“One-pot” Synthesis of Carbamates *via* Curtius Rearrangement

by

Kwaku Kyei-Baffour

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Kwaku Kyei-Baffour

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Dr. Peter Norris, Thesis Advisor Date

Dr. John Jackson, Committee Member Date

Dr. Nina Stourman, Committee Member Date

Dr. Sal Sanders, Associate Dean of Graduate Studies Date

Thesis Abstract

In this thesis, acyl chlorides were successfully converted to their corresponding carbamates via Curtius rearrangement in a novel “one-pot” synthesis procedure that uses *p*-nitrobenzenesulfonyl azide as the azide nucleophile source. In the process alkyl esters were also synthesized as the associated by-product. The thesis also deals with the “one-pot” synthesis of acyl azides from acyl chlorides.

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INTRODUCTION

Organic azides are carbon-containing compounds with an azide group (N_3^-) attached to an alkyl, aryl or acyl group (Figure 1).

Figure 1: Resonance structures for a general organic azide.

Since their discovery in 1864 by Peter Grieβ,[1] these energy-rich and flexible intermediates have become one of the most important and versatile classes of compounds in synthetic chemistry. They have proven to be a very important bridge among the disciplines of chemistry, biology, medicine, and material science.

Organic azides can undergo a wide range of functional group inter-conversions.[2] Due to their ready conversion into amines and isocyanates, and their use in energetic polymers,[3] azides have received more attention in the pharmaceutical industry.[4] The easy polarization of the π-bond of the azide ion, N_3^-, results in a breakdown of the azide ion and leads to the release of molecular nitrogen and a nitrene.[3] They are considered powerful precursors for reactive species such as nitrenes and nitrenium ions as well as nitrogen-rich compounds such as aziridines, azirines, triazoles, triazolines, and triazenes.[3]

Industrial interest in organic azide compounds began with the use of azides for the synthesis of heterocycles such as triazoles and tetrazoles as well as with their use as blowing agents and as functional groups in pharmaceuticals. Thus, for example, azidonucleosides attracted international interest in the treatment of AIDS.[5]

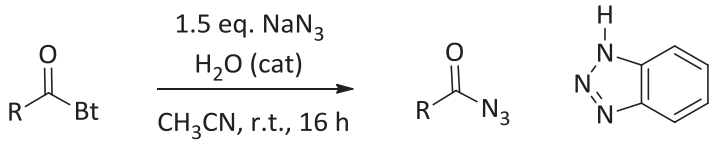
Like hydrogen azide most other azides are also explosive substances that decompose with the release of nitrogen through the slightest input of external energy, for example,

pressure, impact, or heat. The heavy-metal azides are used, for example, in explosive technology, in which they serve as detonators. Due to the explosive nature of azides and their high sensitivity to heat, sodium azide is used in automobile airbags. The organic azides, particularly methyl azide, often decompose explosively.[1]

The major route to organic azides that most researchers use involves sodium azide (NaN_3) and substrates bearing leaving groups such as sulfonates and halides. There has been development of numerous synthetic pathways over the past years for the synthesis of organic azides, however, most of the routes are considered unsafe and can be expensive and time-consuming. Although, there are a lot of indirect methods in the literature, few direct methods are known.[4] The main focus, for the purpose of this thesis, will be acyl azides and their application in carbamate synthesis via the Curtius rearrangement.

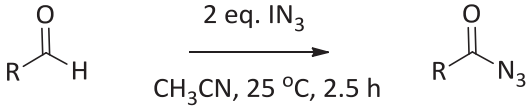
Acyl azides have widespread utility in organic synthesis.[6] They are extensively used in the synthesis of amides, nitriles, in cycloaddition reactions, and also in heterocyclic chemistry.[6,7] The well-known Curtius rearrangement of acyl azides under thermal condition leads to isocyanates, which in turn undergo easy conversion into amines, carbodiimides, ureas, urethanes, thiourethanes, and other derivatives.[8] Several protocols have been reported for the synthesis of acyl azides in the literature. They are generally prepared by the reaction of sodium azide with acid derivatives such as acid chlorides, mixed anhydrides which in turn are prepared using acid activators like $SOCl_2$/DMF, [9] cyanuric chloride/*N*-methylmorpholine,[10] triphosgene/triethylamine,[11] ethyl chloroformate/*N*-methylmorpholine.[12,13] Acyl azides can also be prepared from hydrazides by nitrosation with sodium nitrite in acidic media.[14-16] Hydrazide nitrosation to give acyl azides is applied for a large-scale synthesis.[17]

A. R. Katritzsky et al. recently reported a simple and safe synthesis of acyl azides from the corresponding *N*-acyl benzotriazoles and sodium azide in a two-step protocol[18] (**Equation 1**). This procedure avoids the use of acid activators and NO^+ equivalents typically employed to synthesize these compounds from acid chlorides and hydrazides, respectively.



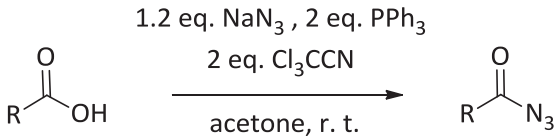
Equation 1: General synthesis of acyl azides from the corresponding *N*-acyl benzotriazoles.

Aliphatic and aromatic aldehydes can be converted to acyl azides by treatment with iodine azide, as azide source, (**Equation 2**) which is formed *in situ* by mixing ICl and NaN_3.[19] Even though yields obtained from this process are good, extreme caution is always required since IN_3 is potentially explosive and definitely so in the solid form. The reagent should be generated in solution and destroyed with thiosulfate wash before work up. However, when solid NaN_3 and ICl are mixed an explosion can occur.



Equation 2: General synthesis acyl azides from aliphatic and aromatic aldehydes.

Various carboxylic acids can also be converted into acyl azides in excellent yields in the presence of trichloroacetonitrile, triphenylphosphine, and sodium azide at room temperature (**Equation 3**). The reaction allows the preparation of dipeptides without deprotection or rearrangement during the reaction.[20] However, this procedure is not material efficient.



Equation 3: Synthesis of acyl azides from carboxylic acids.

Direct conversion of carboxylic acids to acyl azides is accomplished using diphenylphosphoryl azide (DPPA) which is expensive.[21,22]

Although these methods are available for the preparation of acyl azides, there are still drawbacks such as long reaction time, by-product formation, hazardous and expensive reagents, multi-step protocol, and tedious reaction conditions. Therefore, additional methods for acyl azide formation are still useful. This led to the development of our procedure.

The first part of this research is to find a novel way to synthesize acyl azides, from which the carbamates will be synthesized. The acyl azides will be synthesized from acyl chlorides using arylsulfonyl azides. *p*-Nitrobenzenesulfonyl azide (*p*-NBSA) (**Figure 2**) will be the arylsulfonyl azide source. *p*-NBSA is the arylsulfonyl azide of choice because of its relatively high solubility in acetonitrile.

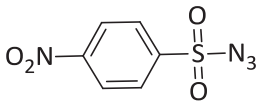
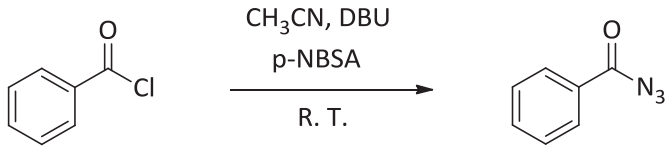


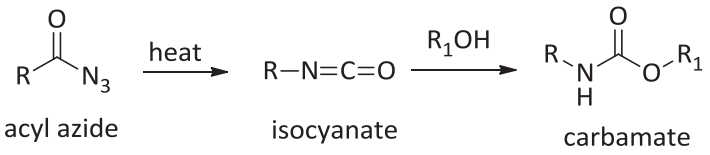
Figure 2: Structure of p-nitrobenzenesulfonyl azide (*p*-NBSA).

In the development of our method, CH_3CN was chosen as the solvent because it is inexpensive, readily available and because smaller amounts are required to dissolve *p*-NBSA when 1, 8-diazobicyclo [5.4.0] undec-7-ene (DBU) is used as the base.



Equation 4: Proposed method for the synthesis of acyl azides from acyl chlorides using p-NBSA.

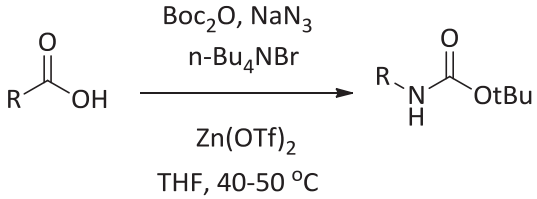
Upon pyrolysis of the acyl azides, isocyanates are formed (**Equation 5**). Isocyanates can then be trapped by a variety of nucleophiles, such as alcohols, providing a convenient method for the synthesis of amine derivatives, such as carbamates. The rearrangement of acyl azides into isocyanates is well known as the Curtius rearrangement. This important reaction is the best way to convert acyl azides to carbamates and it has been used to synthesize many complex natural products.



Equation 5: Curtius rearrangement of acyl azide to carbamates.

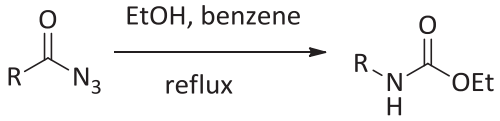
Organic carbamates represent an important class of compounds showing various interesting properties. They find wide utility in areas such as pharmaceuticals,[23] agrochemicals,[24] as intermediates in organic synthesis,[25] for the protection of amino groups in peptide chemistry,[26] and as linkers in combinatorial chemistry.[27] Organic carbamates have been extensively used as intermediates for the synthesis of structurally diverse synthetic intermediates/molecules of biological importance.[28] In recent years, much interest has been developed among chemists to develop an efficient and safe methodology for carbamate synthesis through the Curtius rearrangement by trapping of the isocyanate intermediate with an alcohol.

Lebel and Leogane have reported an efficient one-pot protocol for the preparation of *tert*-butyl carbamates from the corresponding acids (**Equation 6**).[29] The reaction of carboxylic acids with di-*tert*-butyl dicarbonate and sodium azide allowed the formation of the acyl azides, which undergo a Curtius rearrangement in the presence of tetrabutylammonium bromide and zinc (II) triflate to afford the corresponding carbamates through trapping of the isocyanate intermediate. They have extended the same protocol to the direct synthesis of carbamates of aromatic amines using aromatic acids.



Equation 6: "One-pot" protocol for the preparation of *tert*-butyl carbamates (Lebel and Leogane).

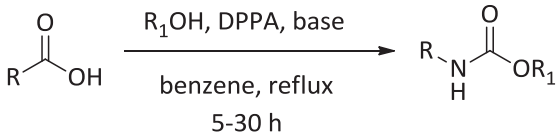
Dussault and Xu have also reported a direct conversion of various acid azides into their corresponding carbamates through a Curtius rearrangement using ethanol (**Equation 7**).[30] A similar kind of approach was adopted by Saigo and co-workers for the synthesis of fullerene carbamates through the reaction of the corresponding fullerene acid azide with an alcohol.[31]



Equation 7: Conversion of acyl azides into carbamates (Dussault and Xu).

Iklegami and co-workers also reported a synthesis of carbamates of various sugar and other functionalities using the corresponding acids. *In situ* conversion of acids to the corresponding azides was achieved using diphenyl phosphoryl azide (DPPA) as azide source,

followed by the addition of an alcohol to afford the corresponding carbamates (**Equation 8**).[32] They have further explored this methodology for the synthesis of carbamates linked glycoconjugates using various kinds of sugar acids and diphenylphosphorazidate (DPPA).[33] The use of this reagent is potentially complicated by the high temperatures required to achieve conversion to the desired carbamate, which could compromise the stability of sensitive functionalities. Also, toxicity considerations limit its usage.

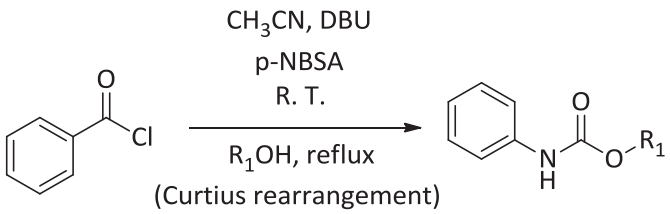


Equation 8: Synthesis of carbamates of various sugar and other functionalities using their corresponding acids (Iklegami and co-workers).

There has been increasing interest in the synthesis of carbamates and most procedures as seen in the literature are multistep. These traditional methods result in the formation of intermediates which need work-up and isolation. This makes them expensive, tedious and time-consuming. Some of the procedures are also dangerous due to the use of compounds that are very prone to explosion.

From the above review, "one-pot" synthesis of carbamates as proven by Lebel and Leogane, and Iklegami and co-workers is possible. Although their protocols avoided the tedious work of intermediate isolation, they were material-consuming, expensive and in some cases dangerous.

The main goal of this research is to develop an efficient, safe, and inexpensive "one-pot" process for the synthesis of carbamates from acyl azides, using arylsulfonyl azides as the azide source, which is also rapid as well as material efficient (**Equation 9**).



Equation 9: Proposed method for the "one-pot" synthesis of carbamates via Curtius rearrangement.

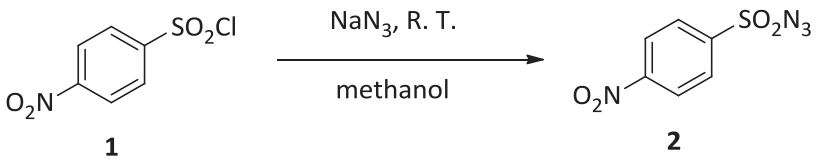
STATEMENT OF PROBLEM

The synthesis of organic carbamates has drawn the attention of numerous researchers due to their wide biological significance. The most common procedures employed for their synthesis are the indirect methods. These methods involve separate procedures which can be tedious, time-consuming, and expensive. The “one-pot” procedures currently in use for the synthesis of carbamates are also expensive, inefficient, time-consuming, and potentially dangerous.

This research is geared towards developing an efficient, safe, and inexpensive “one-pot” protocol for carbamate synthesis from acyl azides via Curtius rearrangement. In the process of doing so, a useful, safe, and inexpensive “one-pot” procedure for the synthesis of acyl azides will also be developed.

RESULTS AND DISCUSSION

We began the research by synthesizing *para*-nitrobenzenesulfonyl azide, *p*-NBSA (**2, Equation 10**). This was easily synthesized from *para*-nitrobenzenesulfonyl chloride (**1**) and NaN_3 using methanol as solvent. The reaction was left to stir overnight at room temperatature and TLC of the reaction mixture showed a new spot (R_f = 0.29) which appeared yellow upon heating when *p*-anisaldehyde was used as the TLC stain. Most azides in general produce yellow color upon heating when stained with *p*-anisaldehyde. The IR spectrum of the recrystallized product showed a signal at 2143 cm^{-1} which corresponds to an azide functional group. ^{1}H NMR and ^{13}C NMR spectra of the product showed that *p*-NBSA had been successfully synthesized.



1 **2**

Equation 10: Conversion of *para*-nitrobenzenesulfonyl chloride (**1**) to *para*-nitrobenzenesulfonyl azide (**2**).

SYNTHESIS OF ACYL AZIDES

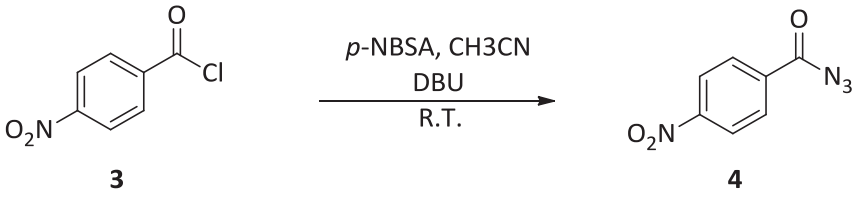
The first part of the research involved the synthesis of acyl azides from acyl chlorides using *p*-NBSA as the azide source. In doing so, the right solvent had to be determined. In choosing the solvent, consideration was given to the ability to readily dissolve *p*-NBSA, ready availability, low boiling point, and the ability to not interfere in the reaction process by enabling the formation of many by- products.

Polar aprotic solvents (tetrahydrofuran (THF), dimethylformamide (DMF), and acetonitrile (CH_3CN)) were considered. Although all the solvents relatively dissolved p-NBSA

readily, upon addition of 1, 8-diazobicyclo [5.4.0] undec-7-ene (DBU), the base of choice, stirring became very difficult and extra solvent was required in the case of THF. Also the anionic azide took extra time to form as compared to DMF and CH_3CN. Although DMF took less time to help in the formation of the anionic azide, its high boiling point (153 ^oC) makes its evaporation very difficult. CH_3CN was then settled upon as the solvent of choice because of its low boiling point as compared to DMF, its ability to help form the anionic azide faster and in lower amounts as compared to THF, its ready availability, and also because its triple bond does not react with azides.

The first acyl chloride that was used for this research was 4-nitrobenzoyl chloride (**3**, **Equation 11**). 4-Nitrobenzoyl azide (**4**, **Equation 11**) was made by first reacting *p*-NBSA dissolved in CH_3CN with **3**, using 1, 8-diazobicyclo [5.4.0] undec-7-ene (DBU), as the base. The reaction was left overnight till TLC confirmed the disappearance of the *p*-NBSA spot. The IR spectrum indicated a shift of the covalently bonded azide functional group at 2143 cm^{-1} to the anionic azide functional group form at 2019 cm^{-1}. Acid chloride **3** dissolved in CH_3CN was then added, and the reaction mixture was left to sit at room temperature overnight. TLC showed the appearance of a new spot (R_f = 0.79) of yellow color upon heating when *p*-anisaldehyde was used as the TLC stain. The IR spectrum of the mixture showed the reappearance of the signal at 2143 cm^{-1} indicating a covalently bonded azide functional group. This indicated that the acyl azide product might have been synthesized. Aqueous work-up on the product gave a dark yellow syrupy solid as the crude product. Although ^1H NMR and ^{13}C NMR of the crude product indicated the presence of the acyl azide product, they also showed it was impure. Subsequent purification by silica gel flash column chromatography (5:1 hexane: ethyl acetate) afforded **4**. ^{13}C NMR analysis of the white solid (product **4**, isolated in 52 % yield) proved the presence of the azide in **4** due to the movement of the carbonyl group signal in **3** further downfield from 167.00

ppm to 170.84 ppm which corresponds to that of literature.[34] The IR spectrum of the purified product which showed absorption at 2138 cm^{-1}, is in good agreement with literature.[34] Finally, the melting point value of 64-65 ^{o}C also corresponds to that of literature.[34]

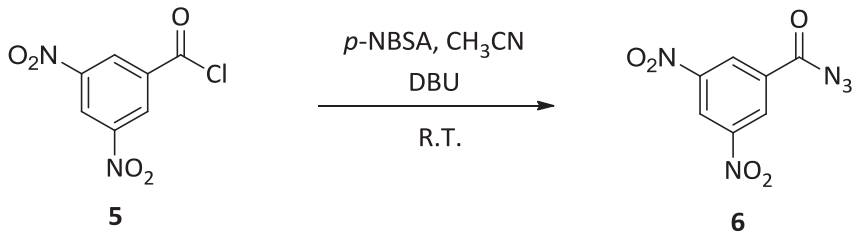


3 **4**

Equation 11: Conversion of 4-nitrobenzoyl chloride (**3**) to 4-nitrobenzoyl azide (**4**).

