Attempted “One Pot” Synthesis of Carbamates of Carboxylic Acids via Curtius Rearrangement

by

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Thesis Abstract

This thesis reports the attempted synthesis of carbamates from carboxylic acids via Curtius rearrangement of acyl azide intermediates. Successful synthesis of carbamates of some common alcohols such as ethanol, isopropyl alcohol and cholesterol were achieved adopting the use of diphenyl phosphoryl azide as the azide substrate. The products were confirmed by infra-red spectroscopy, proton nuclear magnetic resonance (^{1}H) and carbon-13 nuclear magnetic resonance (^{13}C).

A possible double Curtius rearrangement reaction and product was observed using terephthalic acid as the carboxylic acid and this was confirmed with infra-red spectroscopy and nuclear magnetic resonance as well. Less toxic azides used could not be proven to have worked or not due to the insufficient data obtained from their reactions.

Acknowledgement

Foremost, I would like to express my deep and sincere appreciation to my research advisor, Dr. Peter Norris for the opportunity to do research and his patience in providing me with invaluable guidance throughout this research.

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Finally, I would like to thank the Almighty God for His bountiful blessings over my life and for granting me the enabling knowledge and strength to be able to follow through with my dreams of studying at this height to attain this enviable feat.

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List of Abbreviations

Abbreviations	Description
AIDS	acquired immune deficiency syndrome
^{13}C	Carbon-13
$CDCl_3$	deuterated chloroform
δ	chemical shift in parts per million (ppm)
d	doublet
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMSO-d_6	deuterated dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
Et_3N	triethylamine
g	gram
^{1}H	Proton-1
h	hour
Hz	Hertz
J	coupling constant
q	quartet
IR	infra-red
m	multiplet
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimoles
mp	melting point
NMR	nuclear magnetic resonance
OH	hydroxyl
o-NBSA	ortho nitrobenzene sulfonyl azide
p-NBSA	para nitrobenzene sulfonyl azide
ppm	parts per million

R_f	retention factor
s	singlet
t	triplet
TLC	thin layer chromatography
UV	ultraviolet

INTRODUCTION

Azides

Generally, azides are compounds containing three nitrogen atoms linearly bonded together as $-N_3$. They can be found in either inorganic or organic forms and are usually produced from hydrazoic acid (HN_3), certain inorganic salts such as sodium azide (NaN_3) or organic derivatives such as diphenyl phosphoryl azide (DPPA). A general structure of azide ion has both positive and negative charges distributed on the nitrogen atoms as illustrated by the resonance structures in **Figure 1**. This distribution of electrons on the nitrogen atoms makes azides very essential in organic chemical synthesis; they can act as nucleophiles, electrophiles and undergo addition reaction making it versatile.

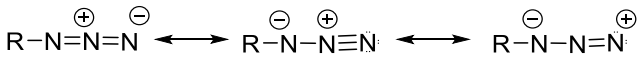


Figure 1: General structure of azide showing resonance.

Organic azides are carbon compounds that have the azide group, $-N_3$, as the main functional group represented as RN_3 where the R could be an alkyl, aryl or acyl group.

The chemistry of organic azides is of much importance to scientists because of their wide usage as versatile intermediates and precursors in the synthesis of biologically active compounds and in other industries. Derivatives of azides are used as drugs in the treatment of various diseases. A typical example of azide which has been widely used is 3-azido-3-deoxythymidine (**Figure 2**), which has been internationally administered as an antiviral drug for the treatment of Acquired Immune Deficiency Syndrome (AIDS) and its associated diseases.[1,2]

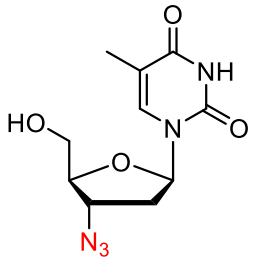


Figure 2: Structure of 3-azido-3-deoxythymidine.[1]

Organic azides, like other azides, are highly unstable due to the polarizability of the pi (π) electrons between the nitrogen atoms and, hence, decompose rapidly to produce nitrogen gas upon the application of heat or electric shock. Evolution of nitrogen gas upon decomposition makes these azides highly explosive; the inorganic and some alkyl forms are therefore used as explosives in detonators and percussion caps. The high reactivity of azides makes them capable of forming many different compounds.[2,3]

Acyl Azides

Acyl azides are usually more stable than the other organic azides, due to resonance contribution from the carbonyl oxygen, and are highly versatile organic reagents with many uses in the field of chemistry, biology, medicine and material science. They are used in the preparation of nitriles, amides, in cycloaddition reactions and in the synthesis of many heterocyclic compounds.

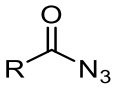


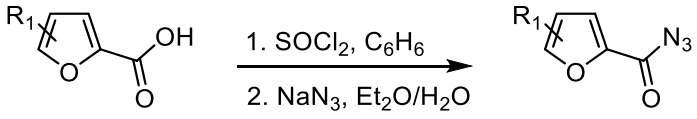
Figure 3: General structure of acyl azides.

The "R" group could be an alkyl (straight chain compounds) or aryl (aromatic ring compounds). With an increased industrial interest in organic azide compounds, several

syntheses of heterocycles have been made such as triazoles and tetrazoles which have been used as blowing agents and as functional groups in pharmaceuticals.[1]

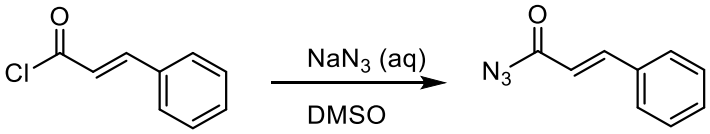
The main synthetic methods used in forming azides require the using of sodium azide and other harmful and easily degraded substrates such as halides which are dangerous and harmful to the environment. Several methods and projects have been designed which are geared towards the formation of acyl azides including; a) reaction of carboxylic acids and sodium azide using various bases such as triphenylphosphine (PPh_3),[1] b) treatment of acid chlorides with mixed anhydrides,[4] c) treatment of acid chlorides with azide ions such as sodium azide,[5] d) reaction of acyl hydrazine with nitrosyl precursors,[6] e) acid activators such as thionyl chloride and dimethyl formamide mixture ($SOCl_2$ / DMF) or cyanuric chloride / *N*-methyl morpholine mixture,[7] f) triphosgene and triethylamine with aryl or alkyl carboxylic acids,[8] g) Dess-Martin periodinane (DMP) and sodium azide, which convert aldehydes to acyl azides at reduced temperatures (below 0 °C).[9]

Padwa et al. in 1999 reported the systematic synthesis of acyl azides from furoic acid and sodium azide by first treating the acid with thionyl chloride in benzene and then reacting the acyl chloride formed with sodium azide[5] (**Equation 1**). This procedure involves multiple steps and uses benzene as a solvent, which has been known to be carcinogenic. Thionyl chloride used is also known to be highly reactive, corrosive, irritant and poses the danger of explosion.



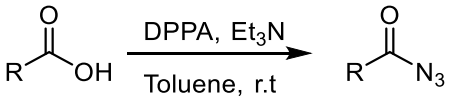
Equation 1: Acyl azide from furoic acid.[5]

Watts et al. reported in 2017 the synthesis of acyl azides from acyl chlorides and sodium azide.[10] (**Equation 2**). This step involves the use of an acyl halide which is known to be harmful to the environment and is also difficult to handle due to its instability.



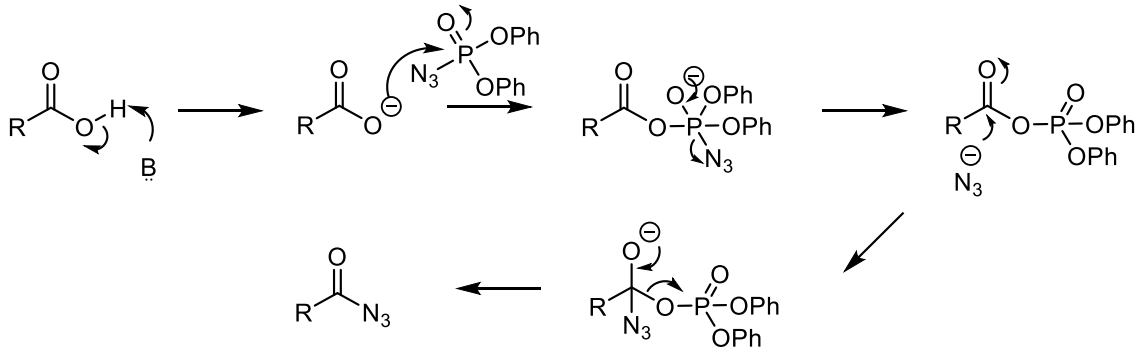
Equation 2: Acyl azide from acyl chloride.[10]

Acyl azides have also been produced from the direct treatment of carboxylic acids with diphenyl phosphoryl azide (DPPA) with triethyl amine (Et_3N) (**Equation 3**). This method is useful in the synthesis of derivatives of acyl azides in a "one pot" system, which saves time and operational costs.



Equation 3: Synthesis of acyl azides from carboxylic acids.[5]

When the alcohol or carboxylic acid is treated with DPPA in the right solvent, and in the presence of a base, the hydroxyl group (OH) of the alcohol (or carboxylic acid) is displaced by the $-N_3$ of the DPPA in a nucleophilic acyl substitution reaction yielding the corresponding azide compound (**Scheme 1**).

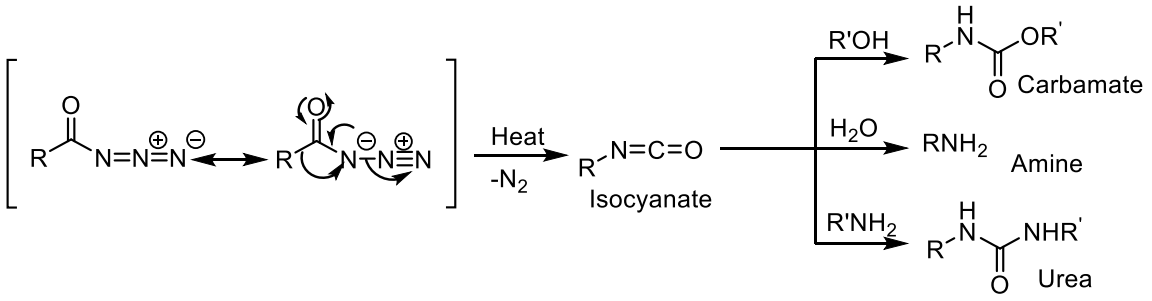


Scheme 1: Mechanism of DPPA with carboxylic acid.[5,6]

The azide formed is essential in organic chemistry due to its versatility in transformation to various needed products.

Rearrangement

In the presence of heat, acyl azides usually undergo degradation through the Curtius rearrangement to form isocyanates by releasing nitrogen gas. This isocyanate formed is highly versatile and can further react with other reagents to form products such as carbamates (urethanes), amines, carbodiimides, ureas, thiourethanes and other useful products (**Scheme 2**).[4,5]



Scheme 2: Isocyanate and its derivatives.

Carbamates

Isocyanates react with alcohol substrates to yield carbamates. Organic carbamates have been manipulated in the synthesis of several drug moieties. Carbamate (urethane) containing molecules are essential in the fields of chemistry and biology and play significant roles in medicinal chemistry and modern-day drug discovery.[11] (**Figure 4**) The strong intramolecular hydrogen bonding makes them highly stable and capable of permeating cell membranes, hence affording their usage as replicas to peptide bonds in proteins and protecting groups for amine and amino acid processes.[12]

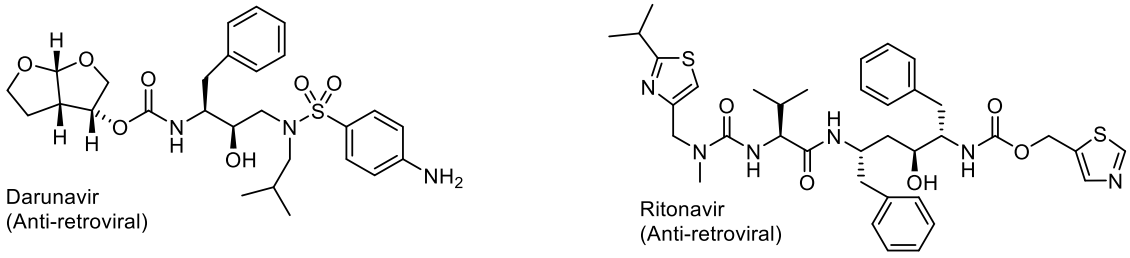
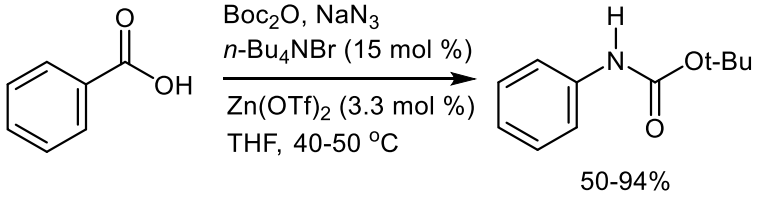


Figure 4: Carbamates commonly used in medicine.

They are also applied in the paint industry as preservatives or reacting starting materials, intermediates, or solvents in product formulation.[13,14] Carbamates are used in agrochemicals as pesticides such as fungicides and herbicides (**Figure 5**).[3,14]

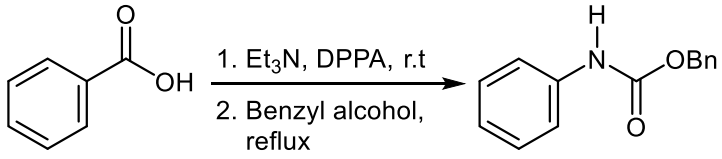
Figure 5: Carbamates commonly used in Agriculture.

Over the years, various scientists have utilized isocyanates formed in Curtius rearrangements in the synthesis of very useful carbamates. Helëne Lebel and coworkers used this method in synthesizing carbamates and ureas.[3] Sodium azide was used to convert the carboxylic acid to azide which was degraded thermally to form the isocyanate and trapped with di-t*ert*-butyl dicarbonate to yield the desired carbamate (**Equation 4**).[3]



Equation 4: Synthesis of carbamates by Lebel and coworkers.[3]

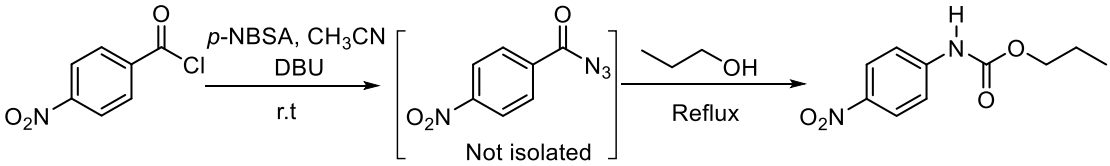
One reagent that has been utilized greatly in successfully converting carboxylic acids to azides is diphenyl phosphoryl azide (DPPA). This acts as a carbonyl activator and azide donor for the carboxylic acid thus no other reagent is required to activate the acid, as in the case of sodium azide. This method has been utilized by Jacobi and coworkers in the formal total syntheses of the β-lactam antibiotics thienamycin and PS-5.[15] Evans et al employed this route in the synthesis of amino acids and derivatives of succinic acids. Triethylamine was used to deprotonate the acid, which was activated by DPPA to form the azide at room temperature. Elevating the temperature formed the isocyanate and then carbamate by reacting with benzyl alcohol (**Equation 5**).[16]



Equation 5: Carbamate synthesis by Evans et al (1999).[16]

Though this method has proven to be efficient in the synthesis of carbamates, there are several unavoidable setbacks with this reagent.

Previous work done by Kyei Baffour utilized *p*-NBSA to convert acyl chlorides into carbamates in good yields in a "one pot" manner. The acyl chloride was first converted to the respective azide, which was not isolated, and then heated to form isocyanate which was then trapped with various alcohols to form the corresponding carbamate. The system is safer since it utilizes the less toxic *p*-NBSA. (**Equation 6**).[17]



Equation 6: Synthesis of carbamate by Kyei Baffour.[17]

The first part of this project is to convert various carboxylic acids into azides using DPPA, and then degrade the azides thermally to form isocyanates which can then be trapped with various alcohol substrates to form possibly useful carbamates.

Ortho-Nitrobenzene sulfonyl azide or the isomeric *para*-nitrobenzene sulfonyl azide, synthesized in the laboratory, will then be tested as the azide source for the synthesis of acyl azides which will then be converted to the corresponding carbamates upon treatment with various alcohol substrates. This azide source is less toxic, more environmentally friendly, and easy to synthesize and will be a good alternative to DPPA for the azidation if successful.

Statement of Purpose

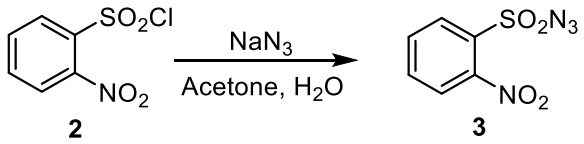
Most of the known methods of synthesizing carbamates involve multiple steps with the isolation of intermediates. Isocyanate conversion to carbamate has been utilized greatly in synthesis due to the high reactivity of the intermediate. Most of the known methods of synthesizing the acyl azides involve multiple steps and the use of toxic and unfriendly reagents. They also involve the formation of acid chloride intermediates which are difficult to obtain from substrates which have sensitive substituents like hydroxyl (OH) or amine (-NH_2) groups. The acid chlorides are also highly reactive to moisture and are therefore difficult to store or handle. In addition, little or no information is available on azide synthesis using di- and tricarboxylic acids.

The main azide source used in these processes is the inorganic sodium azide which is insoluble in organic solvents and so must be used in excess. Sodium azide is acutely toxic and poses an explosive hazard at high temperatures. Also, because sodium azide is inorganic, it is mostly dissolved in water for synthetic purposes. This makes it difficult to use sodium azide in carbamate synthesis since the isocyanate formed can react with water to form an unwanted amine product.

There is the need to find a synthetic route with reduced steps as much as possible and reagents that would minimize toxicity as much as possible. From **Scheme 1** above, we observe a straightforward nucleophilic acyl substitution reaction between DPPA and carboxylic acid. This would be applied in the one pot synthesis of carbamates via Curtius rearrangement, and then compared with similar reactions using aryl sulfonyl azides.

RESULTS AND DISCUSSION

The research began with the synthesis of *ortho*-nitrobenzene sulfonyl azide, *o*-NBSA (**3**), and *para*-nitrobenzene sulfonyl azide, *p*-NBSA (**5**), to be used as the azide moiety in the synthesis of the acyl azides. Acetone was chosen as the organic solvent due to its low boiling point and ability to dissolve the various sulfonyl chlorides used. *Ortho*-nitrobenzene sulfonyl azide was prepared using *ortho*-nitrobenzene sulfonyl chloride (**2**) and sodium azide (**1**) with acetone and water as the solvent (**Equation 7**). The reaction was then left to stir overnight at room temperature until TLC (1:1 hexane: ethyl acetate) confirmed the formation of the product (R_f = 0.47), which appeared yellow upon heating with *p*-anisaldehyde as the staining solution. The product was purified by recrystallisation using hot ethanol and an IR spectrum was run (**Figure 8**). This showed a signal at 2149 cm^{-1} representing the band expected for a covalently bonded azide functional group. ^{1}H NMR (**Figure 6**) and ^{13}C NMR (**Figure 7**) spectra of the product further confirmed the successful formation of *o*-NBSA in a good yield.

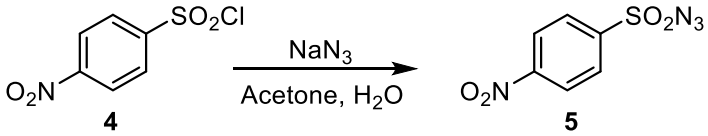


2 **3**

Equation 7: Synthesis of *ortho*-nitrobenzene sulfonyl azide, *o*-NBSA (**3**).

Para-Nitrobenzene sulfonyl azide, *p*-NBSA (**5**) was equally synthesized from *para*-nitrobenzene sulfonyl chloride (**4**) and NaN_3 (**1**) using acetone and water as solvents (**Equation 8**). The reaction was left to stir overnight at room temperature until TLC (1:1 hexane: ethyl acetate) of the reaction mixture showed a new spot, R_f = 0.30, that appeared

yellow upon heating when *p*-anisaldehyde was used as the staining solution. The azide formed was purified with hot ethanol and IR spectrum (**Figure 11**) of the recrystallized product showed a signal at 2143 cm^{-1} which is consistent with IR bands for an azide functional group. ^{1}H NMR (**Figure 9**) and ^{13}C NMR (**Figure 10**) spectra of the product showed that *p*-NBSA had been successfully synthesized.



Equation 8: Synthesis of *para*-nitrobenzene sulfonyl azide, *p*-NBSA (**5**).

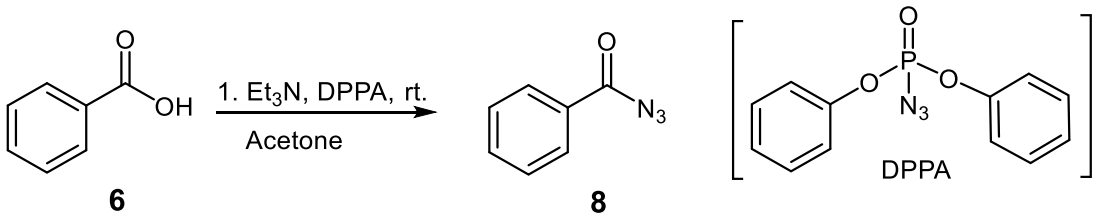
SYNTHESIS OF ACYL AZIDES

The first part of the research involved the synthesis of acyl azides from a carboxylic acid (benzoic acid) using DPPA as the azide source. This was done to confirm the reproducibility of results for the method adopted by Evans *et al*.[16] in the synthesis of carbamates and to extend it to our approach for the method development using the azides synthesized in our laboratory (either *o*-NBSA or *p*-NBSA). The success of every experiment depends greatly on the reaction conditions and one significant factor is the choice of solvent. In selecting the appropriate solvent, consideration was given to the easy solubility of the starting materials and the azide moiety, availability, low boiling point, and the ability to not cause any side reaction in the overall process by enabling the formation of main products.

For the synthesis of the acyl azides, the suitable solvent settled on is acetone. The solubility of the benzoic acid used was considered in various organic solvents and toluene, ethanol and acetone were considered. Although all the solvents dissolved the benzoic acid

readily, toluene was quite difficult to remove from the azide product formed due to its high boiling point. Organic azides pose explosion hazard and therefore the temperature of the evaporator could not be raised enough to remove the toluene, if used as solvent. Alcohol has the potential of reacting with the azide at high temperatures to form carbamates hence it was not chosen as solvent for the azide.

