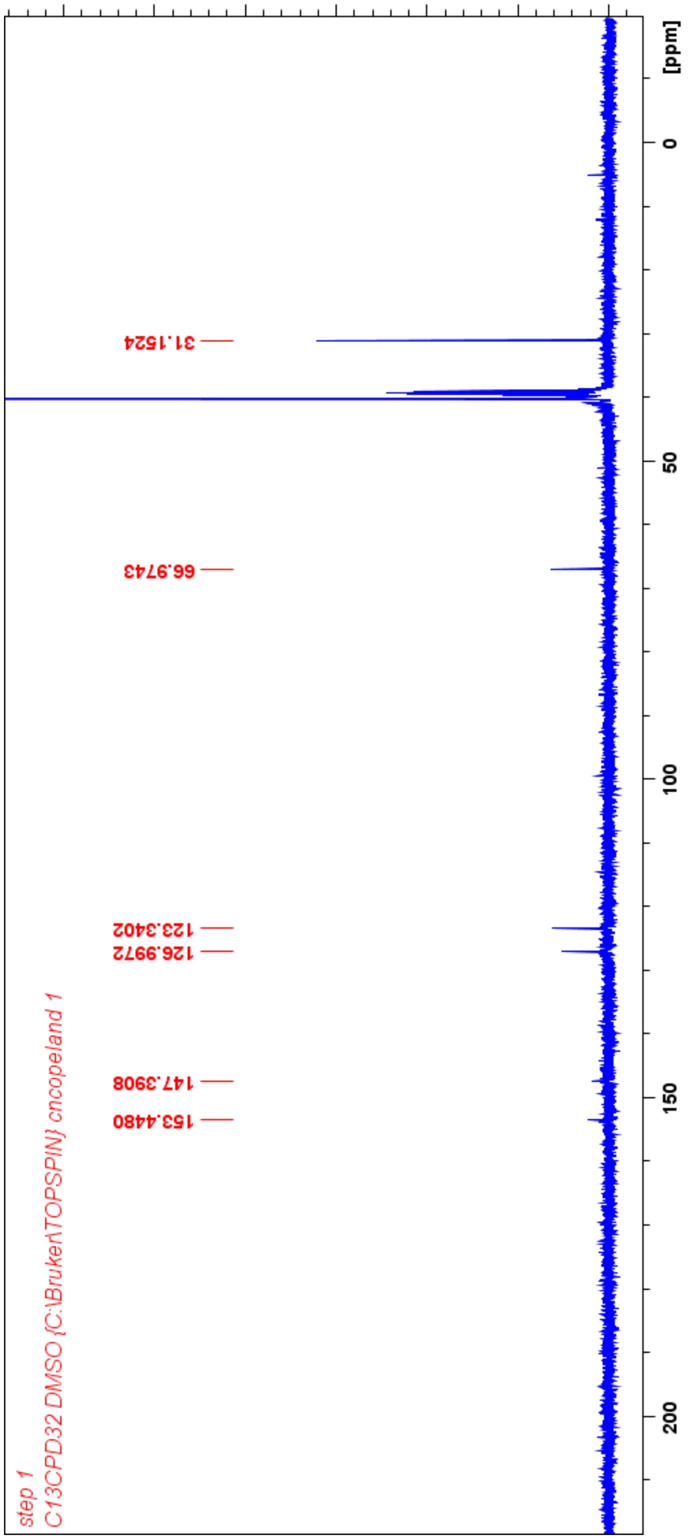

Figure 15: ^{13}C NMR of tert-butyl 4-nitrobenzenesulfonate (**3**)

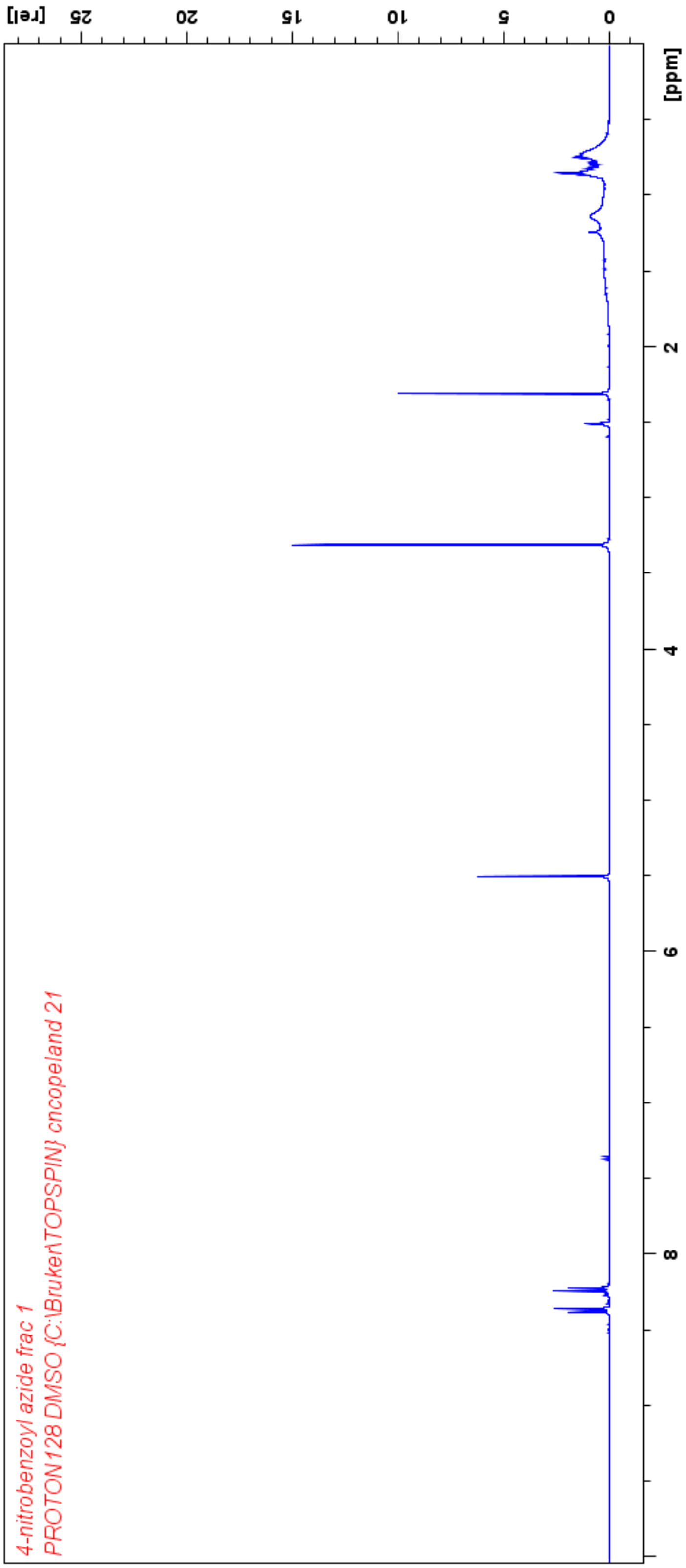

Figure 16: ^{1}H NMR of 4-nitrobenzoyl azide (**7**)

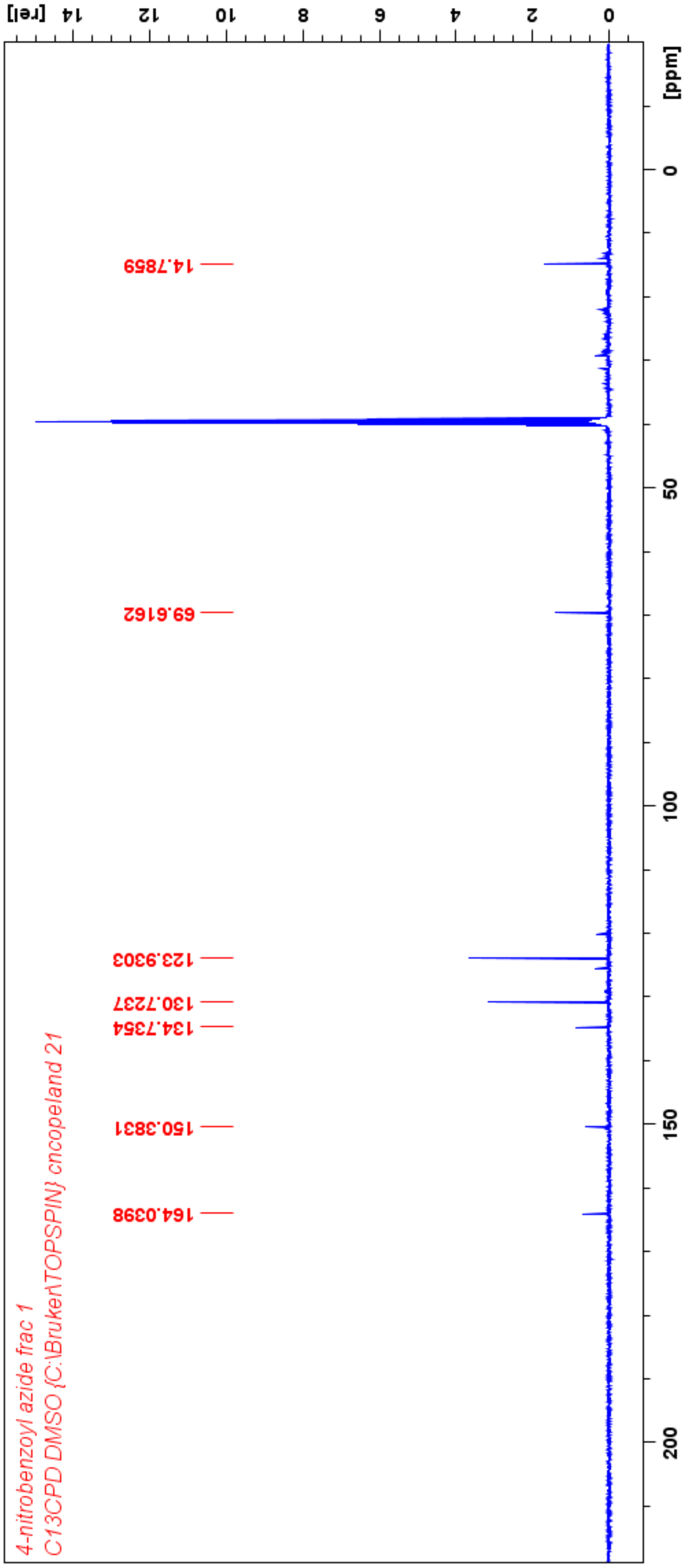

Figure 17: ^{13}C NMR of 4-nitrobenzoyl azide (**7**)

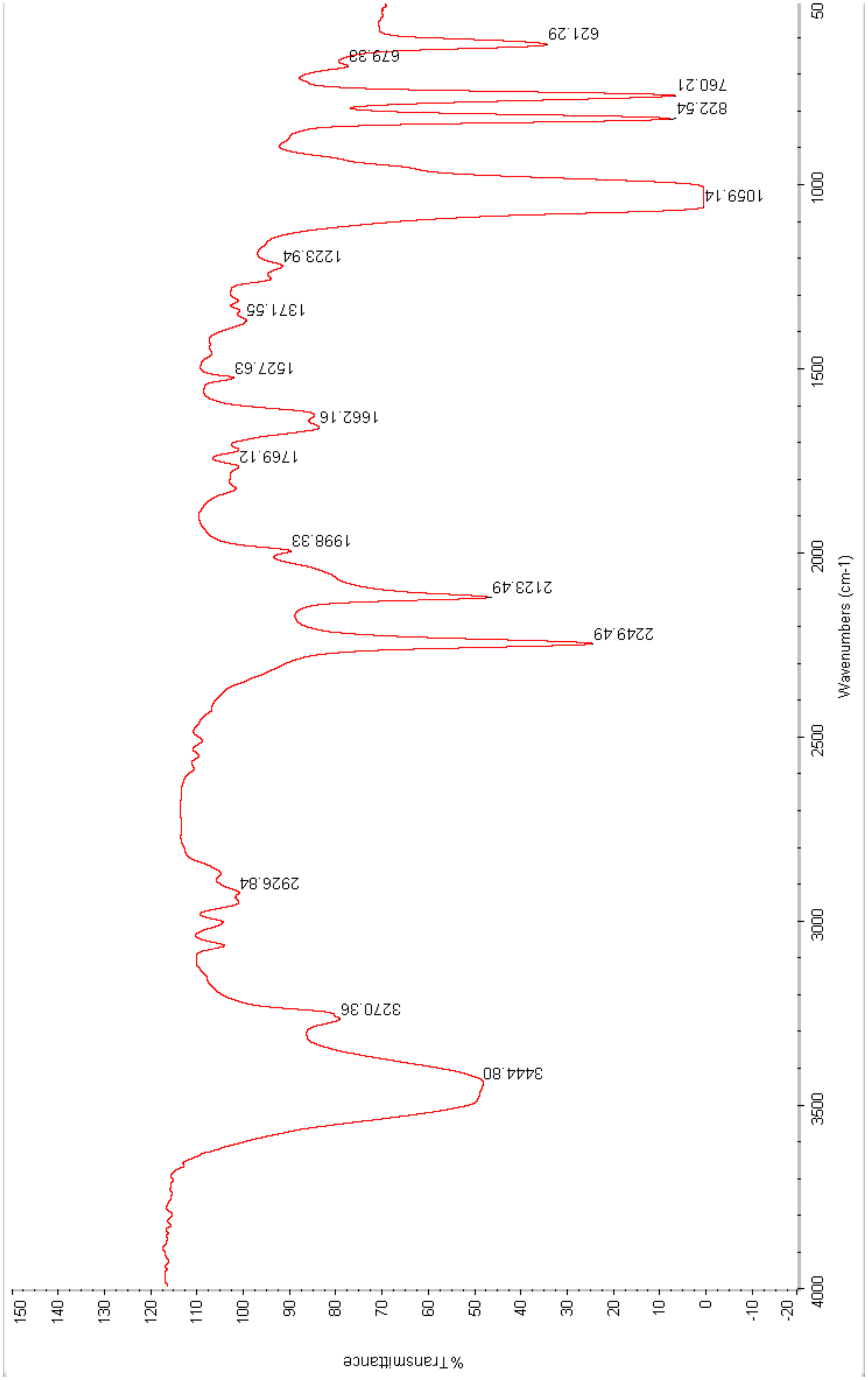

Figure 18: IR spectrum of 4-nitrobenzoyl azide (**7**)