The next stage was to adapt the methodology for the synthesis of other acyl azides from their corresponding acyl chlorides.

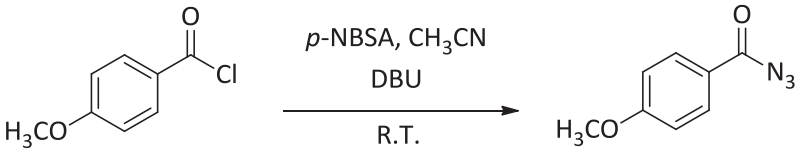
The next acyl chloride used was 3, 5-dinitrobenzoyl chloride (**5**). Upon the confirmation of the formation of the anionic azide which showed IR peak at 2019 cm^{-1}, **5** was then added. The reaction mixture was allowed to sit at room temperature overnight. TLC showed the appearance of a new yellow spot (R_f = 0.75) upon heating when *p*-anisaldehyde was used as the TLC stain. The IR spectrum of the mixture showed the reappearance of the signal at 2153 cm^{-1} indicating a covalently bonded azide functional group. Aqueous work-up followed by purification by flash column chromatography (5:1 hexane: ethyl acetate) afforded **6**. ^{13}C NMR analysis of the pale yellow solid (product **6**, isolated in 66.2 % yield) proved the presence of the azide in **6** due to the movement of the carbonyl group ^{13}C NMR signal in **5** further downfield from 165.11 ppm to 168.71 ppm which corresponds to that of literature. The IR spectrum of the purified product showed absorption at 2153 cm^{-1} which is in good agreement with the literature. Finally the melting point value was found to be 96-99 ^{o}C.



5 **6**

Equation 12: Conversion of 3,5-dinitrobenzoyl chloride (**5**) to 3,5-dinitrobenzoyl azide (**6**).

4-methoxybenzoyl azide (**7**) was also synthesized from 4-methoxybenzoyl chloride (**6**). Upon the confirmation of the formation of the anionic azide which showed IR signal at 2019 cm^{-1}, **6** was added and allowed to sit at room temperature overnight. TLC showed the appearance of a new yellow spot (R_f = 0.69) upon heating when *p*-anisaldehyde was used as the TLC stain. The IR spectrum of the mixture showed the reappearance of the signal at 2136 cm^{-1} indicating a covalently bonded azide functional group. Aqueous work-up on the product followed by purification by flash column chromatography (3:1 hexane: ethyl acetate) afforded **7**. ^{13}C NMR analysis of the white solid (product **7**, isolated in 60 % yield) proved the presence of the azide in **7** due to the movement of the carbonyl group signal in **5** further downfield field from 166.97 ppm to 168.71 ppm which corresponds to that of literature.[34] The IR spectrum of the purified product showed absorption at 2136 cm^{-1} is in good agreement with literature.[34] Finally, the melting point value of 68-70 ^{o}C also corresponds to that of literature.[34]

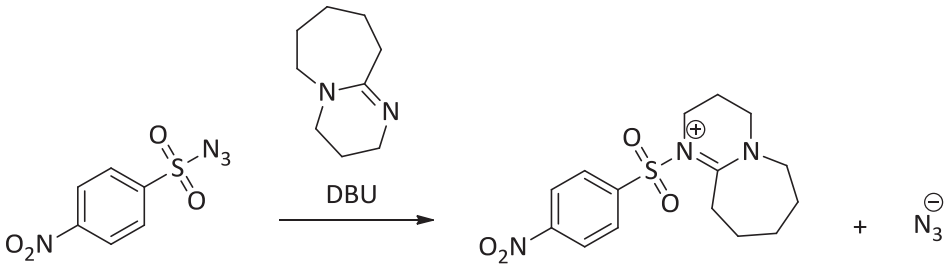


7 **8**

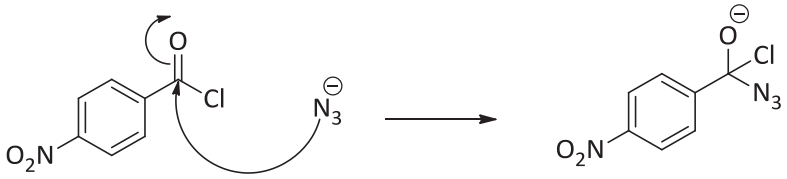
Equation 13: Conversion of 4-methoxybenzoyl chloride (**7**) to 4-methoxybenzoyl azide (**8**).

PROPOSED MECHANISM FOR ACYL AZIDE FORMATION

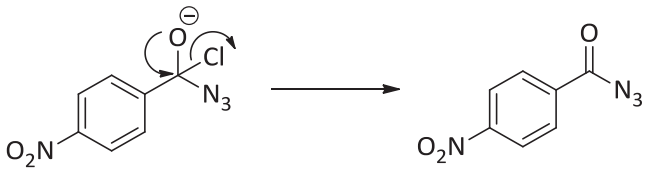
1. Generation of the azide anion.



2. Nucleophilic attack on carbonyl carbon by the azide nucleophile.



3. Removal of the chlorine leaving group to form the acyl azide product.



Scheme 1: Proposed mechanism for acyl azide formation.

"ONE-POT" SYNTHESIS OF THE CARBAMATES

The main essence of the synthesis of the acyl azides was to show the presence of the acyl azides before proceeding to the "one-pot" synthesis of the carbamates from acyl chlorides via Curtius rearrangement.

Following the synthesis of the acyl azides, various alcohol nucleophiles were used to successfully effect Curtius rearrangement to obtain the corresponding carbamates.

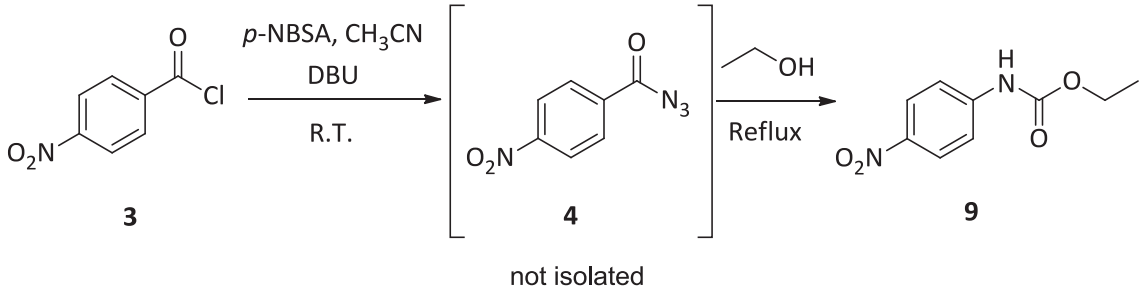
Conversion of 4-nitrobenzoyl chloride to ethyl (4-nitrophenyl) carbamate

The reaction process was done as that of the synthesis of the acyl azide. Upon the addition of the 4-nitrobenzoyl chloride the reaction was allowed to sit overnight and monitored for completion using TLC (hexane: ethyl acetate 1:1). Upon confirmation of the presence of **4**, ethanol was added and a reflux condenser was attached. The reaction mixture was heated to 75-78 ^{o}C. The progress of the reaction was monitored by TLC and IR. IR was used to check for the disappearance of the covalently bonded azide peak at 2138 cm $^{-1}$ which will occur as a result of a successful Curtius rearrangement. This happened on the third day of reflux. However, TLC confirmed an impure crude product with two spots of R_f 0.56 and 0.47 respectively. Aqueous work-up on the product gave a dark yellow syrupy solid. Although ^{1}H NMR and ^{13}C NMR of the crude product indicated the absence of the acyl azide, they also showed the presence of a by-product. Subsequent purification by silica gel flash column chromatography (5:1 hexane: ethyl acetate) afforded carbamate **9** and an alkyl ester. The proof of the reaction product was made using ^{13}C and ^{1}H NMR.

^{13}C NMR analysis of the pale yellow solid (product **9**, isolated in 36 % yield) showed the movement of the carbonyl group signal in **9** further upfield from 167.00 ppm to 152.81 ppm

which is within the range for a carbonyl carbon of an aliphatic or an aromatic carbamate. The aromatic carbons are seen at 117.67 ppm, 125.22 ppm, 143.03 ppm, and 143.97 ppm. The aliphatic carbon signals downfield at 62.01 ppm and upfield at 14.41 ppm are indicative of the methylene carbon, which is closest to the electronegative oxygen, and the methyl carbon of the ethyl group, respectively.

^{1}H NMR analysis of the product shows the proton on the nitrogen heteroatom of the carbamate appearing as a distinct singlet at 6.95 ppm. The methylene protons and methyl protons rightly occurred as a quartet and triplet and at 4.27 ppm and 1.34 ppm, respectively. Conjugation with the *N* –acyl group makes the phenyl protons more shielded, hence their upfield movement from 8.37 ppm and 8.31 ppm for the chloride to 8.20 ppm and 7.55 ppm for the carbamate.



Equation 14: Conversion of 4-nitrobenzoyl chloride (**3**) to ethyl (4-nitrophenyl)carbamate (**9**).

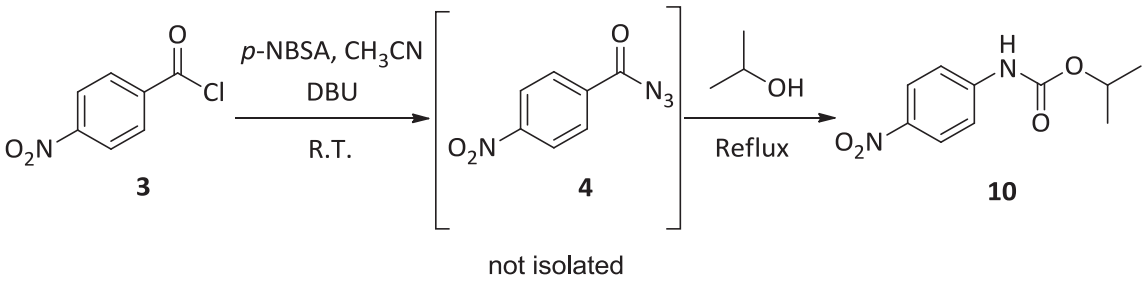
This procedure was then adapted for the “one-pot” synthesis of other carbamates by varying the alcohols. Isopropanol, propanol, butanol were the other alcohols used.

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

Upon confirmation of the presence of the 4-nitrobenzoyl azide via TLC, isopropanol was added and reflux condenser attached. The solution was heated to 80-82 ^{o}C for three days. IR confirmed the completion of the rearrangement and TLC confirmed an impure crude product with two very distinct spots of R_f 0.70 and 0.63, respectively. Aqueous work-up and purification by flash column chromatography (5:1 hexane: ethyl acetate) afforded **10** as the carbamate as well as an alkyl ester.

^{13}C NMR analysis of the white solid (product **10**, isolated in 40 % yield) showed the carbonyl group signal in **10** further upfield from 167.00 ppm to 152.52 ppm. The aryl ring carbons are seen at 117.66 ppm, 125.18 ppm, 142.87 ppm, and 144.26 ppm. The aliphatic carbon signals are seen downfield 69.84 ppm and upfield at 21.94 ppm, with the signal at 69.84 ppm being that of the secondary carbon, which is closest to the electronegative oxygen and 21.94 ppm being that of the methyl carbons.

^{1}H NMR analysis of the product shows the secondary carbon proton and the two sets of equivalent methyl protons occurring as a septet and doublet and at 5.05 ppm and 1.32 ppm, respectively. The proton on the nitrogen heteroatom of the carbamate appears as a distinct singlet at 7.08 ppm. The phenyl protons are shielded as a result of conjugation with the *N*-acyl group moved downfield from 8.37 ppm and 8.31 ppm for the chloride to 8.19 ppm and 7.57 ppm for the carbamate.



Equation 15: Conversion of 4-nitrobenzoyl chloride (**3**) to isopropyl (4-nitrophenyl)carbamate (**10**).

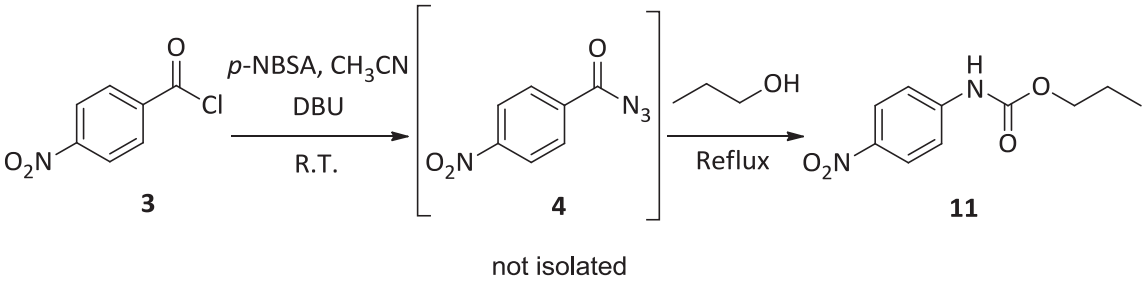
Conversion of 4-nitrobenzoyl chloride to propyl (4-nitrophenyl) carbamate

Propanol was added as the nucleophilic solvent after the confirmation of the presence of the 4-nitrobenzoyl azide by TLC. Reflux condenser was then attached and the mixture was heated to 95-97 ^{o}C for three days. IR confirmed the completion of the rearrangement and TLC confirmed an impure crude product with two very distinct spots of R_f 0.85 and 0.72, respectively. Aqueous work-up and purification by flash column chromatography (5:1 hexane: ethyl acetate) afforded **11** as the carbamate as well as an alkyl ester.

^{13}C NMR analysis of the white solid (product **11**, isolated in 31 % yield) also showed the aryl ring carbons at 117.68 ppm, 125.26 ppm, 143.97 ppm, and 144.93 ppm. The carbonyl group signal in **11** moved further upfield from 167.00 ppm to 152.90 ppm which is within the range for a carbonyl carbon of an aliphatic or an aromatic carbamate. The aliphatic carbon signals are the downfield signal at 67.64 ppm symptomatic of the methylene carbon closest to the

electronegative O, and upfield signals at 22.18 ppm and 10.29 ppm which shows the methylene carbon further away from the O and the methyl carbon, respectively.

Conjugation with the *N*-acyl group also made the phenyl protons more shielded, hence the ^{1}H NMR analysis showed an upfield movement from 8.37 ppm and 8.31 ppm for the chloride to 8.20 ppm and 7.55 ppm for the carbamate. The proton on the nitrogen heteroatom of the carbamate appeared as a singlet at 6.89 ppm. The methylene protons and methyl protons rightly occurred as a triplet, sextet, and triplet at 4.17 ppm, 1.73 ppm and 0.99 ppm, respectively.



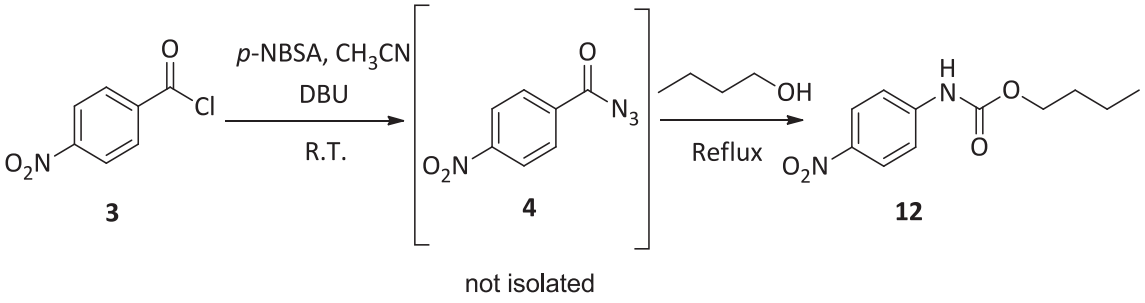
Equation 16: Conversion of 4-nitrobenzoylchloride (**3**) to propyl (4-nitrophenyl)carbamate (**11**).

Conversion of 4-nitrobenzoyl chloride to butyl (4-nitrophenyl) carbamate

Refluxing in butanol as the solvent for three days was done after confirmation of the presence of the 4-nitrobenzoyl azide via TLC. Butanol was added and a reflux condenser attached. The mixture was then heated to 115-117 ^{o}C. IR confirmed the completion of the rearrangement and TLC confirmed an impure crude product with two distinct spots of R_f 0.70 and 0.55, respectively. Aqueous work-up and purification by flash column chromatography (5:1 hexane: ethyl acetate) afforded **12** as the carbamate, as a white solid isolated in 34% yield along with an alkyl ester.

^{13}C NMR again showed the movement of the carbonyl group signal in **12** further upfield from 167.00 ppm to 152.90 ppm. The signals for the aromatic carbons appear at 117.65 ppm, 125.23 ppm, 143.97 ppm, and 144.97 ppm. The aliphatic carbon signals downfield at 65.89 ppm, 30.82 ppm, 19.02 ppm, and upfield at 13.65 ppm are representative of the methylene carbon directly bonded to electronegative oxygen, the secondary methylene carbons, and the methyl carbon, respectively.

The proton on the nitrogen heteroatom of the carbamate was shown by ^{1}H NMR to appear as a clear singlet at 6.90 ppm. The phenyl protons as expected were more shielded hence appeared upfield from 8.37 ppm and 8.31 ppm for the chloride to 8.20 ppm and 7.55 ppm for the carbamate. The methylene protons and methyl protons rightly occurred as a triplet, quintet, sextet, and triplet at 4.22 ppm, 1.68 ppm, 1.43 ppm, and 0.97 ppm, respectively.



Equation 17: Conversion of 4-nitrobenzoyl chloride (**3**) to butyl (4-nitrophenyl)carbamate (**12**).

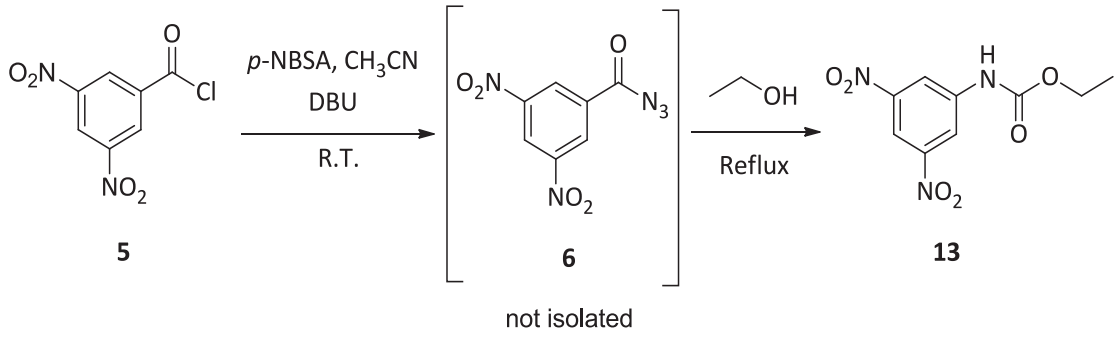
The one-pot procedure was then used to synthesize other carbamates from a different acyl chloride.