Benzoyl azide (8)



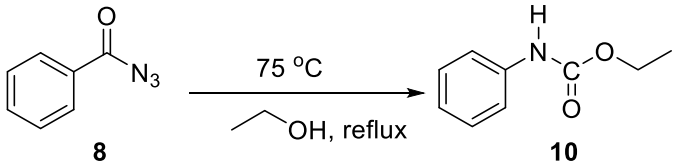
6 **8**

Equation 9: Synthesis of benzoyl azide using DPPA (**8**).

Benzoyl azide (**8**, **Equation 9**) was synthesized from benzoic acid (**6**) dissolved in acetone and DPPA (**7**) using triethylamine as the base. The triethylamine used was to deprotonate the carboxylic acid to enable the attack on DPPA. TLC confirmed the disappearance of the azide spot for the DPPA and the formation of a new spot ($R_f = 0.67$) of yellow color upon heating when *p*-anisaldehyde was used as the TLC staining solution. The IR spectrum was run for the reaction and a new signal which indicated the formation of a new covalently bonded azide functional group, at 2134.58 cm^{-1}, was observed which is different from that of DPPA, which shows at 2169.73 cm^{-1} (**Figure 15**). This was an indication that the benzoyl azide product might have been synthesized, hence aqueous work-up on the product gave a white crystalline solid as the crude product. After recrystallization using 3:1 hexane: ethyl acetate solvent, ^{1}H NMR and ^{13}C NMR of the product further confirmed the presence of the acyl azide product (**8**, 2.20g, 74.6%). There was a shift in the carbonyl group signal in benzoic acid, **6** further downfield from 167.80

ppm to 172.40 ppm which corresponds to that of literature value for carbonyls of azide compounds[16] in ^{13}C NMR analysis (**Figure 13**). The disappearance of the signal at 12.9 ppm observed in ^{1}H NMR for the hydroxyl proton in benzoic acid as observed in the benzoyl azide further confirmed the product (**Figure 12**). The IR spectrum of the purified product, which showed absorption at 2134.62 cm^{-1} (**Figure 14**), is in good agreement with literature.[16] The recorded melting point value of 30-32 °C also corresponds to that reported in literature.[16]

CARBAMATES



8 **10**

Equation 10: Synthesis of carbamate (**10**) from benzoyl azide (**8**).

With the main azide successfully synthesized for the monoacid substrate, the next thing was to attempt to make carbamates of the azide and later repeat in a "one-pot" manner. The first carbamate that was synthesized is ethyl phenyl carbamate, **10** from benzoyl azide, **8** and ethanol using toluene as the solvent. Toluene was used because the temperature of the reaction had to be elevated above the boiling point of acetone, which would make acetone evaporate if used as the reaction solvent. The benzoyl azide was heated at a temperature of 80 °C to enable the degradation of the azide into an isocyanate in a Curtius rearrangement. TLC showed the disappearance of the yellow azide spot upon heating with *p*-anisaldehyde as the TLC staining solution. This was confirmed by IR by the disappearance of the azide band at 2134.58 cm^{-1} and the formation of a new band at 2260.35 cm^{-1} (**Figure 18**) which is consistent with literature for isocyanate.[16] The reaction

was then cooled to 50 ℃ to avoid immediate evaporation of the ethanol when added, and to also allow the isocyanate species to react with the ethanol. Ethanol was added, and the reaction heated at 110 ℃ for 72 hours to enhance complete consumption of the isocyanate. TLC showed the appearance of a new pinkish red spot (R_f=0.67) upon heating when *p*-anisaldehyde was used as the TLC staining solution. The IR spectrum of the mixture showed the disappearance of the signal at 2260.35 cm^{-1} indicating the consumption of the isocyanate intermediate and the possible formation of the carbamate. Aqueous work-up and then evaporation on the rotavap led to the isolation of the product as pale yellow solid.

NMR (^{1}H and ^{13}C) analysis of the pale yellow solid (74.26% yield) confirmed the successful synthesis of **10**. A unique singlet peak was observed further upfield at 9.50 ppm in the proton NMR (**Figure 16**) which corresponds to the proton on the electro-negative nitrogen atom. This is consistent with the fact that the electronegative atoms pull the electrons towards themselves causing the protons to be deshielded and hence have signals downfield in the proton spectrum. There was a change in chemical shift for the peaks corresponding to the methylene and methyl protons from the ethanol. The methylene and methyl protons were observed as quartet at 4.14 ppm and triplet at 1.25 ppm respectively in the product which was consistent with literature values and spectra predictions for ethyl phenyl carbamate.[16] The phenyl protons were observed as a multiplet from 7.51 ppm to 6.96 ppm.

^{13}C NMR showed a change in chemical shift for the ethyl carbons in the product as compared to ethanol. Two distinct peaks observed further upfield in this spectrum are those occurring at 60.54 ppm and 14.97 ppm which correspond to the shielded alkyl carbons

from the ethanol. The phenyl carbons were observed at 139.69 ppm, 129.17 ppm, 122.75 ppm and 118.74 ppm. The carbonyl carbon was also observed at 154.52 ppm (**Figure 17**).

IR spectrum run for the final product showed the disappearance of the azide and isocyanate signals which further confirms the successful Curtius rearrangement and formation of the carbamate (**Figure 19**).

Isopropyl phenyl carbamate (**12**, 69.67%) was also synthesized from benzoyl azide (**8**) and isopropyl alcohol (**11**) using toluene as the solvent and the product was confirmed by TLC, IR, and NMR. Analysis of the ^{1}H NMR of the pale-yellow solid showed that the methine protons and methyl protons rightly occurred as multiplet from 4.94 ppm to 4.85 ppm and doublet at 1.26 ppm, respectively. The septet peak for the methylene protons is located downfield to the doublet of the methyl group due to the presence of the electronegative oxygen of the carbamate. The intensity of the doublet group further downfield is consistent with the number of protons associated with it. A singlet peak observed further downfield at 9.44 ppm corresponds to the deshielded proton located on the more electronegative nitrogen atom. The aromatic protons of the carbamate were observed as a multiplet from 7.48 ppm to 6.96 ppm for the five protons (**Figure 20**).

Analysis of the ^{13}C NMR showed the movement of the carbonyl group in the azide further upfield from 172.40 ppm to 153.6 5ppm which is rightly within the range for a carbonyl carbon of a carbamate. The difference is because the azide has three nitrogen atoms withdrawing the electrons from the carbonyl and hence greatly deshielded it, causing the signal to be further downfield for the azide. The aromatic carbons are seen at 138.78 ppm, 129.10 ppm, 122.11 ppm, and 118.90 ppm. The aliphatic carbon signals are the downfield signal at 67.84 ppm and upfield signal at 22.43 ppm indicative of the methine

carbon closest to the electronegative oxygen and the methyl carbon, respectively (**Figure 21**).

Another alcohol moiety that was used to trap the isocyanate formed from the rearrangement of the benzoyl azide was cholesterol. This alcohol was used to confirm that carbamates could equally be synthesized for bulky natural product substrates which are commonly available. The benzoyl azide was heated at a temperature of 80 °C on a carousel to enable the degradation of the azide into an isocyanate in a Curtius rearrangement. TLC was run to show the disappearance of the yellow azide spot, upon heating with *p*-anisaldehyde as the TLC staining solution, and the formation of the isocyanate. This was confirmed by IR by the disappearance of the azide band at 2140.32 cm^{-1} and the formation of a new band at 2260.35 cm^{-1} which is consistent with literature value for isocyanates.[16]

The reaction was then cooled to 50 °C and cholesterol was dissolved in toluene and added to the reaction and the reaction heated at 75 ^{o}C for 72 hours to enhance complete consumption of the isocyanate and possible formation of the carbamate product. TLC showed the appearance of a new pinkish red spot (R_f = 0.67) upon heating when *p*-anisaldehyde was used as the TLC staining solution. The IR spectrum of the mixture showed the disappearance of the signal at 2260.35 cm^{-1} indicating the consumption of the isocyanate group. Aqueous work-up of the solution, and then evaporation on the rotavap led to the isolation of the product as pale yellow solid. NMR (^{1}H and ^{13}C) analysis of the pale-yellow solid confirmed the successful synthesis of the cholesterol phenyl carbamate. Due to the bulkiness of cholesterol and the many signals observed, interpretation of the spectra could not be done easily.

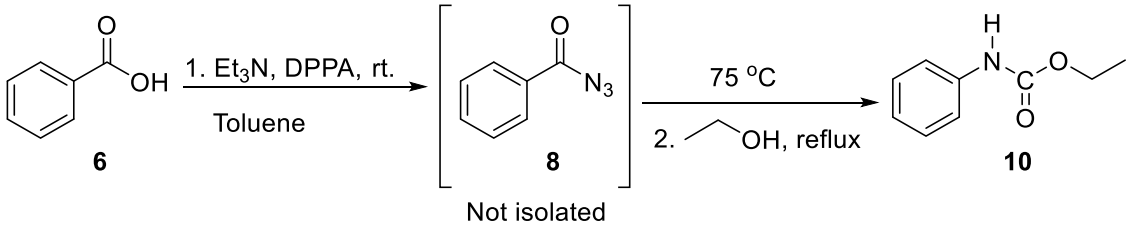
One signal that is distinctive of a carbamate in a ^{1}H NMR is the downfield singlet peak observed for the proton on the electronegative nitrogen atom, this signal was observed for the phenyl carbamate of cholesterol at 9.63 ppm which confirms the formation of the product. The aromatic protons were observed between 7.0 and 7.50 ppm whiles the cluster of peaks for protons on the alkyl groups were observed from 6.0 to 0.4 ppm upfield (**Figure 22**).

^{13}C NMR showed a shift of the signal for the carbonyl group in benzoyl azide further upfield from 172.4 ppm to 154.04 ppm which is expected due to the deshielding effect by the electronegative oxygen atom. The aromatic carbons were observed between 140.17 and 118.74 ppm while the alkyl carbons showed upfield (**Figure 23**).

"ONE-POT" SYNTHESIS OF THE CARBAMATES

With the successful stepwise synthesis of the carbamates, we next proceeded to attempting them in a "one-pot" manner. The main goal of the systematic synthesis of the acyl azides and the corresponding carbamates was to show the presence of the acyl azides before proceeding to the "one-pot" synthesis of the carbamates from the carboxylic acids via Curtius rearrangement.

Ethyl phenyl carbamate (10)



Equation 11: "One pot" synthesis of ethyl phenyl carbamate (**10**).

The synthesis began with the addition of triethylamine to benzoic acid in toluene which causes deprotonation of the acid to make the carboxylate more activated for the attack on the nucleophilic DPPA. DPPA was then added and left to stir for 30 minutes to form the benzoyl azide at room temperature which was confirmed by TLC by the appearance of a new spot which was colored yellow when developed with *p*-anisaldehyde as the TLC staining solution. Formation of the intermediate isocyanate was confirmed by the disappearance of the yellow colored azide spot on TLC (hexane: ethyl acetate 1:1), after heating at 75 °C, and by the observation of an IR signal at 2260.39 cm^{-1} different from the azide signal at 2134.77 cm^{-1}. The reaction was then cooled to 50 °C upon confirmation of isocyanate, and ethanol was added, and the mixture refluxed for 72 hours to afford the formation of the carbamate.

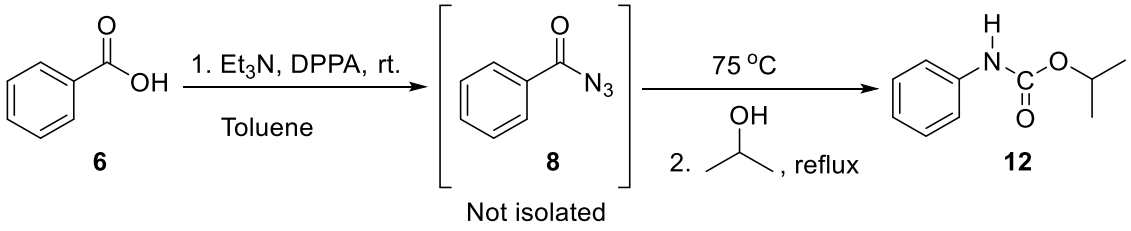
The product was confirmed by the appearance of a pinkish red spot on TLC (hexane: ethyl acetate 1:1). However, TLC confirmed an impure crude product with two spots (R_f=0.68 and 0.52), respectively. Aqueous work-up on the product gave a dark yellow syrupy product. Although ^{1}H NMR and ^{13}C NMR of the crude product indicated the absence of the signal for the acyl azide, and a shift in the chemical shift value of the carbonyl signal. Subsequent purification by silica gel flash column chromatography was set to be done but the product formed pale yellow crystals over time.

^{13}C NMR analysis of the pale yellow solid (0.48 g, 58.55%) showed the movement of the carbonyl group signal the product further upfield from 172.40 ppm to 154.02 ppm which is within the range for a carbonyl carbon of an aliphatic or an aromatic carbamate. The aromatic ring carbons are seen at 139.72 ppm, 129.15 ppm, 122.70 ppm, and 118.61 ppm. The aliphatic carbon signals downfield at 60.55 ppm and upfield at 14.95 ppm are

indicative of the methylene carbon, which is closest to the electronegative oxygen, and the methyl carbon of the ethyl group which came from the ethanol, respectively.

Analysis of the ^{1}H NMR of the product also shows the unique proton on the electronegative nitrogen heteroatom of the carbamate appearing, further downfield as a singlet, at 9.63 ppm. This is consistent with literature because the nitrogen is strongly deshielding.[16] The methylene and methyl protons corresponding to the those from the ethanol rightly occurred as a quartet and triplet at 4.13 ppm and 1.34 ppm, respectively. The phenyl protons were observed between 7.50 ppm and 6.98 ppm. The phenyl protons were observed a little further upfield compared to that observed in the benzoic acid due to the deshielding of the acyl group by the more electronegative nitrogen atom. The absence of the broad signal at 4.55 ppm for the hydroxyl proton in ethanol further confirms the product.

Isopropyl phenyl carbamate (12)



Equation 12: "One pot" synthesis of isopropyl phenyl carbamate (**12**).

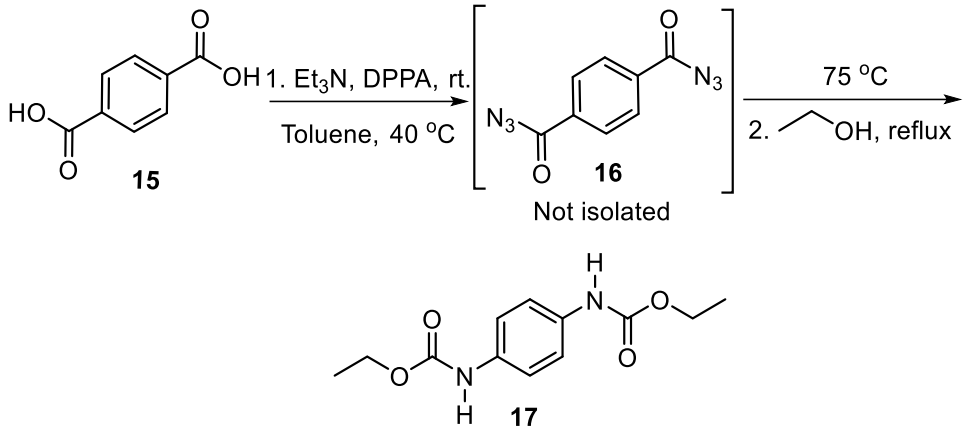
The benzoyl azide synthesis was carried out between benzoic acid and DPPA in toluene, and upon confirmation of the successful synthesis of the azide by TLC, the isopropanol was added to afford the product. IR confirmed the completion of the rearrangement and TLC confirmed an impure crude product with two very distinct spots

of R_f=0.69 and 0.61, respectively. Aqueous work-up and evaporation gave **12** as the carbamate with a possible alkyl ester as an impurity.

Analysis of the ^{13}C NMR spectrum of the off-white solid showed a shift of the carbonyl group signal in benzoic acid further upfield from 167.80 ppm to 153.60 ppm. The aromatic ring carbons are seen at 139.78 ppm, 129.15 ppm, 122.65 ppm, and 118.56 ppm. The aliphatic carbon signals are seen downfield at 67.81 ppm and upfield at 22.45 ppm. The signal observed at 67.81 ppm for the methine carbon is further downfield because of its closeness to the electronegative oxygen atom, and that at 22.45 ppm corresponds to the carbons of the methyl groups.

^1H NMR analysis of the product shows the unique singlet peak downfield at 9.57 ppm representing the deshielded proton connected to the electronegative nitrogen heteroatom. The phenyl protons were observed a little upfield between 7.49 ppm and 6.97 ppm. The secondary carbon proton from the alcohol and the two sets of equivalent methyl protons were observed as a septet and doublet at 4.90 ppm and 1.27 ppm, respectively. The upfield position of the methyl protons at 1.27 ppm is due to the absence of deshielding agents while that at 4.90 ppm is downfield due to the oxygen atom attached. The spectrum showed other peaks which could be attributed to alkyl ester impurity.

Attempted "One-Pot" synthesis of Diethyl 1,4-phenylene dicarbamate (17).



Equation 13: "One pot" synthesis of Diethyl 1,4-phenylene dicarbamate (**17**).

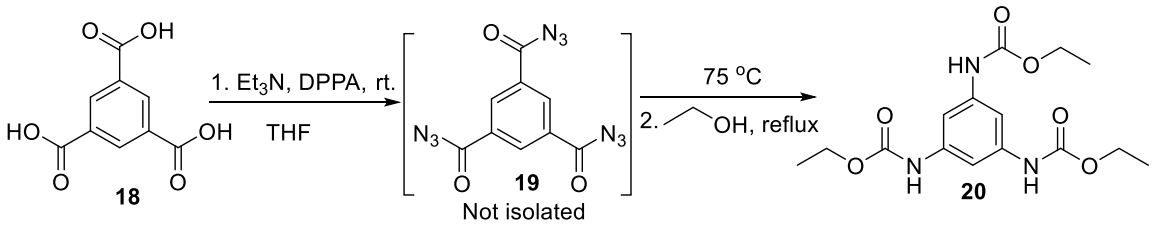
The suitable solvent for terephthalic acid was determined using DMF, DMSO and found to be readily soluble in DMF and DMSO but DMSO was ignored due to the high boiling point and tendency to react in various reactions as both electrophile and nucleophile. Toluene was also useful in dissolving the acid, but the reaction formed a precipitate upon addition of DPPA and so the reaction temperature had to be elevated to 30 °C to avoid the precipitation. The terephthaloyl diazide synthesis was carried out between terephthalic acid and DPPA in toluene at 40 °C, and upon confirmation of the successful synthesis of the azide by TLC, the temperature was elevated to 80 °C to afford the isocyanate. IR confirmed the completion of the rearrangement by the disappearance of the signal at 2138.6 cm^{-1} (**Figure 26**) for the azide and the appearance of a new one at 2270.52 cm^{-1} (**Figure 27**). Ethanol was added to afford the product and TLC confirmed an impure crude product with two spots. Aqueous work-up and evaporation gave a liquid which crystallized to form the possible as the carbamate **16** with a likely alkyl ester as an impurity.

Analysis of the ^{13}C NMR spectrum of the intermediate azide showed a shift of the carbonyl group signal in benzoic acid further downfield from 162.13 ppm to 171.53 ppm.

This is due to the electronegative nitrogen atom deshielding the carbon. The symmetrical aromatic ring carbons are seen at 135.38 ppm and 129.55 ppm. The carbonyl of the final product was observed at 153.19 ppm which possible represents the degradation of the azide and formation of a new product. The signal for the aromatic carbons were observed at 129.11 ppm, 123.05 ppm and 120.32 ppm which do not clearly confirm the product since only 2 signals were expected for the aromatic carbons. The aliphatic carbon signals are seen downfield at 45.62 ppm and upfield at 8.45 ppm, respectively (**Figure 25**). These signals observed are consistent with the expected signals for ethyl group of the ethanol added but they are observed more upfield than what was predicted by ChemDraw and ACDLab.

^{1}H NMR analysis of the intermediate product shows the unique singlet peak downfield at 8.02 ppm representing the four symmetrical protons of the azide (**Figure 24**). The final impure product showed a single proton at 8.96 ppm which could represent the protons of connected to the electronegative nitrogen heteroatoms. The phenyl protons were observed a little upfield from 7.27 ppm to 7.01 ppm which could be due to the presence of the nitrogen atom. Amidst other peaks that could be attributed to impurities, the protons of the methylene group from the alcohol and the methyl groups were observed as a quartet and triplet at 4.21 ppm and 1.24 ppm, respectively (**Figure 28**). The upfield position of the methyl protons at 1.24 ppm is due to the absence of deshielding agents while that at 4.21 ppm is downfield due to the oxygen atom attached. The spectrum showed other peaks which could be attributed to alkyl ester impurity.

Attempted "One-Pot" synthesis of Triethyl benzene-1,3,5-triyltricarbamate (20).



Equation 14: "One pot" synthesis of Triethyl benzene-1,3,5-triyltricarbamate (**20**).

Solvent suitability for 1,3,5 tricarboxylic acid was determined with tetrahydrofuran (THF) and methanol and THF was chosen to be the solvent due to its ease of solubility. Meanwhile due to the low boiling point (below 70 °C) of both solvents, the carbamate could not be successfully synthesized. The isocyanate formation has been reported to occur at 75 °C, also the solution of the carboxylic acid formed a solid paste upon the addition of triethyl amine as a base. The azide formation was carried out in excess THF and was confirmed to be present by TLC. After aqueous work up, IR and NMR also confirmed the product. The presence of a new azide signal at 2143.97 cm^{-1} confirmed the formation of a new product (**Figure 32**).

Analysis of the ^{13}C NMR spectrum of the azide showed a shift of the carbonyl group signal in tricarboxylic acid further downfield from 167.00 ppm to 170.68 ppm. This is due to the electronegative nitrogen atom deshielding the carbon. The aromatic ring carbons are seen at 134.21 ppm, 132.59 ppm and 119.20 ppm (**Figure 31**).

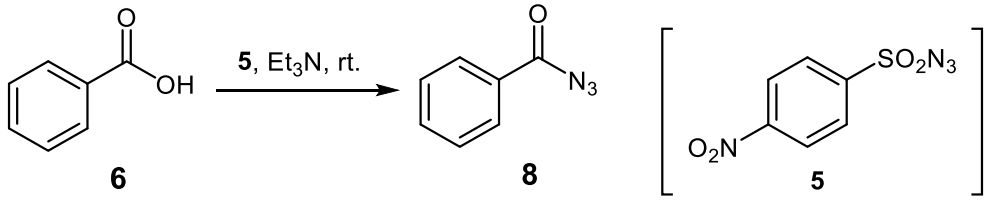
^{1}H NMR analysis of the azide product shows the unique singlet peak downfield at 8.68 ppm representing the three identical protons of the azide. The disappearance of the hydroxyl peak at 13.32 ppm found in the tricarboxylic acid confirms the formation of the azide molecule (**Figure 30**).