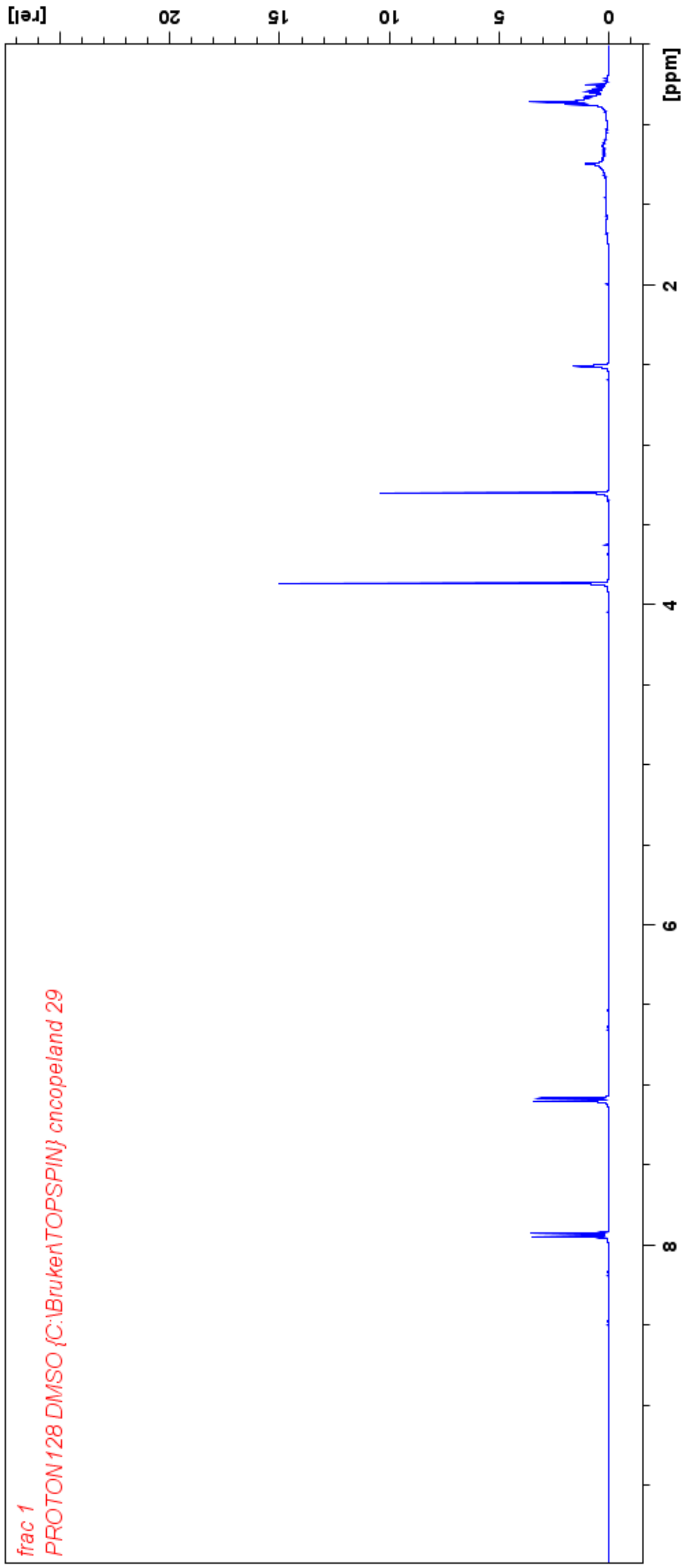

Figure 19: ^{1}H NMR of 4-methoxybenzoyl azide (**5**)

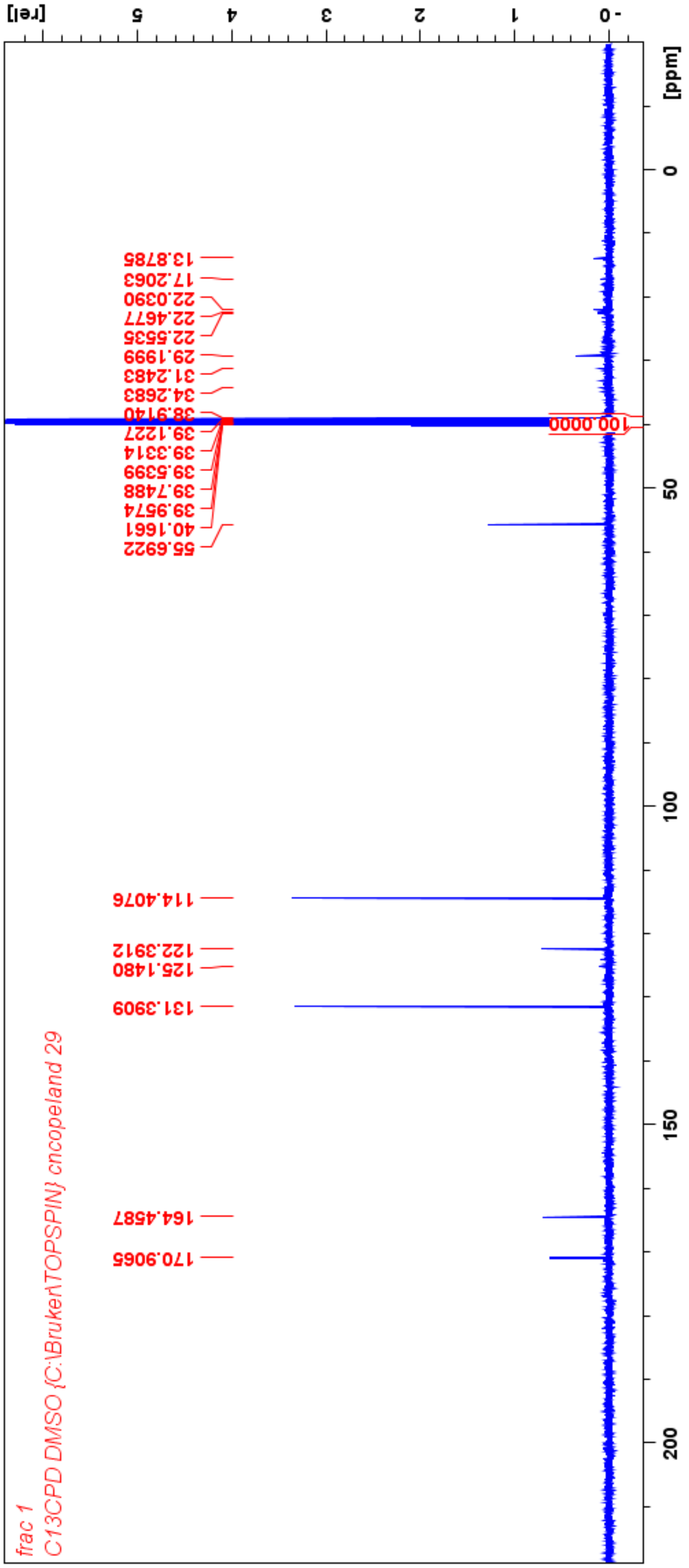

Figure 20: ^{13}C NMR of 4-methoxybenzoyl azide (**5**)

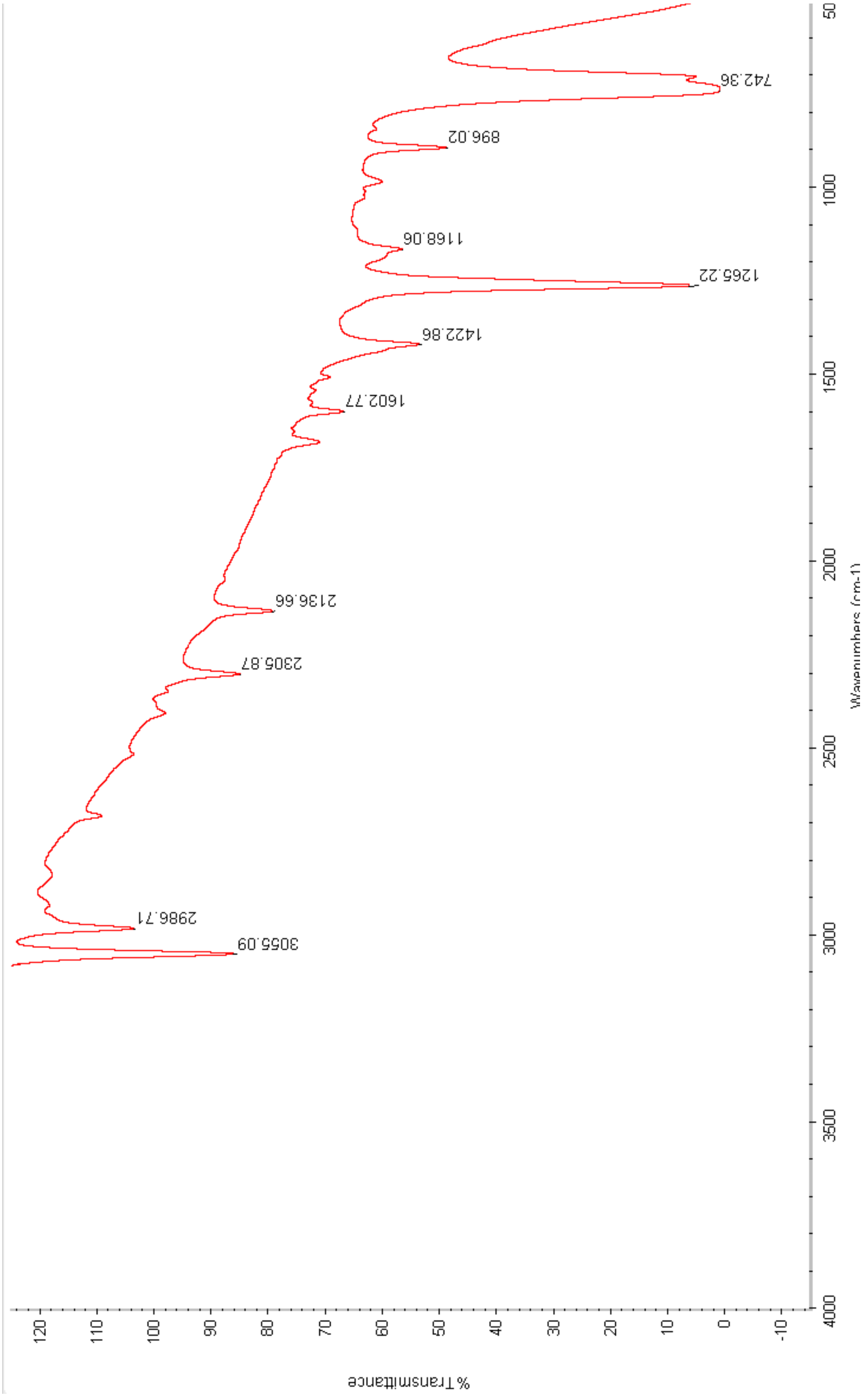

Figure 21: IR of 4-methoxybenzoyl azide (**5**)

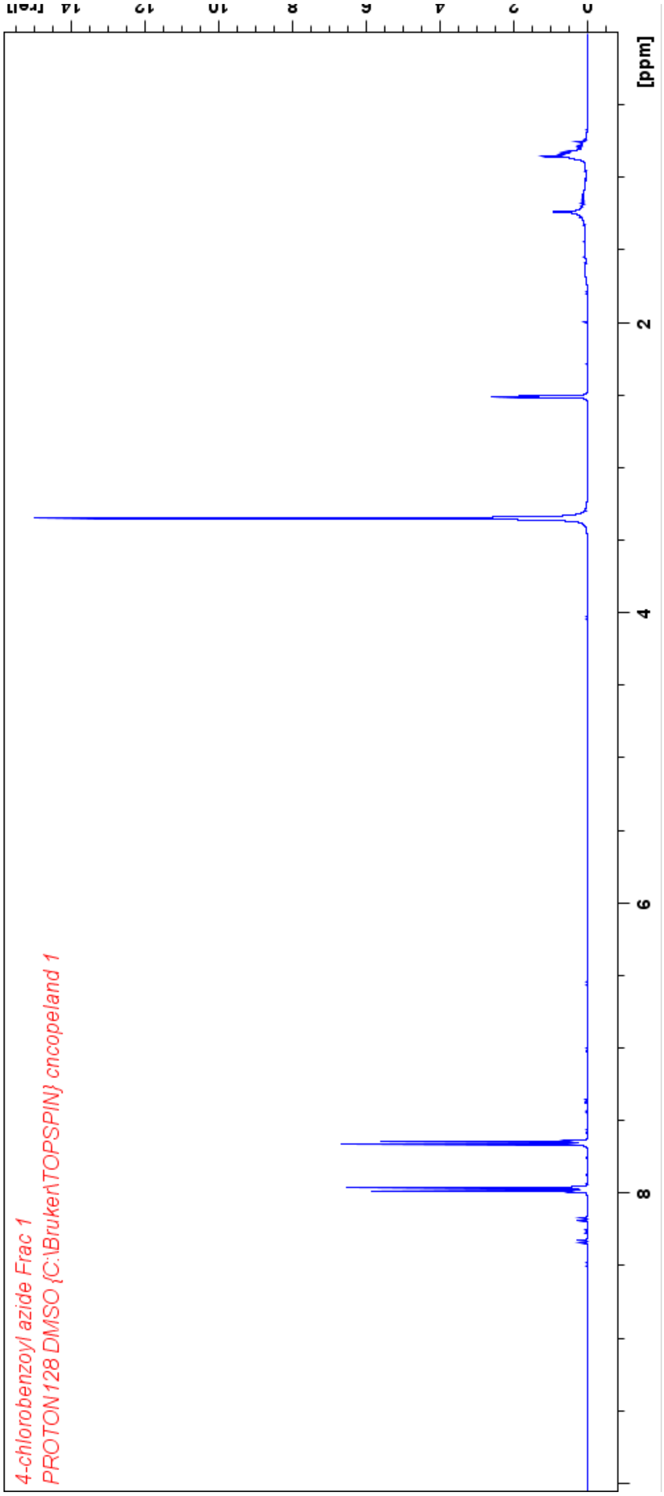

Figure 22: ^{1}H NMR of 4-chlorobenzoyl azide (**9**)

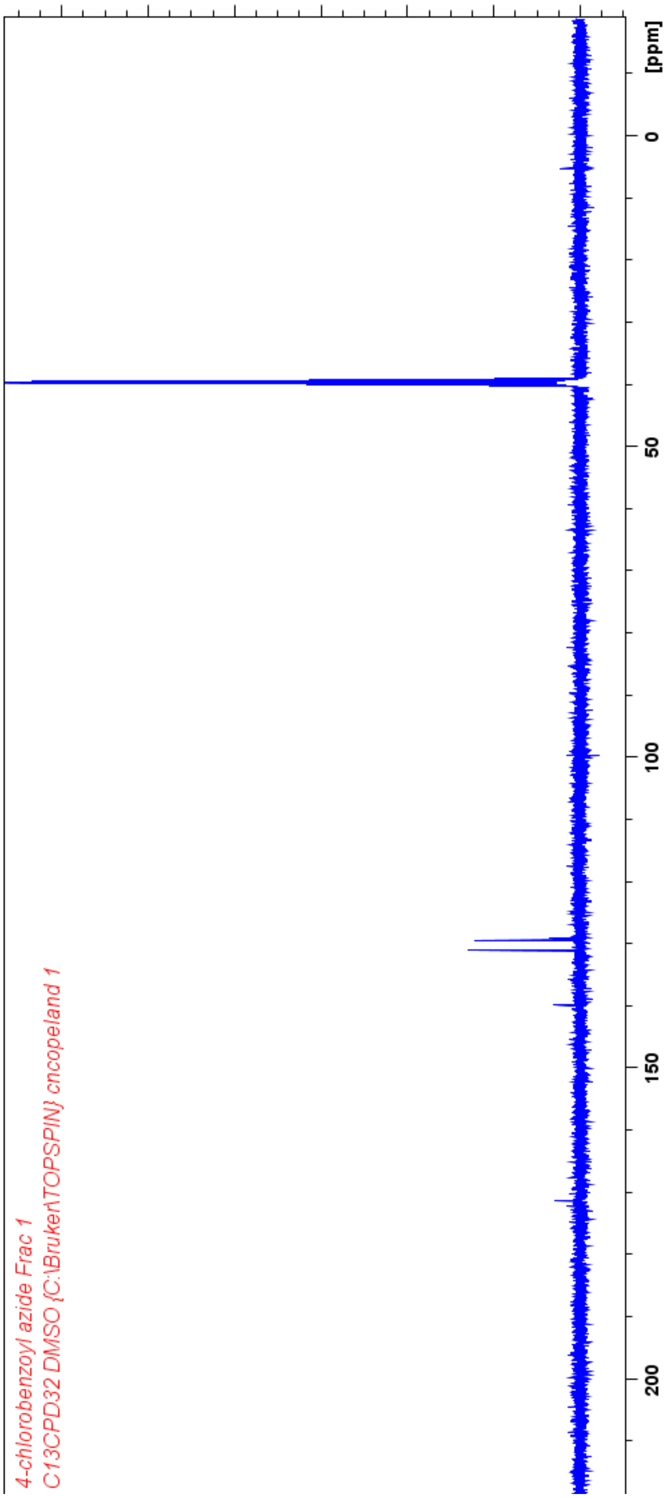

Figure 23: ^{13}C NMR of 4-chlorobenzoyl azide (**9**)