Conversion of 3, 5- dinitrobenzoyl chloride to ethyl (3, 5- dinitrophenyl) carbamate

The reaction process was done as that of the synthesis of the acyl azide. Upon the addition of the 3, 5- dinitrobenzoyl chloride the reaction was allowed to sit overnight and monitored for completion using TLC (hexane: ethyl acetate 1:1). Upon confirmation of the presence of the 4-nitrobenzoyl azide, ethanol was added and a reflux condenser was attached. The reaction mixture was then heated to 75-78 ^{o}C. The progress of the reaction was monitored by TLC and IR. IR was used to check for the disappearance of the covalently bonded azide peak at 2138 cm $^{-1}$ which is indicative of a successful Curtius rearrangement. This happened on the third day of reflux. However, TLC confirmed an impure crude product with two very distinct spots of R_f 0.71 and 0.64, respectively. Aqueous work-up on the product gave a dark yellow syrupy solid. Although ^{1}H NMR and ^{13}C NMR of the crude product indicated the absence of the acyl azide product, they also showed the presence of a by-product. Subsequent purification by silica gel flash column chromatography (5:1 hexane: ethyl acetate) afforded **13** as the carbamate product and an alkyl ester as the by-product. Carbamate **13** was isolated as a pale yellow solid in 38 % yield.

^{1}H NMR analysis showed the proton on the nitrogen heteroatom appearing as a singlet at 7.10 ppm. The quartet and triplet at 4.32 ppm and 1.36 ppm represent the methylene and methyl protons, respectively. The phenyl protons shielded due to conjugation with *N*-acyl group were also seen downfield at 8.70 ppm and 8.65 ppm.

^{13}C NMR showed the movement of the carbonyl group signal to 152.76 ppm. The aromatic carbons are seen at 112.77 ppm, 129.42 ppm, 140.66 ppm, and 149.03 ppm. The aliphatic carbon signals of the methylene carbon which is closest to the electronegative oxygen and the methyl carbon appeared downfield at 63.03 ppm and upfield at 14.40 ppm, respectively.



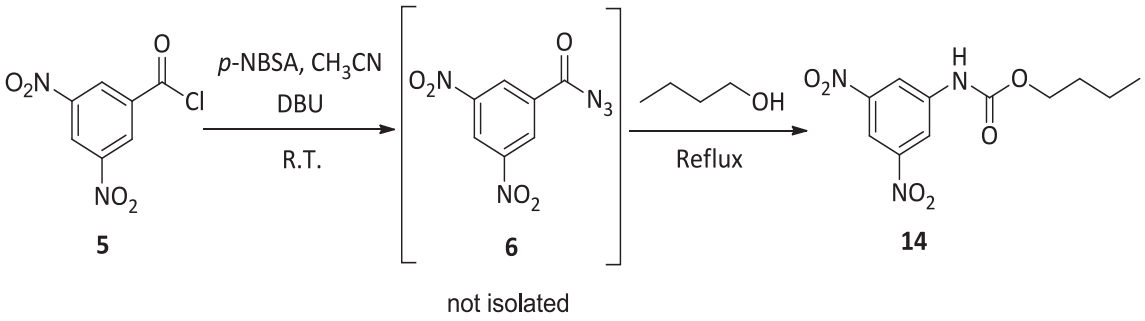
Equation 18: Conversion of 3,5-dinitrobenzoyl chloride (**5**) to ethyl (3,5-dinitrophenyl)carbamate (**13**).

Conversion of 3, 5- dinitrobenzoyl chloride to butyl (3, 5- dinitrophenyl) carbamate

Butanol was added upon confirmation of the presence of the 4-nitrobenzoyl azide via TLC, and a reflux condenser was attached. The reaction mixture was then heated to 115-117 ^{o}C for three days. IR confirmed the completion of the rearrangement and TLC confirmed an impure crude product with two very distinct spots of R_f's 0.71 and 0.64, respectively. Aqueous work-up and subsequent purification by flash column chromatography (5:1 hexane: ethyl acetate) afforded **14** and an alkyl ester by product. **14** was isolated as a white solid and in 40 % yield.

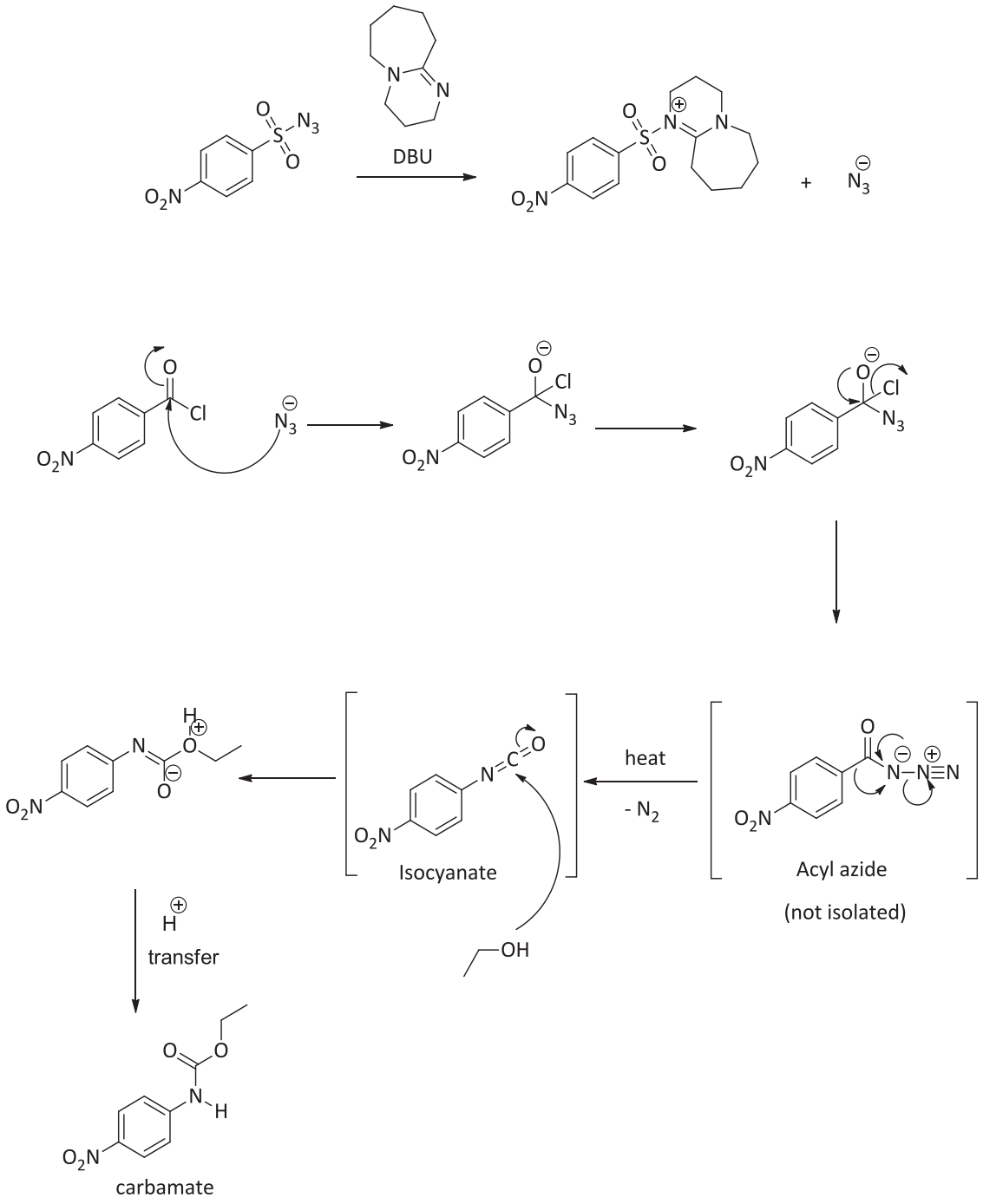
^{13}C NMR showed the carbonyl carbon signal at 152.93 ppm. The aliphatic carbon signals downfield at 66.46 ppm, 30.78 ppm, 19.03 ppm and upfield at 13.66 ppm indicates the methylene carbons which are closest to the electronegative oxygen, the secondary methylene groups, and the methyl carbon, respectively.

^{1}H NMR again showed the proton on the nitrogen heteroatom of the carbamate appearing as a singlet at 7.16 ppm. The triplet, quintet, sextet, and triplet at 4.26 ppm, 1.70 ppm, 1.44 ppm, and 0.98 ppm represent the methylene protons and methyl protons, respectively. The shielded phenyl protons appeared upfield at 8.70 ppm and 8.66 ppm.



Equation 19: Conversion of 3,5-dinitrobenzoyl chloride (**5**) to butyl (3,5-dinitrophenyl)carbamate (**14**).

PROPOSED MECHANISM FOR CARBAMATE FORMATION



Scheme 2: Proposed mechanism for "one-pot" synthesis of carbamate via curtius rearrangement.

SYNTHESIS OF THE ALKYL ESTERS

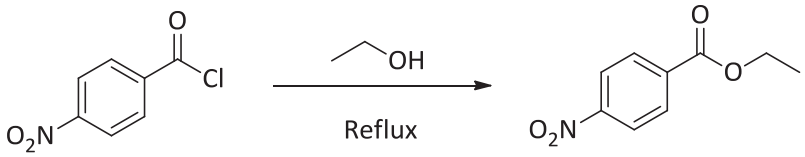
As indicated above, the TLC for the crude products after the addition of the acyl chlorides showed the presence of a by-product. This means that aside the Curtius rearrangement another reaction took place. Isolation and characterization showed the product to be alkyl ester. This, in essence, means that there were still unreacted acid chloride which led to the formation of the ester by-product upon reaction with the alcohol nucleophile. We synthesized these alkyl esters to confirm these.

Conversion of 4-nitrobenzoyl chloride to ethyl 4-nitrobenzoate

Using ethanol as the nucleophile, 4-nitrobenzoyl chloride was converted to ethyl 4-nitrobenzoate (**15**).

^{1}H NMR analysis of the white solid (product **15**, isolated in 29% yield) showed that the methylene protons and methyl protons rightly occurred as quartet and triplet at 4.41 ppm and 1.37 ppm, respectively. It also shows the absence of any carbamate group which would have influence the downfield movement of signals from the aromatic protons.

^{13}C NMR showed the movement of the carbonyl group signal in **15** further upfield from 167.00 ppm to 164.66 ppm which is rightly within the range for a carbonyl carbon of an ester. The aromatic carbons are seen at 123.47 ppm, 130.64 ppm, 135.88 ppm, and 150.51 ppm. The aliphatic carbon signals are the downfield signal at 61.92 ppm and upfield signal at 14.21 ppm indicative of the methylene carbon closest to the electronegative O and the methyl carbon, respectively.



3 **15**

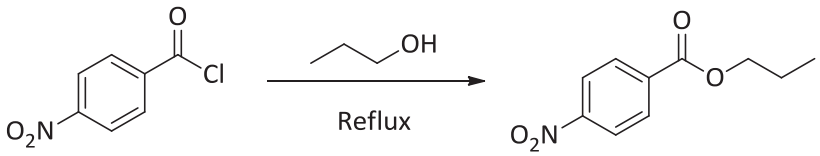
Equation 20: Conversion of 4-nitrobenzoyl chloride (**3**) to ethyl 4-nitrobenzoate (**15**)**.**

Conversion of 4-nitrobenzoyl chloride to propyl 4-nitrobenzoate

When propanol was added as the nucleophile, 4-nitrobenzoyl chloride led to the formation of propyl 4-nitrobenzoate (**16**) which was isolated in 17% yield as a white solid.

^{13}C NMR analysis shows the carbonyl carbon signal downfield at 164.76 ppm. The aromatic carbons appeared at 123.53 ppm, 130.68 ppm, 135.94 ppm, 150.57 ppm, and 164.76 ppm. The aliphatic carbon signals are the downfield signal at 67.51 ppm indicative of the methylene carbon closest to the electronegative O, and upfield signals at 22.05 ppm and 10.46 ppm which shows the methylene carbon further away from the O and the methyl carbon, respectively.

^{1}H NMR analysis of the product shows that the methylene protons and methyl protons correctly occurred as a triplet, sextet, and triplet at 4.34 ppm, 1.83 ppm, and 1.05 ppm, respectively. It also shows the absence of any electronegative N which would have influenced the downfield movement of signals.



3 **16**

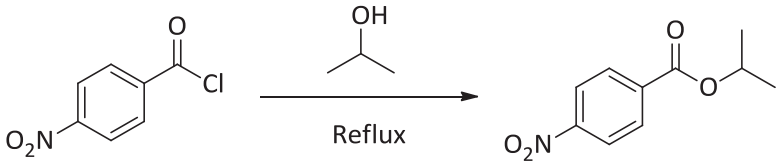
Equation 21: Conversion of 4-nitrobenzoyl chloride (**3**) to propyl 4-nitrobenzoate (**16**)**.**

Conversion of 4-nitrobenzoyl chloride to isopropyl 4-nitrobenzoate.

The product formed when 4-nitrobenzoyl chloride reacted with isopropanol is **17**. It was isolated as a white solid in 19% yield.

The ^{13}C NMR carbonyl group signal occurred at 164.50 ppm. The secondary carbon signal was seen downfield at 69.70 ppm, and the methyl carbons appeared upfield at 21.85 ppm. The aromatic carbons are seen at 123.43 ppm, 130.61 ppm, and 136.31 ppm.

Protons of the secondary carbon and the two sets of methyl protons occurred as a septet and doublet at 5.29 ppm and 1.40 ppm, respectively, on the ^{1}H NMR spectrum.



3 **17**

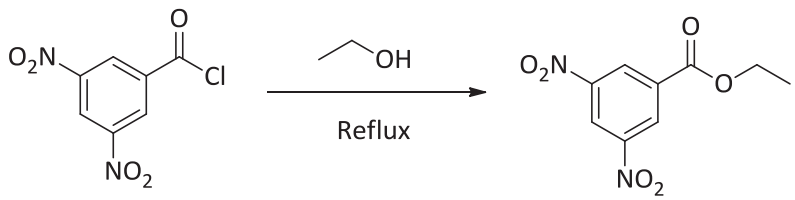
Equation 22: Conversion of 4-nitrobenzoyl chloride (**3**) to isopropyl 4-nitrobenzoate (**17**).

Conversion of 3,5- dinitrobenzoyl chloride to ethyl 3,5- dinitrobenzoate.

3,5- dinitrobenzoyl chloride led to the formation of ethyl 3,5- dinitrobenzoate (**18**) as the side product when ethanol was used as the nucleophile. **18** was isolated a pale yellow solid in 16% yield.

^{13}C NMR analysis showed the carbonyl group signal at 162.57 ppm. The aromatic carbons are seen at 122.29 ppm, 129.42 ppm, 134.22 ppm, and 148.74 ppm, and the methylene and methyl carbons found upfield and downfield at 63.03 ppm and 14.24 ppm, respectively.

^{1}H NMR shows that the methylene protons and methyl protons rightly occurring as a quartet and triplet at 4.52 ppm and 1.48 ppm, respectively.



5 **18**

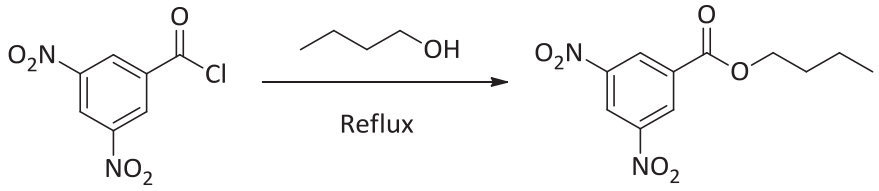
Equation 22: Conversion of 3,5-dinitrobenzoyl chloride (**5**) to ethyl 3,5-dinitrobenzoate (**18**)**.**

Conversion of 3, 5- dinitrobenzoyl chloride to butyl 3,5- dinitrobenzoate

^{13}C NMR and ^{1}H NMR show 3,5- dinitrobenzoate (**19**) as the alkyl ester formed from 3,5-dintrobenzoyl chloride when butanol was used. **19** appeared as a white solid in 24% yield.

^{13}C NMR showed the aromatic carbons at 122.28 ppm, 129.39 ppm, 134.24 ppm, and 148.74 ppm, and the carbonyl group carbon at 162.57. The aliphatic carbon signals downfield at 66.87 ppm, 30.61 ppm, 19.18 ppm and upfield at 13.69 ppm are indicative of the methylene carbons which are closest to the electronegative oxygen and the methyl carbon, respectively.

^{1}H NMR shows that the methylene protons and methyl protons rightly occurred as a triplet, quintet, sextet, and triplet at 4.47 ppm, 1.83 ppm, 1.50 ppm and 1.01 ppm, respectively.

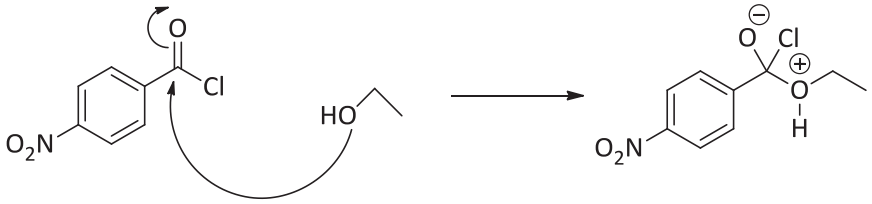


5 **19**

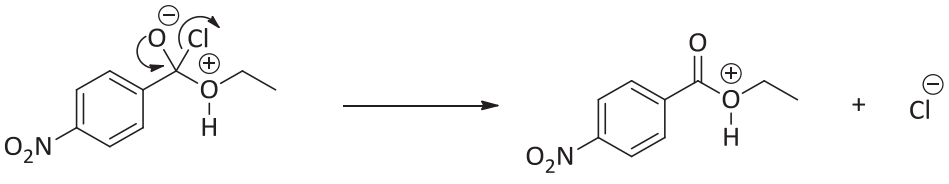
Equation 23: Conversion of 3,5-dinitrobenzoyl chloride (**5**) to butyl 3,5-dinitrobenzoate (**19**)**.**

PROPOSED MECHANISM FOR ALKYL ESTER BY-PRODUCT FORMATION

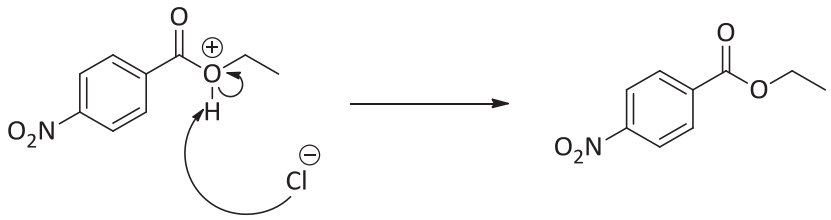
1. Nucleophilic attack on carbonyl carbon by the alcohol nucleophile.