Synthesis of the carbamate can possibly occur for alcohols with boiling points higher than 75 °C. In that regard, the alcohol would act as both the solvent and the

reacting solvent after the formation of the isocyanate, but this would limit the substrate scope to only such alcohols. It might also be difficult to use alcohol moieties which are solids.

With the "one-pot" synthesis of the carbamates of the various alcohols established, the research proceeded with using the less harmful and environmentally friendly azides, synthesized in the laboratory, to attempt forming the benzoyl azide and then possible convert to the carbamate.

Benzoyl azide (8) using *p*-NBSA

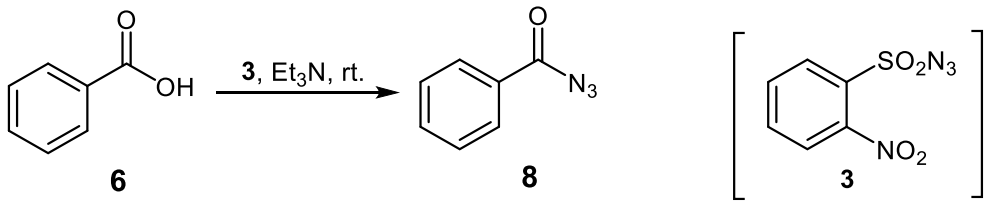


Equation 15: Attempted synthesis of benzoyl azide using *p*-NBSA (**5**).

Attempt to make the benzoyl azide was made with benzoic acid and *p*-NBSA in toluene at temperature. TLC monitoring of the reaction progress showed a single spot in the reaction which had the same retention factor (R_f 0.68) as the retention factor calculated for the *p*-NBSA. This could be attributed to the higher bond strength of sulfur and nitrogen bonds compared to phosphorous and nitrogen bonds. The IR spectrum of the *p*-NBSA (2130.12 cm^{-1}) was almost the same as that of the reaction (2130.57 cm^{-1}). This could mean that the reaction did not produce the expected product or formed an unexpected product or intermediate. It could also mean that the desired product was formed and had the same IR signal for azide as the *p*-NBSA used.

The reaction temperature was elevated to 60 ℃ to enhance product formation by possibly causing a better dissociation of the sulfur nitrogen bond. Though TLC using solvent (5:1 hexane: ethyl acetate) showed the presence of another spot other than the azide substrate with a new retention factor, the IR spectrum showed azide signals (2130.76 cm^{-1}) of similar values to *p*-NBSA (2130.19 cm^{-1}) which presupposed that the expected product was either not formed or formed having the same IR signal as *p*-NBSA (**Figure 34**).

Benzoyl azide (8) using *o*-NBSA



Equation 16: Attempted synthesis of benzoyl azide using *o*-NBSA (**3**).

The already synthesized *o*-NBSA was used to make the benzoyl azide in toluene at room temperature. TLC monitoring of the reaction progress showed two spots in the reaction with one having the same retention factor (R_f 0.47) as the retention factor calculated for the *o*-NBSA and the other one (R_f 0.67) possibly corresponding to the expected product. The IR spectrum of the *o*-NBSA (2149.33 cm^{-1}) was almost the same as that of the reaction (2145.97 cm^{-1}) (**Figure 33**). Though the new IR band for the product is slightly different from the starting material *o*-NBSA, it cannot be concluded to be the product.

CONCLUSION

Carbamates of carboxylic acids such as benzoic acid have been successfully synthesized using DPPA as the main azide substrate. Attempt to extend the synthesis to di- and tricarboxylic acids yielded products with limited substrate scope. Attempt to synthesize carbamates of the tricarboxylic acids only ended with the azide due to the limit with solvent choice.

The safely synthesized *o*-NBSA or *p*-NBSA gave results that seemed encouraging enough to further verify. *p*-NBSA gave some new product with benzoic acid at elevated temperatures though it was not confirmed to be benzoyl azide due to the similarity of the IR signals with the main azide moiety used. *o*-NBSA also showed the formation of a possible azide using the carboxylic acid (benzoic acid) even at room temperature. This could be a starting point for possible further research.

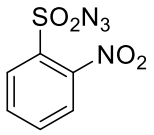
EXPERIMENTAL

General Methods

All reagents used in these experiments were preordered from Sigma-Aldrich and were used without further purification. All reactions were performed in oven-dried glassware at various temperatures including test tubes used in the Radley's carousel system. The progress and completion of all reactions was monitored using TLC on Whatman Silica Gel 60 F254 aluminum-backed plates and ultraviolet light detection for reaction materials that are UV-active. For the azide product determination, the TLC plate was treated with *p*-anisaldehyde solution and dried on a hot plate. .

Nuclear Magnetic resonance (^{1}H and ^{13}C) were recorded for samples dissolved in D_6-DMSO or $CDCl_3$, using a Bruker Avance 400 MHz spectrometer. Proton and carbon chemical shifts are reported in parts per million (ppm). The signals are labelled as singlet (s), doublet (d), triplet (t) and all coupling constants are reported in Hertz (Hz). Infrared spectra were taken on a Thermo Electron Corporation IR 200 spectrophoto-meter and analyzed using EZ-OMNIC software to further confirm the products.

Synthesis of *ortho*-nitrobenzene sulfonyl azide (3).



3

In a 250 mL oven-dried round bottom flask fitted with a rubber septum and magnetic stir bar, sodium azide **1** (3.97 g, 60.0 mmol) was dissolved in deionized water (20 mL) and *o*-nitrobenzene sulfonyl chloride **2** (8.93 g, 40.0 mmol) was dissolved in acetone (20 mL) and then added dropwise to the reaction in an ice bath. The reaction was left to stir overnight and TLC (1:1 hexane: ethyl acetate) was run to show the consumption of starting material and formation of the product (R_f = 0.47). The excess NaN_3 was filtered off and the organic mixture was concentrated under vacuum on a rotary evaporator. The crystals were dissolved in deionized water (50 mL) and then the organic layer was extracted with dichloromethane (3 × 50 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporation to obtain crystals. The product was recrystallized from hot ethyl alcohol to afford pure *o*-NBSA as pale-yellow crystals (8.07 g, 88.40%).

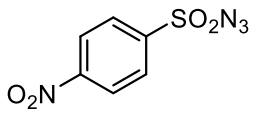
^{1}H NMR (400 MHz, DMSO): δ 8.28 – 8.00 (m, 4H).

^{13}C NMR (100 MHz, DMSO): δ 147.55, 137.55, 134.37, 131.62, 130.98, 126.18.

IR absorption: 2149.33 cm^{-1} for the azide functional group.

Melting Point: 68 - 71 ℃.

Synthesis of *para*-nitrobenzene sulfonyl azide (5).



5

In a 250 mL oven-dried round bottom flask fitted with a septum and magnetic stir bar, sodium azide **1** (4.89 g, 75.0 mmol) was dissolved in deionized water (30 mL) and *p*-nitrobenzene sulfonyl chloride **4** (11.1 g, 50.0 mmol) was dissolved in acetone (30 mL) and then added dropwise to the reaction in an ice bath. The reaction was left to stir overnight and TLC (1:1 hexane: ethyl acetate) was run to show the consumption of starting material and formation of the product (R_f= 0.70). The excess NaN_3 was filtered off and the organic mixture was concentrated under vacuum on a rotary evaporator. The crystals were dissolved in dichloromethane (50 mL) and then the organic layer was extracted with deionized water (3 × 50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporation to obtain crystals. The product was recrystallized from hot ethyl alcohol to afford pure *p*-NBSA as pale-yellow crystals (10.26 g, 89.93%).

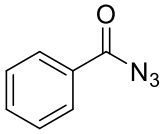
^{1}H NMR (400 MHz, DMSO): δ 8.50 (d, 2H, *J* = 8.00 Hz), 8.31 (d, 2H, *J* = 8.04 Hz).

^{13}C NMR (100 MHz, DMSO): δ 153.2, 143.03, 129.59 (double intensity), 125.78 (double intensity).

IR absorption: 2130.12 cm^{-1} for the azide functional group.

Melting Point: 96 - 99 °C.

Synthesis of benzoyl azide (8) using DPPA.



8

In a 250 mL oven-dried round bottom flask fitted with a septum and magnetic stir bar, benzoic acid **6** (2.46 g, 20.0 mmol) was dissolved in acetone (20 mL) and triethyl amine (3.0 mL, 22 mmol) was added and allowed to stir for 5 mins. DPPA **7** (4.0 mL, 20.0 mmol) was then added and allowed to stir for 30 mins at 0 °C. The progress of the reaction was monitored with TLC (1:1 hexane: ethyl acetate) $R_f = 0.67$. At the confirmation of the product, the reaction was quenched with sodium bicarbonate (30 mL) and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic extract was washed with saturated sodium chloride solution and dried with magnesium sulfate. The solvent was evaporated on a rotavap, and the product obtained as white crystals (2.20 g, 74.60%).

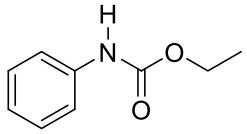
^{1}H NMR (400 MHz, DMSO): δ 7.99 – 7.55 (m, 5H).

^{13}C NMR (100 MHz, DMSO): δ 172.41, 135.20, 130.65, 129.51, 129.49.

IR absorption: 2134.58 cm^{-1} for the azide functional group.

Melting Point: 30-32 °C.

Synthesis of Ethyl phenyl carbamate (10) from Benzoyl azide.



10

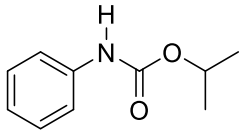
In a 25 mL oven-dried carousel test tube fitted with a septum and magnetic stir bar, benzoyl azide **8** (721 mg, 5.00 mmol) was dissolved in toluene (12 mL) and heated at 80 °C for 3 hours to form isocyanate which was confirmed by IR by the disappearance of the band at 2134.58 cm^{-1} for the benzoyl azide and the appearance of a new band at 2260.35 cm^{-1}. The isocyanate mixture was cooled to about 50 °C, trapped with ethanol **9** (2.5 mL, 5.0 mmol) and refluxed for 3 days until a new reddish spot was seen on TLC (1:1 hexane: ethyl acetate) to confirm the carbamate formation (R_f = 0.59). At the confirmation of the product, the reaction was quenched with saturated aqueous sodium bicarbonate (30 mL) and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic extract was washed with saturated sodium chloride solution and dried with magnesium sulfate. The solvent was evaporated on a rotavap, and pure ethyl phenyl carbamate (448.0 mg, 74.26%) was collected as a pale-yellow solid upon recrystallization with 5:1 hexane: ethyl acetate as solvent.

^{1}H NMR (400 MHz, DMSO): δ 9.63 (s, 1H), 7.51 – 6.96 (m, 5H), 4.13 (q, 2H, J = 7.06 Hz), 1.22 (t, 3H, J = 7.06 Hz).

^{13}C NMR (100 MHz, DMSO): δ 154.04, 139.69, 129.17 (double intensity), 122.75, 118.74 (double intensity), 60.54, 14.97.

Melting Point: 47-51 °C.

Synthesis of Isopropyl phenyl carbamate (12) from Benzoyl azide.



12

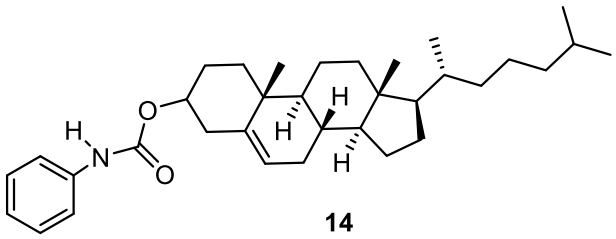
In a 25 mL oven-dried test tube fitted with a septum and magnetic stir bar, benzoyl azide **8** (142.8 mg, 1.0 mmol) was dissolved in toluene (4 mL) and refluxed at 80 ^{o}C to form isocyanate which was confirmed by IR by the disappearance of the band at 2134.58 cm^{-1} for the benzoyl azide and the appearance of a new band at 2260.35 cm^{-1}. The isocyanate mixture was cooled to about 50 ^{o}C, trapped with isopropyl alcohol **11** (0.7 mL, 9.2 mmol) and refluxed until a new reddish spot was seen on TLC (1:1 hexane: ethyl acetate) R_f = 0.60 to confirm the carbamate formation. At the confirmation of the product, the reaction was quenched with sodium bicarbonate (30 mL) and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic extract was washed with saturated sodium chloride (30 mL) solution and dried with magnesium sulfate. The solvent was evaporated on a rotavap, and the product obtained as a brownish liquid. NMR was done to confirm the product.

^{1}H NMR (400 MHz, DMSO): δ 9.44 (s, 1H), 7.48 – 6.96 (m, 5H), 4.94 - 4.84 (m, 1H,), 1.27 (d, 6H, J = 6.20 Hz).

^{13}C NMR (100 MHz, DMSO): δ 153.65, 139.78, 129.10 (double intensity), 122.67, 118.70 (double intensity), 67.84, 22.43 (double intensity).

Melting Point: 86-89 °C.

Synthesis of (8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl phenyl carbamate (14) from benzoic acid.



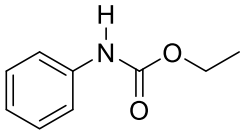
14

In a 25 mL oven-dried test tube fitted with a septum and magnetic stir bar, benzoyl azide **8** (143.8 mg, 1 mmol) was dissolved in toluene (4 mL) and heated at 80 ℃ to form isocyanate which was confirmed by IR by the disappearance of the band at 2134.58 for the benzoyl azide and the appearance of a new band at 2260.35. The isocyanate mixture was cooled to about 50 ℃, trapped with cholesterol **13** (386.9 mg, 1 mmol in 4 mL toluene) and refluxed at 110 ℃ for 72 hours until a new reddish spot was seen on TLC (1:1 hexane: ethyl acetate) R_f = 0.69 to confirm the carbamate formation. At the confirmation of the product, the reaction was quenched with sodium bicarbonate (30 mL) and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic extract was washed with saturated sodium chloride (30 mL) solution and dried with magnesium sulfate. The solvent was evaporated on a rotavap, and the product obtained as a brownish liquid. NMR was done to confirm the product.

Selected ^{1}H NMR (400 MHz, DMSO): δ 9.63 (s, 1H), 7.46 – 6.96 (m, 5H)

Selected ^{13}C NMR (100 MHz, DMSO): δ 154.04, 140.17, 138.62, 129.86, 124.25, 118.74

“One Pot” synthesis of Ethyl phenyl carbamate (10) from benzoic acid.



10

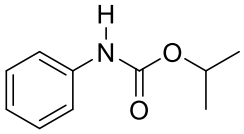
In a 25 mL oven dried test tube, benzoic acid **6** (675.2 mg, 5.0 mmol) was dissolved in toluene (15 mL) and triethylamine (0.75 mL, 5.5 mmol) was added and stirred for 2 min. DPPA **7** (1.0 mL, 5.5 mmol) was added and stirred for 30 minutes. The consumption of starting materials and the formation of the azide was confirmed by TLC (1:1 hexane: ethyl acetate) $R_f = 0.68$ and developed with *p*-anisaldehyde to form yellow spot. The reaction temperature was elevated to 80 ℃ for the formation of isocyanate which was confirmed by the disappearance of the yellow azide spot and the formation of a new spot. The reaction was then cooled to 50 ℃ and ethanol **9** (2.5 mL, 42.4 mmol) was added and allowed to refluxed at 110 ℃ until TLC (1: 1 hexane: ethyl acetate) $R_f = 0.59$ confirmed the formation of the carbamate. The mixture was then allowed to cool down to room temperature. The reaction mixture was diluted with 20 mL distilled water, and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed by rotary evaporation.

^{1}H NMR (400 MHz, DMSO): δ 9.63 (s, 1H), 7.51 – 6.96 (m, 5H), 4.13 (q, 2H, J = 7.06 Hz), 1.22 (t, 3H, J = 7.1 Hz).

^{13}C NMR (100 MHz, DMSO): δ 154.02, 139.72, 129.15 (double intensity), 122.70, 118.59, 60.55, 14.95.

Melting Point: 47-51 ℃.

“One-Pot” synthesis of Isopropyl phenyl carbamate (12) from benzoic acid.



12

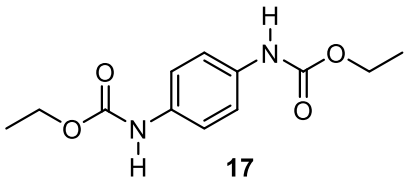
In a 25 mL oven-dried carousel test tube, benzoic acid **6** (677.2 mg, 5.0 mmol) was dissolved in toluene (16 mL) and triethylamine (5.5 mmol, 0.75 mL) was added and stirred for 2 mins. DPPA **7** (1.0 mL, 5.5 mmol) was added and stirred for 30 minutes at room temperature. The consumption of starting materials and the formation of the acyl azide was confirmed by TLC (1:1 hexane: ethyl acetate) and developed with *p*-anisaldehyde to form yellow spot with R_f=0.68. The reaction was heated at 80 ℃ for the formation of isocyanate which was confirmed by the disappearance of the yellow azide spot and the formation of a new spot. The reaction was then cooled to 50 ℃ and isopropanol **11** (3.5 mL, 46 mmol) was added and allowed to reflux at 110 ℃ until TLC (1: 1 hexane: ethyl acetate) confirmed the formation of the carbamate (R_f = 0.59). The mixture was then allowed to cool down to room temperature. The reaction mixture was diluted with 20 mL distilled water, and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed by rotary evaporation at 60 ℃.

^{1}H NMR (400 MHz, DMSO): δ 9.57 (s, 1H), 7.48 – 6.95 (m, 5H), 4.97 – 4.86 (m, 1H), 1.26 (d, 6H, J = 6.28 Hz).

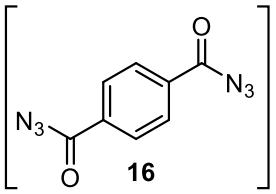
^{13}C NMR (100 MHz, DMSO): δ 153.60, 139.78, 129.15 (double intensity), 122.65, 118.56, 67.81, 22.45 (double intensity).

Melting Point: 86-89 ℃.

Attempted "One-Pot" synthesis of Diethyl 1,4-phenylene dicarbamate (17).



17



16

Not isolated

In a 25 mL oven-dried carousel test tube, terephthalic acid **15** (167.8 mg, 1 mmol) was dissolved in DMF (4 mL) and triethylamine (0.3 mL, 3 mmol) was added and stirred for 2 mins. DPPA **6** (0.6 mL, 2 mmol) was added and stirred for 30 minutes at room temperature. The consumption of starting materials and the formation of the diazide was confirmed by TLC (1:1 hexane: ethyl acetate) and developed with *p*-anisaldehyde to form yellow spot (R_f = 0.68). The reaction was heated at 80 ℃ for the formation of isocyanate which was confirmed by the disappearance of the yellow azide spot and the formation of a new spot. The reaction was then cooled to 50 ℃ and ethanol (1 mL, 11.5 mmol) was added and allowed to heat at 110 ℃ until TLC (1: 1 hexane: ethyl acetate) confirmed the formation of a new product. The mixture was then allowed to cool down to room temperature. The reaction mixture was diluted with 20 mL of distilled water, and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed by rotary evaporation to form the product. NMR was run to ascertain the formation of the carbamate product.

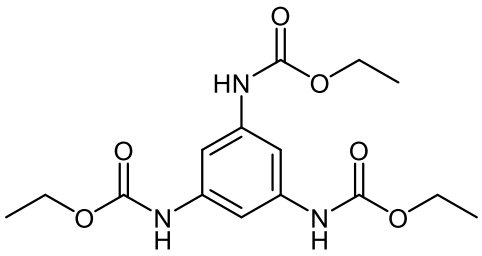
^{1}H NMR (400 MHz, $CDCl_3$) of azide: δ 8.02 (s, 4H).

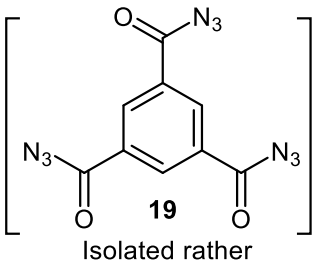
^{13}C NMR (100 MHz, DMSO) of azide: δ 171.53, 135.38, 129.55 (double intensity).

^{1}H NMR (400 MHz, $CDCl_3$) of new product: δ 8.96 (s, 1H), 7.29-7.23 (m, 3 H).

^{13}C NMR (100 MHz, DMSO) of new product: δ 153.19, 129.11, 123.05, 120.32, 45.62, 8.45.

Attempted "One-Pot" synthesis of Triethyl benzene-1,3,5-triyltricarbamate (20).





Isolated rather

In a 25 mL oven-dried carousel test tube, 1,3,5 benzene tricarboxylic acid **18** (216.1 mg, 1 mmol) was dissolved in THF (4 mL) and triethylamine (0.6 mL, 4 mmol) was added and stirred for 2 mins. The mixture formed a paste so THF (4 mL) was added and DPPA **6** (0.9 mL, 4 mmol) was added and stirred for 30 minutes at room temperature. The consumption of starting materials and the formation of the triazide was confirmed by TLC (1:1 hexane: ethyl acetate) and developed with *p*-anisaldehyde to form yellow spot (R_f = 0.76). The reaction was heated at 60 ℃ for the formation of isocyanate but the solvent evaporated so the process was discontinued. The mixture was then allowed to cool down to room temperature. The reaction mixture was diluted with 20 mL of distilled water, and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed by rotary evaporation to form the product. NMR was run to confirm the product formed as the triazide.

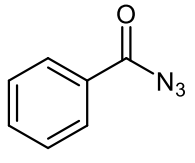
IR absorption: 2143.97 cm^{-1} for the azide functional group of the product.

^{1}H NMR (400 MHz, $CDCl_3$) of azide: δ 8.68 (s, 3H).

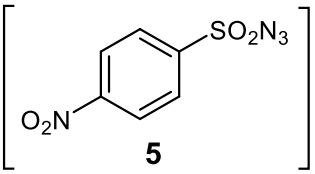
^{13}C NMR (100 MHz, DMSO) of azide: δ 170.68, 134.21 (double intensity), 132.59, 119.20.

Acyl azide using *o*-NBSA or *p*-NBSA as azide substrate

Using *P*-NBSA



8



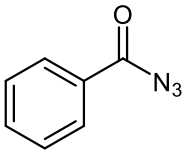
5

In a 25 mL oven-dried , benzoic acid **6** (123.0 mg, 1 mmol) and *p*-NBSA **5** (228.2 mg, 1 mmol) was dissolved in toluene (4 mL) and triethylamine (0.15 mL, 1 mmol) was added and stirred for 30 minutes at room temperature. The consumption of starting materials and the formation of the azide was monitored by TLC (1:1 hexane: ethyl acetate) and developed with *p*-anisaldehyde to form yellow spot. After 24 hours, TLC (R_f=0.70) showed a single spot which had the same retention factor as that of the *p*-NBSA used.