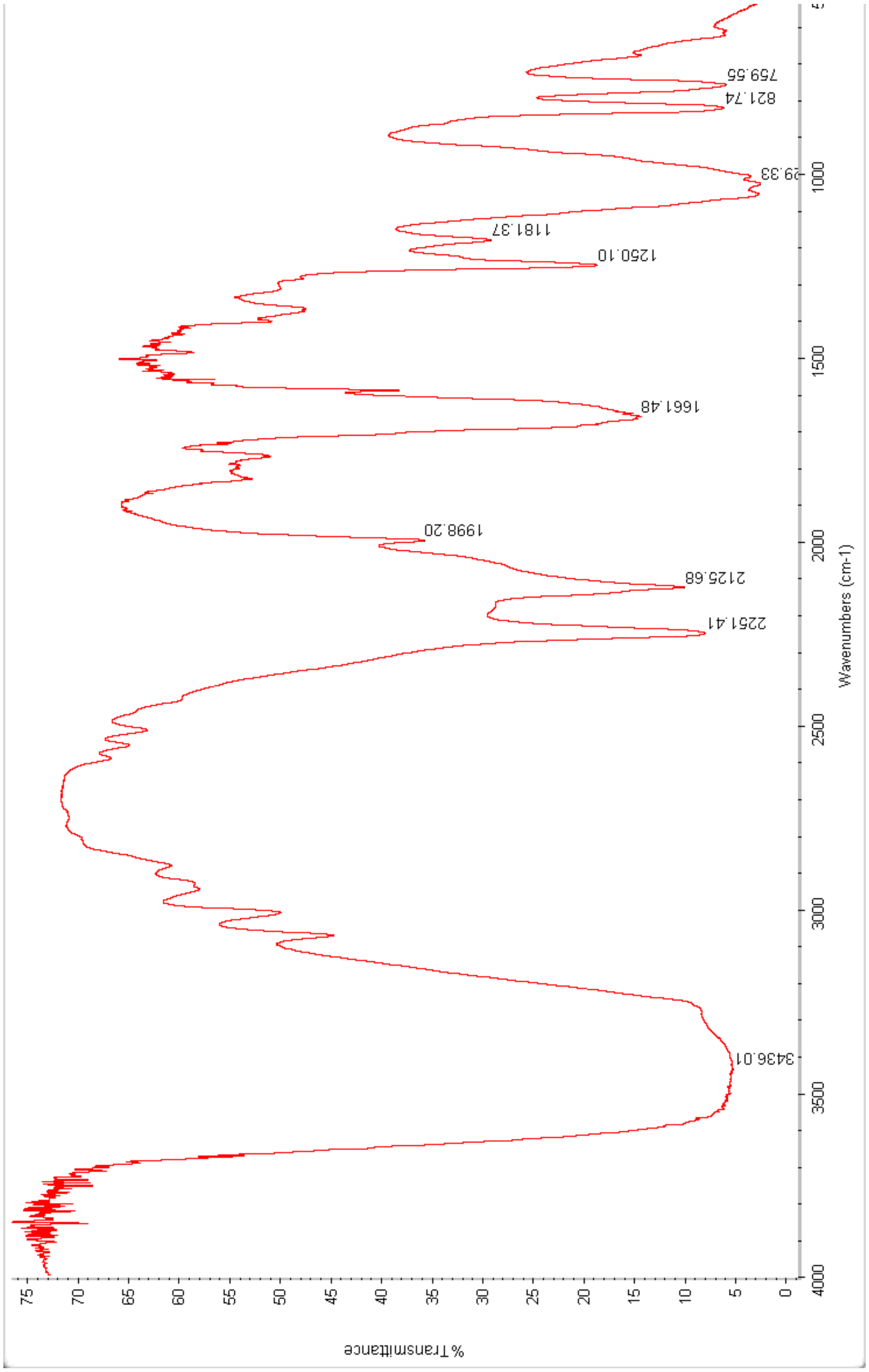

Figure 24: IR of 4-chlorobenzoyl azide (**9**)

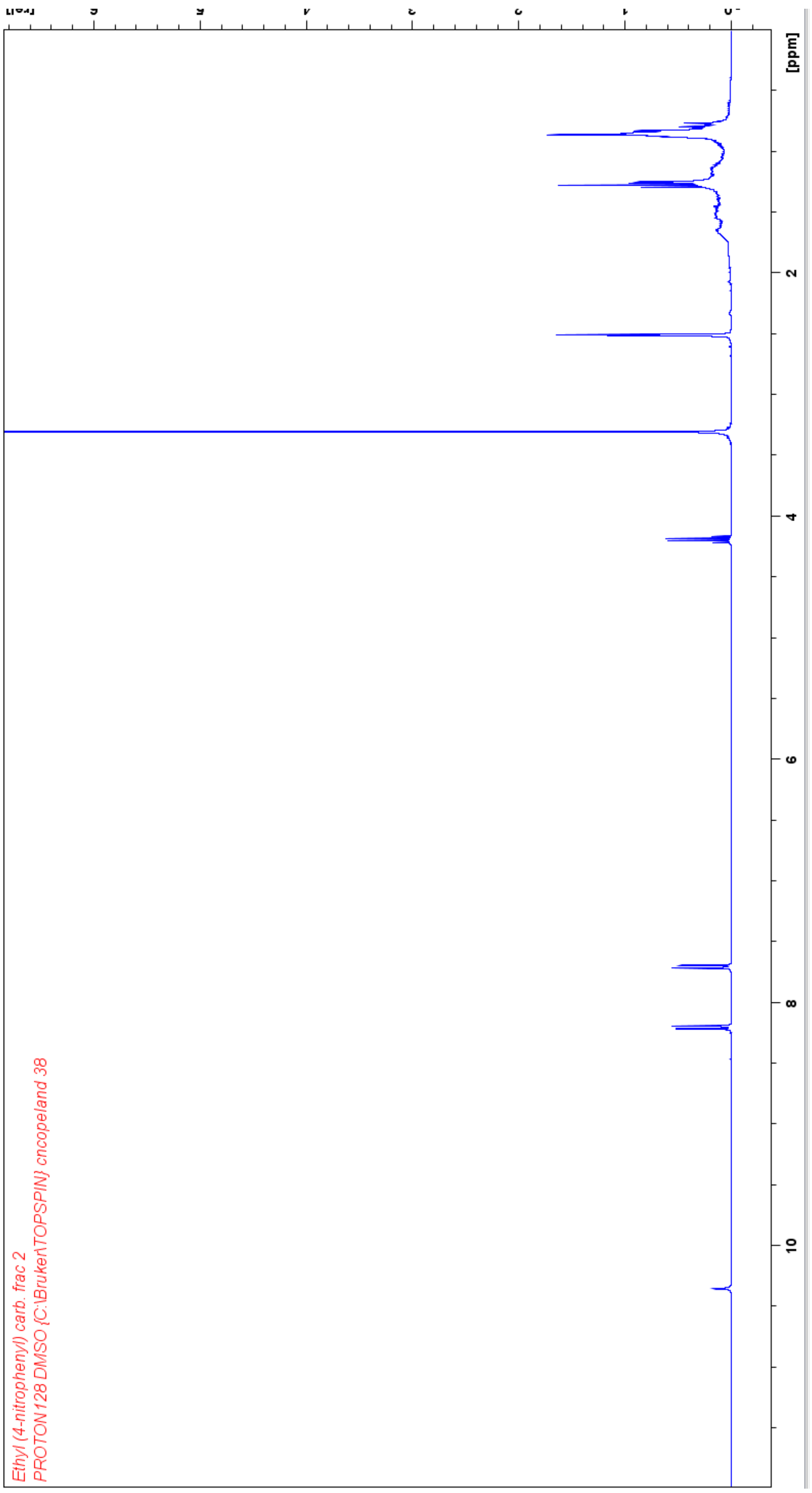

Figure 25: ^{1}H NMR of ethyl (4-nitrophenyl) carbamate (**13**)

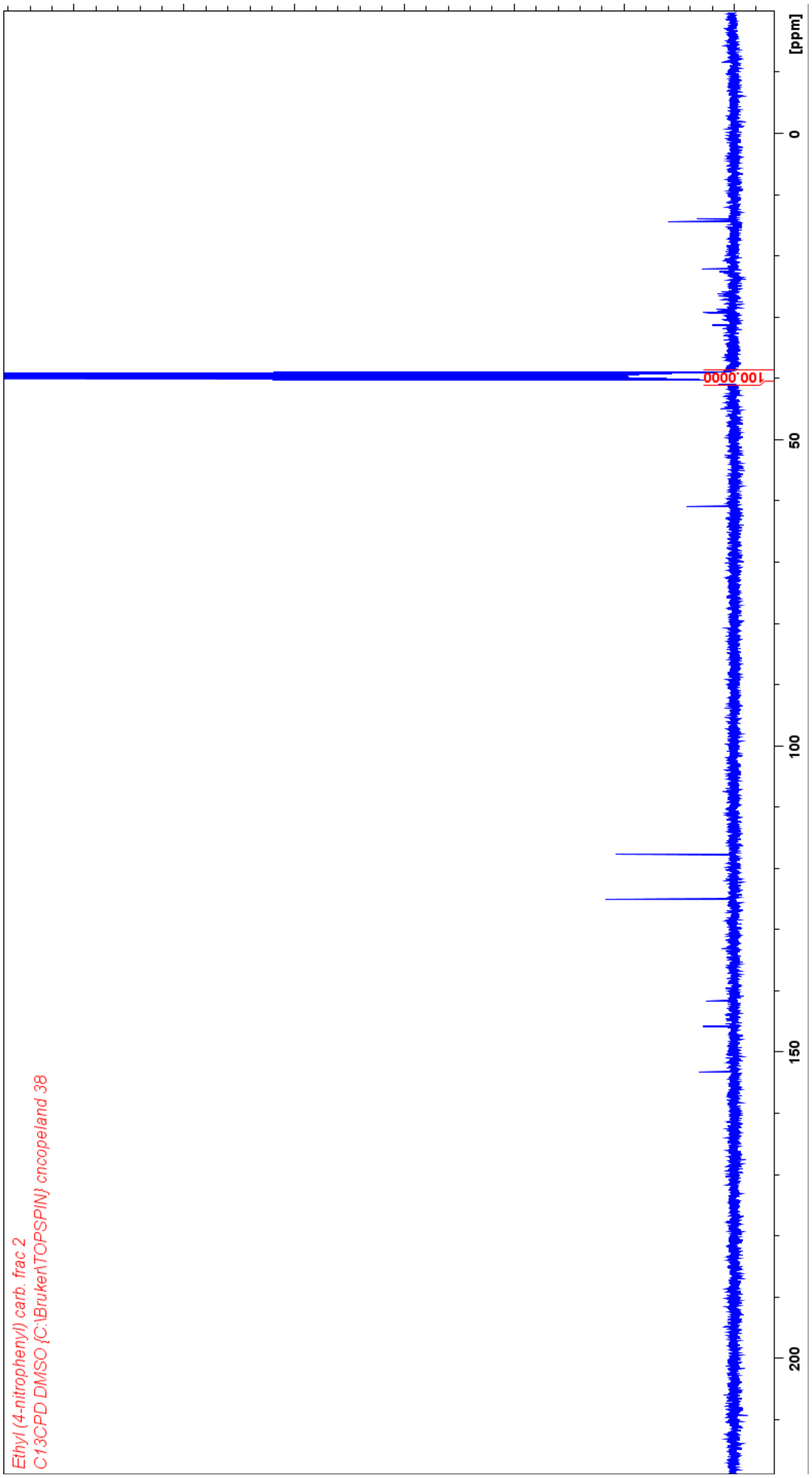

Figure 26: ^{13}C NMR of ethyl (4-nitrophenyl) carbamate (**13**)

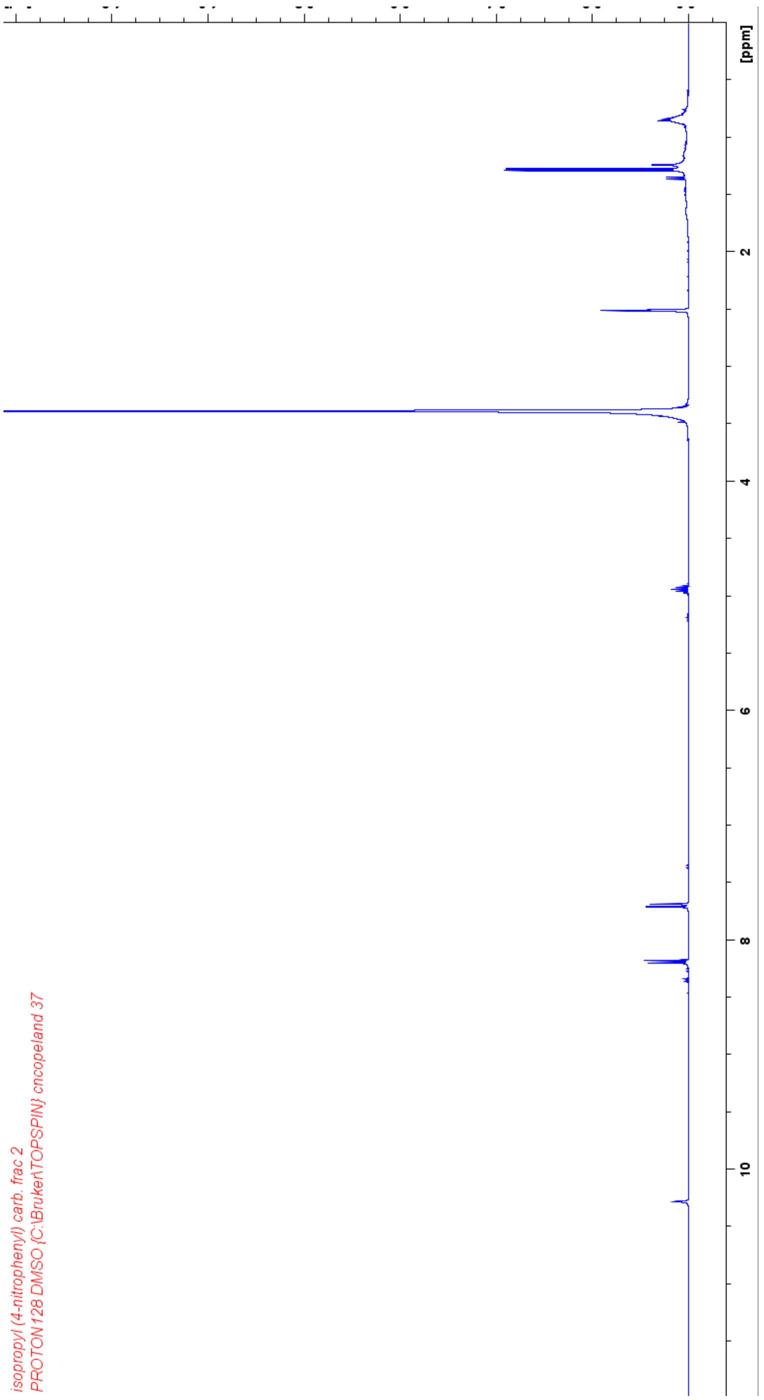

Figure 27: ^{1}H NMR of isopropyl (4-nitrophenyl) carbamate (**14**)