2. Removal of leaving group and reformation of the carbon-oxygen double bond.



3. Abstraction of the proton to form the ester product.



Scheme 3: Proposed mechanism for alkyl ester formation.

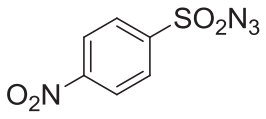
As proven, various alcohol nucleophiles have been successfully used to effect Curtius rearrangement to obtain carbamates from their corresponding acyl chlorides via a “one-pot” procedure. For each carbamate synthesized, an associated by-product was also produced. As shown above, the by-products are alkyl esters which occurred as a result of an esterification reaction between the acyl chlorides and the alcohols.

EXPERIMENTAL

General Experimental Procedure for Synthesis

Reactions were analyzed by Thin Layer Chromatography on Whatman aluminum-backed plates with varying eluent systems. Purifications *via* flash column chromatography were performed using 32-60 Å silica gel with varying eluent systems. Nuclear Magnetic Resonance spectra were recorded on samples dissolved in $CDCl_3$ using Bruker Avance II and Avance III systems, at a frequency of 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C spectra. All chemical shifts were recorded in parts per million (ppm). Signals are labeled as follows: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (multiplet) and coupling constants (*J*) are measured in Hertz (Hz). Infrared spectra were taken on a Thermo Electron Corporation IR 200 spectrophotometer and analyzed using EZ-OMNIC software.

Conversion of *para*-nitrobenzenesulfonyl chloride to *para*-nitrobenzenesulfonyl azide



2

In a 250 mL oven-dried round bottom flask fitted with a septum and magnetic stir bar, *p*-nitrobenzensulfonyl chloride (5.002 g, 22.6 mmol) was dissolved in methanol (100 mL). Sodium azide (2.93 g, 45.12 mmol) was then added. The reaction was left to stir overnight. TLC (1:1 hexane: ethyl acetate) R_f = 0.29 showed complete consumption of starting material. The excess NaN_3 was filtered off and the organic mixture was concentrated under vacuum. The crystals were dissolved in deionized water (50 mL) and then the organic material was extracted with ethyl acetate (3 × 50 mL). The combined organic extract was dried over anhydrous $MgSO_4$,

filtered, and the solvent was removed under vacuum. The product was recrystallized from hot ethyl alcohol to afford *p*-NBSA as pale yellow crystals (3.65 g, 70.6 %).

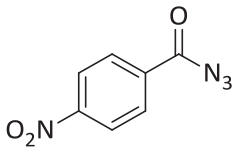
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, 2H, *J* = 9.08 Hz, 2H), 8.48 (d, 2H, *J* = 4.66 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 143.7, 128.9 (double intensity), 124.9 (double intensity).

IR absorption: 2141 cm^{-1} for the azide functional group.

Melting Point: 95-98 °C

Conversion of 4-Nitrobenzoyl chloride to 4-Nitrobenzoyl azide



4

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.456 g, 2.00 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-Nitrobenzoyl chloride (0.372 g 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) R_f = 0.79 showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, 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 removed

by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure 4-nitrobenzoyl azide (0.200 g, 52%) was collected as a white solid.

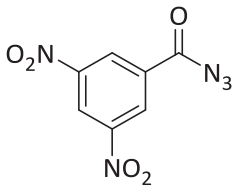
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84, 151.27, 135.71, 135.40, 123.80.

IR absorption: 2138 cm^{-1} for azide functional group.

Melting point: 64-65 ^{o}C.

Conversion of 3,5-dinitrobenzoyl chloride to 3,5-dinitrobenzoyl azide



6

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 3,5- dinitrobenzoyl chloride (0.461 g, 1.999 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) R_f = 0.75 showed the appearance of **6**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure 3,5-dinitrobenzoyl azide (0.314 g, 66.2%) was collected as a pale yellow solid.

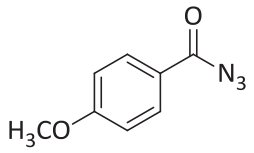
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (t, *J* = 2 Hz, 1H), 9.16 (d, *J* = 2.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.71, 148.89, 134.10, 129.02, 123.27.

IR absorption: 2153 cm^{-1} for azide functional group.

Melting point: 96-99 ^{o}C.

Conversion of 4-methoxybenzoyl chloride to 4-methoxybenzoyl azide



8

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.456 g, 1.998 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1 : 1 hexane : ethyl acetate) showed complete consumption of starting material. 4-methoxybenzoyl chloride (0.28 mL, 2.034 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) R_f = 0.69 showed the appearance of **8**, by showing a yellow spot when stained in

p-anisaldehyde upon heating. Upon completion, 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5 : 1 hexane : ethyl acetate solvent system. Pure 4-methoxybenzoyl azide (0.2163 g, 60 %) was collected as a white solid.

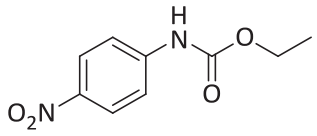
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 9.1 Hz, 2H), 6.93 (d, *J* = 9.1 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.68, 164.65, 131.76, 123.30, 113.98.

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

Melting point: 68-70 ^{o}C.

One-pot conversion of 4-nitrobenzoyl chloride to ethyl (4-nitrophenyl carbamate).



9

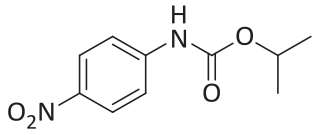
In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to reflux at 75-78 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.47 showed the presence of **9** and that of a an alkyl ester by-product R_f = 0.56. The mixture was then allowed to cool down to room temperature and diluted with 20 mL distilled water. The mixture was then extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure ethyl (4-nitrophenyl) carbamate (0.1518 g, 36%) was collected as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 9.1 Hz, 2H), 7.55 (d, *J* = 9.1 Hz, 2H), 6.95 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.15 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.80, 143.97, 143.03, 125.22, 117.67, 62.01, 14.41.

IR absorption: 3432 cm^{-1}, 1741 cm^{-1}.

One-pot conversion of 4-nitrobenzoyl chloride to isopropyl (4-nitrophenyl carbamate).



10

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to reflux at 80-82 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.63 showed the presence of **10** and that of a an alkyl ester by-product R_f = 0.70. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was

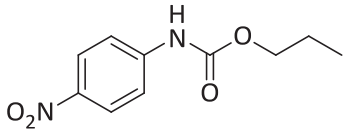
then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure ethyl (4-nitrophenyl) carbamate (0.1797 g, 40%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 9.3 Hz, 2H), 7.57 (d, *J* = 9.2 Hz, 2H), 7.08 (s, 1H), 5.05 (septet, *J* = 6.2 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.23, 144.26, 142.87, 125.18, 117.66, 69.84, 29.66, 21.94.

IR absorption: 3394 cm^{-1}, 1717 cm^{-1}.

One-pot conversion of 4-nitrobenzoyl chloride to propyl (4-nitrophenyl carbamate).



11

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane : ethyl acetate) showed complete consumption of starting material. 4-nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then heated to 95-97 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.72 showed the presence of **11** and that of a an alkyl ester by-

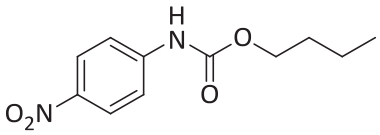
product R_f = 0.85. The mixture was then allowed to cool down to room temperature. The reaction mixture was diluted with 20 mL distilled water, and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent removed by rotary evaporation at 40 ^oC. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure propyl (4-nitrophenyl) carbamate (0.1394 g, 31%) was collected as a pale yellow solid.

^1H NMR (400 MHz, CDCl3): δ 8.20 (d, *J* = 9.3 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 6.89 (s, 1H), 4.17 (t, *J* = 6.7 Hz, 2H), 1.73 (sextet, *J* = 7.12 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.90, 144.93, 143.97, 125.26, 117.68, 67.64, 22.18, 10.29.

IR absorption: 3429 cm^{-1}, 1741 cm^{-1}.

One-pot conversion of 4-nitrobenzoyl chloride to butyl (4-nitrophenyl carbamate).



12

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.456 g, 1.998 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-Nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane:

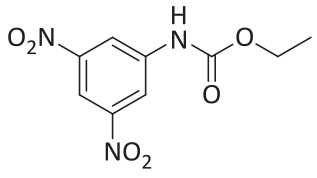
ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then heated to 115-117 ^{o}C for three days. TLC (1 : 1 hexane : ethyl acetate) R_f = 0.55 showed the presence of **12** and that of a an alkyl ester by-product R_f = 0.70. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure butyl (4-nitrophenyl) carbamate (0.1624 g, 34%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 9.3 Hz, 2H), 7.55 (d, *J* = 9.2 Hz, 3H), 6.90 (s, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 1.68 (quintet, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.90, 144.93, 143.96, 125.23, 117.65, 65.89, 30.82, 19.02, 13.65.

IR absorption: 3429 cm^{-1}, 1740 cm^{-1}.

One-pot conversion of 3,5-dinitrobenzoyl chloride to ethyl (3,5-dinitrophenyl) carbamate.



13

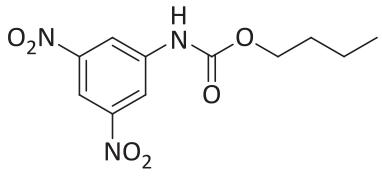
In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.456 g, 1.998 mmol) was dissolved in CH_3CN (6 mL) at room

temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 3, 5 -Dinitrobenzoyl chloride (0.461 g, 1.999 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of 4, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to reflux at 75-78 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.64 showed the presence of **13** and that of the carbamate by-product R_f = 0.71. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5 : 1 hexane : ethyl acetate solvent system. Pure ethyl (3,5-dinitrophenyl) carbamate (0.1824 g, 38%) was collected as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (t, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 2.1 Hz, 2H), 7.10 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.76, 149.03, 140.66, 129.42, 112.78, 63.03, 14.40.

One-pot conversion of 3,5-dinitrobenzoyl chloride to butyl (3,5-Dinitrophenyl) carbamate.



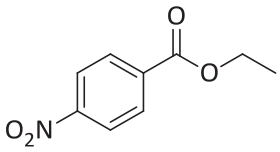
14

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, para-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 3,5-Dinitrobenzoyl chloride (0.461 g, 1.999 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then heated to 115-117 ^{o}C for three days. TLC (1 : 1 hexane : ethyl acetate) R_f = 0.64 showed the presence of **14** and that of a an alkyl ester by-product, R_f = 0.71. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure butyl (3,5-dinitrophenyl) carbamate (0.2145 g, 40%) was collected as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (t, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 9.2 Hz, 2H), 7.16 (s, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 1.70 (quintet, *J* = 7.1 Hz, 2H), 1.44 (sextet, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.93, 149.02, 140.70, 126.69, 117.91, 112.75, 66.46, 30.78, 19.03, 13.66

Conversion of 4-nitrobenzoyl chloride to ethyl 4-nitrobenzoate.



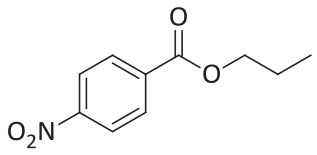
15

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-Nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-Nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to heat to 75-78 ^{o}C for three days. TLC (1: 1 hexane: ethyl acetate) R_f = 0.47 showed the presence of **15** and that of the alkyl ester by-product, R_f = 0.56. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5: 1 hexane: ethyl acetate solvent system. Pure ethyl 4-nitrobenzoate (0.1135 g, 29%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.8 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H), 4.44 (q, *J* = 7.2 Hz, 1H), 1.43 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.65, 150.51, 135.88, 130.64, 123.47, 61.92, 14.21.

Conversion of 4-nitrobenzoyl chloride to propyl 4-nitrobenzoate.



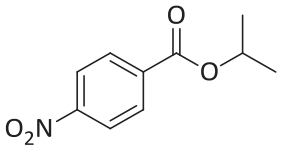
16

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-Nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to reflux at 75-78 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.85 showed the presence of **16** and that of the carbamate R_f = 0.72. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure propyl 4-nitrobenzoate (0.07132 g, 17%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H), 4.34 (t, *J* = 6.7 Hz, 2H), 1.83 (sextet, *J* = 7.1 Hz, 2H), 1.05 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.76, 150.56, 135.94, 130.67, 123.53, 67.51, 22.05, 10.46.

Conversion of 4-nitrobenzoyl chloride to isopropyl 4-nitrobenzoate.



17

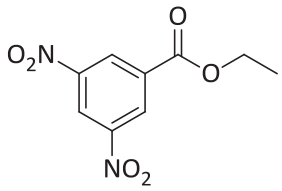
In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-Nitrobenzoyl chloride (0.372 g mL, 2.005 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to reflux at 75-78 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.70 showed the presence of **17** and that of the carbamate, R_f = 0.63. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by

flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure isopropyl 4-nitrobenzoate (0.0797 g, 19%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 5.29 (septet, *J* = 6.2 Hz, 1H), 1.40 (d, *J* = 6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.49, 150.56, 136.31, 130.61, 123.43, 69.71, 21.85.

Conversion of 3,5-dinitrobenzoyl chloride to ethyl 3,5-dinitrobenzoate.



18

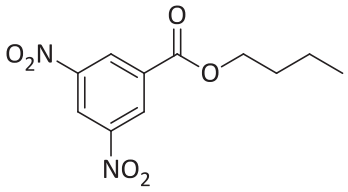
In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.456 g, 1.998 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 3,5-Dinitrobenzoyl chloride (0.461 g, 1.999 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a reflux condenser attached. The mixture was then allowed to reflux at 75-78 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.71 showed the presence of **18** and that of the carbamate R_f = 0.64. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure ethyl 3,5-dinitrobenzoate (0.07681 g, 16%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (t, *J* = 2.2 Hz, 1H), 9.17 (d, *J* = 2.3 Hz, 2H), 4.52 (t, *J* = 7.2 Hz, 2H), 1.83 1.48 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.50, 148.74, 134.22, 129.42, 122.29, 63.02, 14.24.

Conversion of 3,5-dinitrobenzoyl chloride to butyl 3,5-dinitrobenzoate.



19

In a 50 mL oven-dried round bottom flask fitted with a septum and a magnetic stir bar, *para*-nitrobenzenesulfonyl azide (0.457 g, 2.003 mmol) was dissolved in CH_3CN (6 mL) at room temperature. DBU (0.37 mL, 2.5 mmol) was added drop-wise. The reaction was left to stir overnight until TLC (1:1 hexane: ethyl acetate) showed complete consumption of starting material. 4-Nitrobenzoyl chloride (0.461 g, 1.999 mmol) dissolved in CH_3CN (6 mL) was then added drop-wise to the reaction mixture. The reaction was left overnight until TLC (1:1 hexane: ethyl acetate) showed the appearance of **4**, by showing a yellow spot when stained in *p*-anisaldehyde upon heating. Upon completion, as shown by TLC, ethanol (6 mL) was added and a

reflux condenser attached. The mixture was then allowed to reflux at 75-78 ^{o}C for three days. TLC (1:1 hexane: ethyl acetate) R_f = 0.70 showed the presence of **19** and that of the carbamate, R_f = 0.55. 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 removed by rotary evaporation at 40 ^{o}C. The crude product was then purified by flash column chromatography using a 5:1 hexane: ethyl acetate solvent system. Pure butyl 3,5-dinitrobenzoate (0.1287 g, 24%) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (t, *J* = 2.2 Hz, 1H), 9.16 (d, *J* = 2.3 Hz, 2H), 4.47 (t, *J* = 6.8 Hz, 2H), 1.83 (quintet, *J* = 7.2 Hz, 2H), 1.50 (sextet, *J* = 7.5 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.57, 148.74, 134.24, 129.39, 122.28, 66.87, 30.61, 19.18, 13.69.

REFERENCES

1. Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V., "Organic Azides: An Exploding Diversity of a Unique Class of Compounds," *Angew. Chem. Int Ed.* **2005**, *44*, 5188-5240.
2. Katritzky, R. A.; Oniciu, C. D.; Ghiviriga, I., "The Mitsunobu Reaction: An Alternative Synthesis of 1-(Primary alkyl)benzotriazoles," *Synth. Commun*. **1997**, *27*, 1613-1621.
3. Banert, K.; Brase S., Organic Azides: Syntheses and Applications, John Wiley and Sons: United Kingdom. **2010**, 29-32.
4. Rokhum, L.; Bez, G., "A Practical One-Pot Synthesis of Azides Directly from Alcohols," *J. Chem. Sci.* **2012**, *124*, 687–691.
5. Scriven, E.F.V.; Turnbull, K., "Azides: Their preparation and synthetic uses", *Chem. Rev.,* **1988**, *88*, 297-368.
6. Viaud, M. C.; Rollin, P., "Zinc Azide Mediated Mitsunobu Substitution: An Expedient Method for the One-Pot Azidation of Alcohols," *Synthesis*, **1990**, 130-132.
7. Brase, S.; Zimmermann, V.; Gil, C; Knepper. K., "Organic azides: An exploding diversity of a unique class of compounds", *Angew. Chem Int. Ed.* **2005**, *44*, 5188-5240.
8. Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. J., "Several Convenient Methods for the Synthesis of 2-Amido Substituted Furans", *J. Org. Chem.* **2003**, *68*, 2609-2617.
9. Arrieta, A.; Aizpurua, J. M.; Palomo, C., "N,N-Dimethylchlorosulfitemethaniminium chloride ($SOCl_2$-DMF) a versatile dehydrating reagent",*Tetrahedron Lett.* **1984**, *25*, 3365-3368.
10. Bandgar, B. P.; Pandit, S. S., "Synthesis of acyl azides from carboxylic acids using cyanuric chloride", *Tetrahedron Lett*, **2002**, *43*, 3413-3414.

11. Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R., "A mild and efficient method for the preparation of acyl azides from carboxylic acids using triphosgene", *Tetrahedron Lett*, **2002**, *43*, 1345-1346.
12. Wilder, R.; Mobashery, S. J., "The use of triphosgene in preparation of N-carboxy .alpha.-amino acid anhydrides", *J. Org. Chem.* **1992**, *57*, 2755-27556.
13. Kuramochi, K.; Watanabe, H.; Kitahara, T., "Synthetic Study on Oximidines: A Concise Synthesis of (Z)-Enamides", *Synlett*, **2000**, *3*, 397-399.
14. Latthe, P. R.; Shinge, P. S.; Badami, B. V.; Patil, P. B.; Holihosur, S. N., "Curtius rearrangement reactions of 3-(4-azidocarbonyl)phenylsydnone. Synthesis of 4-(sydnon-3-yl) phenyl carbamates, N-aryl-N''-[4-(sydnon-3-yl)] phenyl ureas and their antimicrobial and insecticidal activities", *J. Chem. Sci.* **2006**, *118*, 249-256.
15. Kim, H. S.; Kim, T, E.; Lee, S. U.; Kim, D. I.; Han, S. W.; Okamoto, Y.; Mitomi, T.; Kurasawa, Y. J., "A convenient synthesis of 2-amino-4*H*-1,3,4-oxadiazino[5,6-*b*]-quinoxaline derivatives"
Heterocyclic Chem. **1998**, *35*, 1515-1520.
16. Papeo, G.; Posteri, H.; Vianello, P.; Varassi, M., "Nicotinoyl azide (NCA)-mediated Mitsunobu reaction: An expedient one-pot transformation of alcohols into azides", *Synthesis,* **2004**, *17*, 2886-2893.
17. Rumi, L.; Pfleger, C.; Spurr, P.; Klinkhammer, U.; Bannwarth, W., "An Adaptation of an exothermic and acylazide-involving synthesis sequence to microreactor technology", *Org. Process Res. Dev.* **2009**, *13*, 747-750.

18. Katritzky, A. R.; Widyan, K.; Kirichenko, K., "Preparation of Polyfunctional Acyl Azides," *J. Org. Chem*. **2007**, *72*, 5802-5804.

19. Marinescu, L.; Thinggard, J.; Thomsen, I. B.; Bols, M., "Radical Azidonation of Aldehydes," *J. Org. Chem*. **2003**, *68*, 9453-9455.

20. Kim, J. G.; Jang, D. O., "Direct Synthesis of Acyl Azides from Carboxylic Acids by the Combination of Trichloroacetonitrile, Triphenylphosphine and Sodium Azide", *Synlett*, **2008**, 2072-2074.

21. Pawia, M. R.; Lobbestead, S. J.; Taylor, C. P.; Hershenson, F. M.; Miskell, D. L., "N-Phenyl-N'-pyridinylureas as anticonvulsant agents," *J. Med. Chem.* **1990**, *33*, 854-861.

22. Sureshbabu, V. V.; Chennakrishna, G.; Narendra, N., "A facile and one-pot synthesis of N^{α}-Fmoc/Bsmoc/Boc/Z-protected ureidopeptides and peptidyl ureas employing diphenylphosphoryl azide [DPPA]", *Tetrahedron Lett.* **2008**, *49*, 1408-1412.

23. Ray, S.; Charturvedi, D., "Application of Organic Carbamates in Drus Design. Part 1: Anticancer agents recent reports", *Drugs future*, **2004**, *29*, 343-357.

24. *The Pesticidal manual*, 10th ed.; Thomlin. C. D. S. Ed.; Crop. Protection Publication; Farnham, UK, **1994**.

25. Wills, A. J.; Ghosh, T. K.; Balasubramanian, S., "Synthesis of a Polymer-Supported Oxazolidine Aldehyde for Asymmetric Chemistry", *J. Org. Chem.* **2002**, *67*, 6646-6652.

26. Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*, 4th ed.; John: New York, NY, **2007.**

27. Mayer, J. P.; Lewis, G. S.; Curtius, M. J.; Zhang, J., "Solid Phase Synthesis of Quinazolinones", *Tetrahedron Lett*. **1997**, *38*, 8445-8449.

28. Chedid, R. B.; Brummer, M.; Wibbeling, B.; Fohlich, R.; Hoppe, D., “Stereo- and Regiochemical Divergence in the Substitution of a Lithiated Alk-1-en-3-yn-2-yl Carbamate: Synthesis of Highly Enantioenriched Vinylallenes or Alk-3-en-5-yn-1-ols”, *Angew. Chem., Int. Ed*. **2007**, *46*, 3131-3134.
29. Lebel, H.; Leogane, O. "Boc-protected amines via a mild and efficient one-pot Curtius rearrangement". *Org. Lett.* **2005**, *7*, 4107–4110.
30. Dussault, P. H.; Xu, C., “Curtius rearrangement and Wolff homologation of functionalized peroxides”, *Tetrahedron Lett.* **2004**, *45*, 7455-7457.
31. Tada, T.; Ishida, Y.; Saigo, K., “Synthesis of 2,2-[60]Fullerenoalkylamines via the Curtius Rearrangement”, *Synlett.* **2007**, *2*, 235-238.
32. Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S., “A new and facile synthesis of carbamate- and urea-linked glycoconjugate using modified Curtius Rearrangement”,*Tetrahedron Lett.* **2006**, *47*, 7219-7233.
33. Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S., “Novel synthesis of oligosaccharides linked with carbamate and urea bonds utilizing modified Curtius rearrangement,”*Tetrahedron,* **2008,** *64*, 8780-8788.
34. Akhlaghinia, B.; Rouhi-Saadabad, H., “Direct and facile synthesis of acyl azides from carboxylic acids using the trichloroisocyanuric acid–triphenylphosphine system”, *Can. J. Chem*. **2013**, *91*, 181-185.

Appendix A

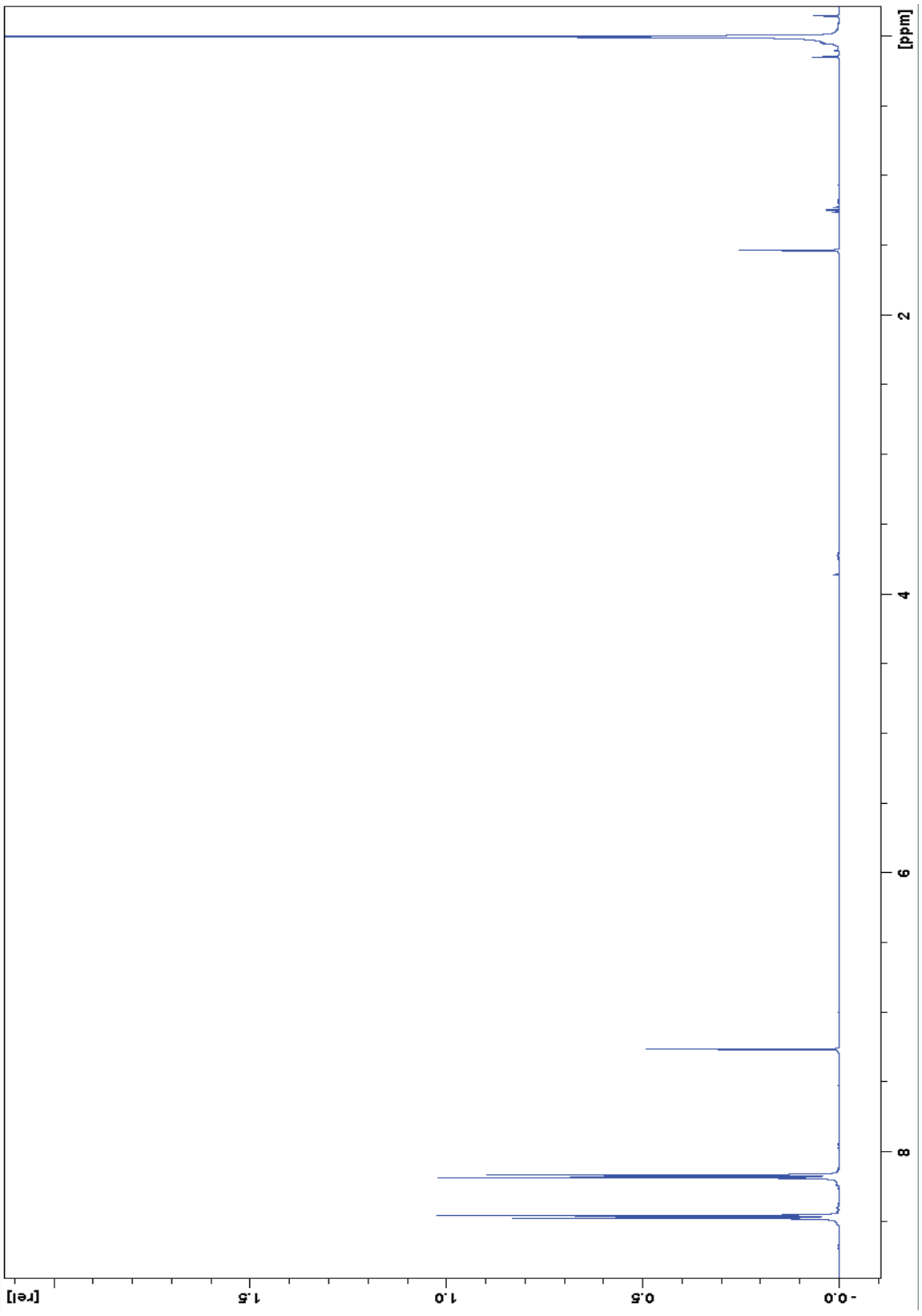


Figure 3: ^{1}H NMR of *para*-nitrobenzenesulfonyl azide (**2**)

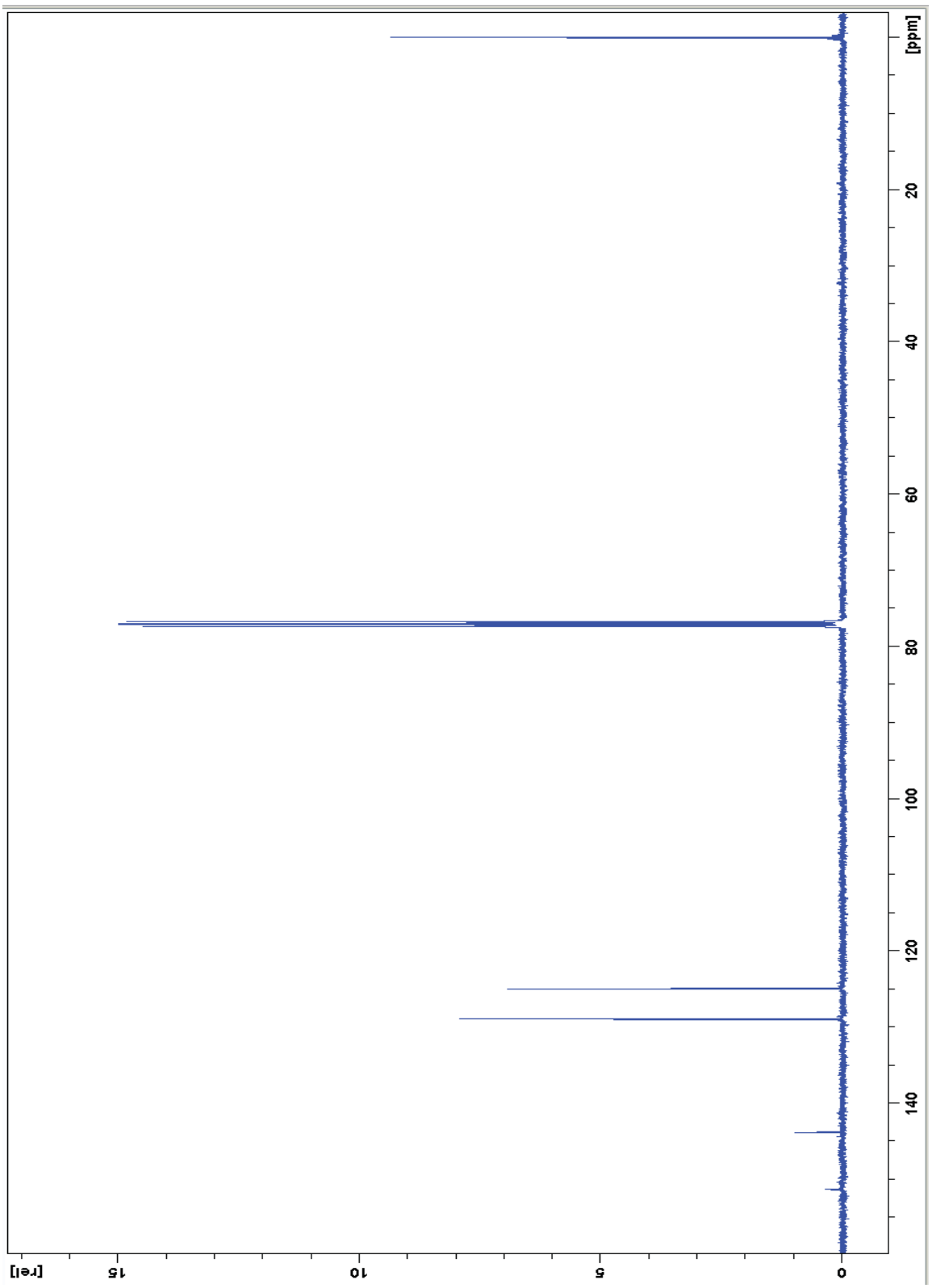


Figure 4: ^{13}C NMR of *para*-nitrobenzenesulfonyl azide (**2**).

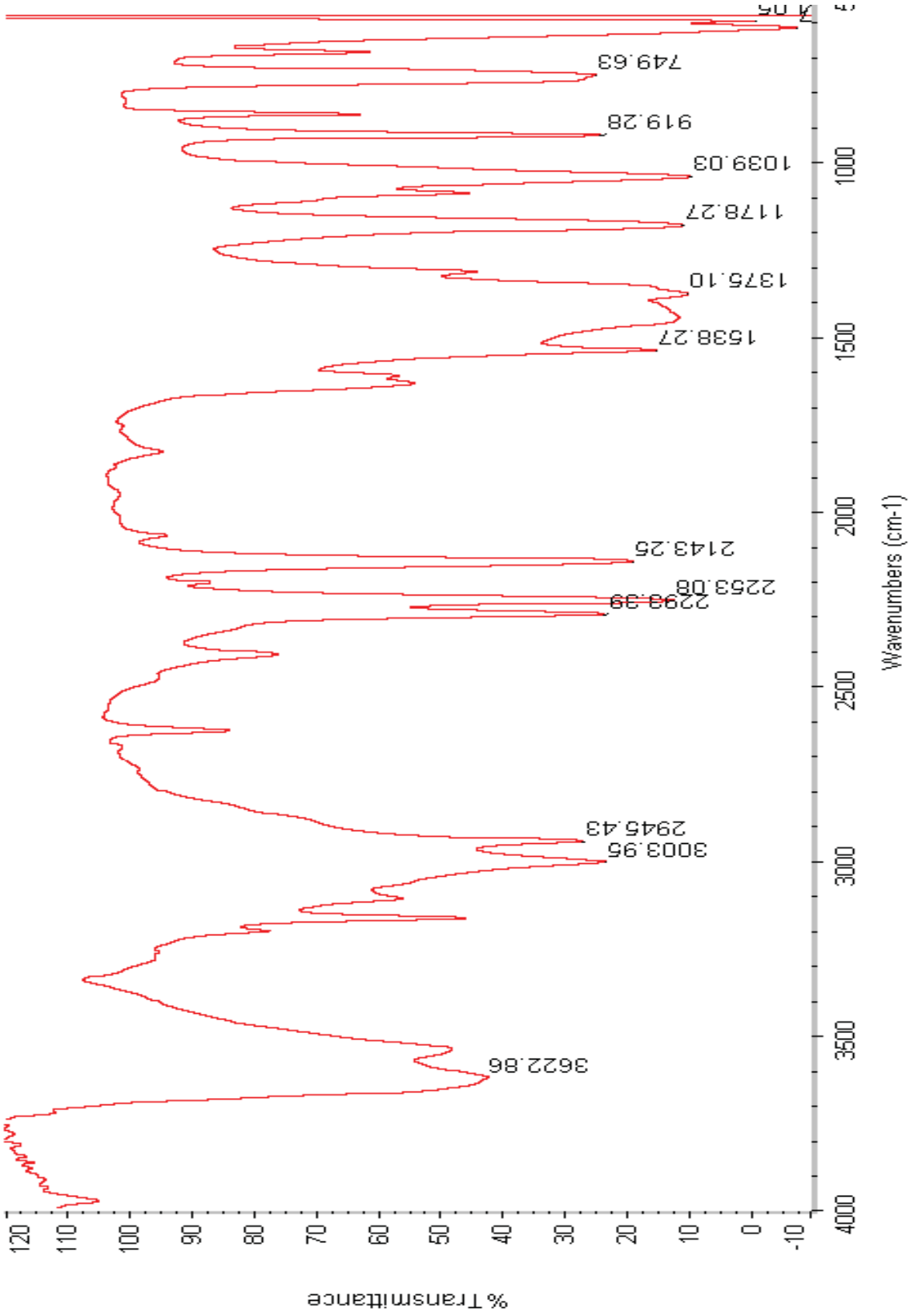


Figure 5: IR spectrum of para-nitrobenzenesulfonyl azide (**2**).

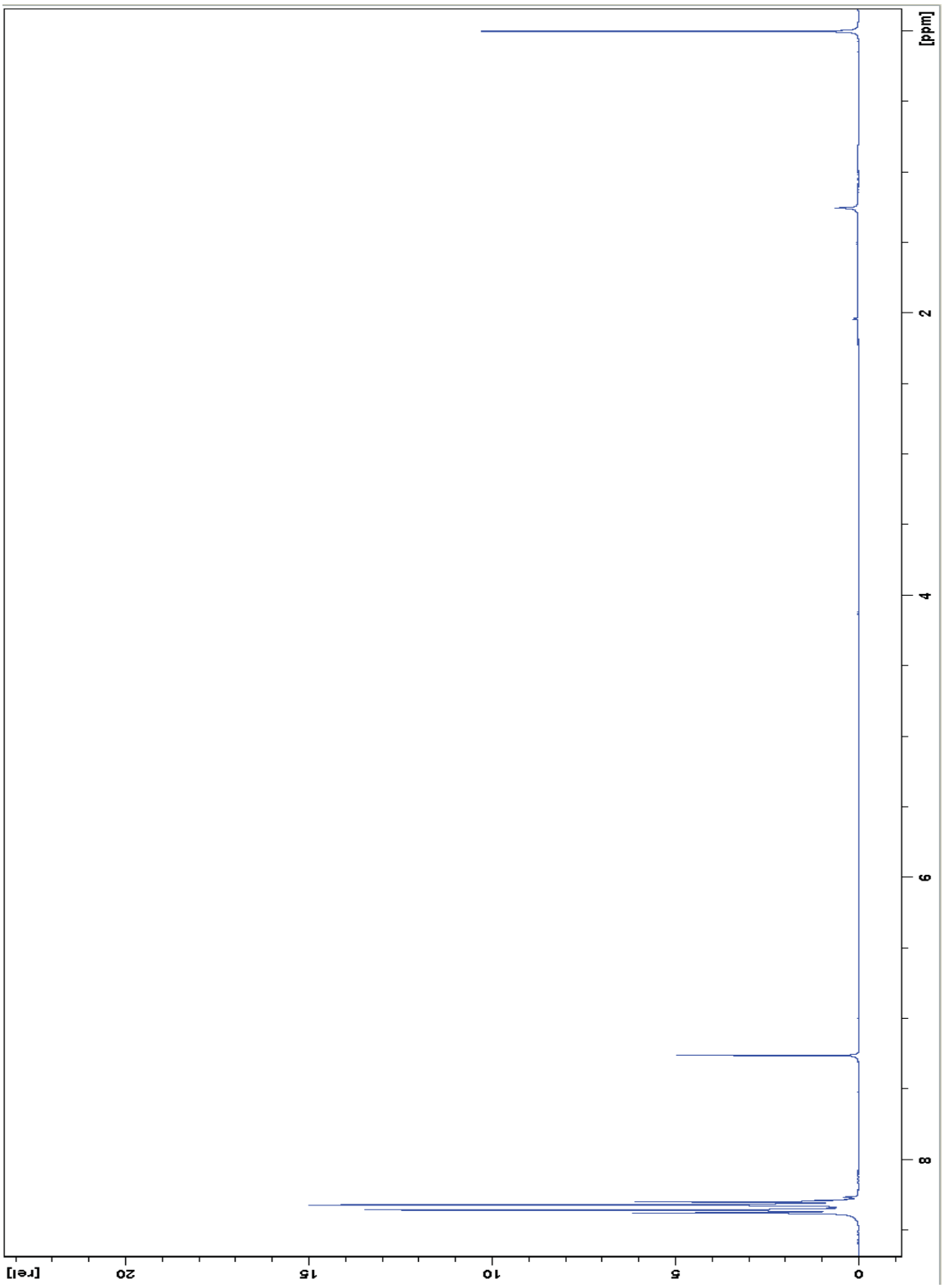


Figure 6: ^{1}H NMR of 4-nitrobenzoyl chloride (**3**).