IR absorption: 2130.78 cm^{-1} for the azide functional group of the product.

IR absorption: 2130.45 cm^{-1} for the azide functional group of *p*-NBSA.

Using *o*-NBSA



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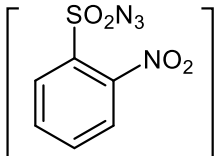

3

In a 25 mL oven-dried carousel test tube, benzoic acid **6** (123.5 mg, 1 mmol) and o-NBSA **3** (228.7mg, 1 mmol) was dissolved in toluene (4 mL) and triethylamine (0.15 mL, 1 mmol) was added and stirred for 30 minutes at room temperature. The consumption of starting materials and the formation of the azide was monitored by TLC (1:1 hexane: ethyl acetate) and developed with *p*-anisaldehyde to form yellow spot. After 1 hour, TLC showed two spots (R_f = 0.47 and 0.67) corresponding to *o*-NBSA and a possible new product. At the confirmation of the product, the reaction was quenched with saturated aqueous sodium bicarbonate (10 mL) and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extract was washed with saturated sodium chloride solution and dried with magnesium sulfate. The solvent was evaporated on a rotavap for further evaluation to be done.

IR absorption: 2145.97 cm^{-1} for the azide functional group of the product.

IR absorption: 2149.33 cm^{-1} for the azide functional group of *o*-NBSA.

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APPENDIX A

NMR and IR Spectra

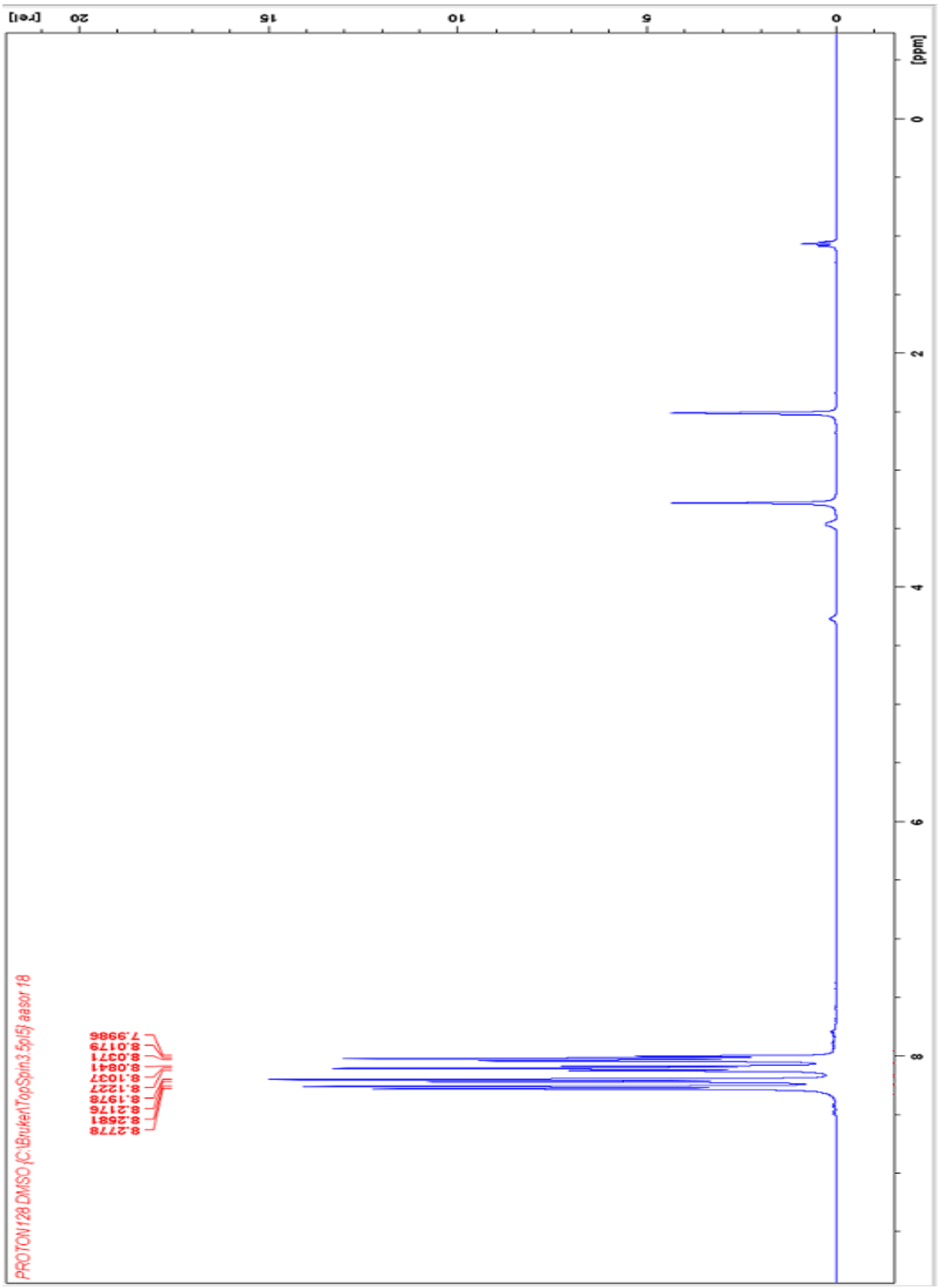

Figure 6: ^{1}H NMR Spectrum of *o*-NBSA (**3**).

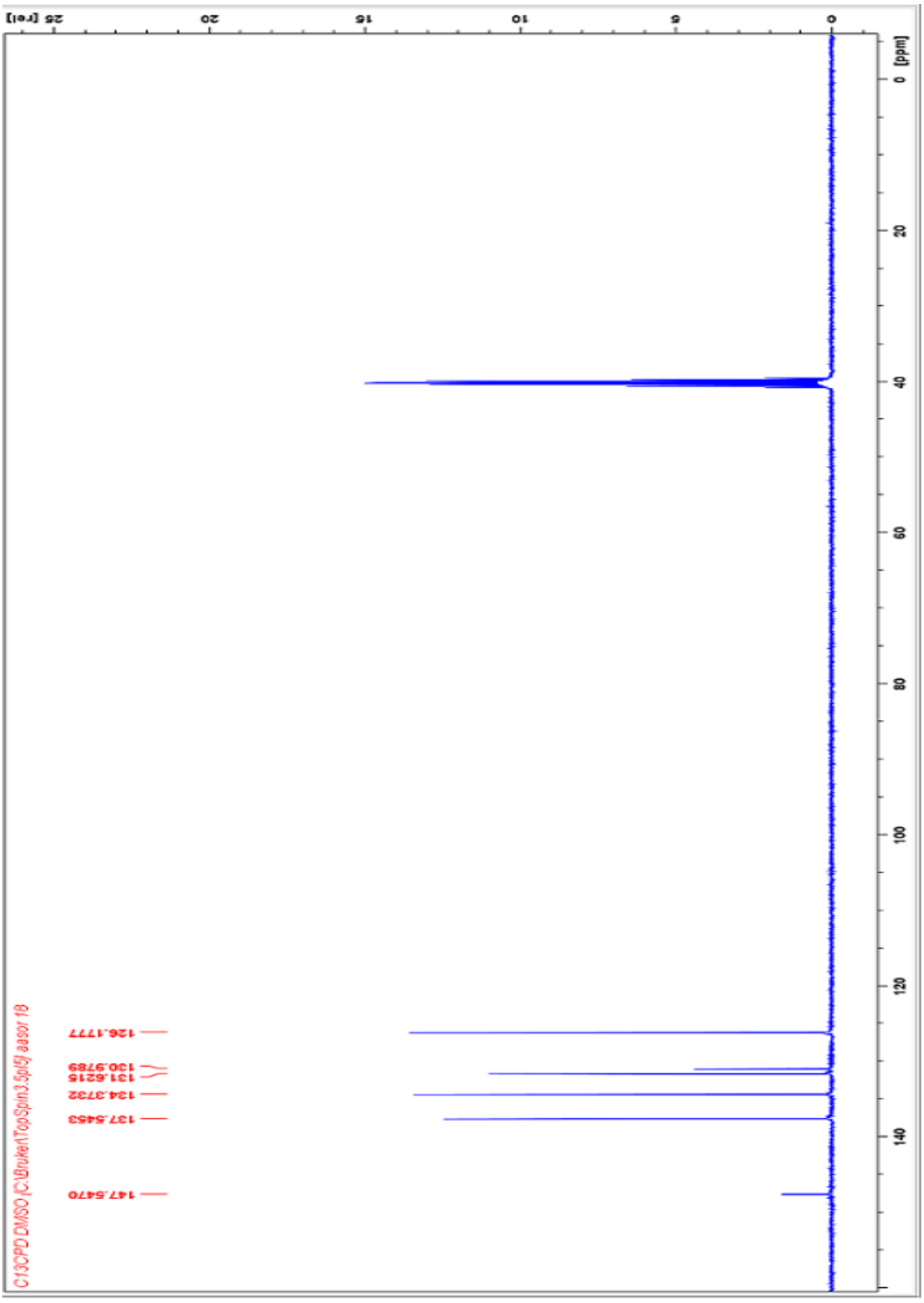

Figure 7: ^{13}C NMR of *o*-NBSA (**5**).

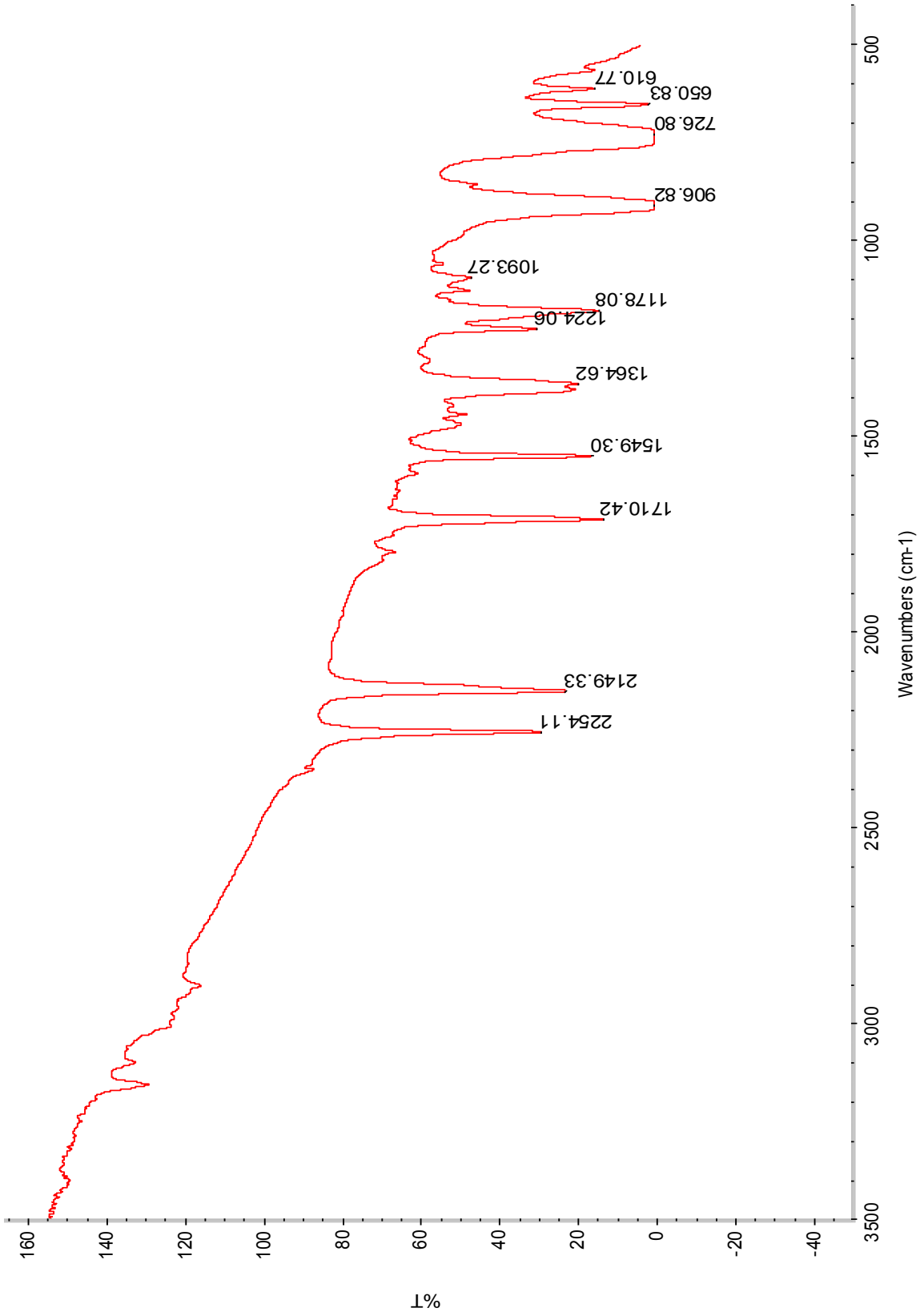

Figure 8: IR spectrum of *o*-NBSA (**3**) in $CDCl_3$.

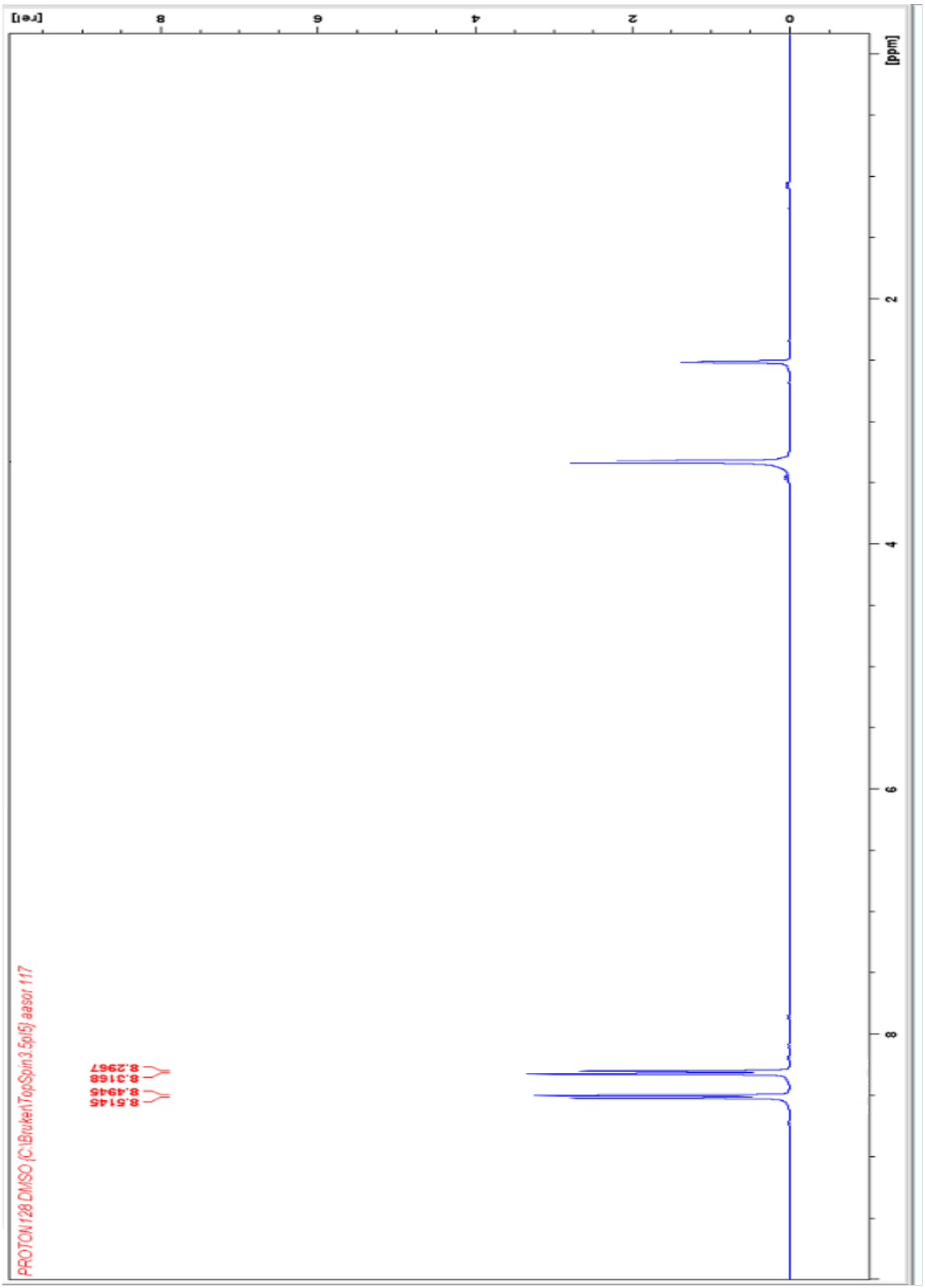

Figure 9: ^{1}H NMR Spectrum of *p*-NBSA (**5**).

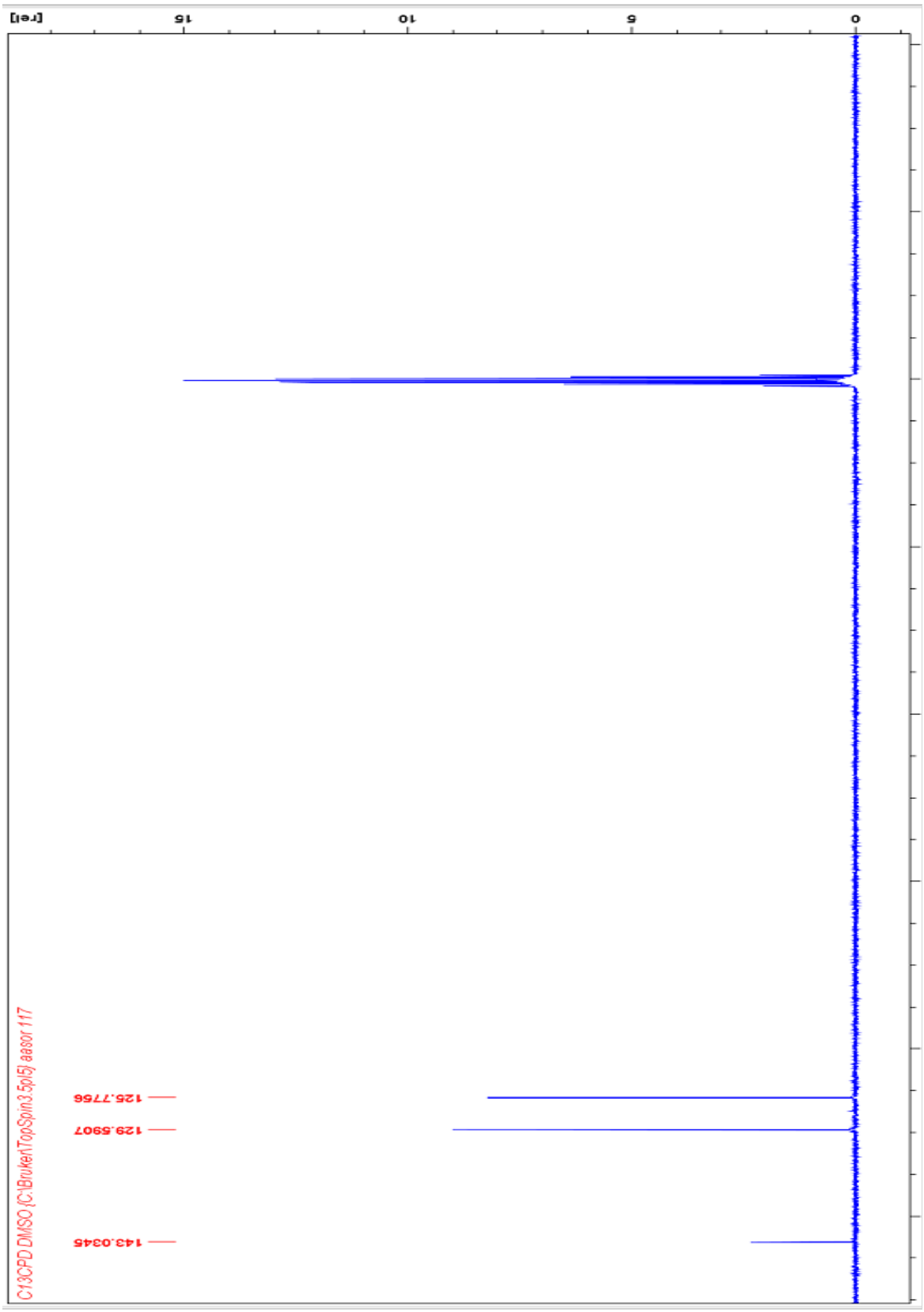

Figure 10: ^{13}C NMR of *p*-NBSA (**5**).