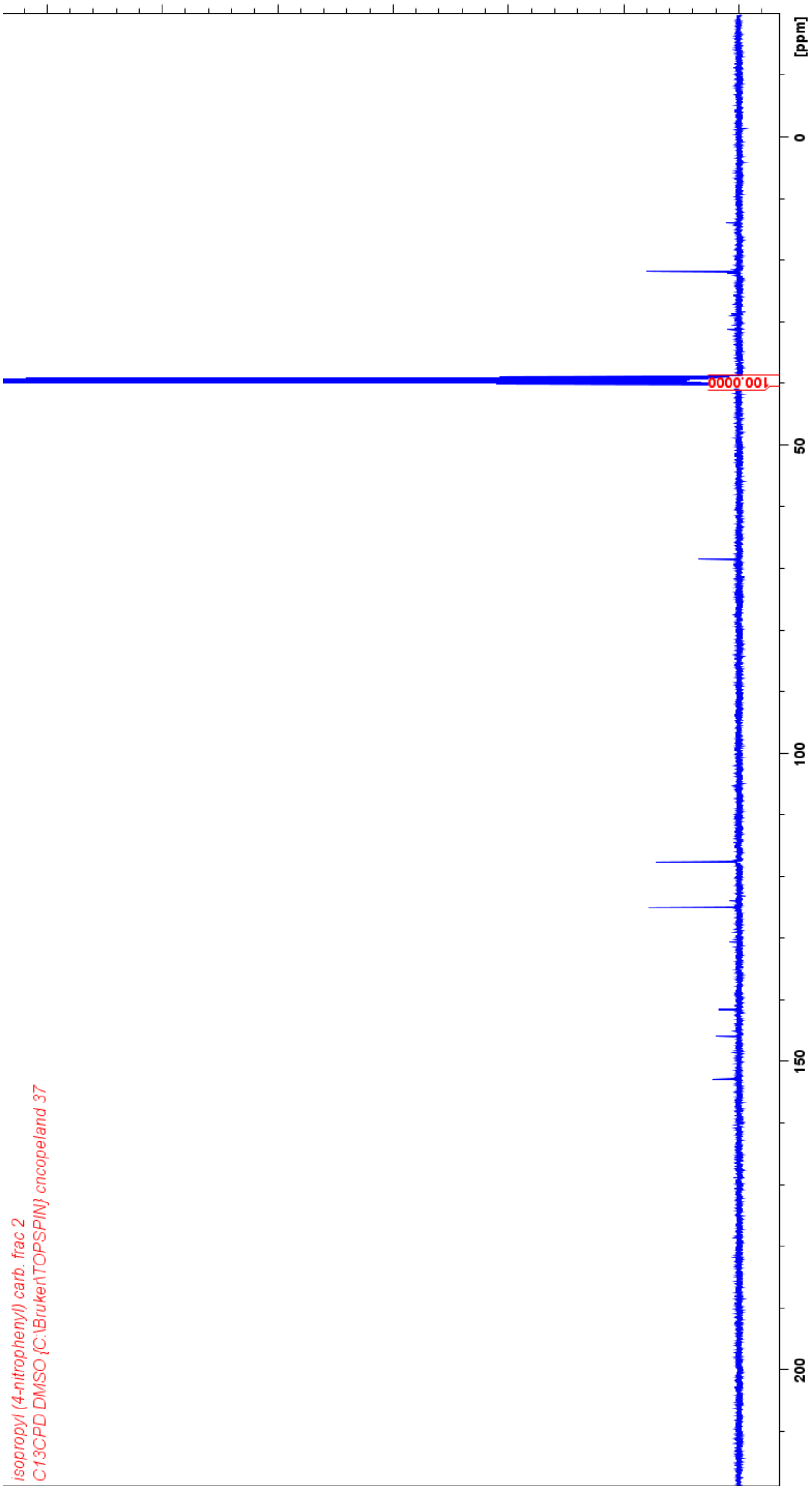

Figure 28: ^{13}C NMR of isopropyl (4-nitrophenyl) carbamate (**14**)

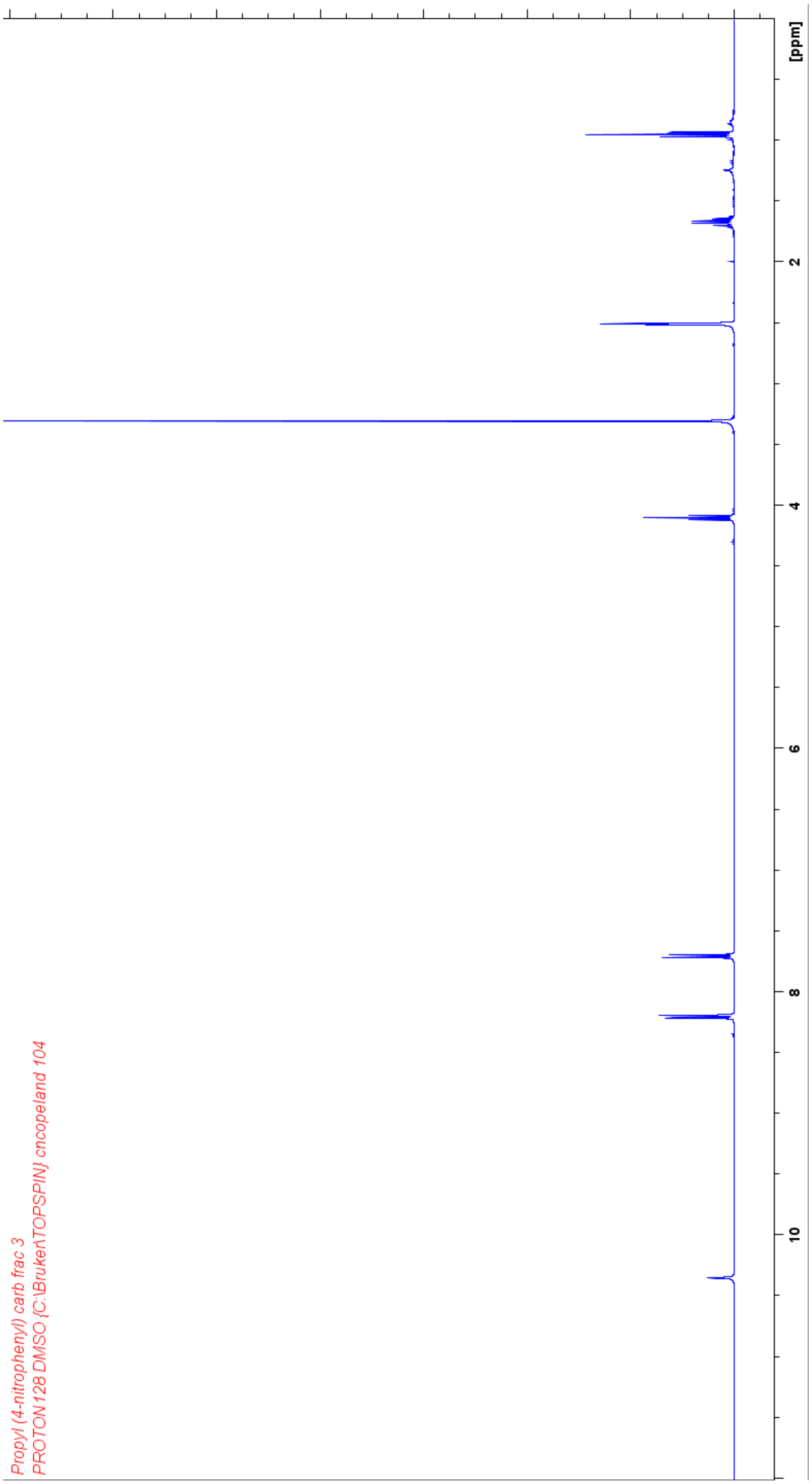

Figure 29: ^{1}H NMR of propyl (4-nitrophenyl) carbamate (**10**)

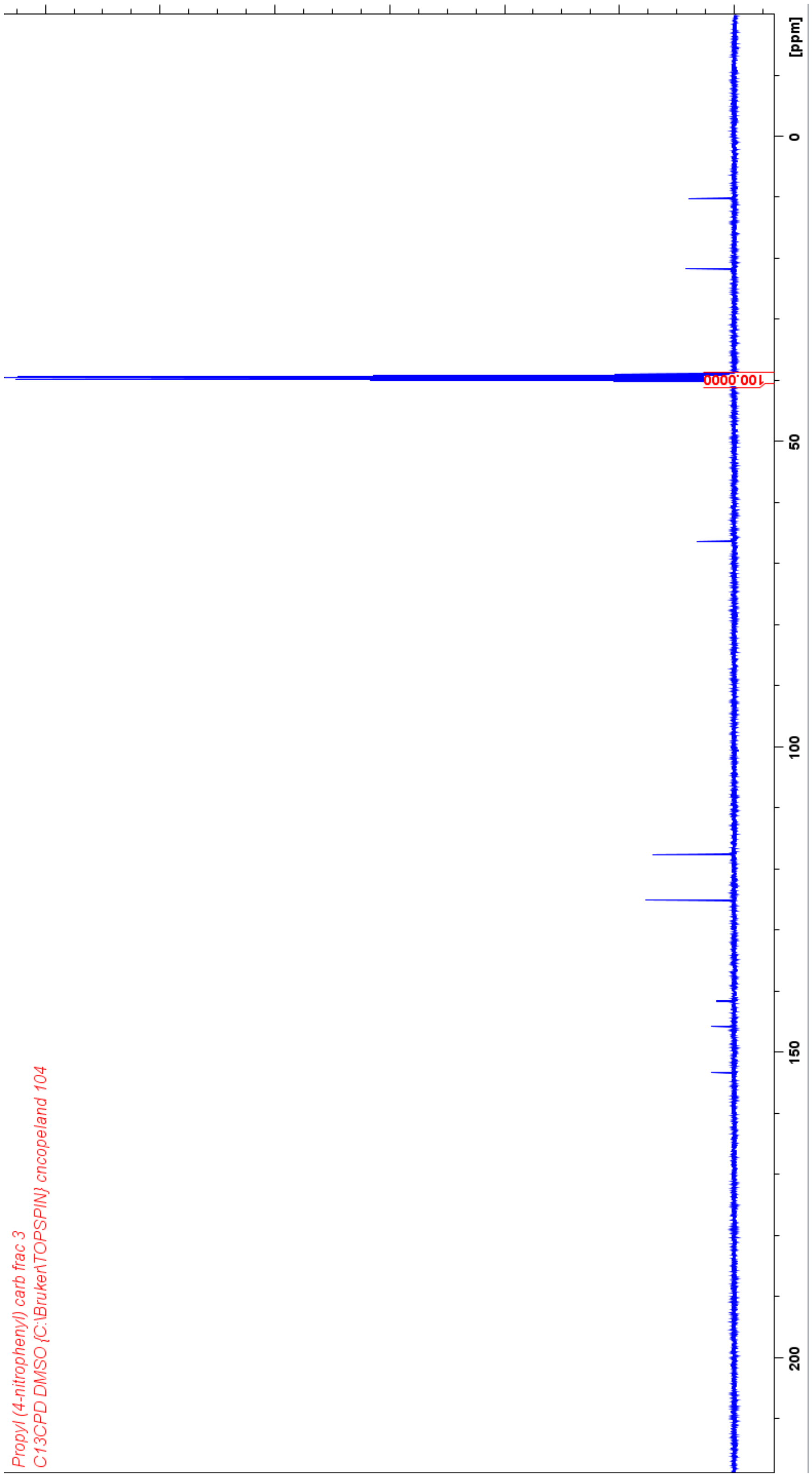

Figure 30: ^{13}C NMR of propyl (4-nitrophenyl) carbamate (**10**)

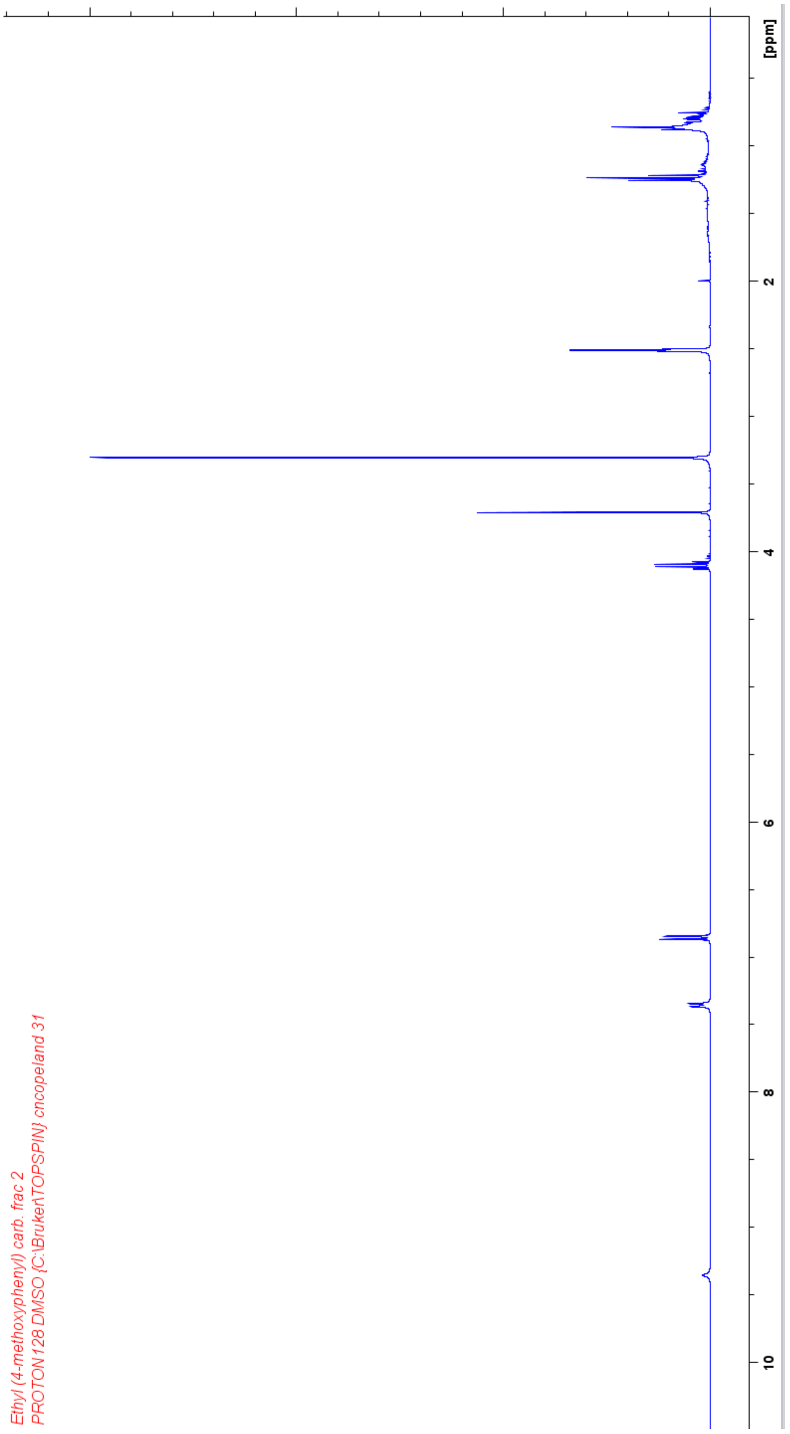

Figure 31: ^{1}H NMR of ethyl (4-methoxyphenyl) carbamate (**11**)