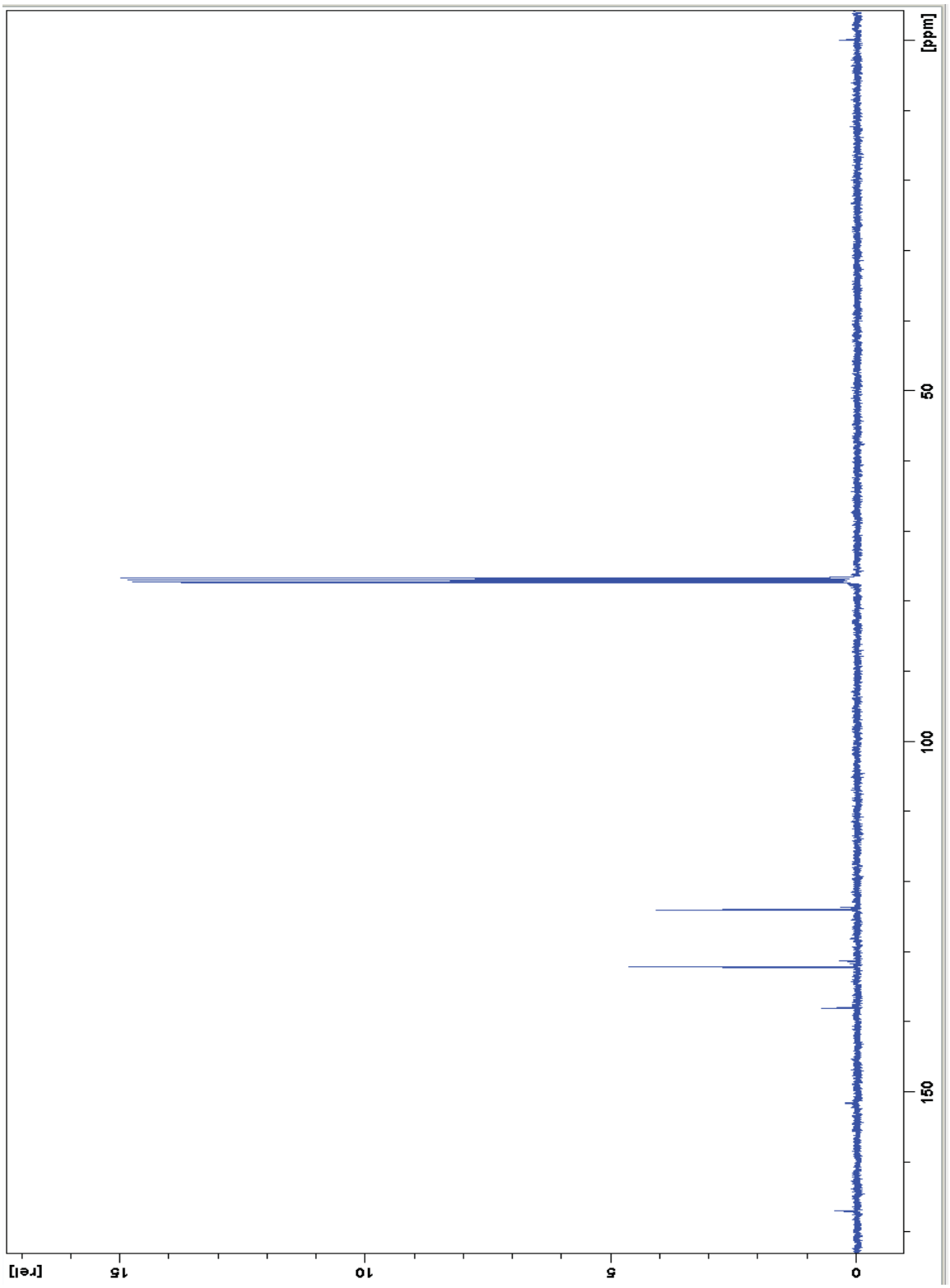


Figure 7: ^{13}C NMR of 4-nitrobenzoyl chloride (**3**).

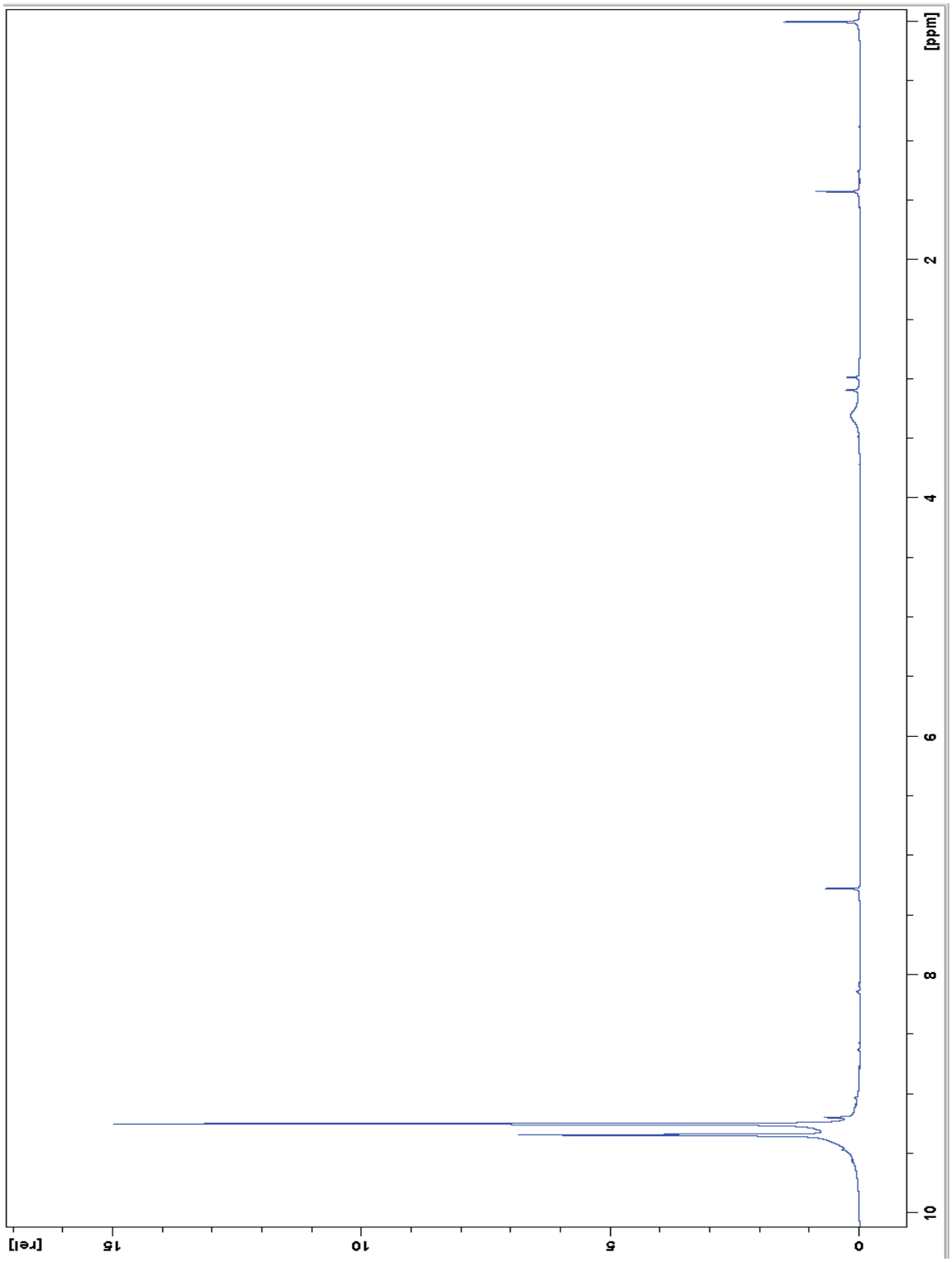


Figure 8: ^{1}H NMR of 3,5-dinitrobenzoyl chloride (**5**).

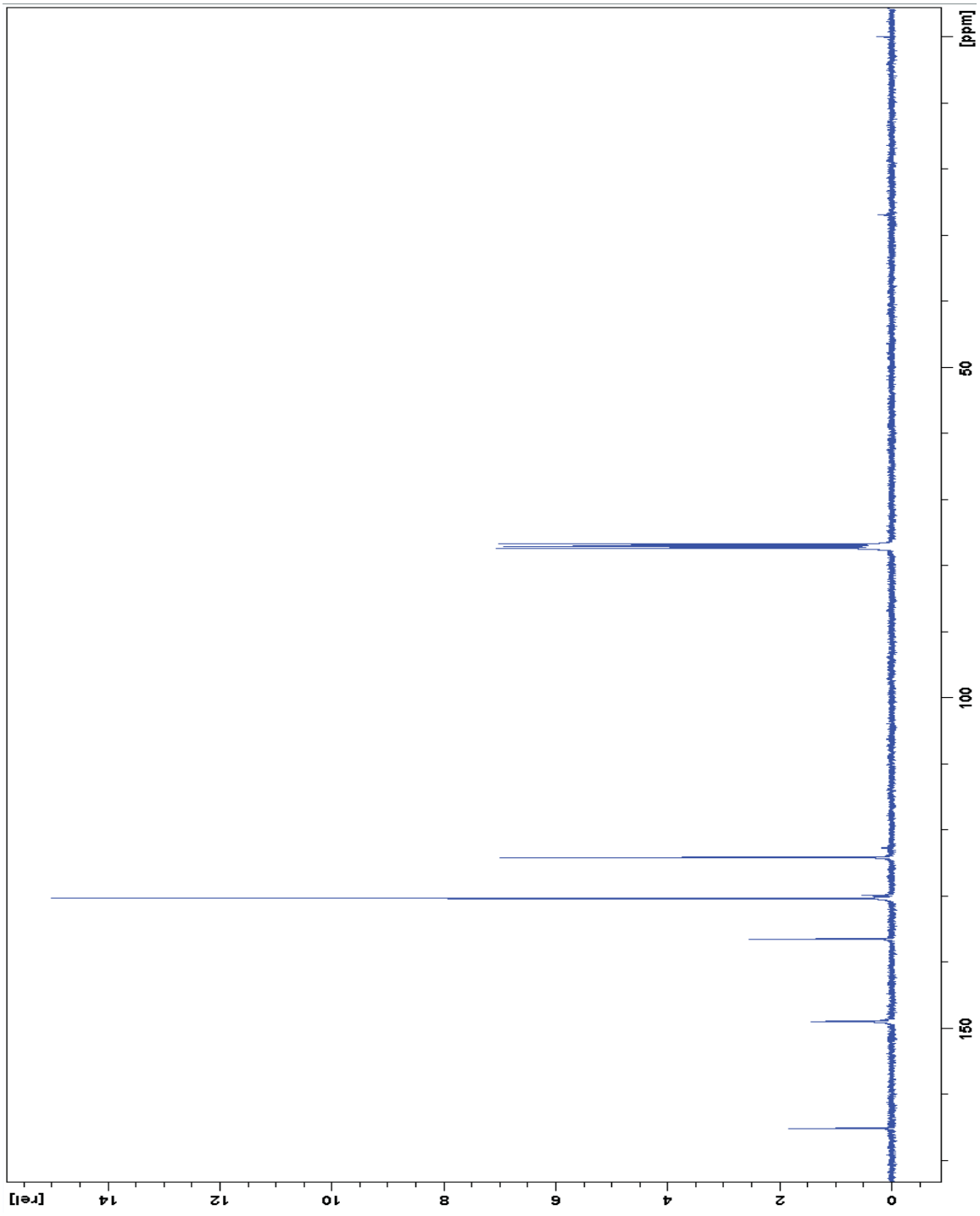


Figure 9: ^{13}C NMR of 3,5-dinitrobenzoyl chloride (**5**).

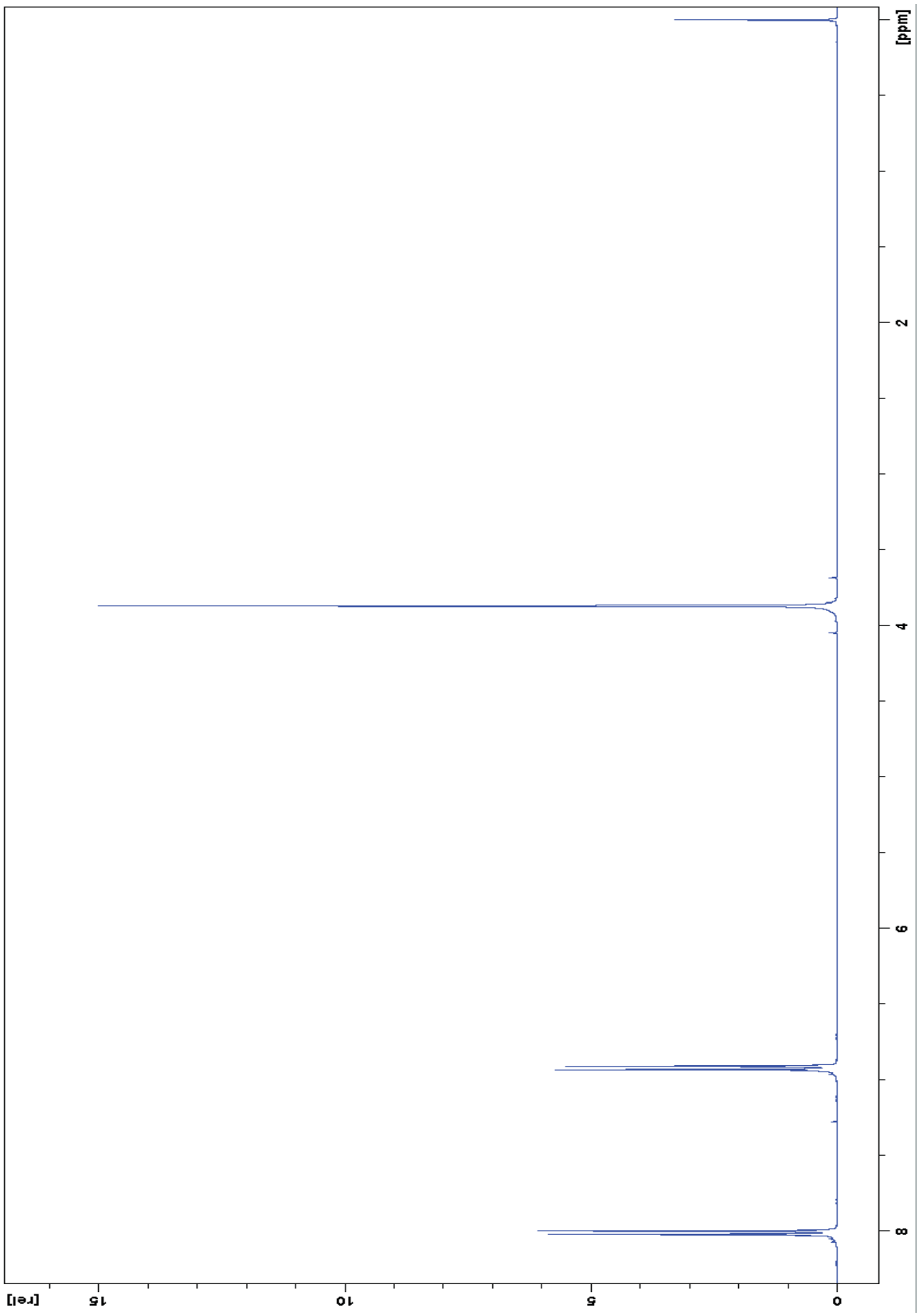


Figure 10: ^{1}H NMR of 4-methoxybenzoyl chloride (**7**).