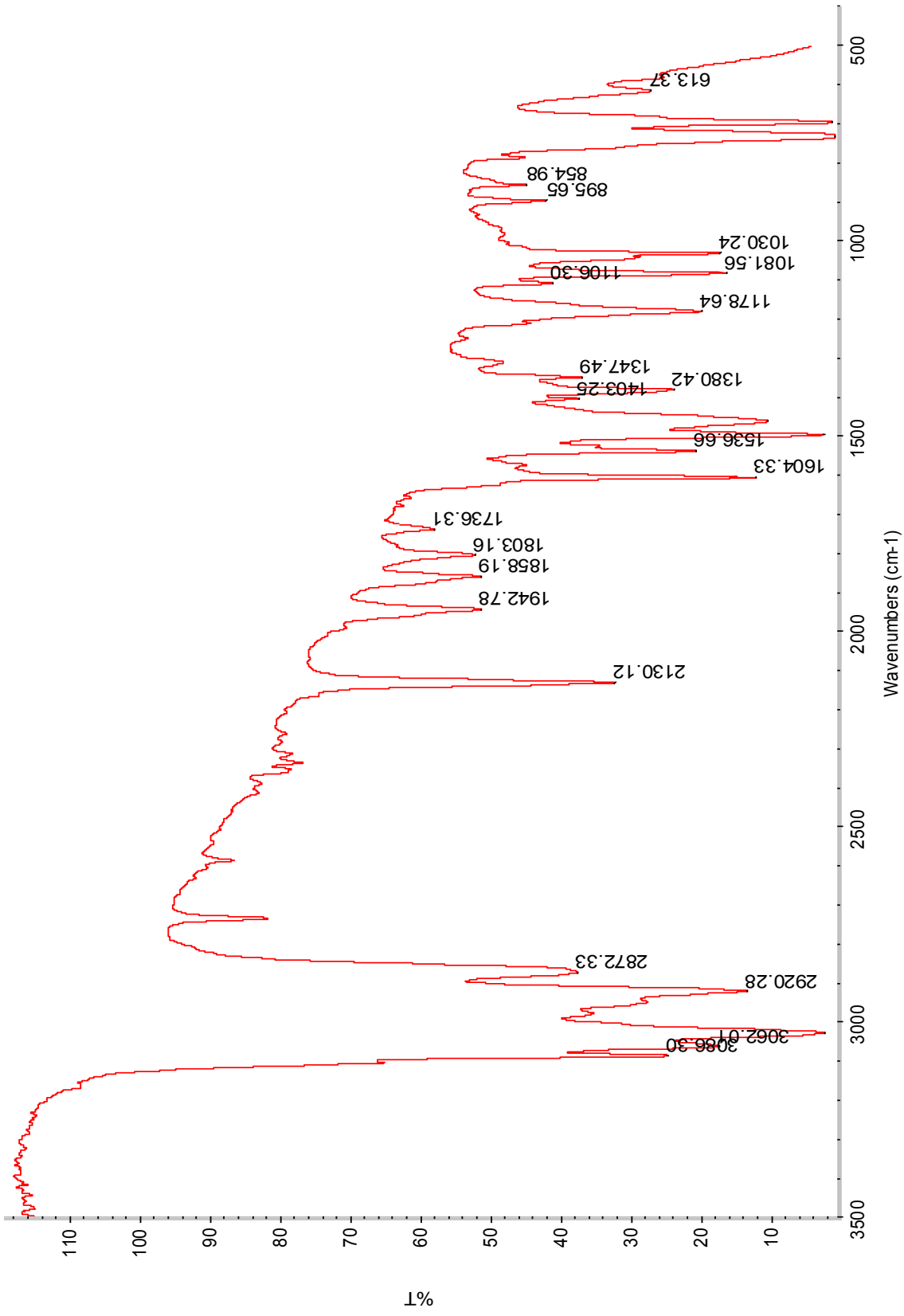

Figure 11: IR spectrum of *p*-NBSA (**5**).

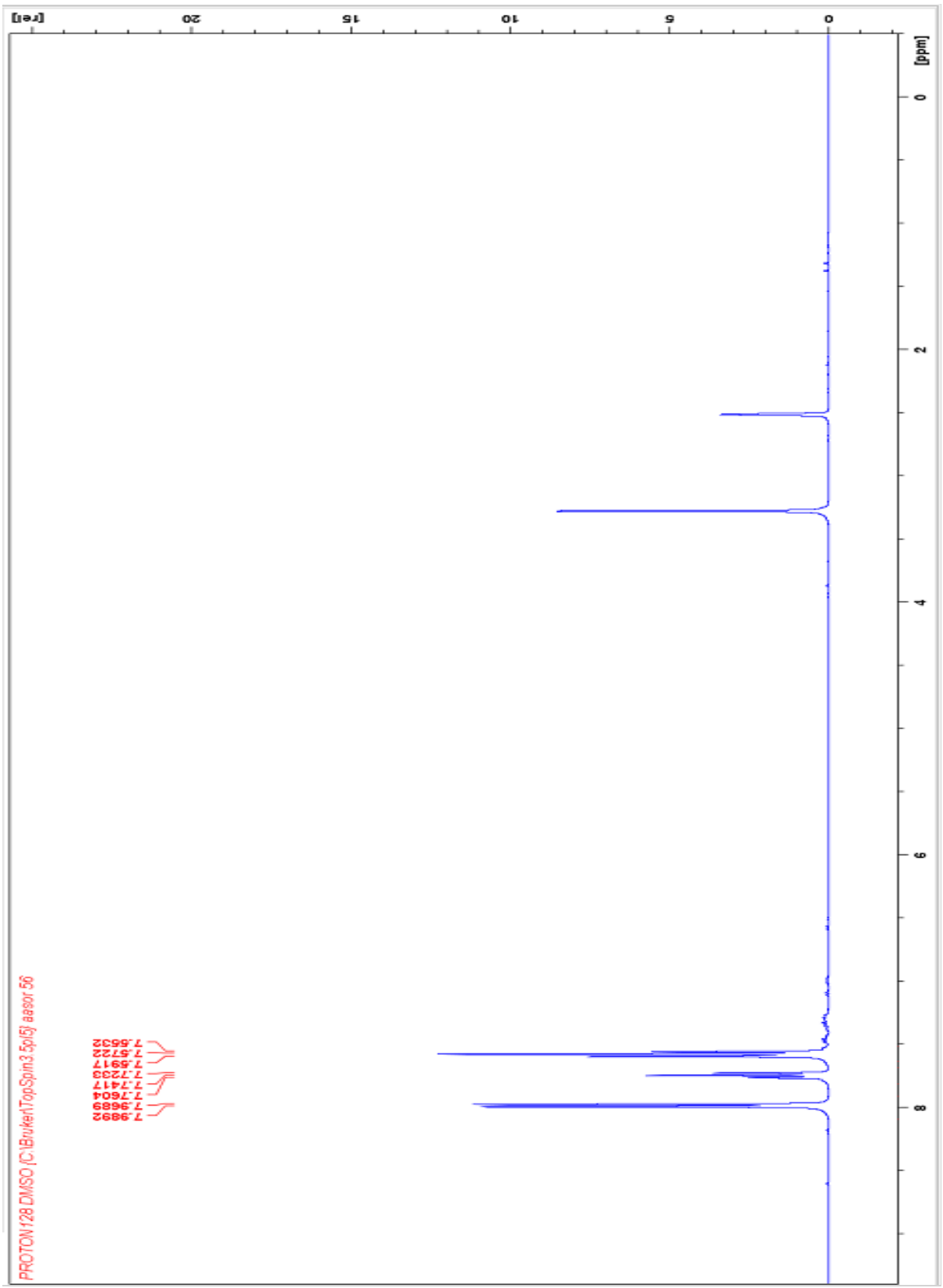

Figure 12: ^{1}H NMR Spectrum of benzoyl azide (**8**).

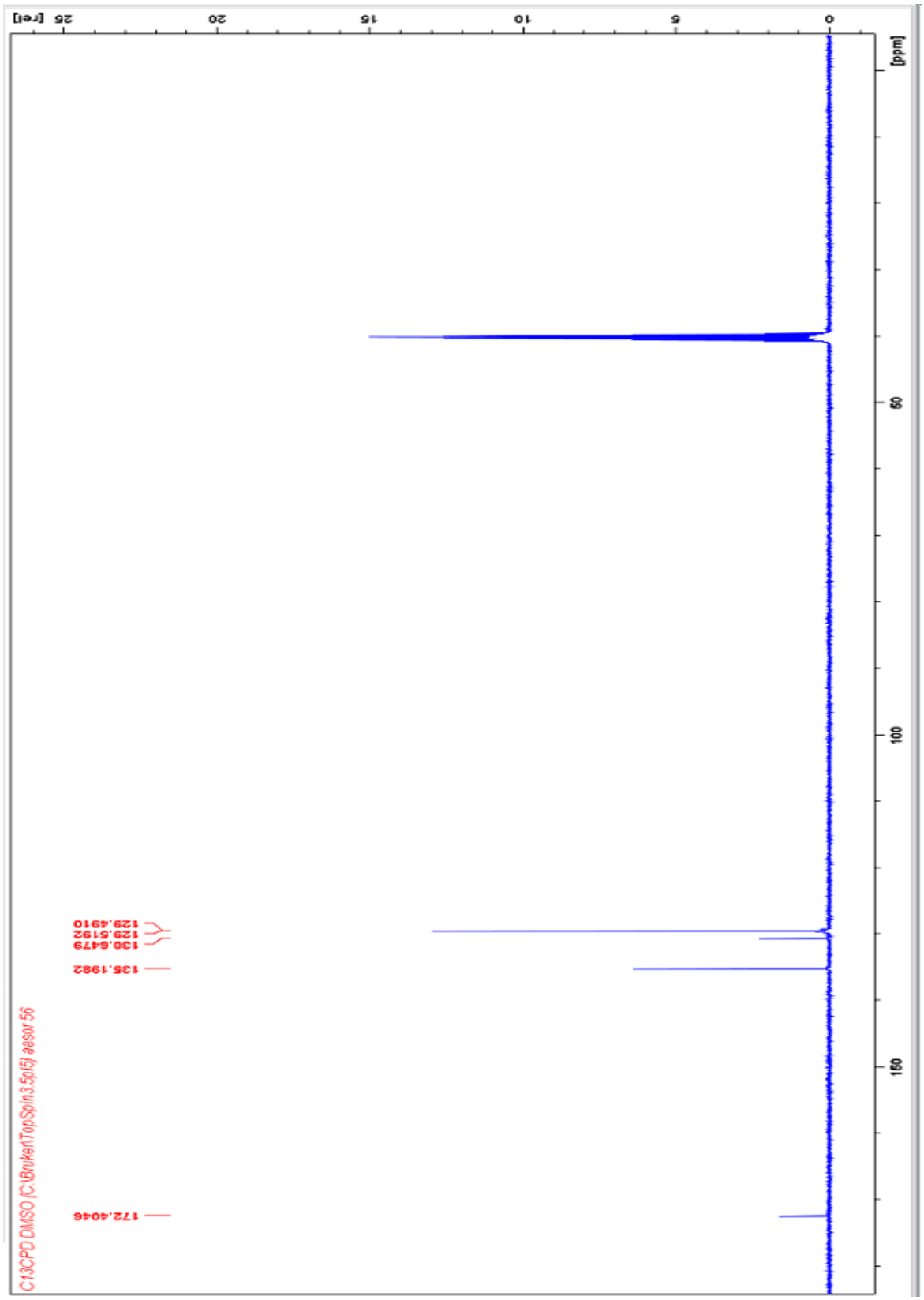

Figure 13: ^{13}C NMR of benzoyl azide (**8**).

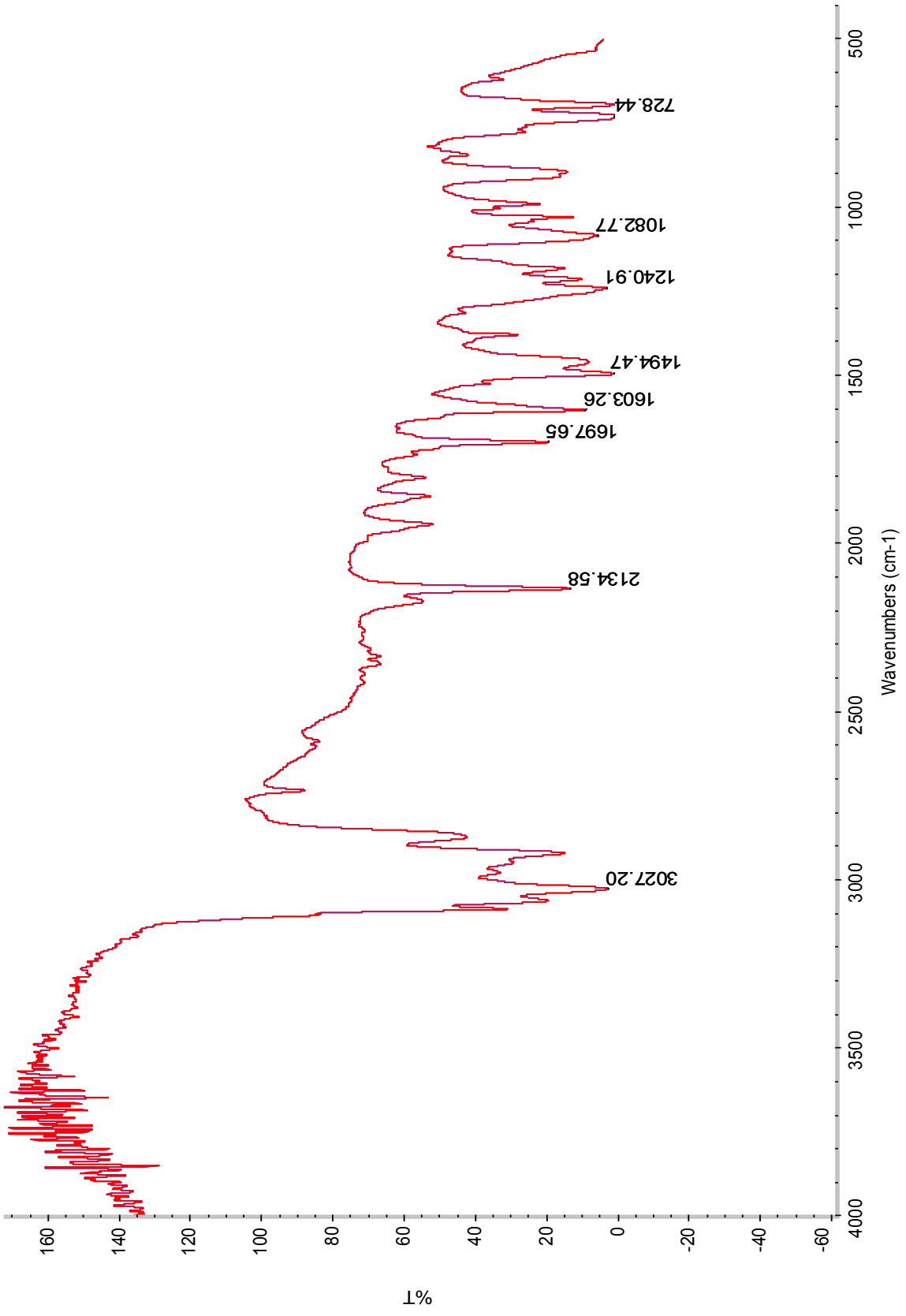

Figure 14: IR spectrum of benzoyl azide (**8**).

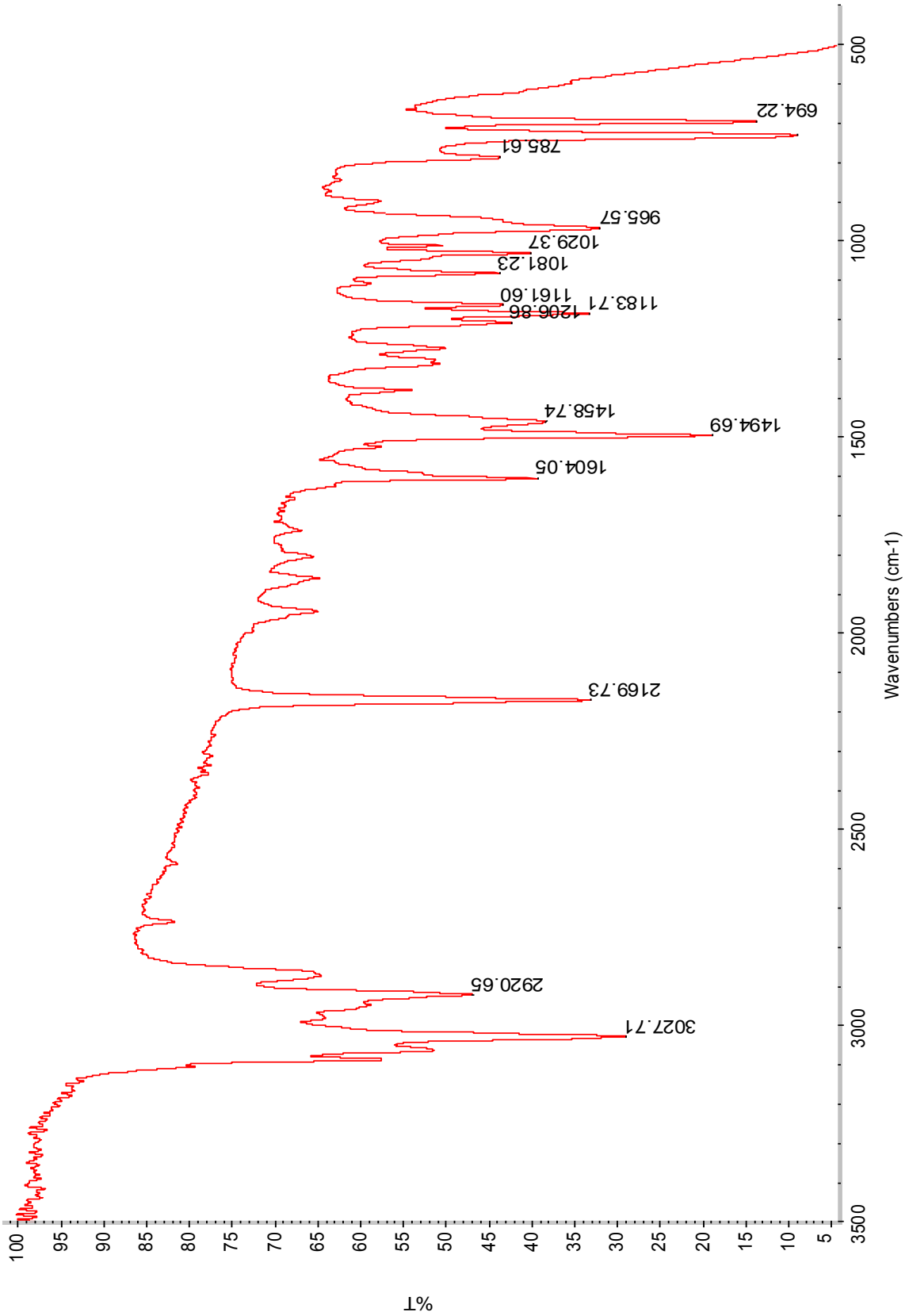

Figure 15: IR spectrum of DPPA in toluene.

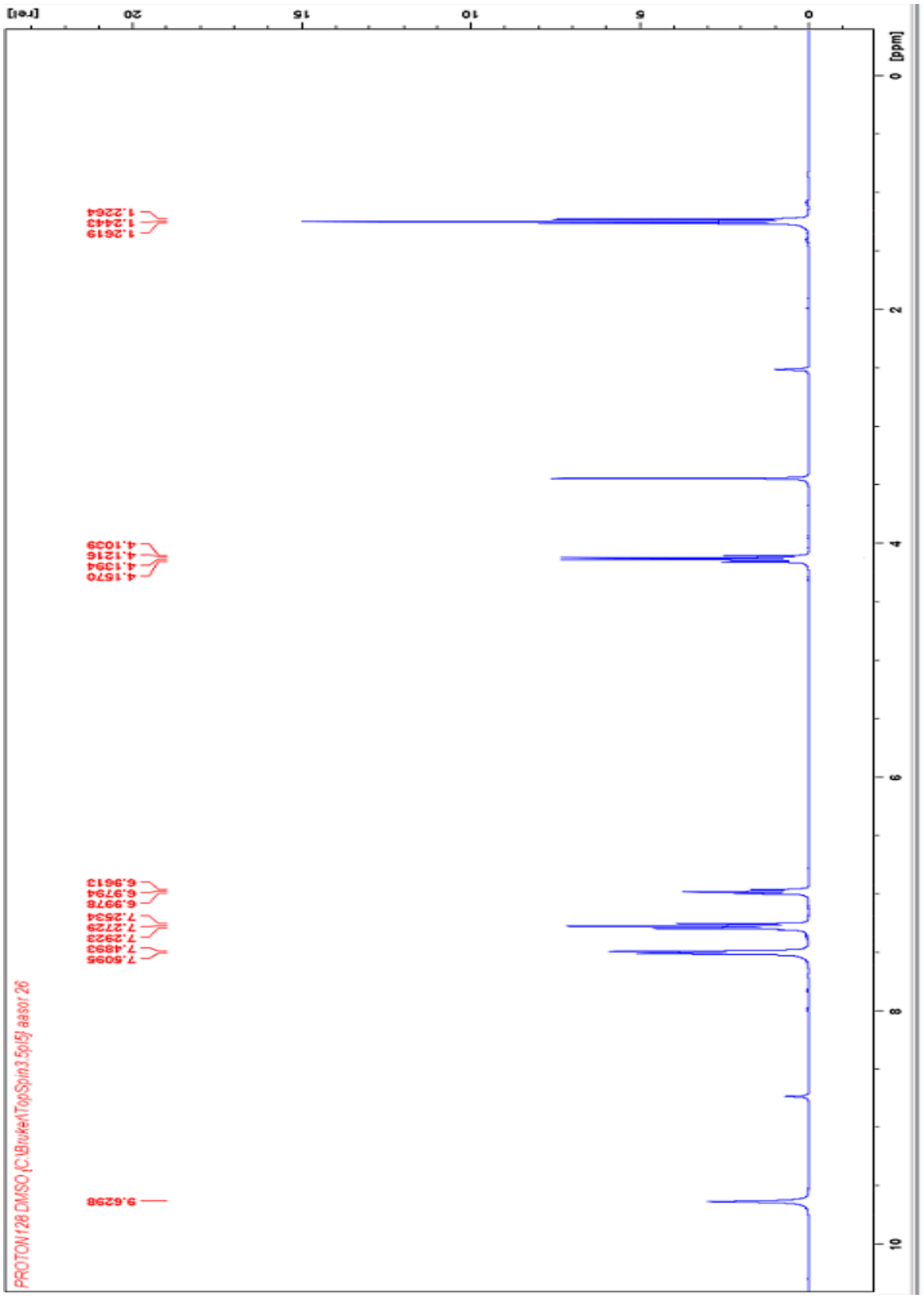

Figure 16: ^{1}H NMR of ethyl phenyl carbamate (**10**).