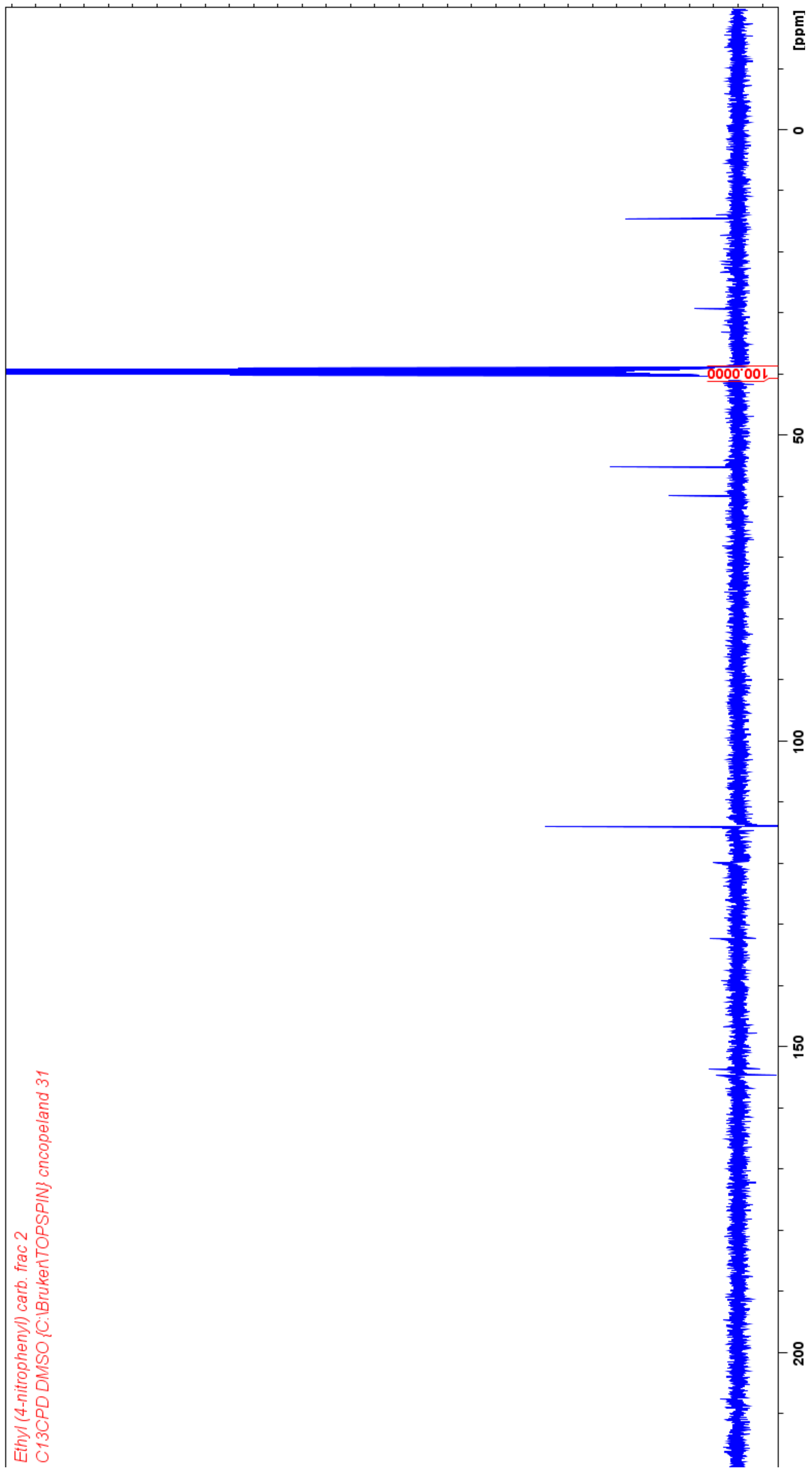

Figure 32: ^{13}C NMR of ethyl (4-methoxyphenyl) carbamate (**11**)

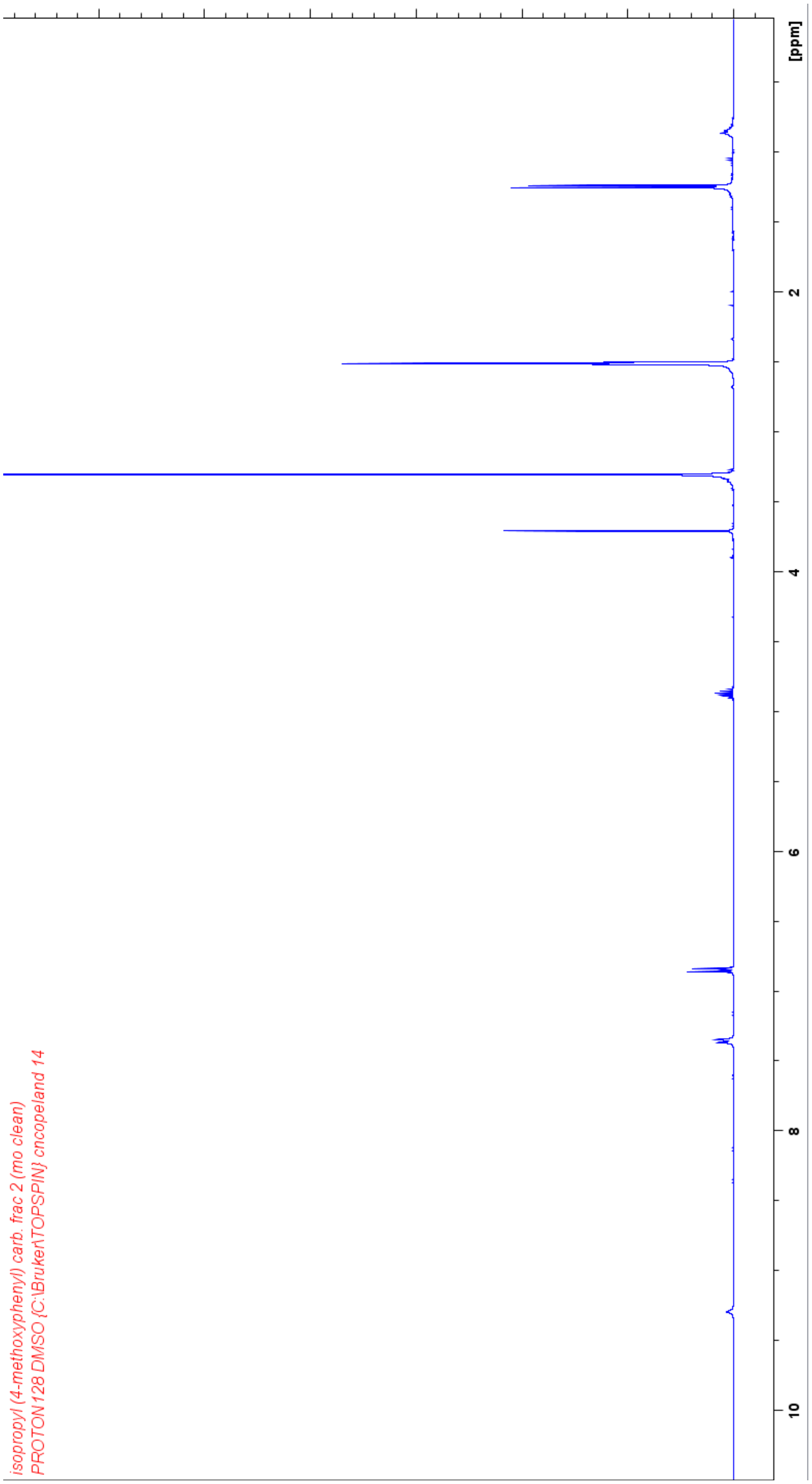

Figure 33: ^{1}H NMR of isopropyl (4-methoxyphenyl) carbamate (**15**)

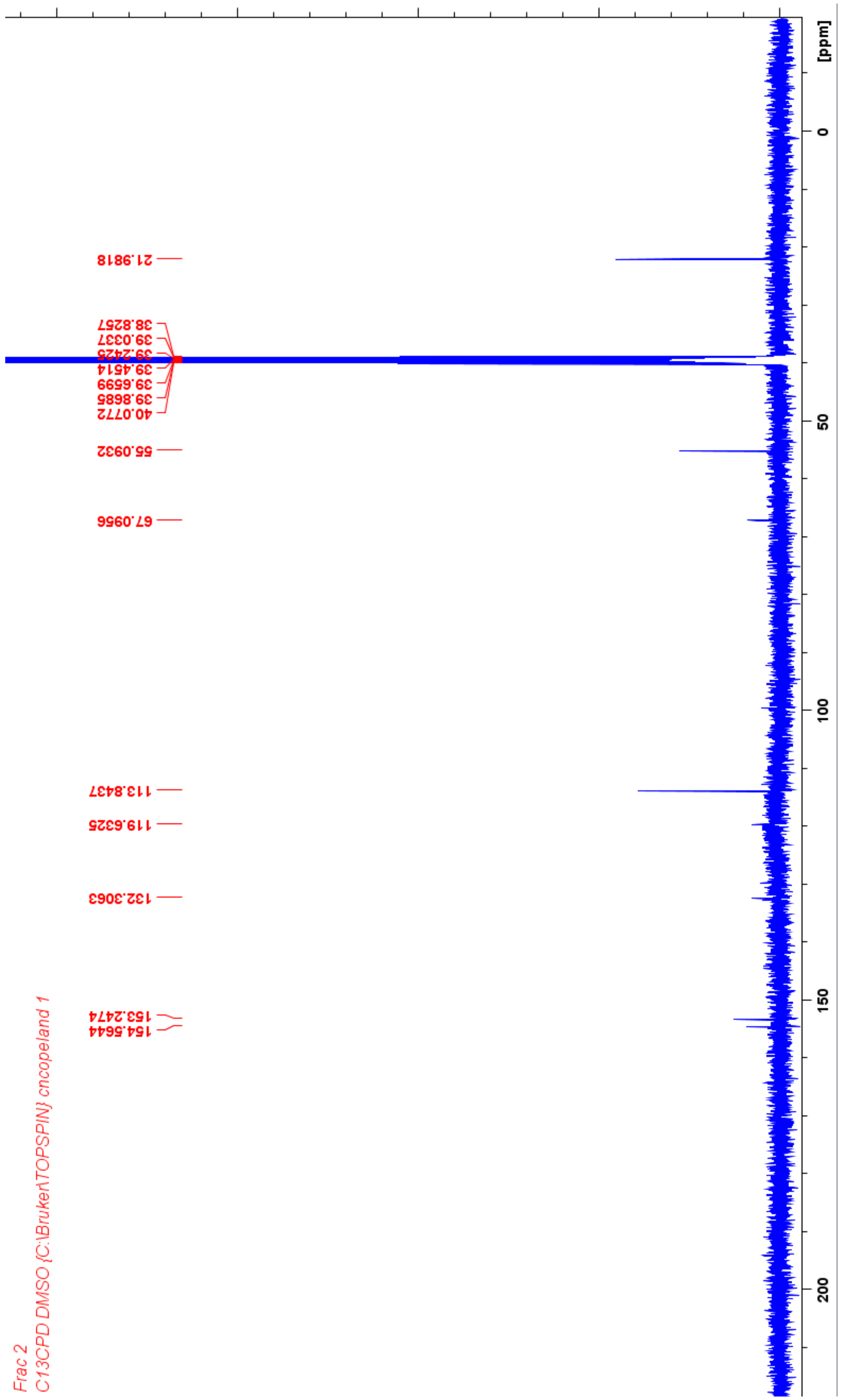

Figure 34: ^{13}C NMR of isopropyl (4-methoxyphenyl) carbamate (**15**)

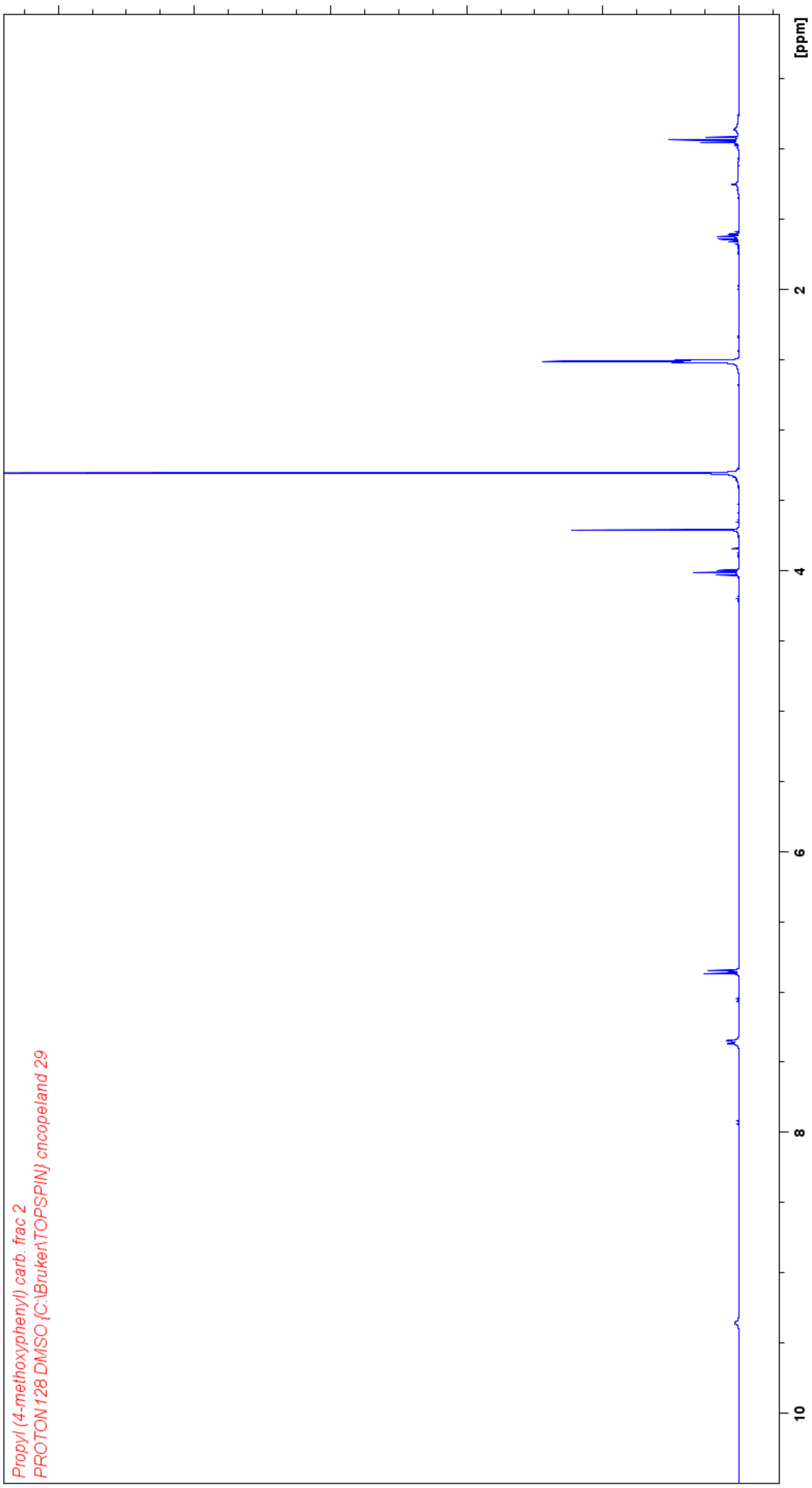

Figure 35: ^{1}H NMR of propyl (4-methoxyphenyl) carbamate (**16**)

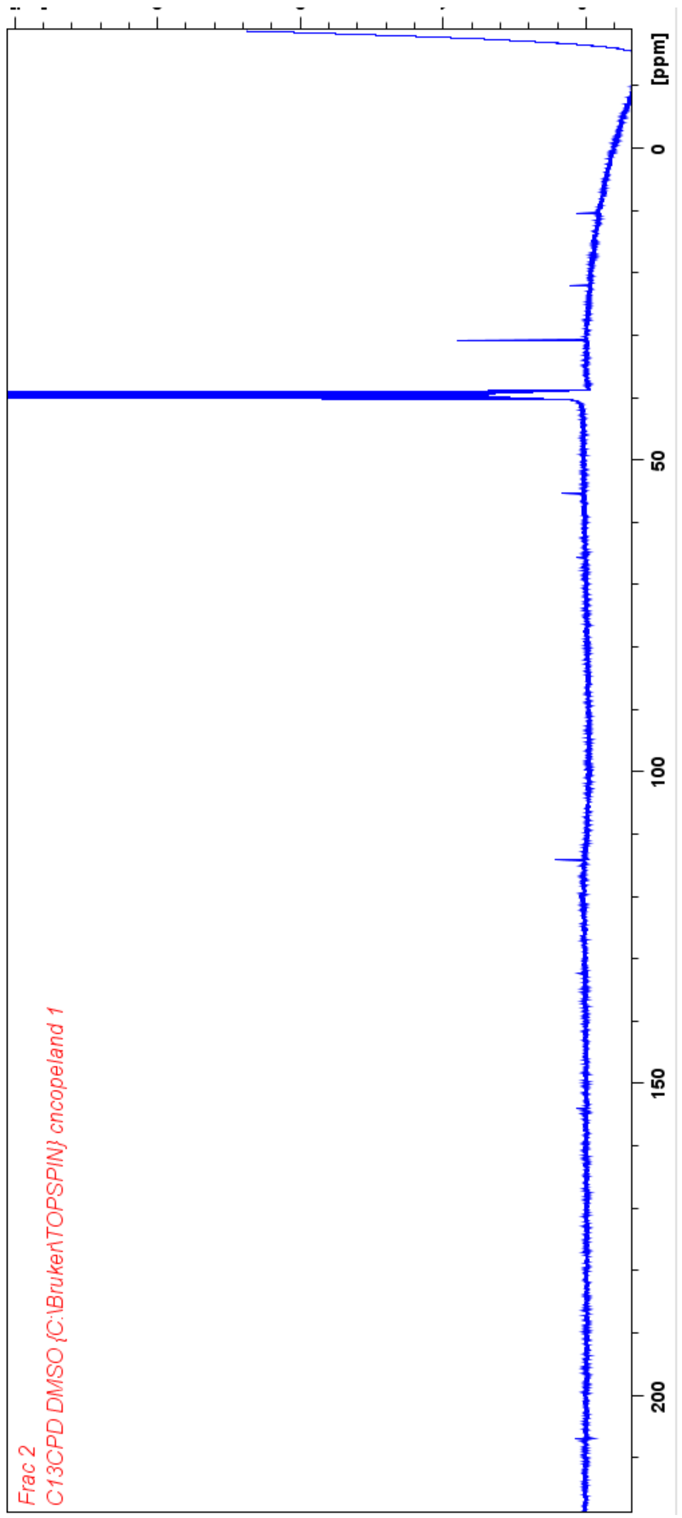

Figure 36: ^{13}C NMR of propyl (4-methoxyphenyl) carbamate (**16**)