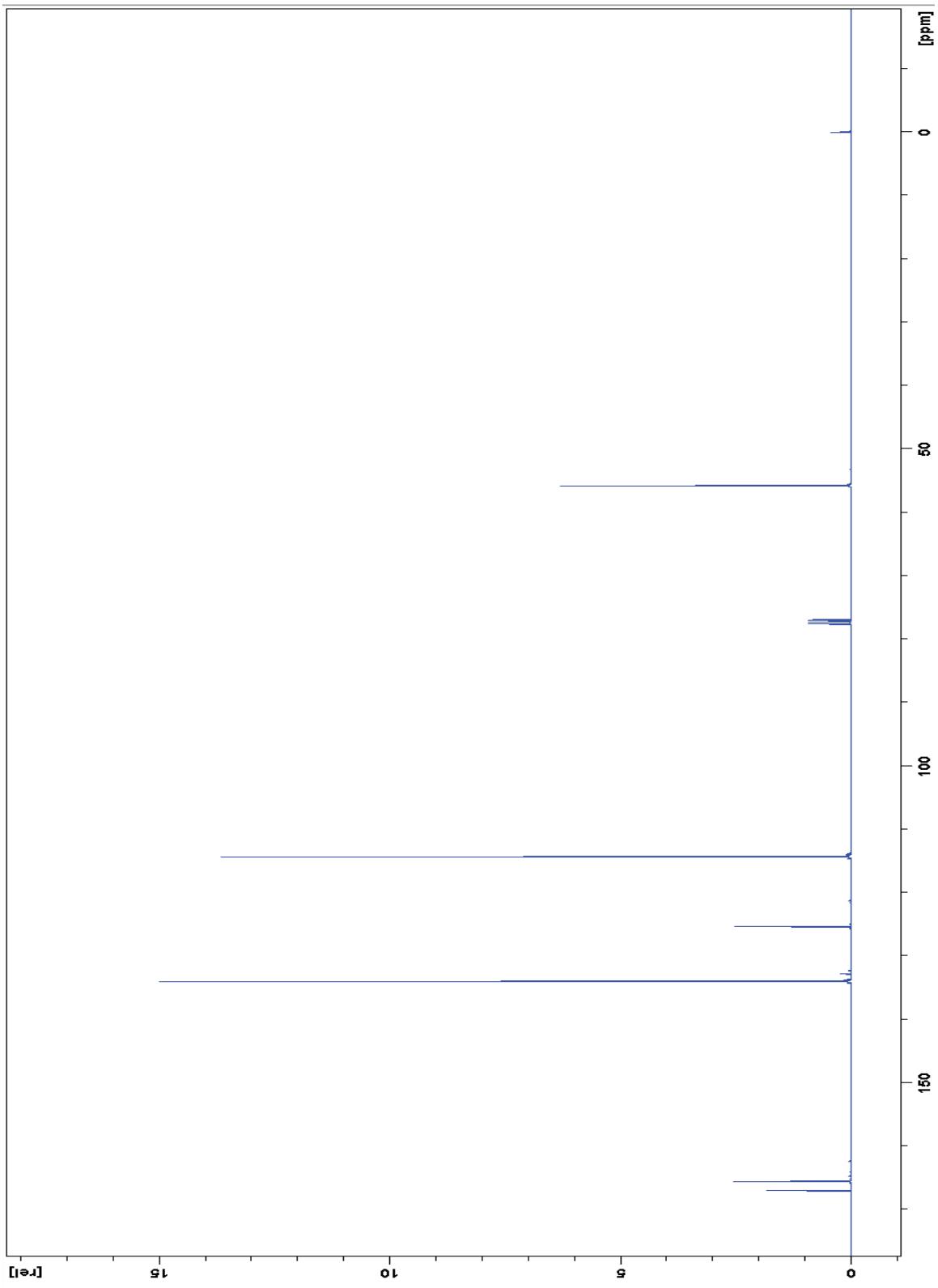


Figure 11: ^{13}C NMR of 4-methoxybenzoyl chloride (**7**).

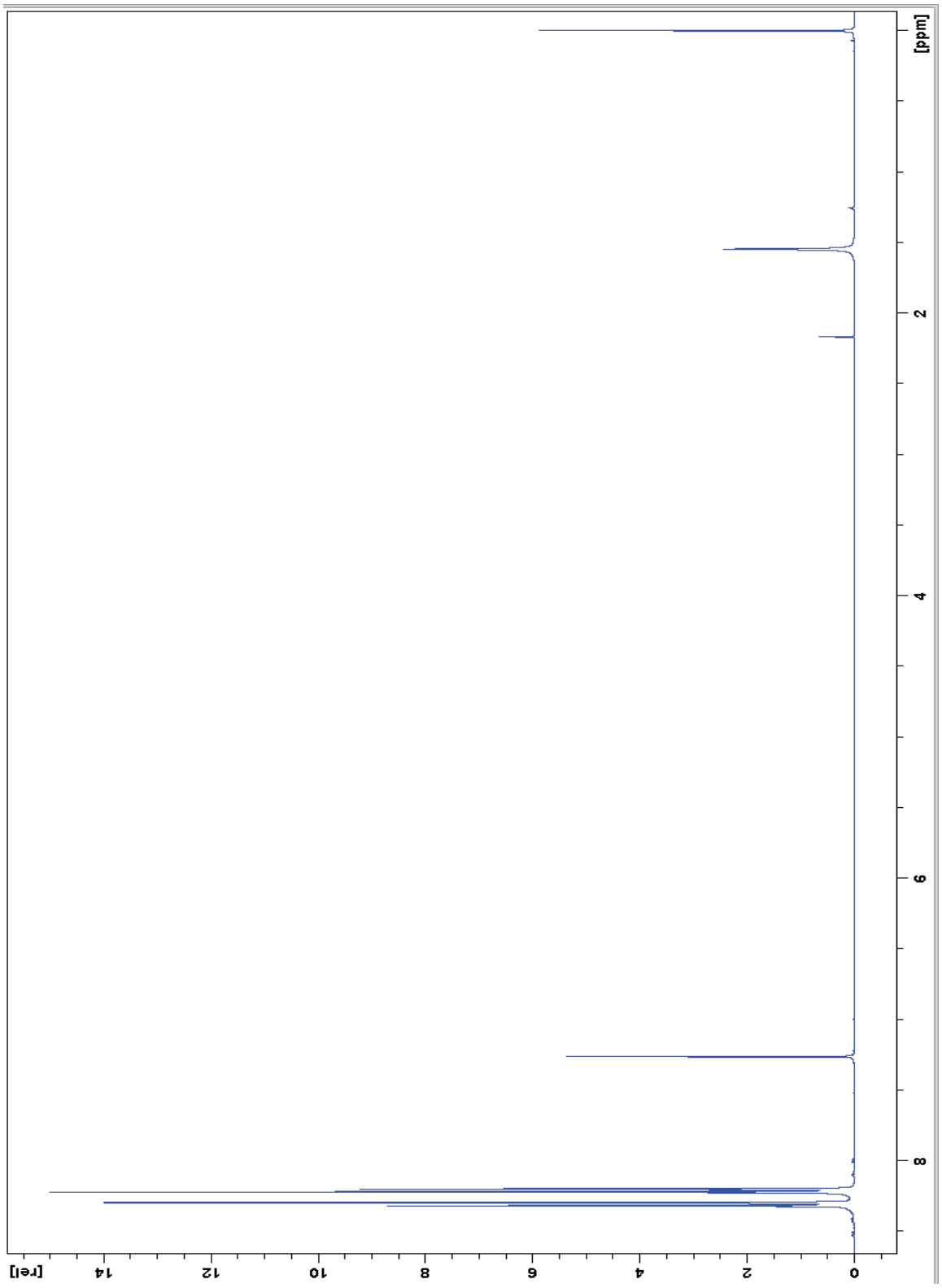


Figure 12: ^{1}H NMR of 4-nitrobenzoyl azide (**4**).

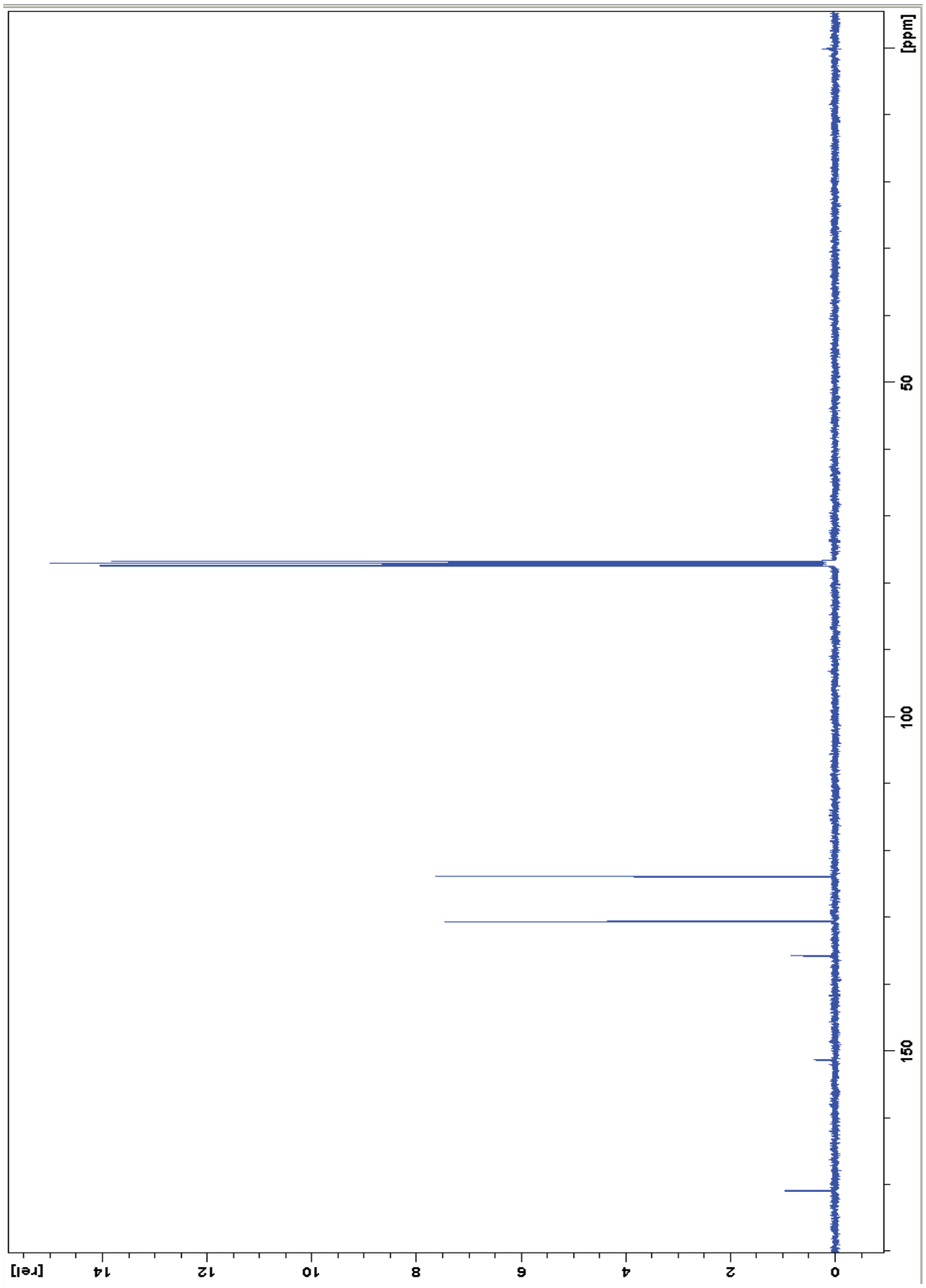


Figure 13: ^{13}C NMR of 4-nitrobenzoyl azide (**4**).

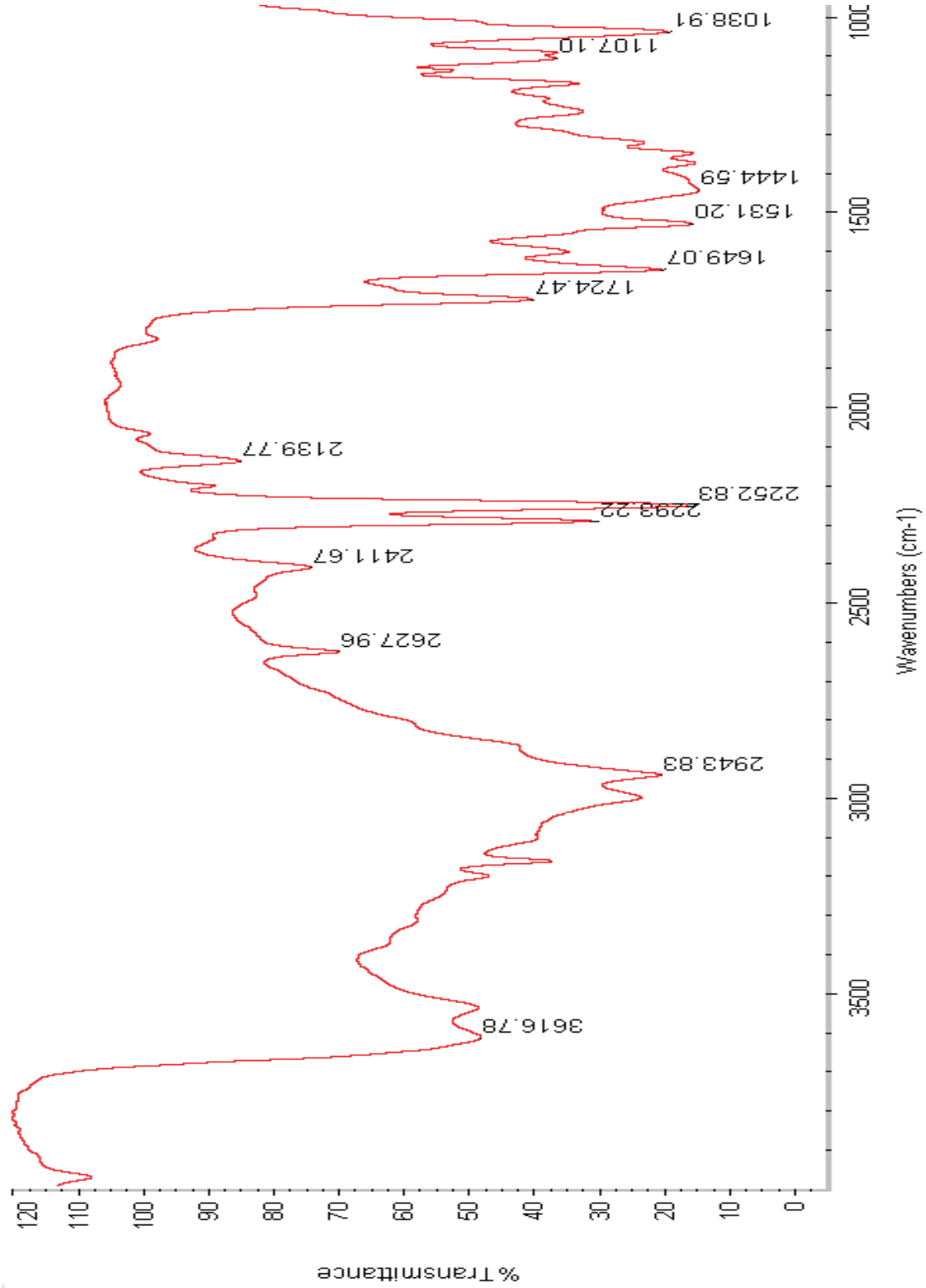


Figure 14: ^{13}C NMR of 4-nitrobenzoyl azide (**4**).

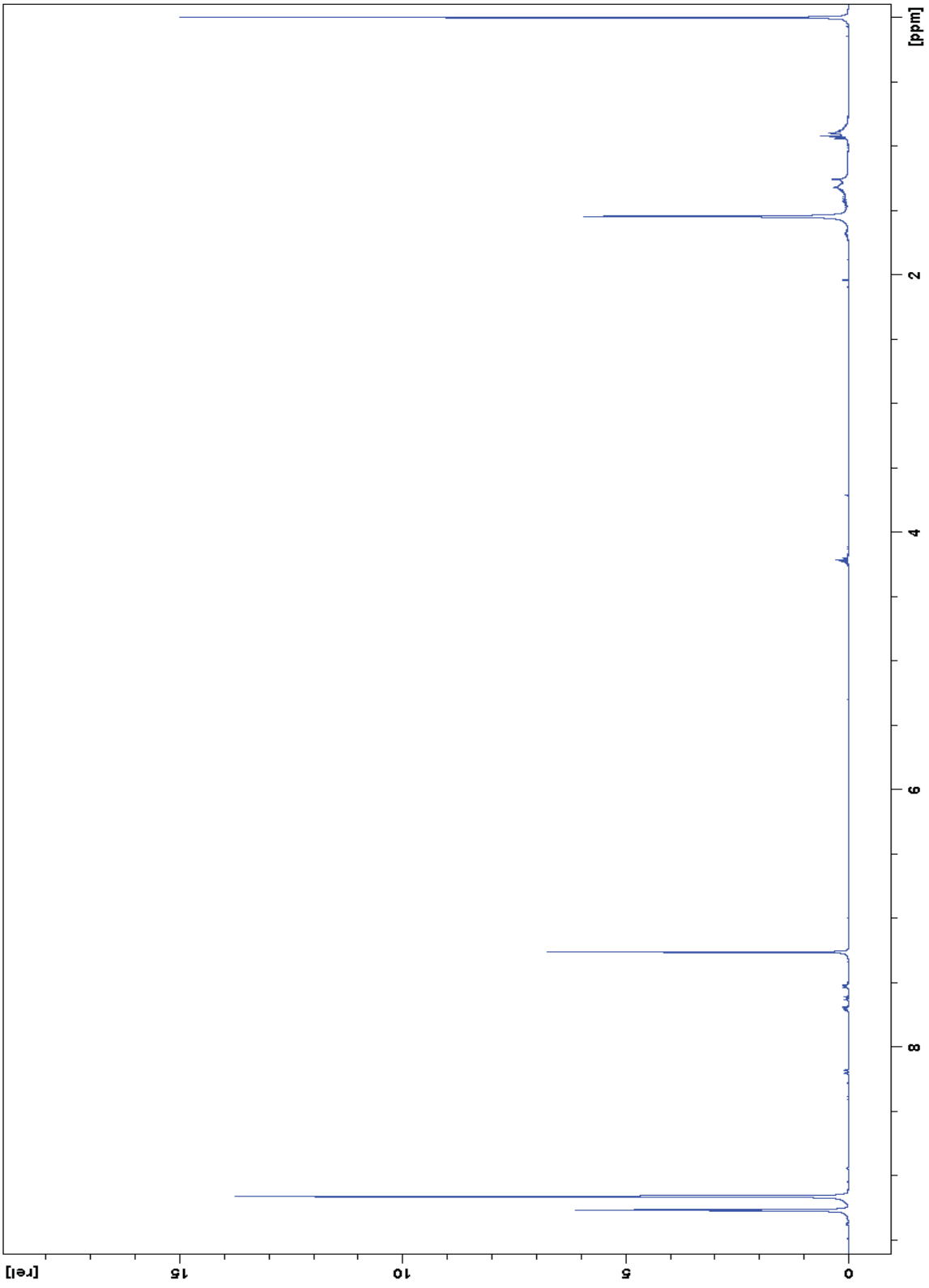


Figure 15: ^{1}H NMR of 3,5-dinitrobenzoyl azide (**6**).