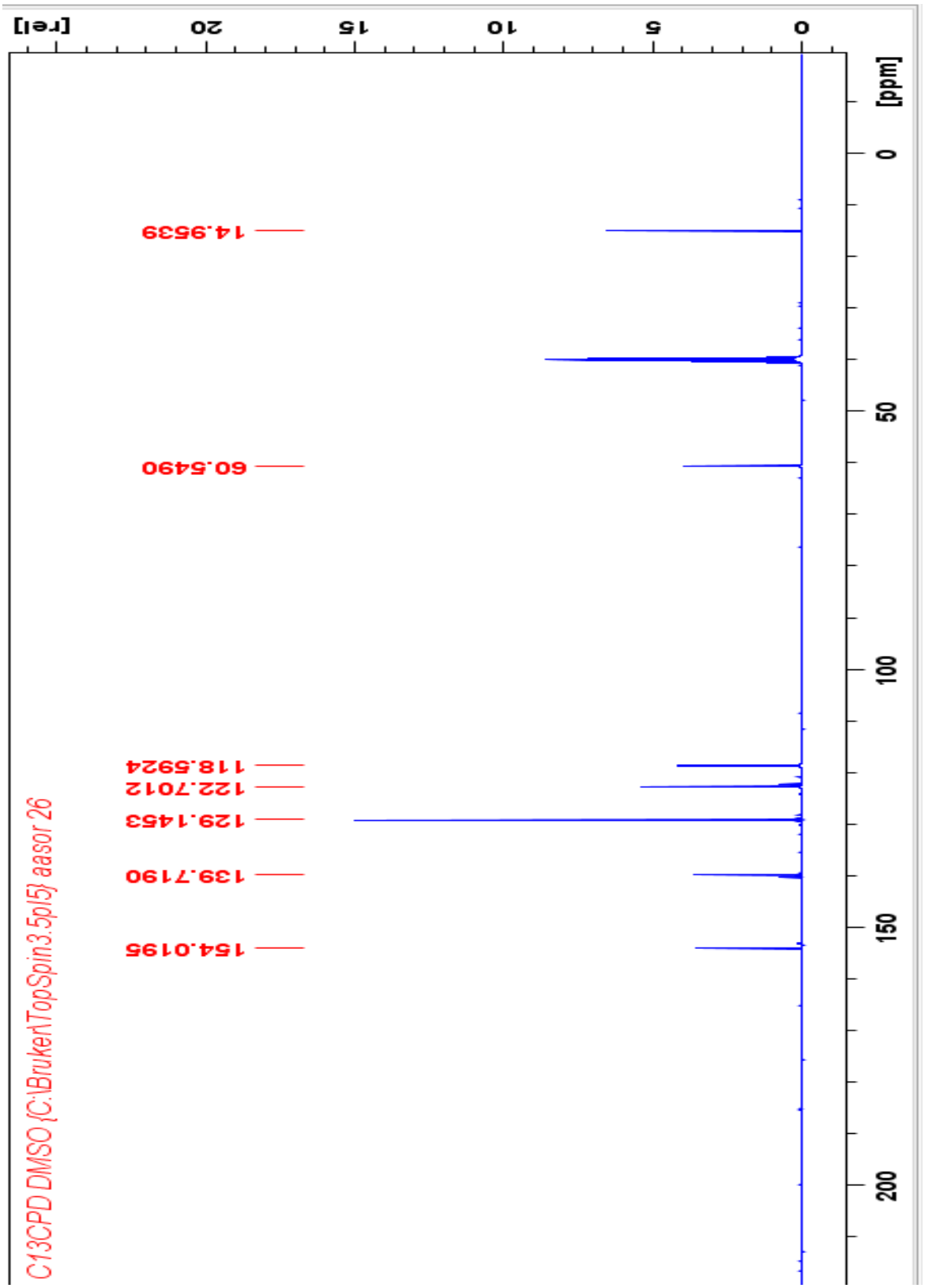

Figure 17: ^{13}C NMR of ethyl phenyl carbamate (**10**).

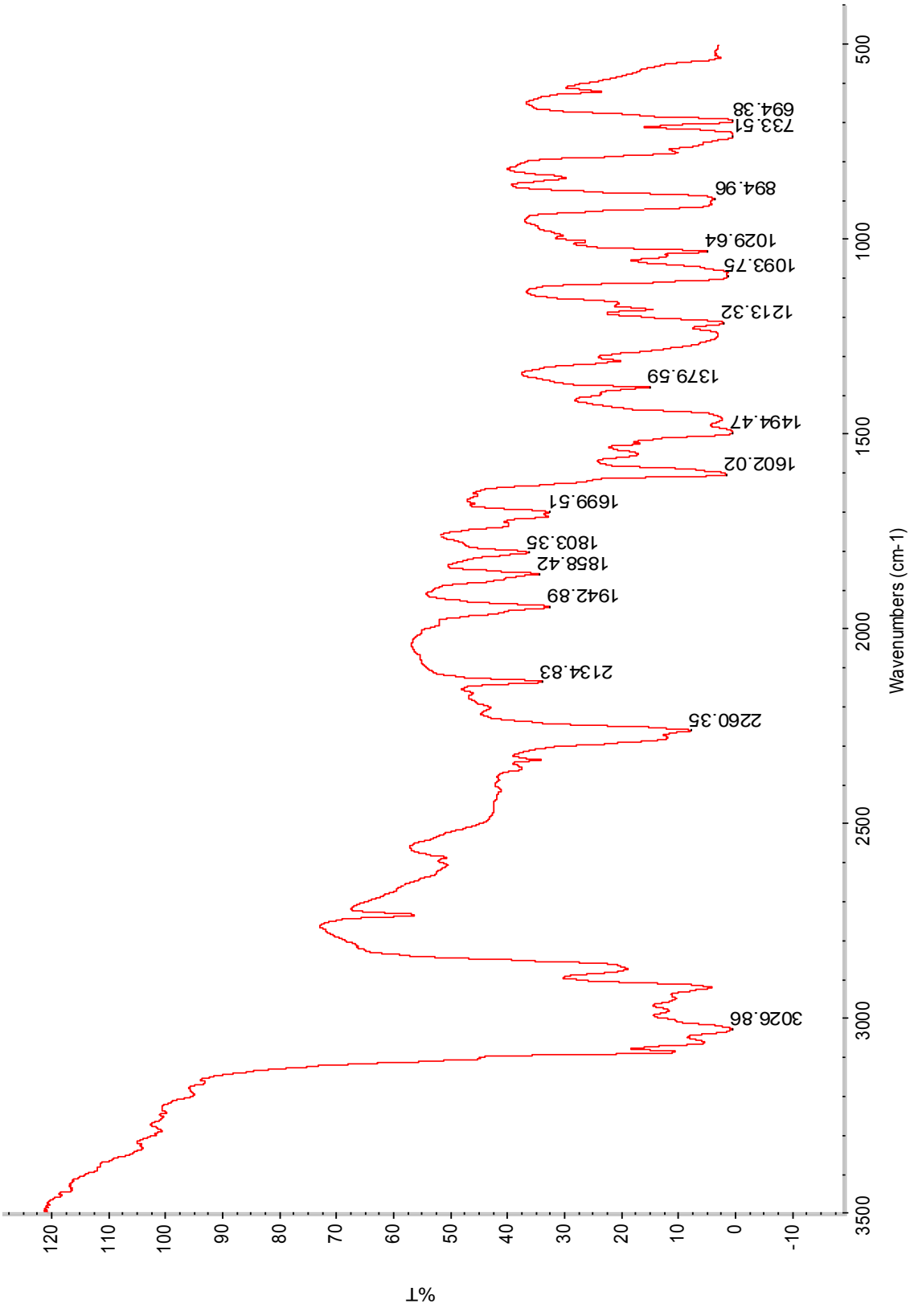

Figure 18: IR spectrum of benzene isocyanate.

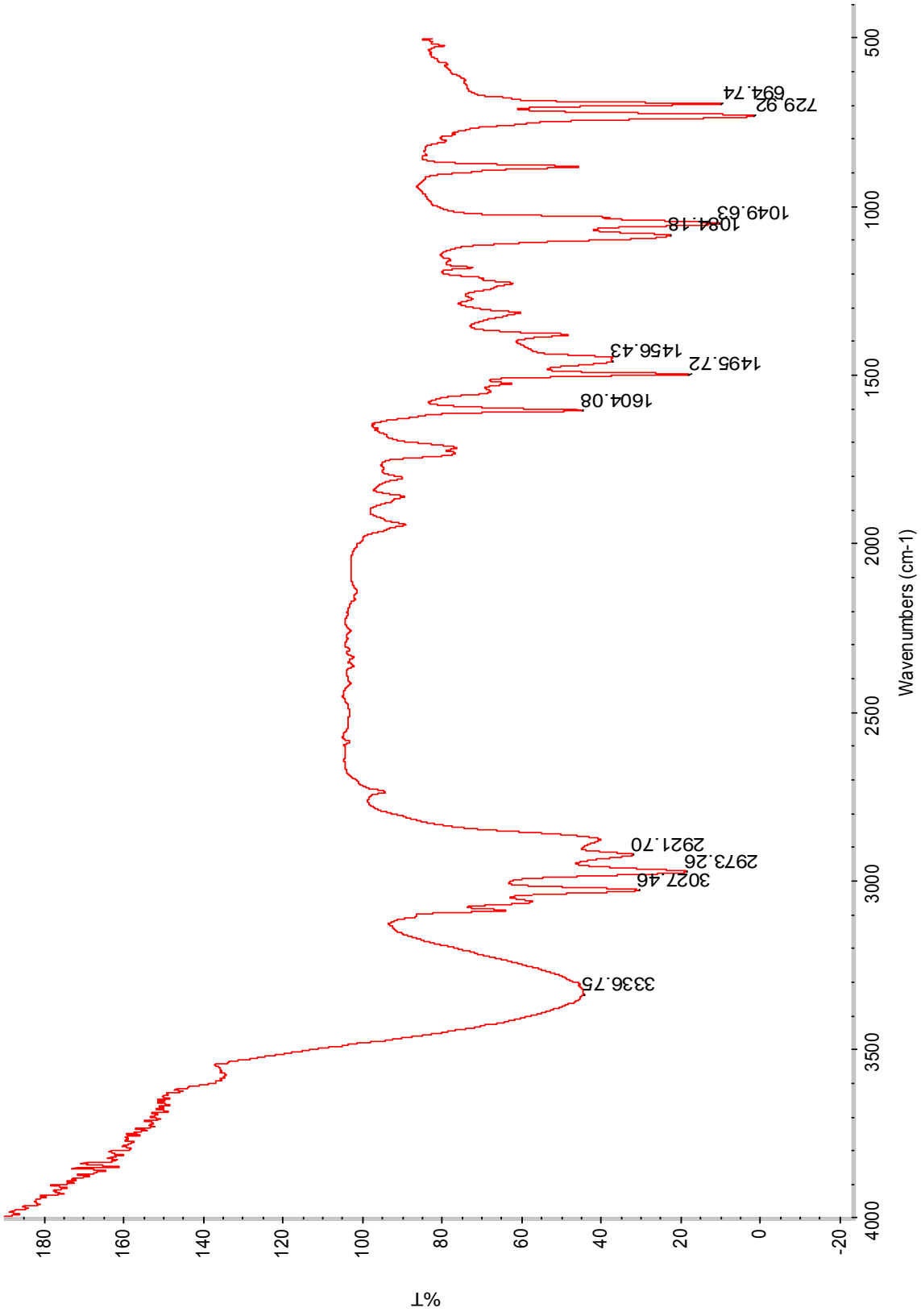

Figure 19: IR spectrum of ethyl phenyl carbamate (**10**).

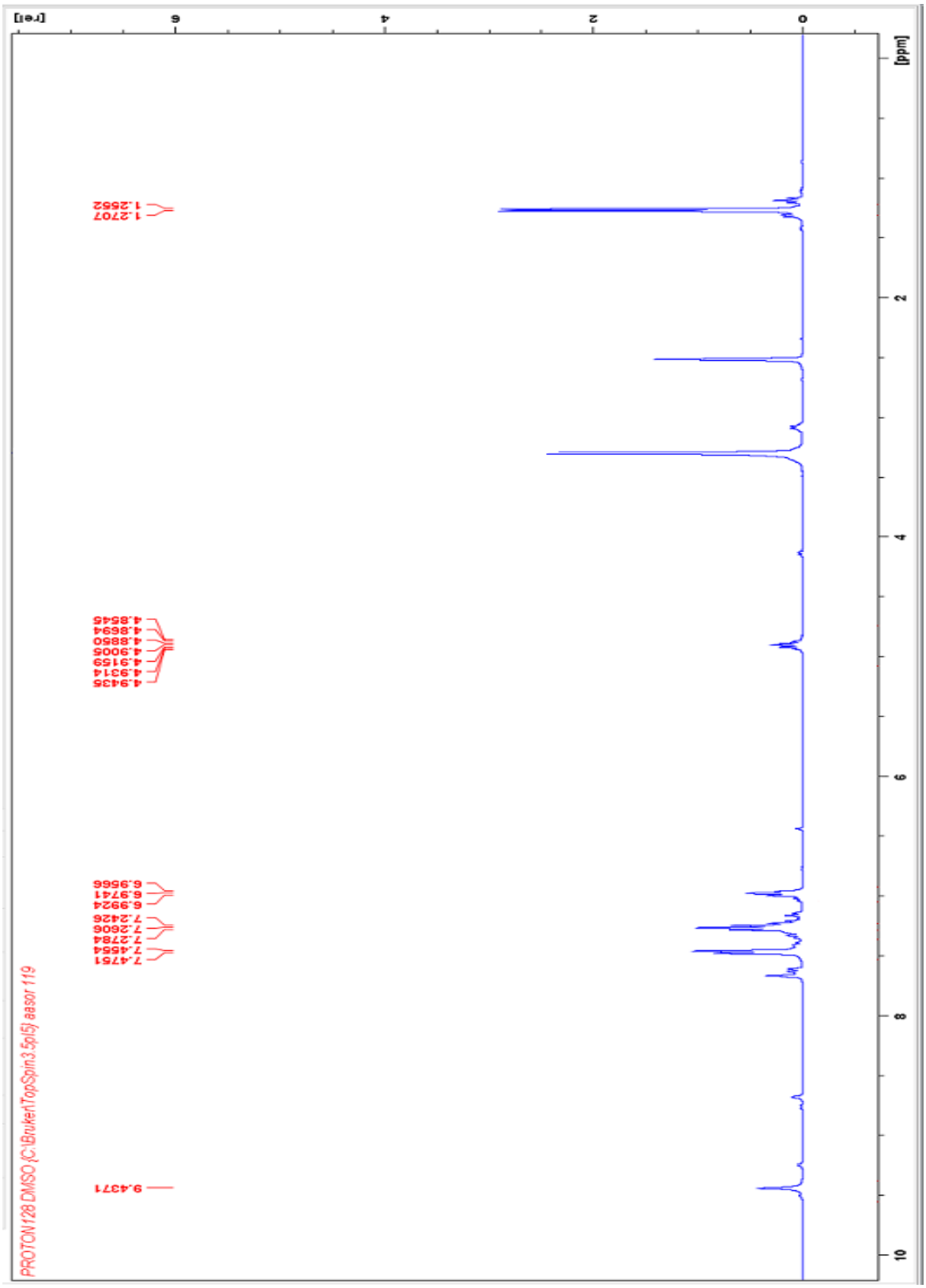

Figure 20: ^{1}H NMR of isopropyl phenyl carbamate (**12**).

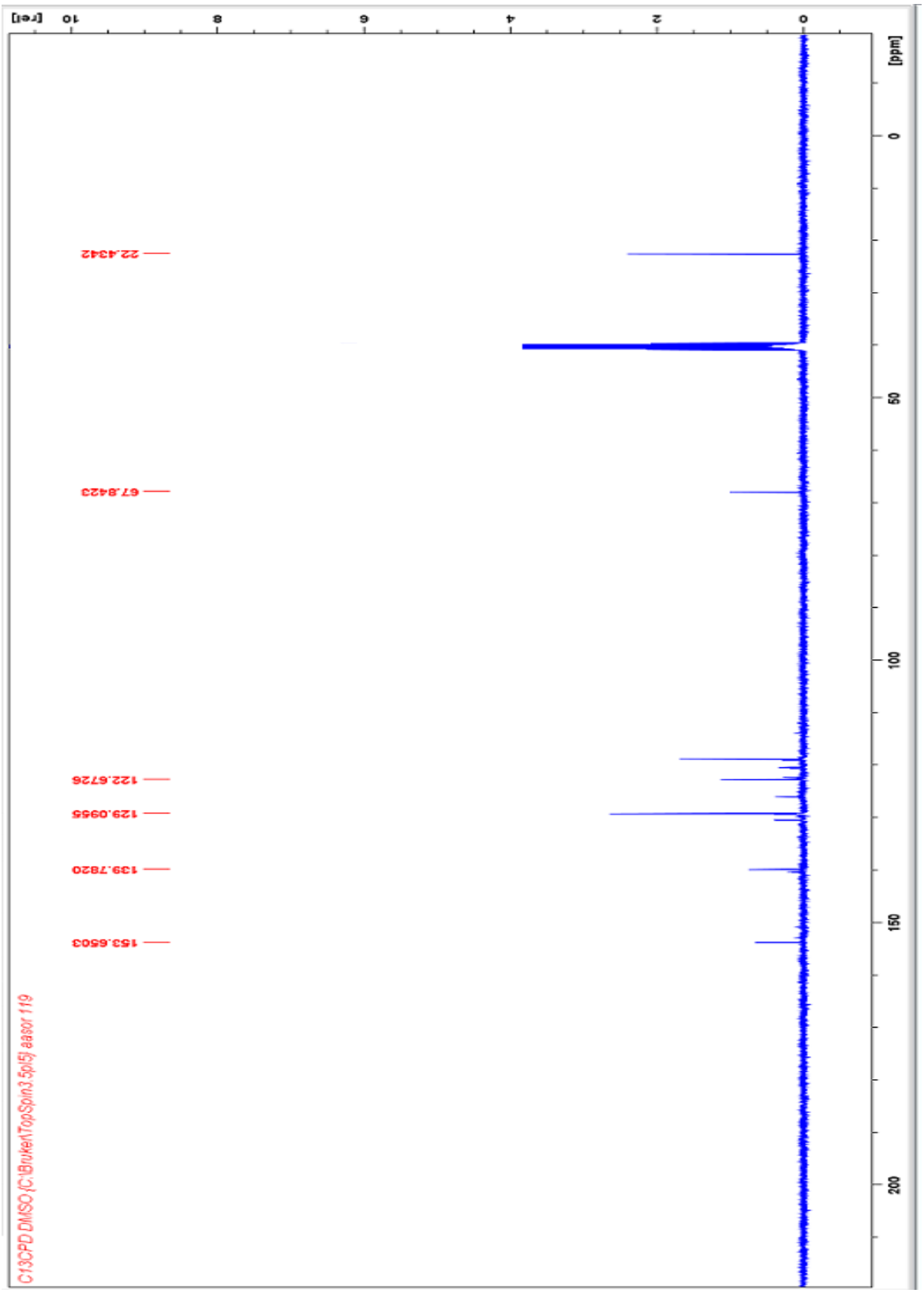

Figure 21: ^{13}C NMR of isopropyl phenyl carbamate (**12**).

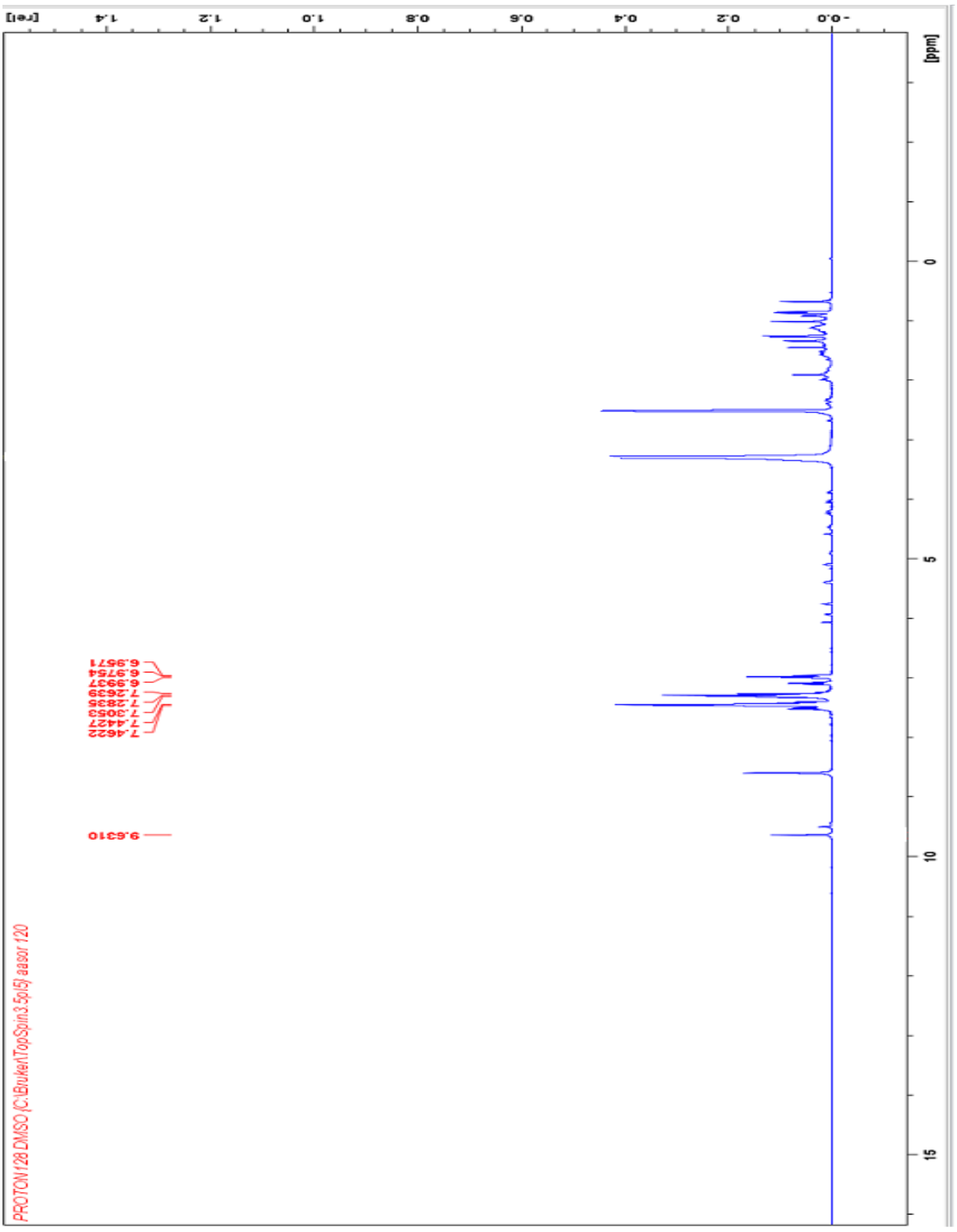

Figure 22: ^{1}H NMR of (8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl phenyl carbamate (**14**).