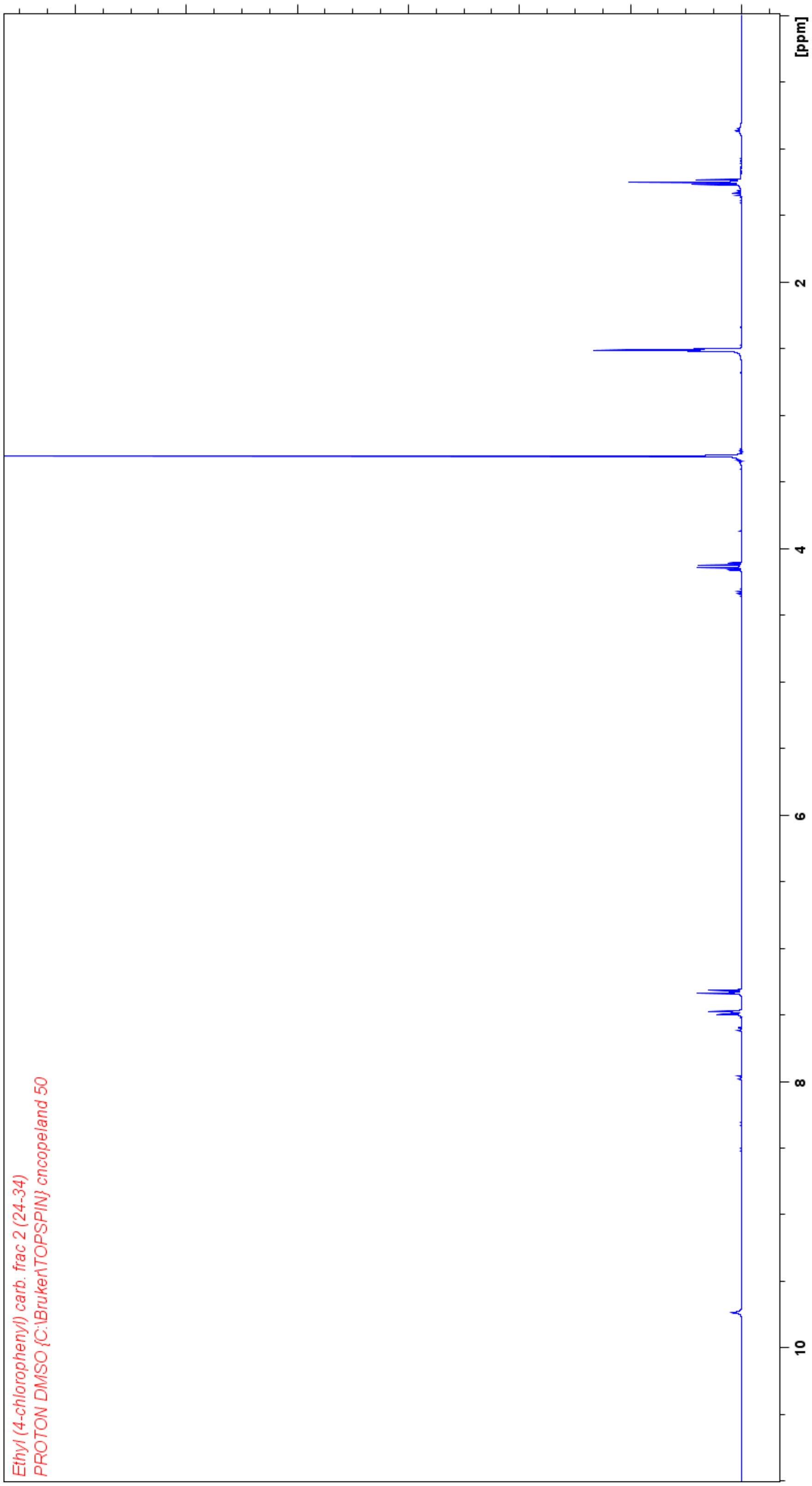

Figure 37: ^{1}H NMR of ethyl (4-chlorophenyl) carbamate (**17**)

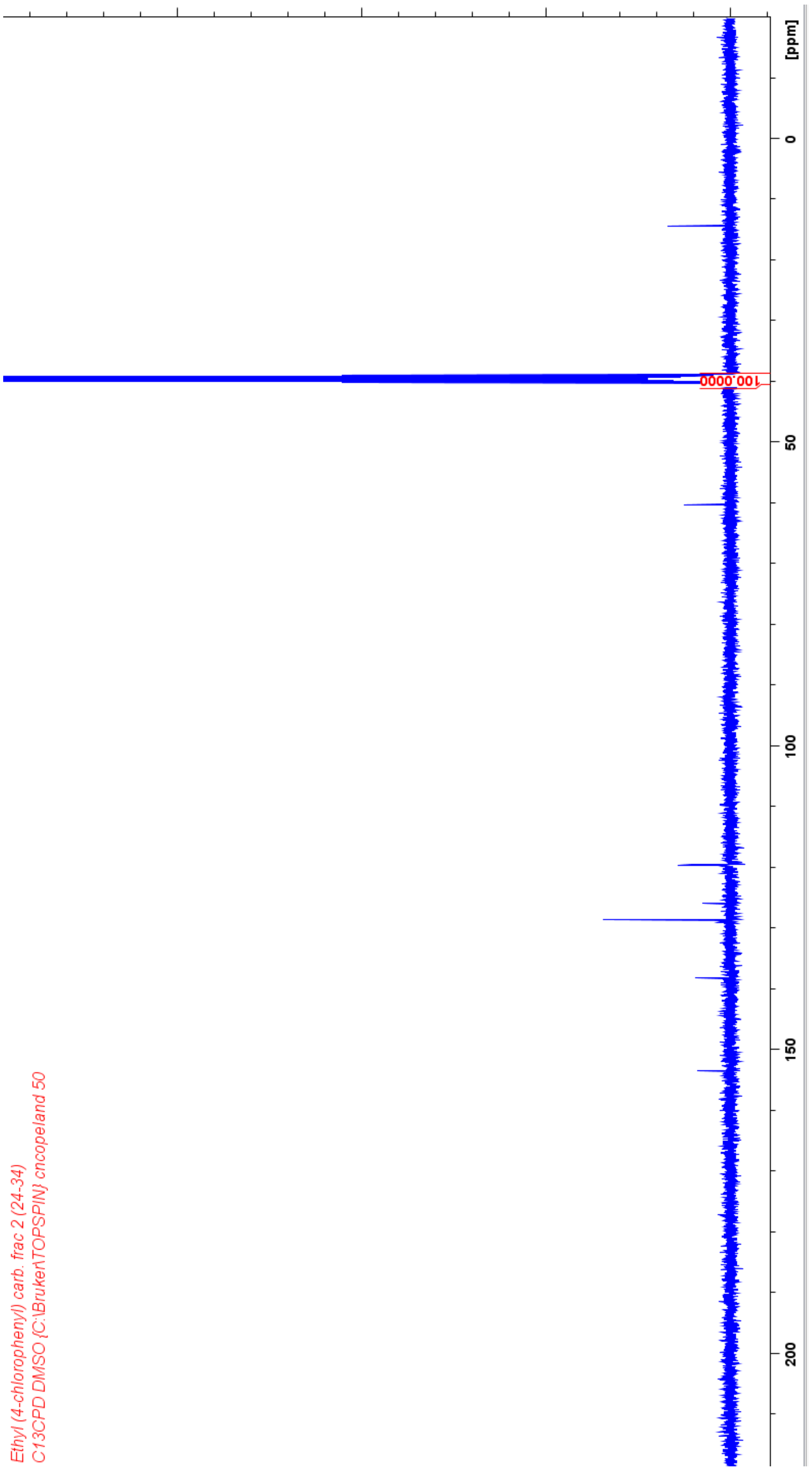

Figure 38: ^{13}C NMR of ethyl (4-chlorophenyl) carbamate (**17**)

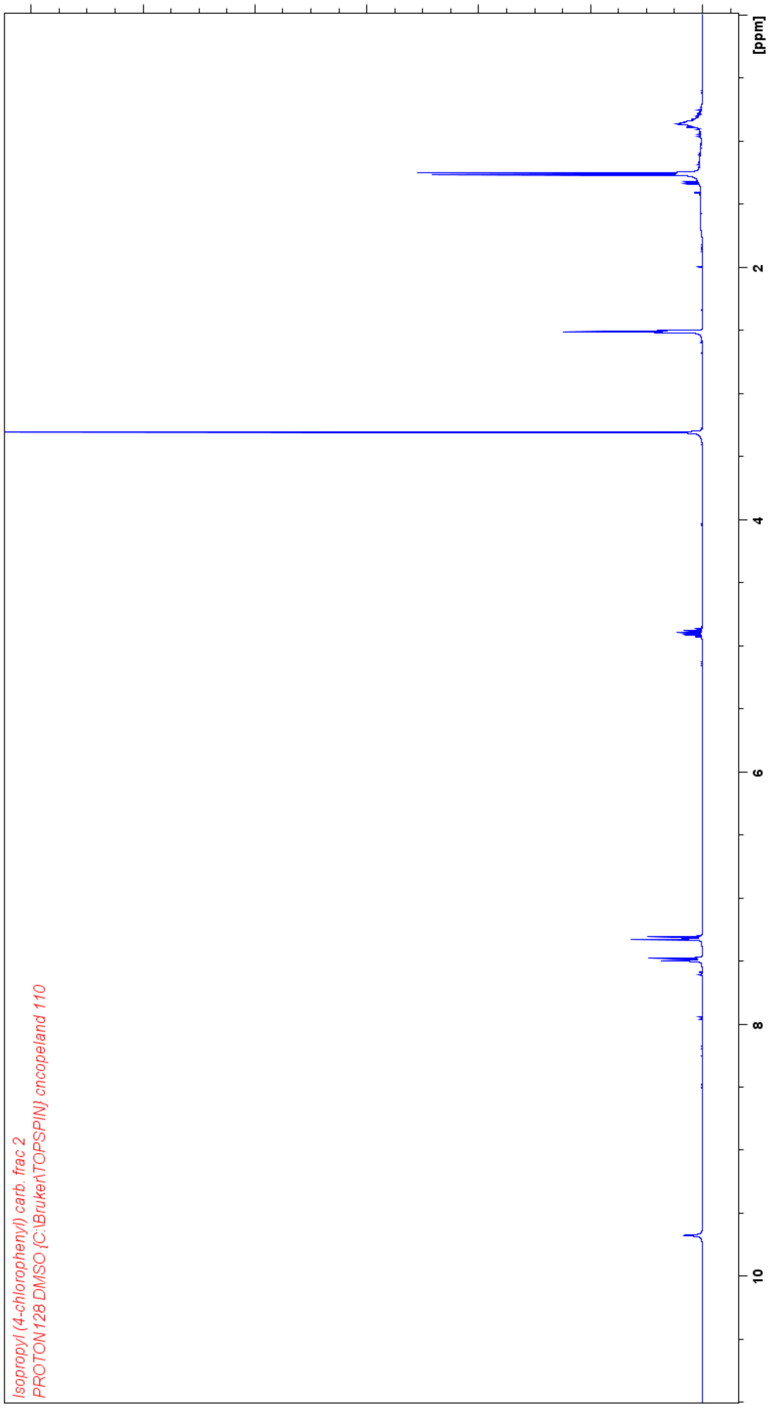

Figure 39: ^{1}H NMR of isopropyl (4-chlorophenyl) carbamate (**12**)

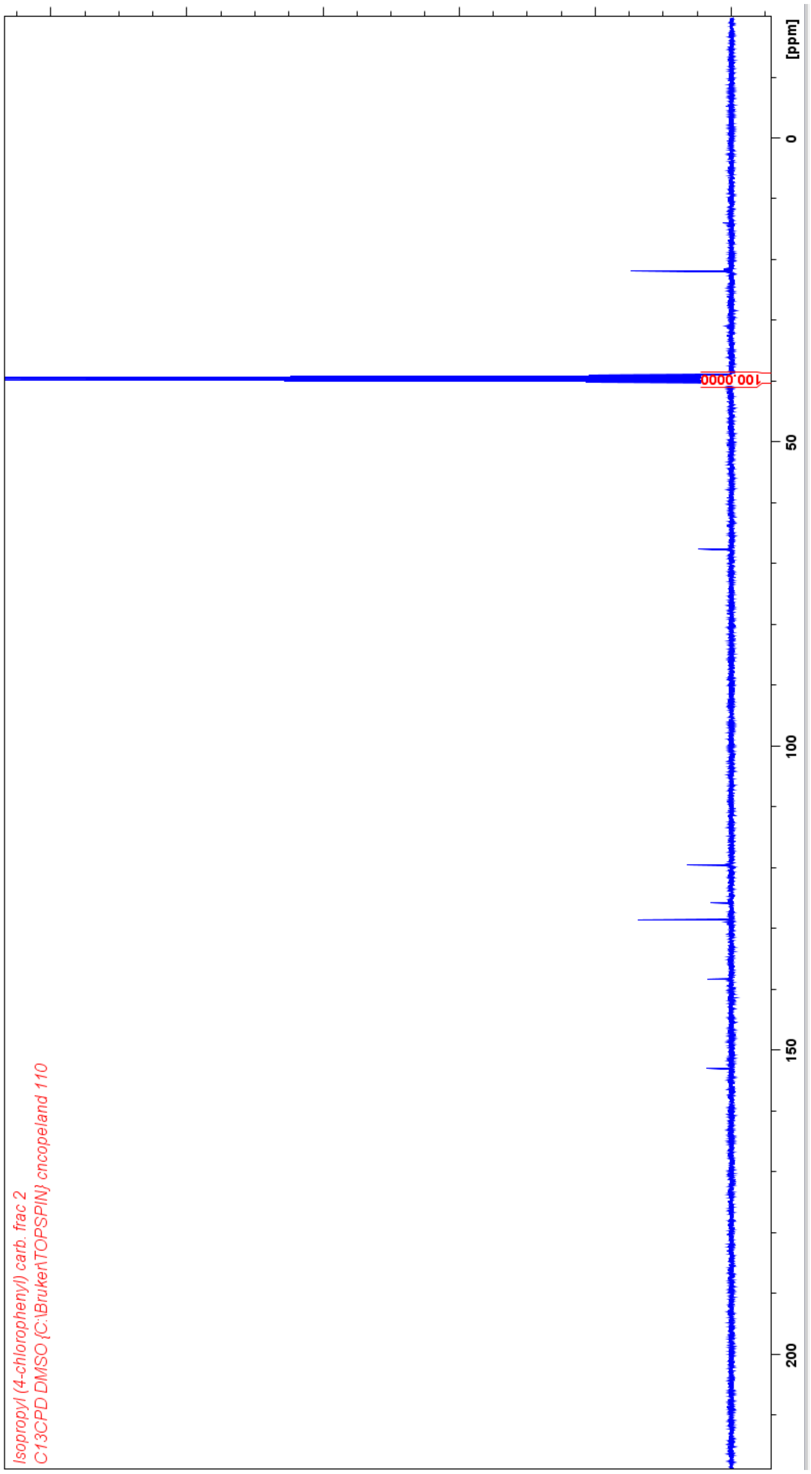

Figure 40: ^{13}C NMR of isopropyl (4-chlorophenyl) carbamate (**12**)