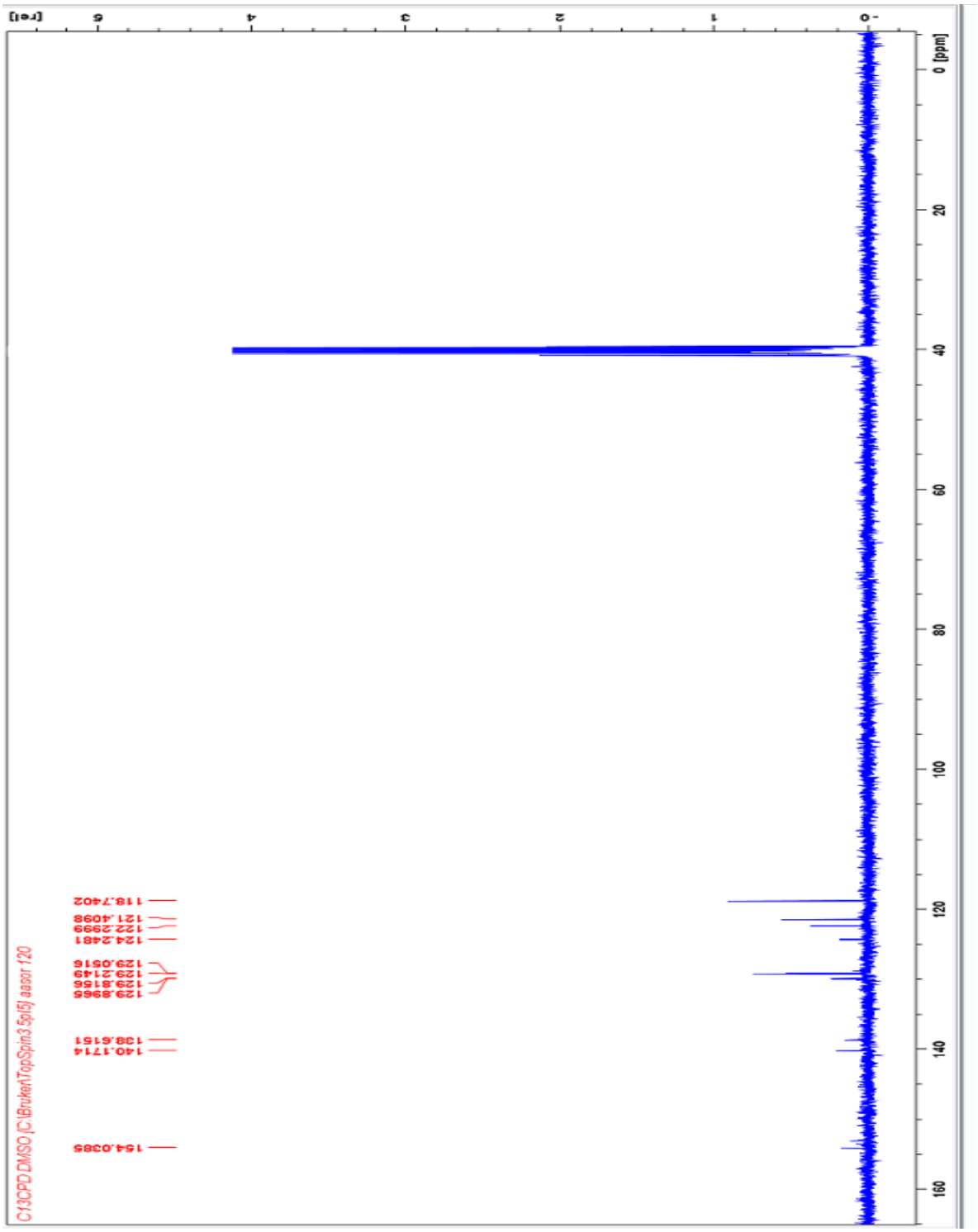

Figure 23: ^{13}C NMR of (8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl phenyl carbamate (**14**).

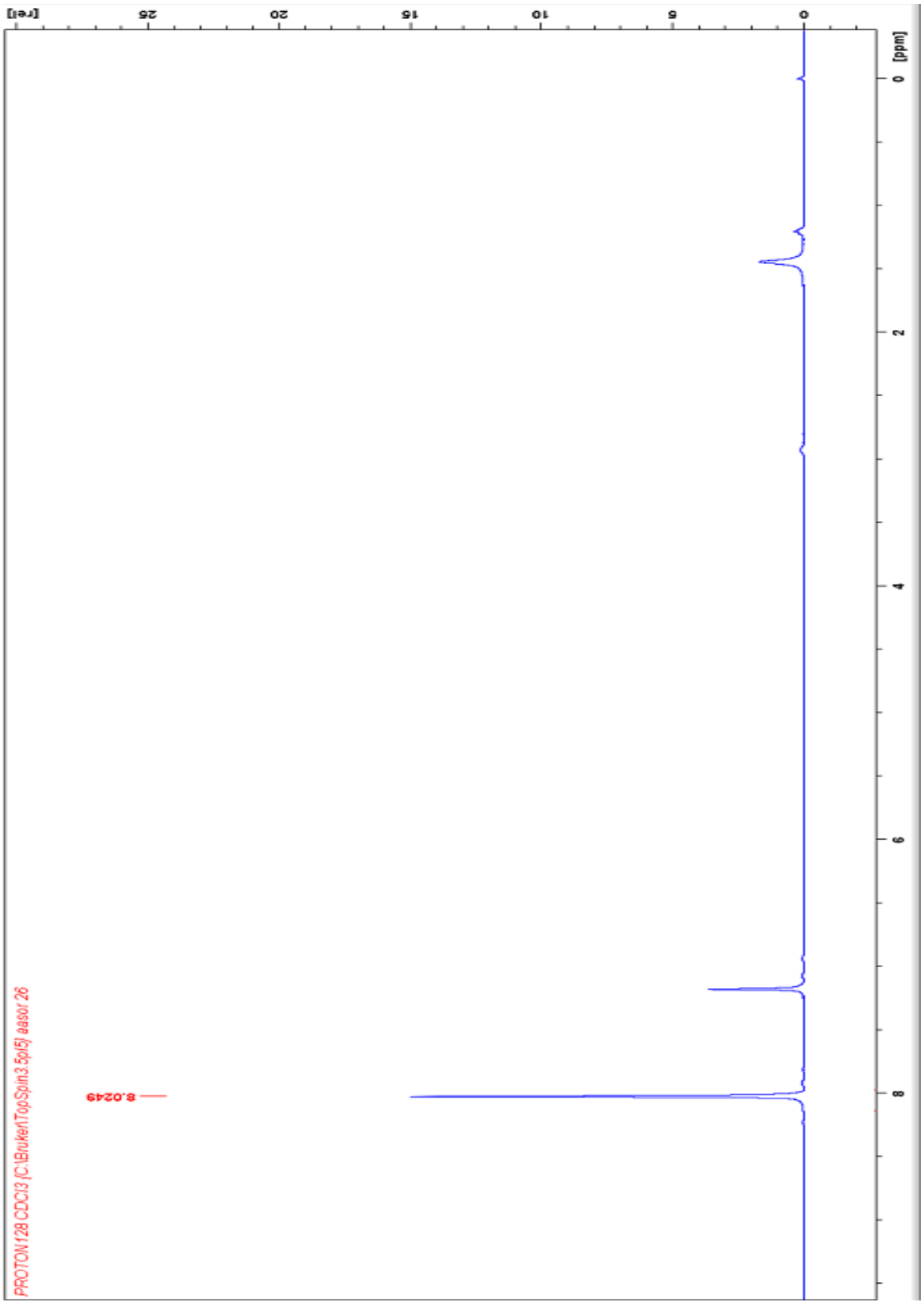

Figure 24: ^{1}H NMR of terephthaloyl diazide (**16**).

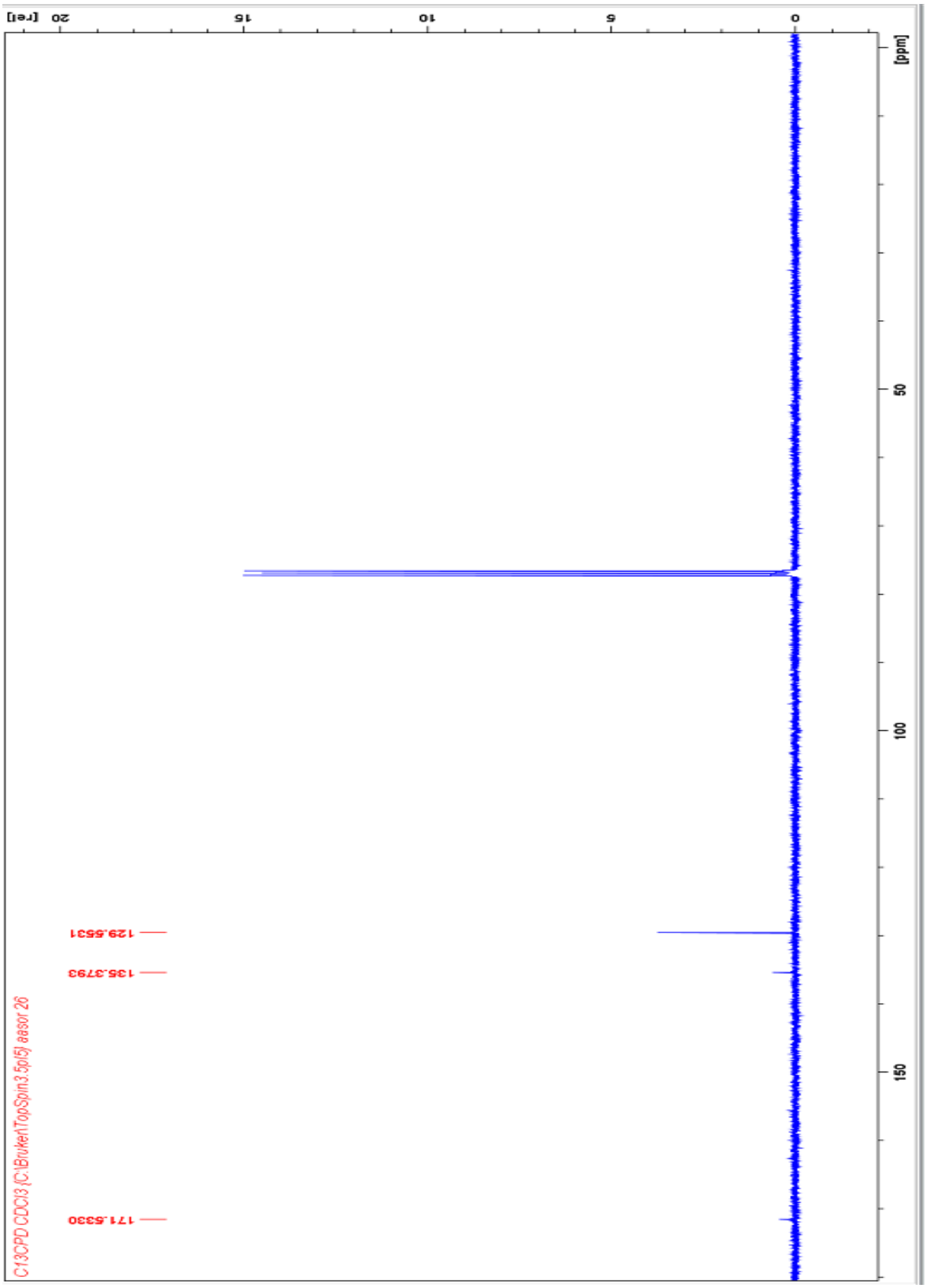

Figure 25: ^{13}C NMR of terephthaloyl diazide (**16**).

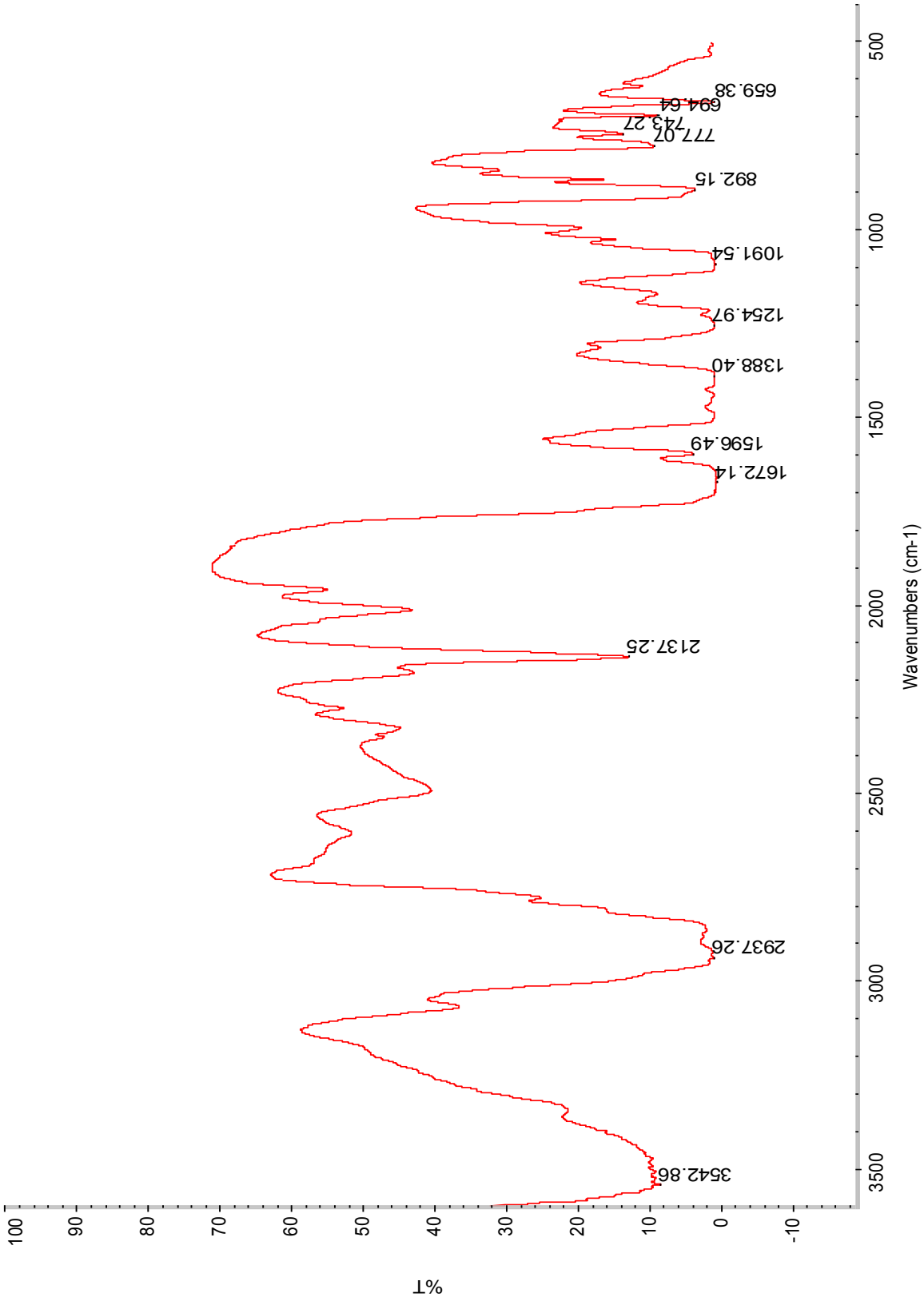

Figure 26: IR spectrum of terephthaloyl diazide (**16**).

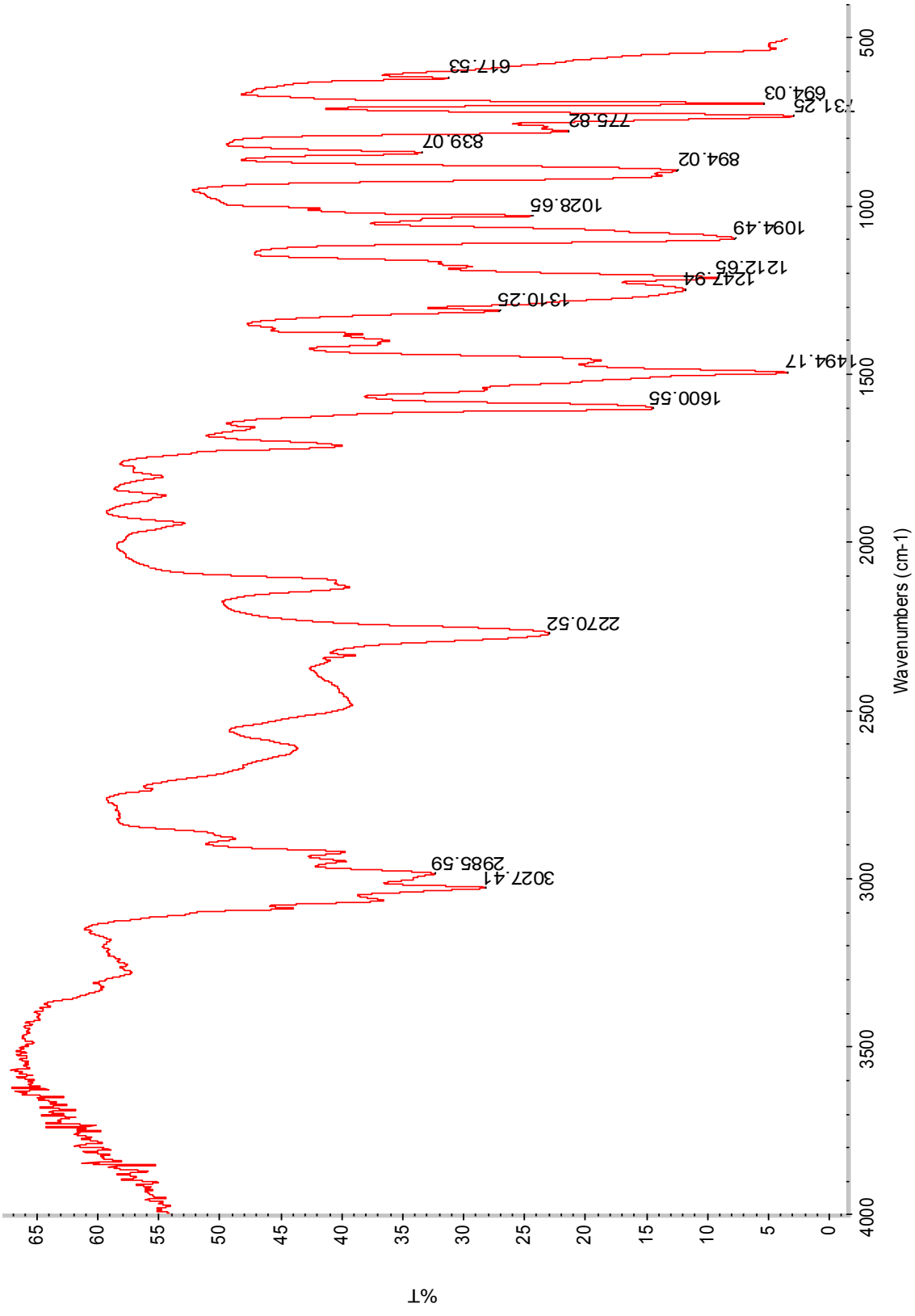

Figure 27: IR spectrum of 1,4-diisocyanatobenzene.

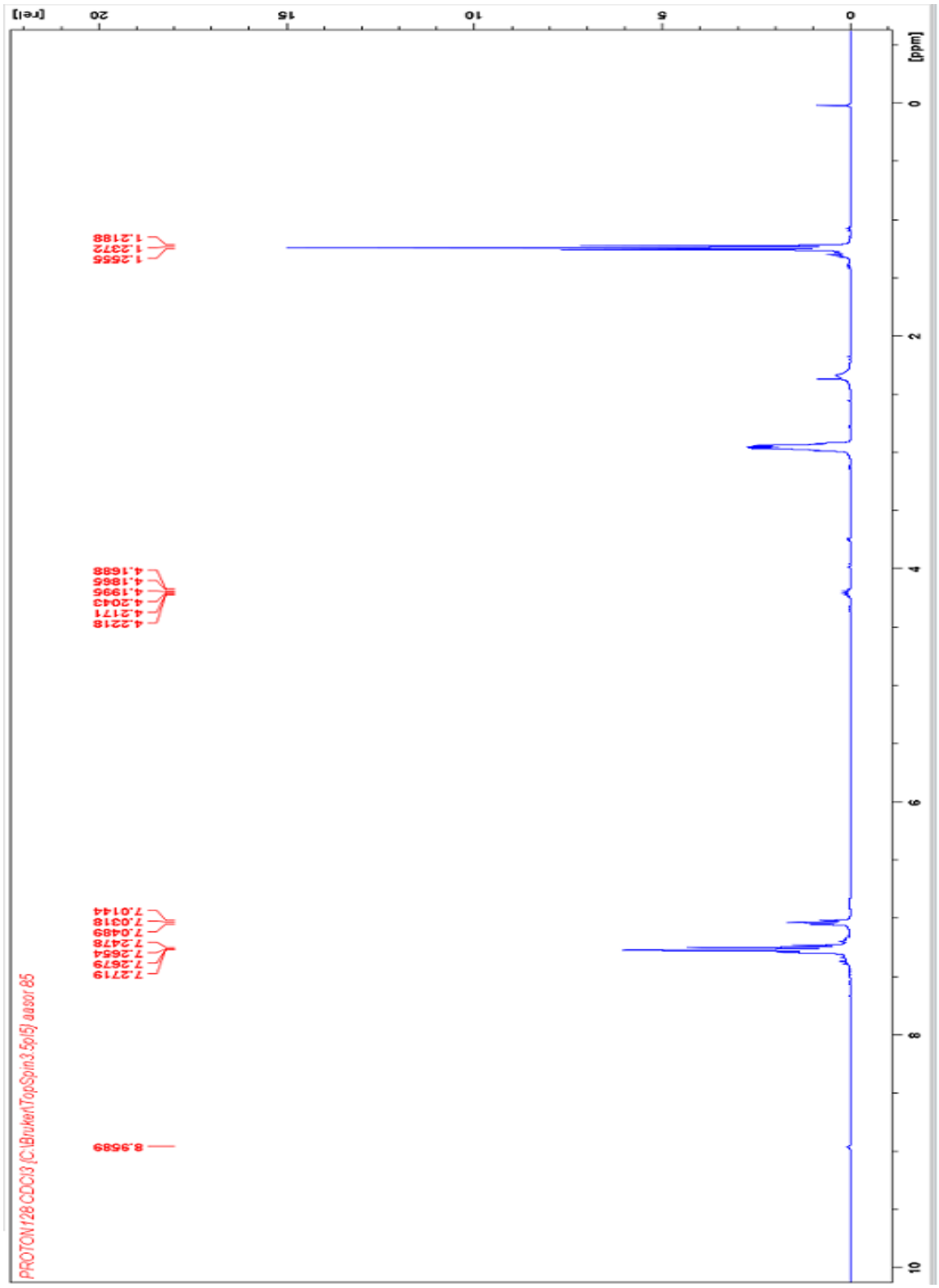

Figure 28: ^{1}H NMR of diethyl 1,4-phenylene dicarbamate (**17**).