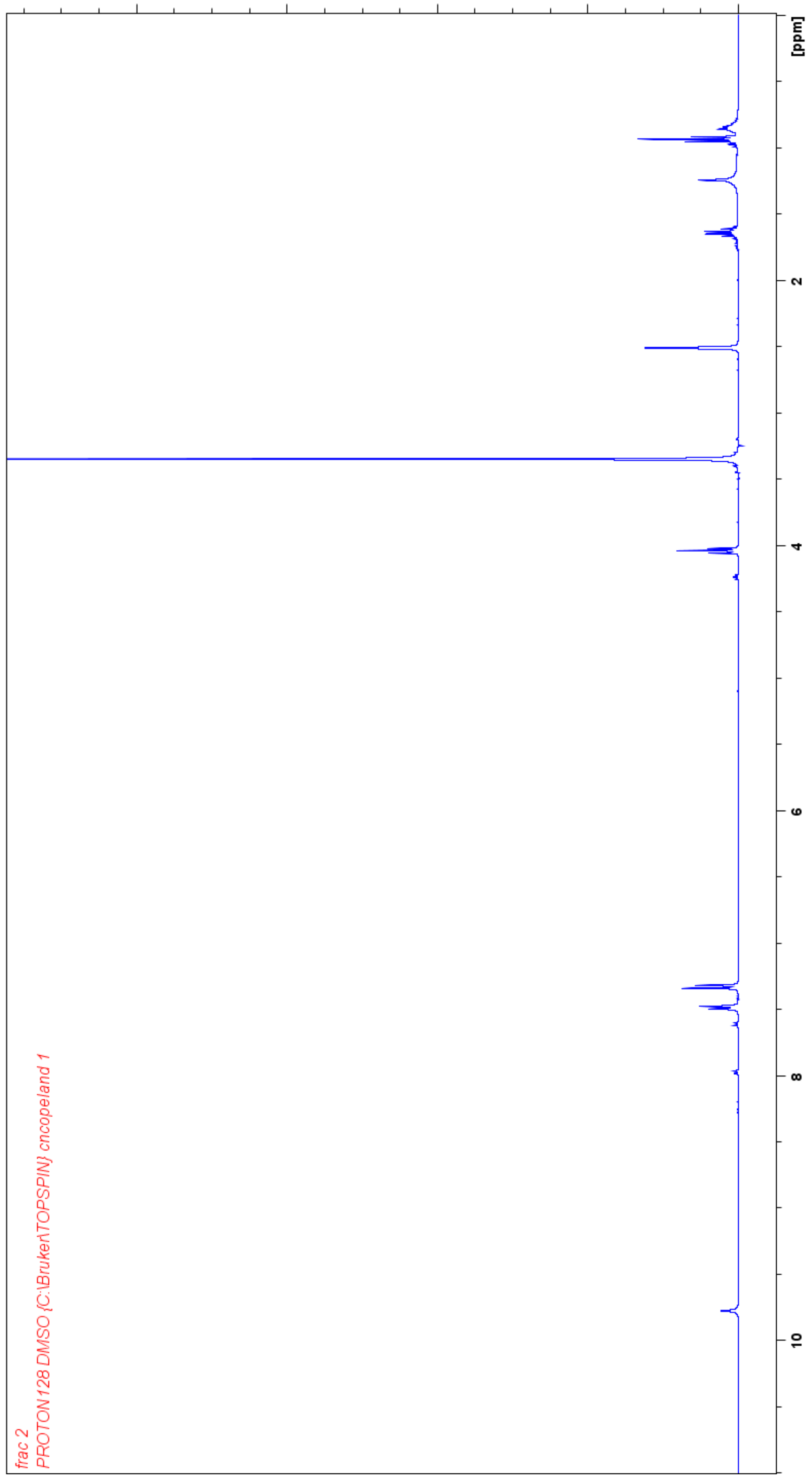

Figure 41: ^{1}H NMR of propyl (4-chlorophenyl) carbamate (**18**)

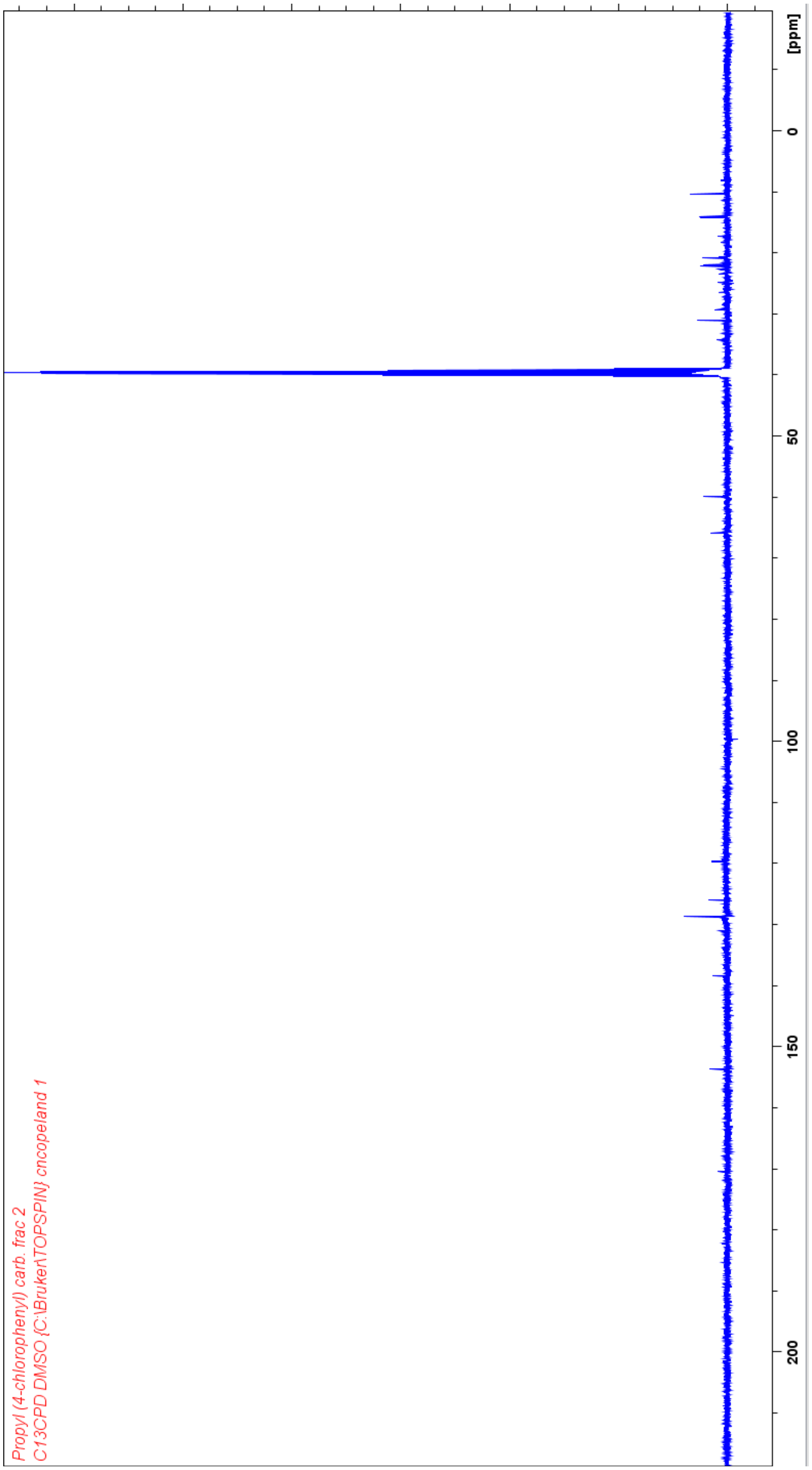

Figure 42: ^{13}C NMR of propyl (4-chlorophenyl) carbamate (**18**)

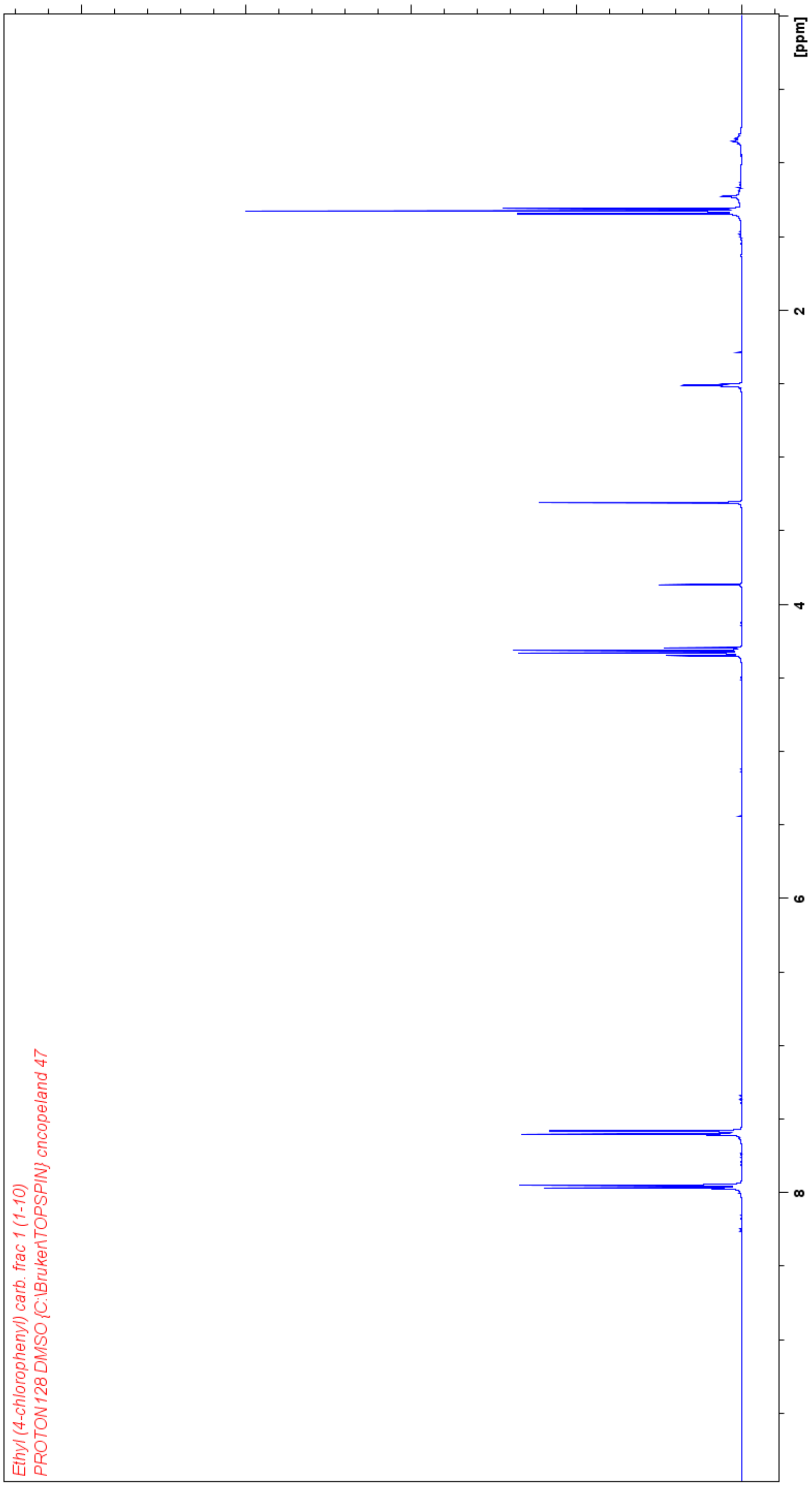

Figure 43: ^{1}H NMR of ethyl 4-chlorobenzoate (**19**)

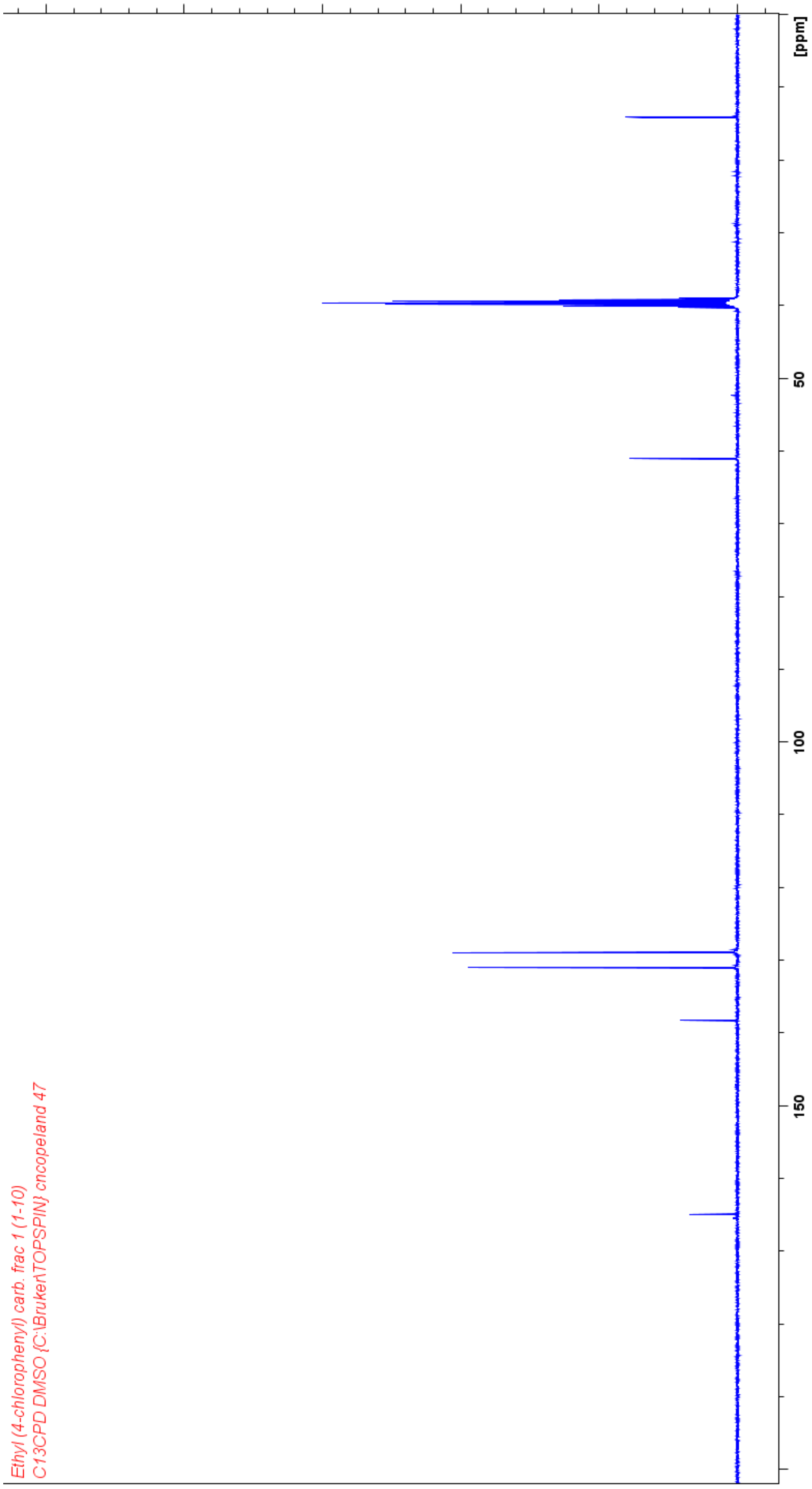

Figure 44: ^{13}C NMR of ethyl 4-chlorobenzoate (**19**)