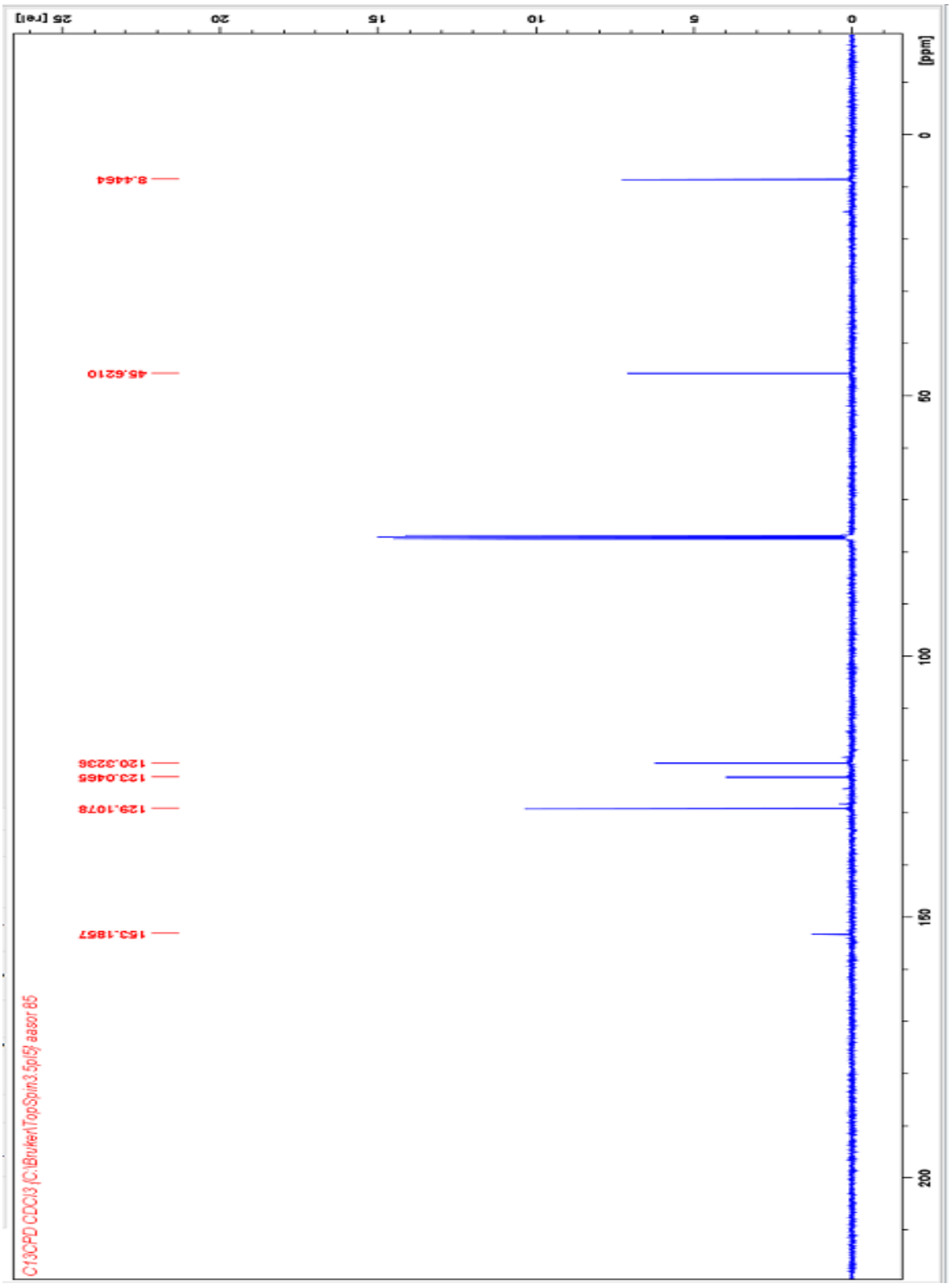

Figure 29: ^{13}C NMR of diethyl 1,4-phenylene dicarbamate (**17**).

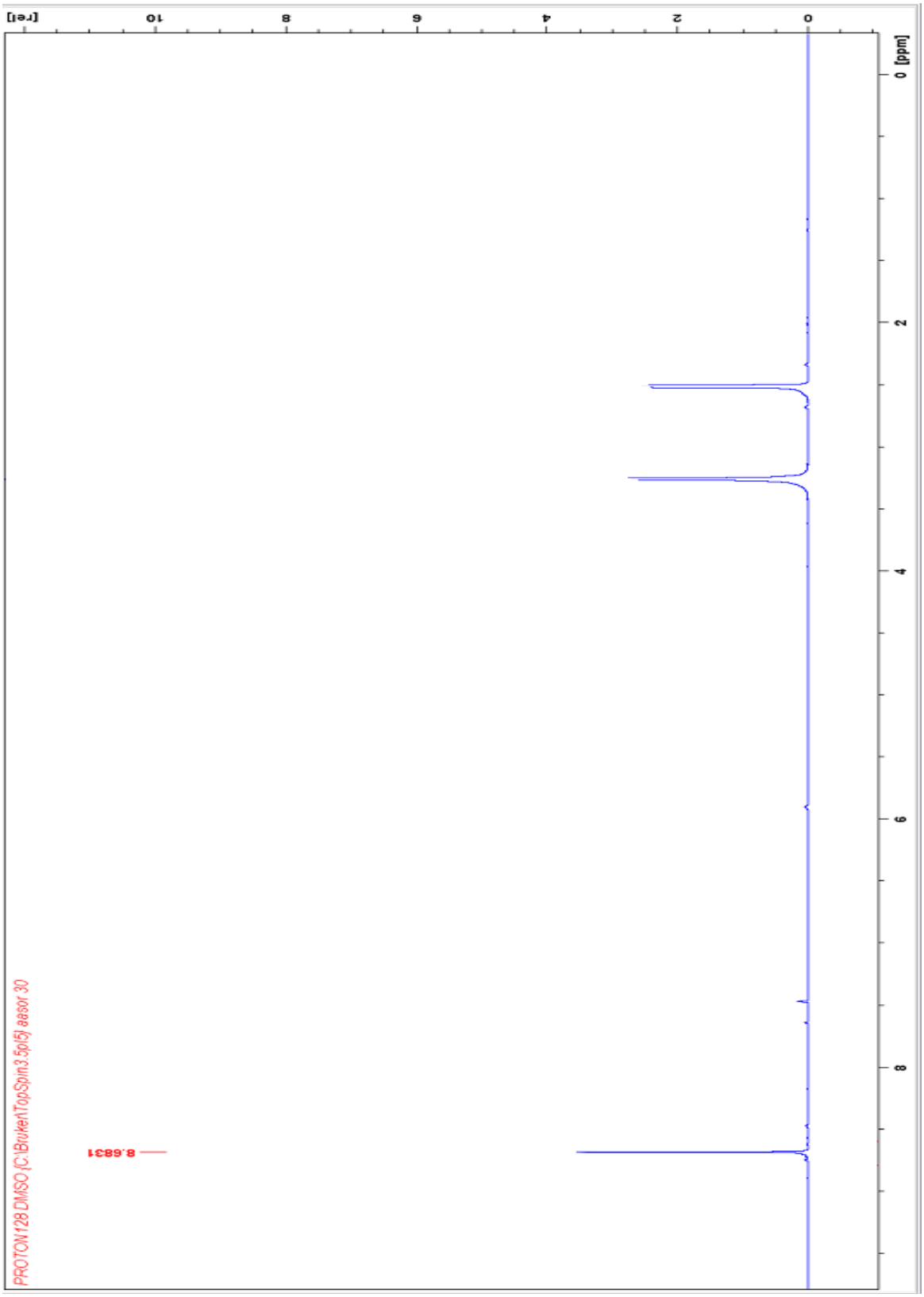

Figure 30: ^{1}H NMR of benzene 1,3,5 tricarbonyl azide (**19**).

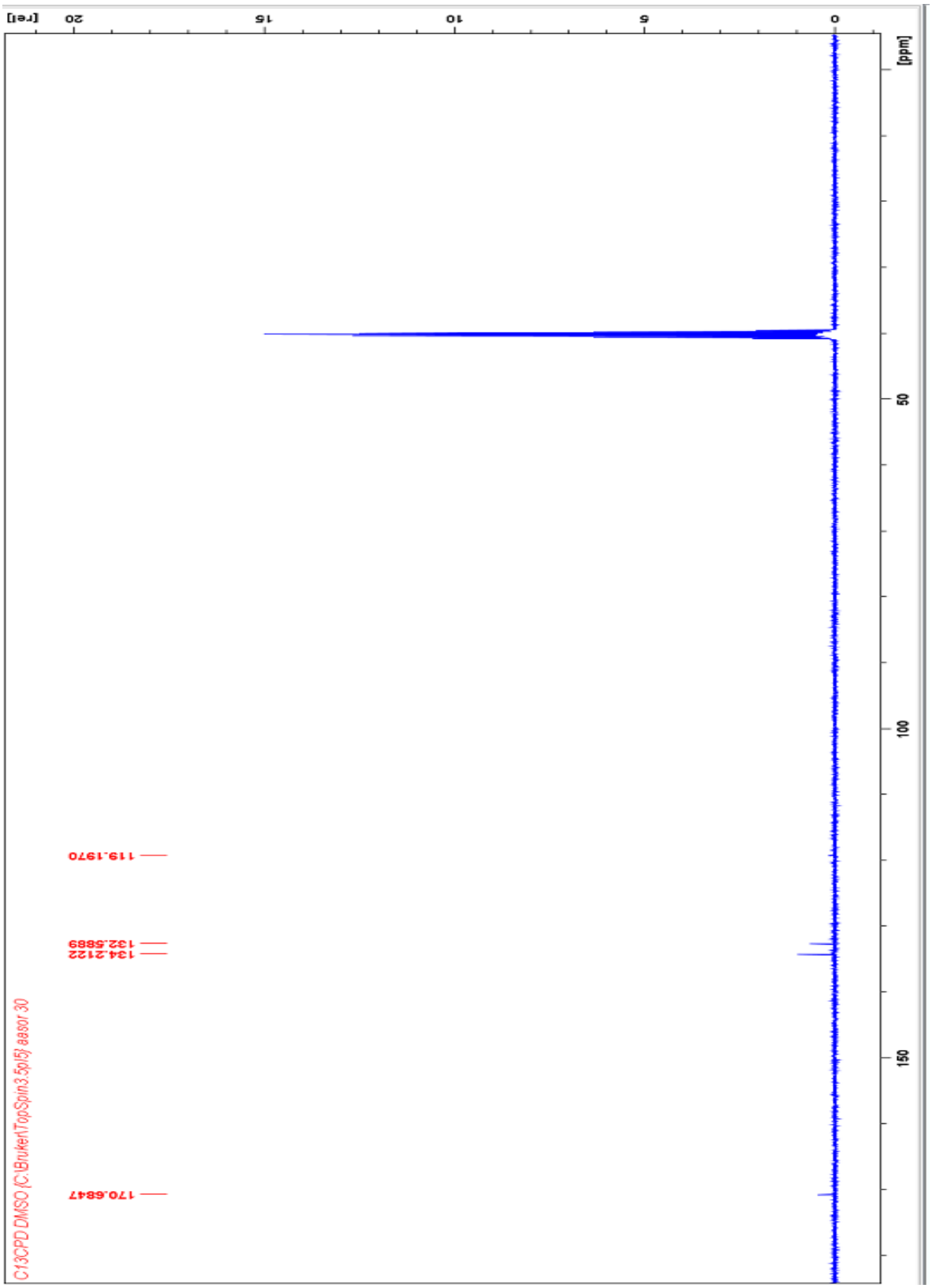

Figure 31: ^{13}C NMR of benzene 1,3,5 tricarbonyl azide (**19**).

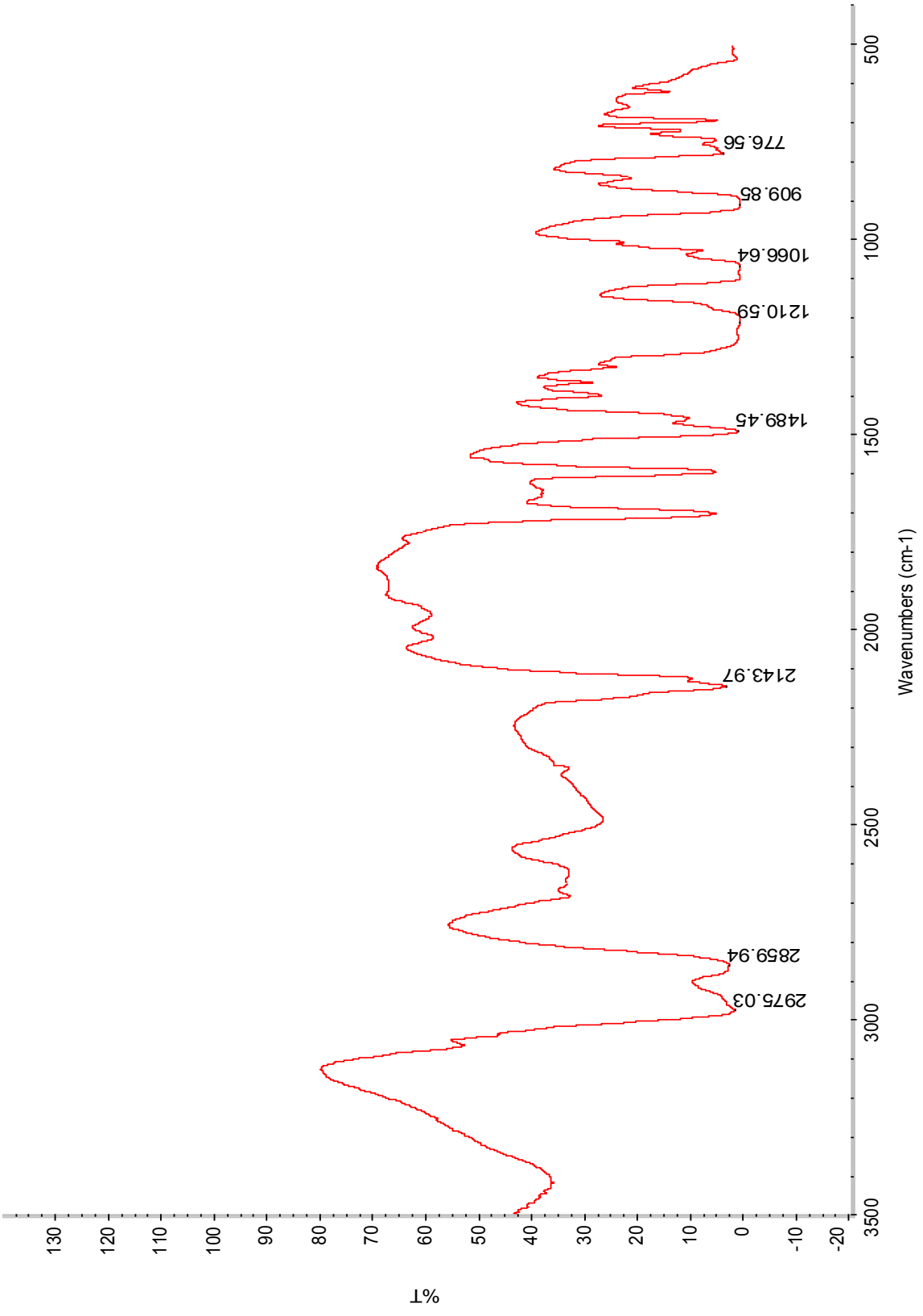

Figure 32: IR spectrum of benzene 1,3,5 tricarbonyl azide (**19**).

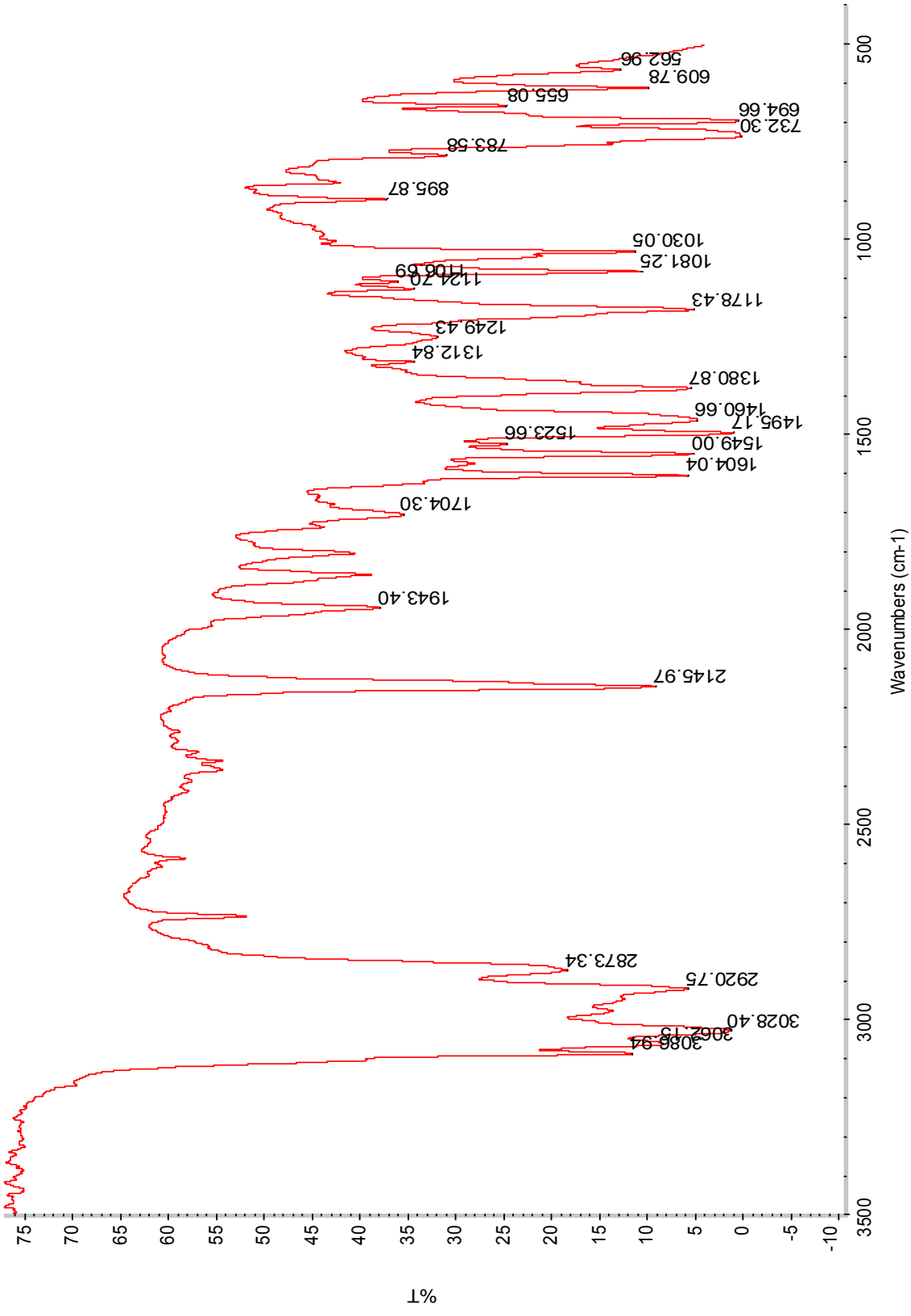

Figure 33: IR spectrum of benzoyl azide (**8**) using *o*-NBSA.

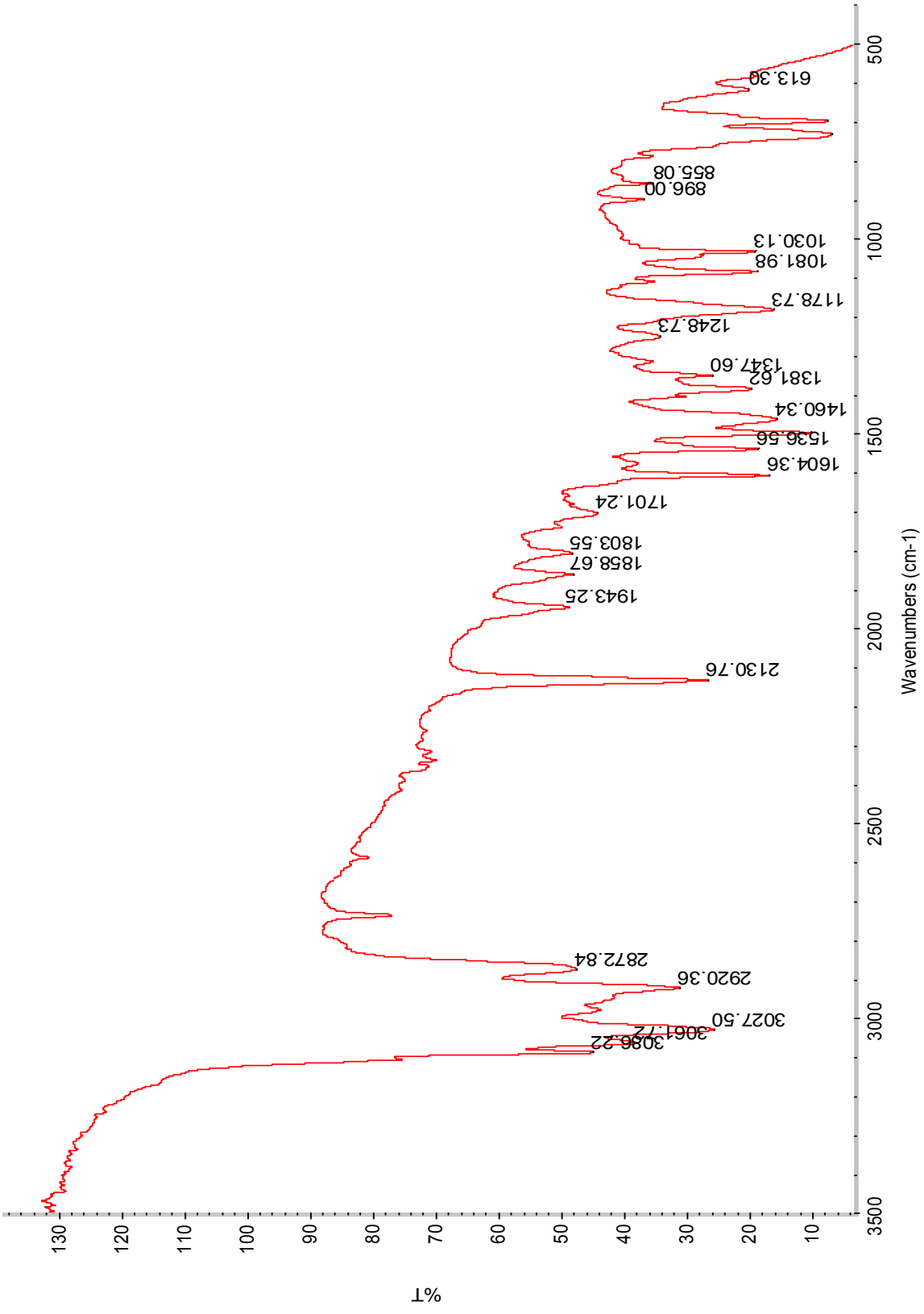

Figure 34: IR spectrum of benzoyl azide (**8**) using *p*-NBSA.