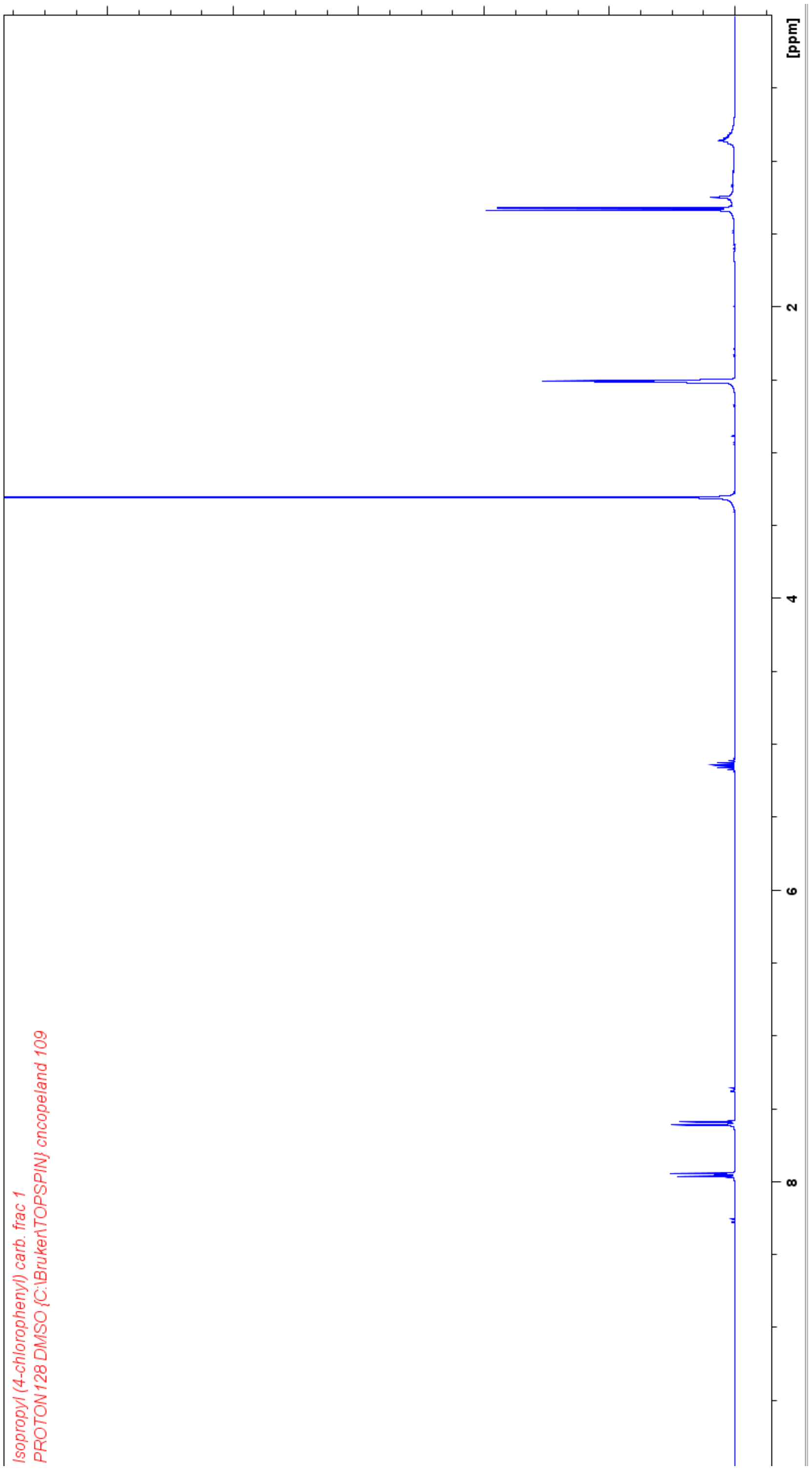

Figure 45: ^{1}H NMR of isopropyl 4-chlorobenzoate (**21**)

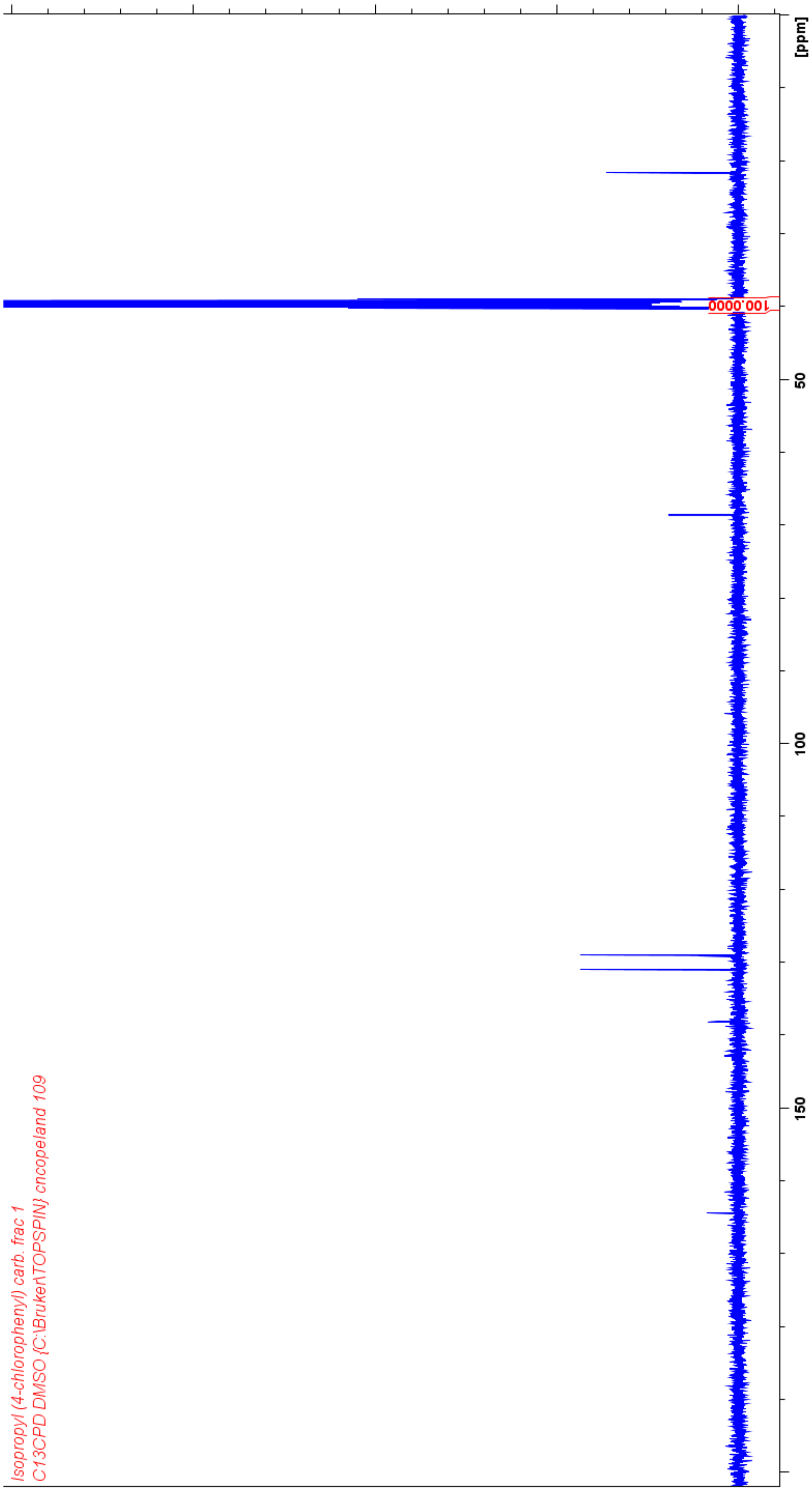

Figure 46: ^{13}C NMR of isopropyl 4-chlorobenzoate (**21**)

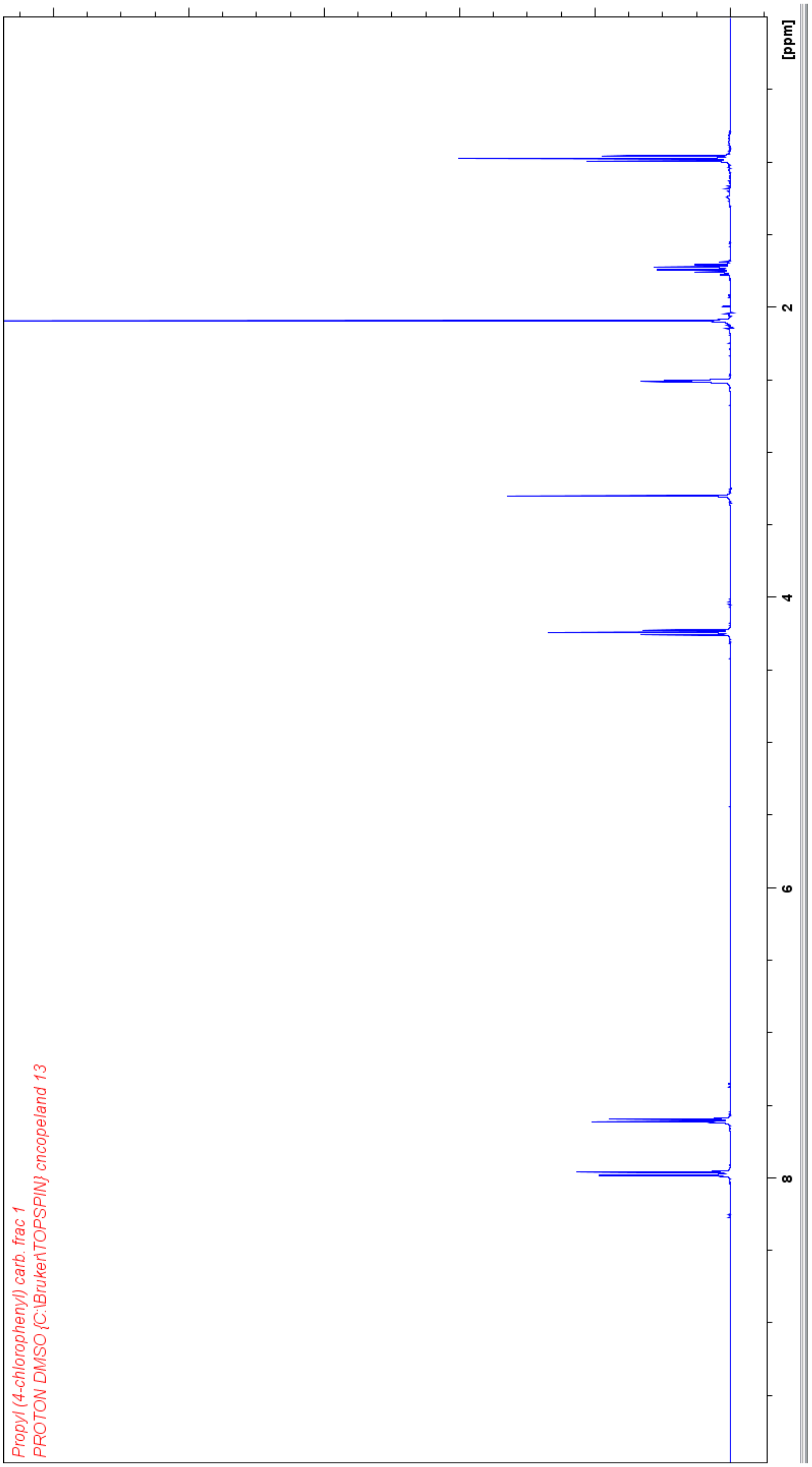

Figure 47: ^{1}H NMR of propyl 4-chlorobenzoate (**20**)

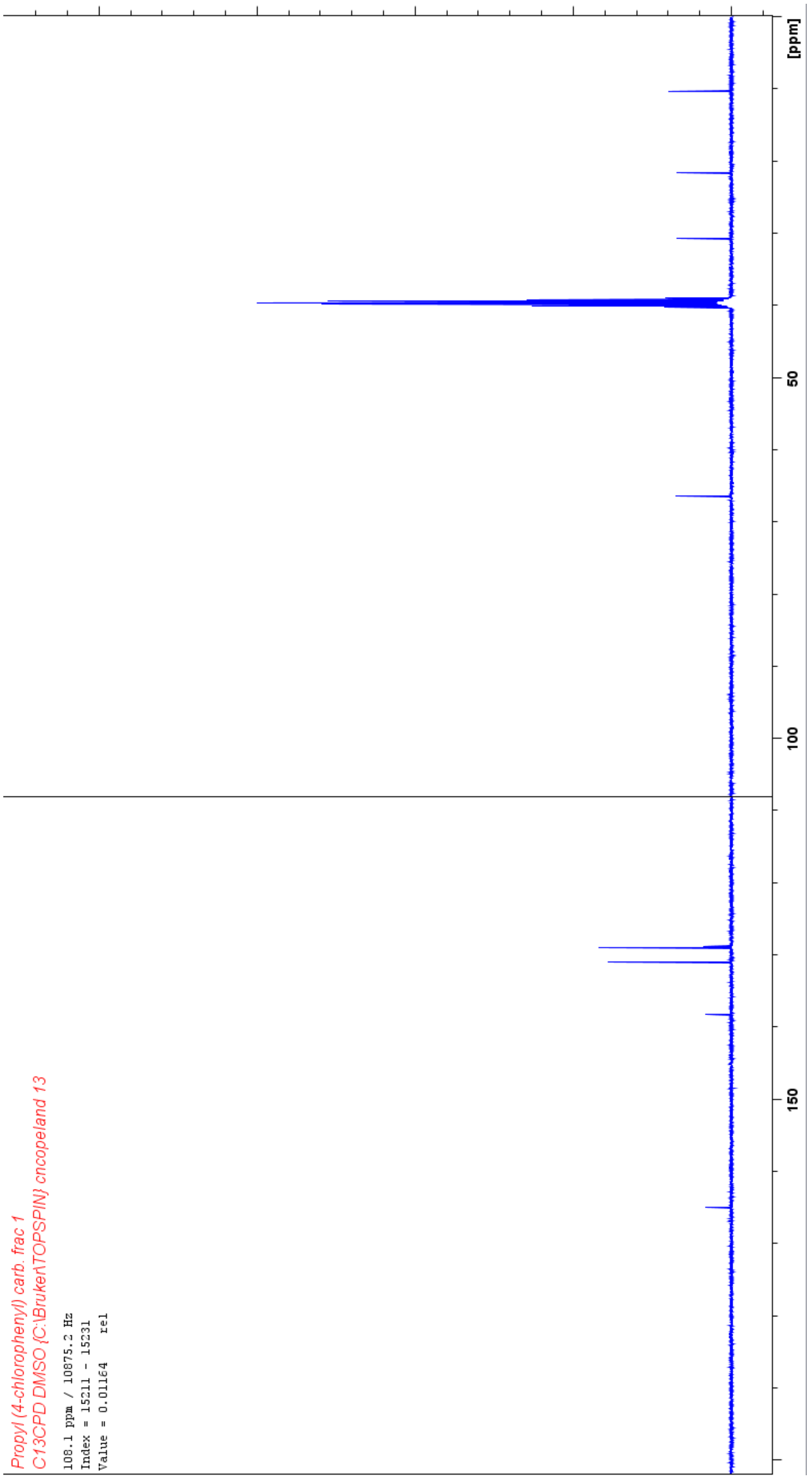

Figure 48: ^{13}C NMR of propyl 4-chlorobenzoate (**20**)