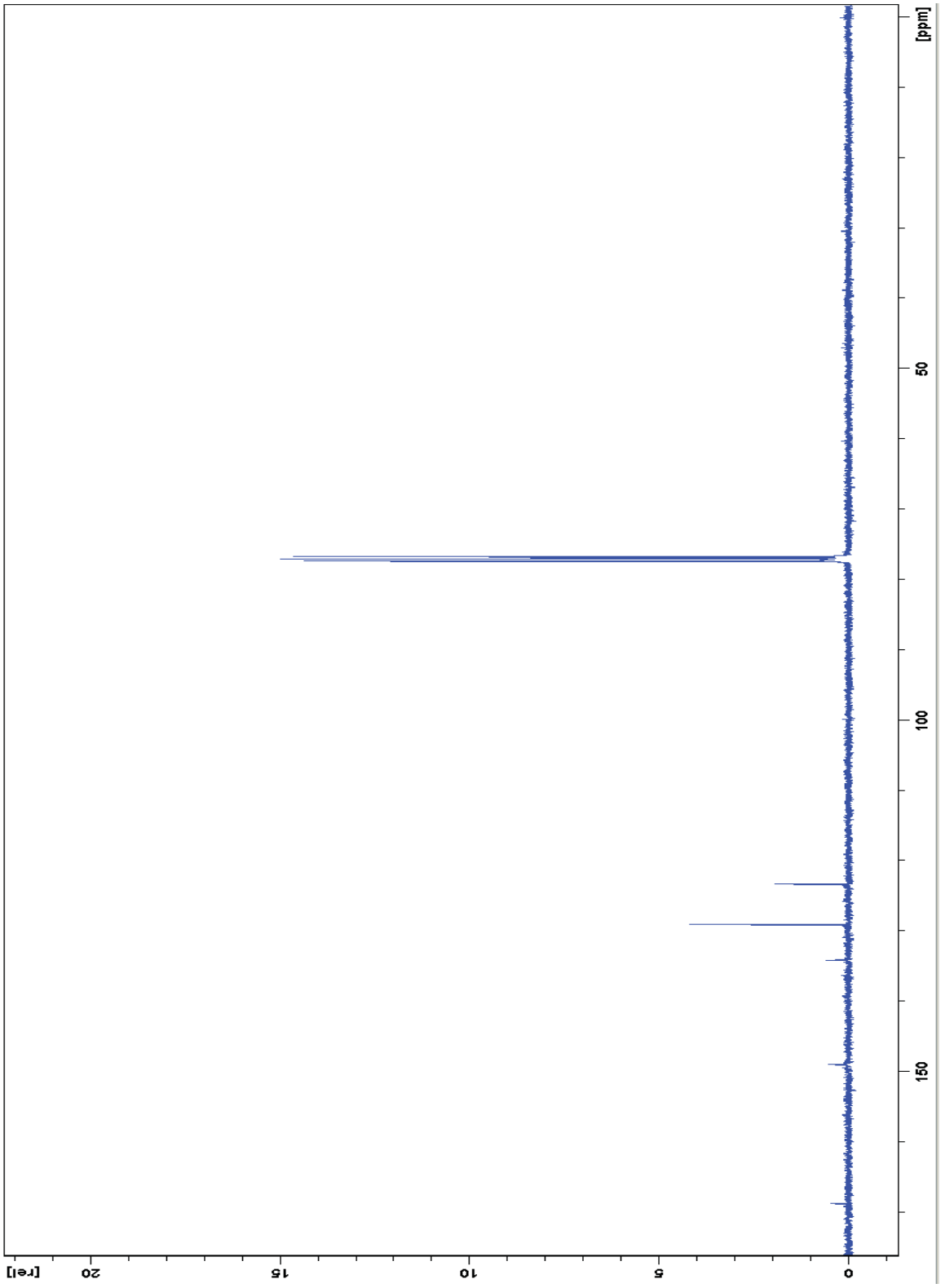


Figure 16: ^{13}C NMR of 3,5-dinitrobenzoyl azide (**6**).

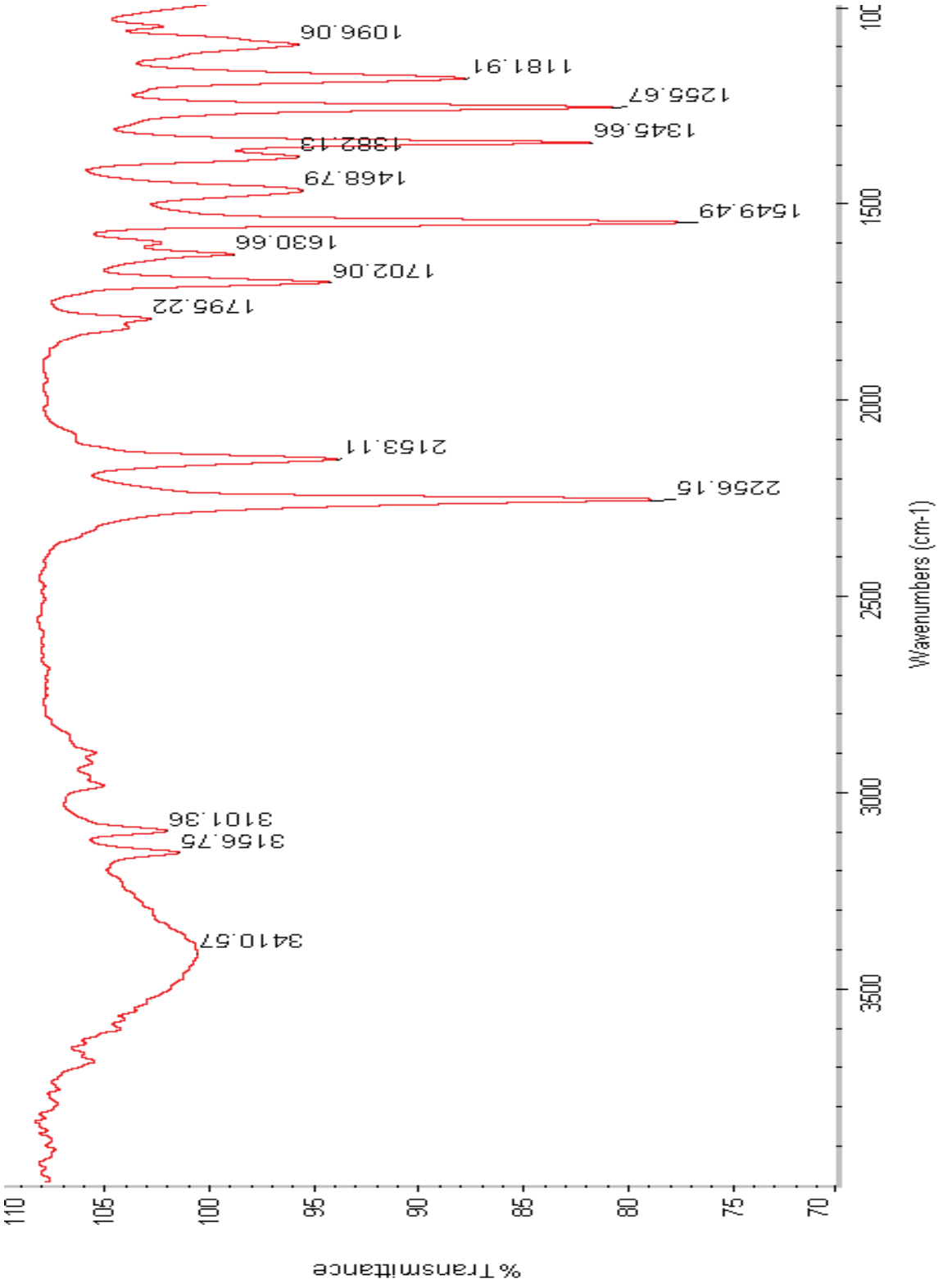


Figure 17: ^{13}C NMR of 3,5-dinitrobenzoyl azide (**6**).

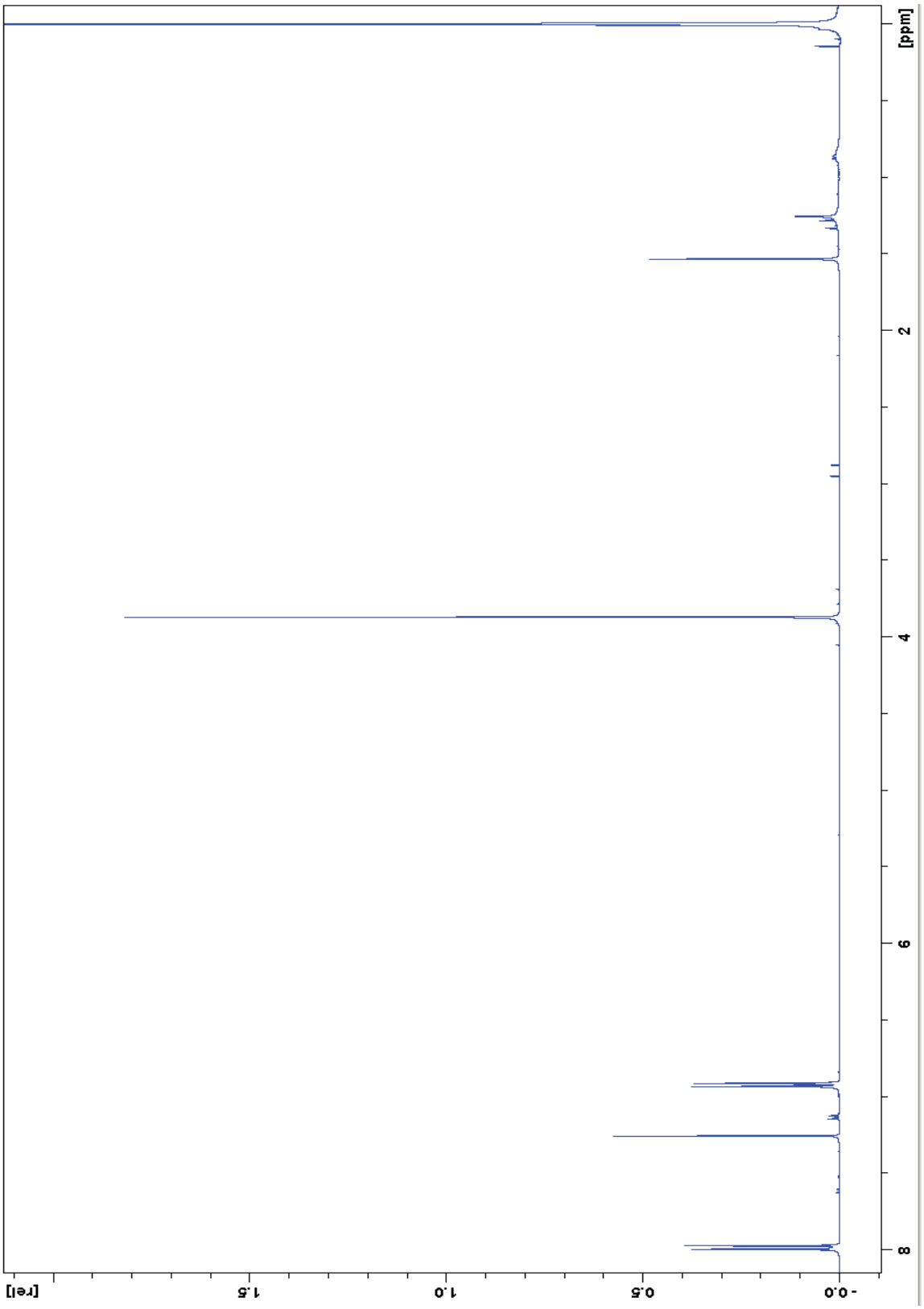


Figure 18: ^{1}H NMR of 4-methoxybenzoyl azide (**8**).

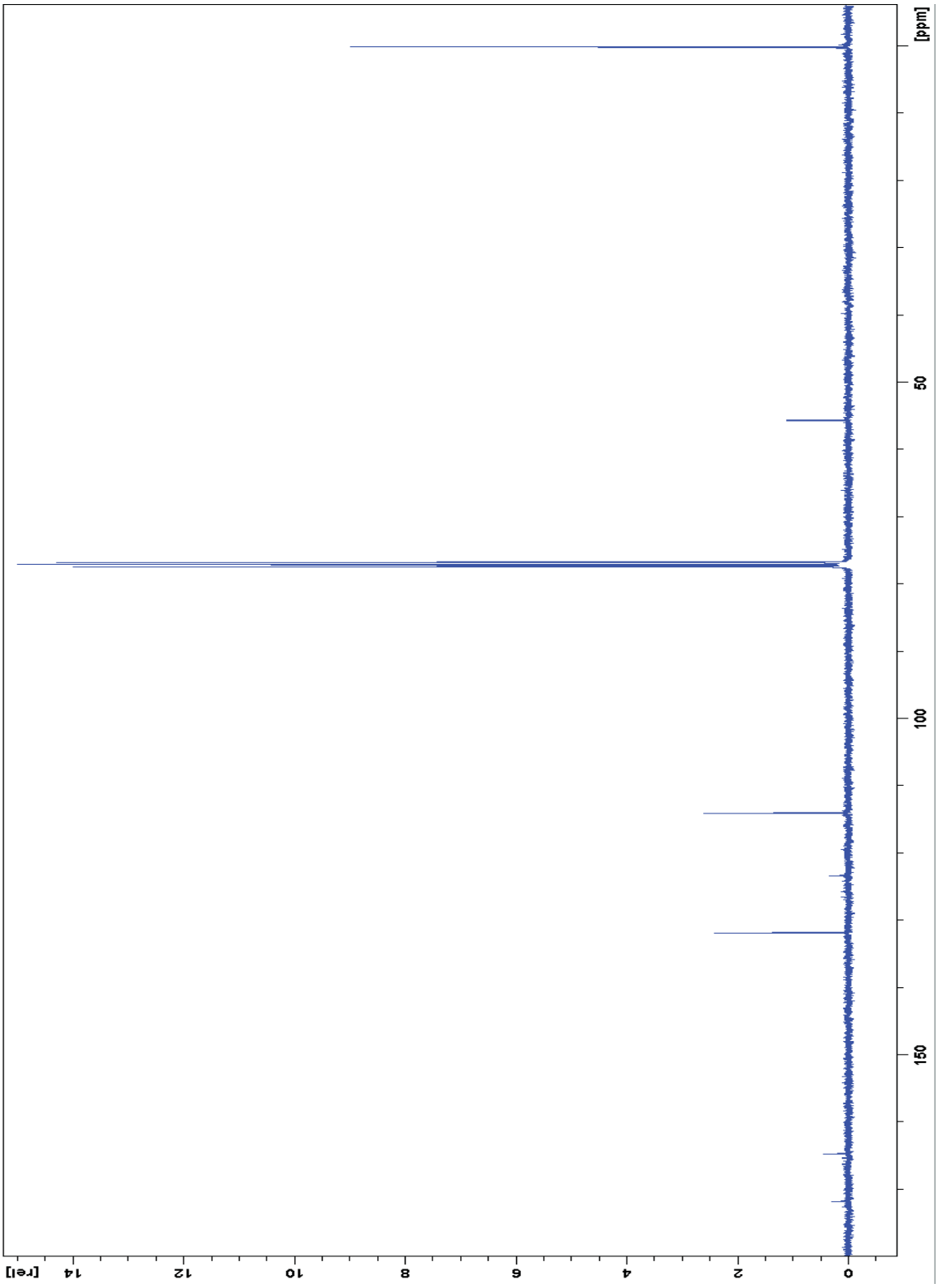


Figure 19: ^{13}C NMR of 4-methoxybenzoyl azide (**8**).

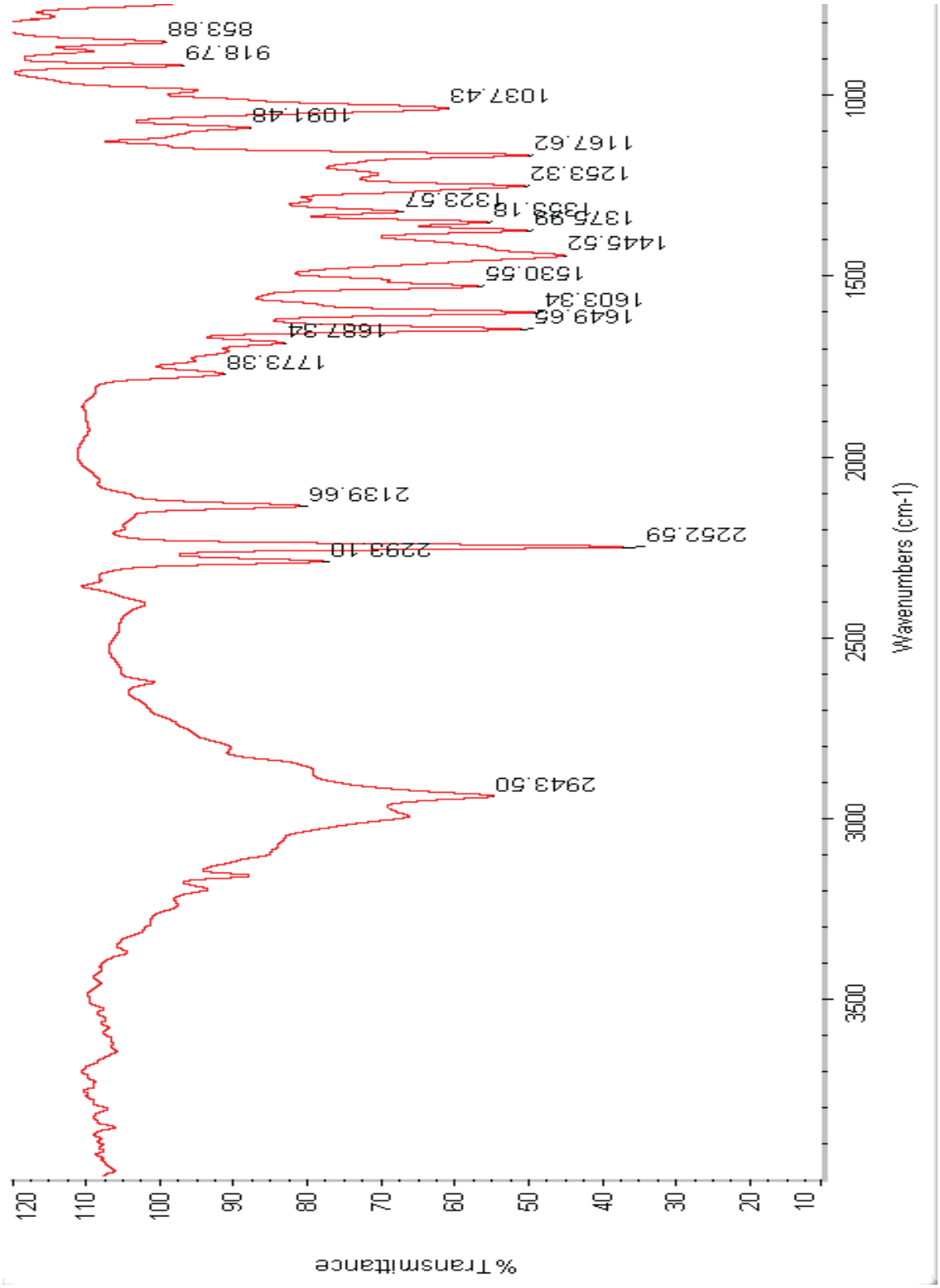


Figure 20: IR spectrum of 4-methoxybenzoyl azide (**8**).

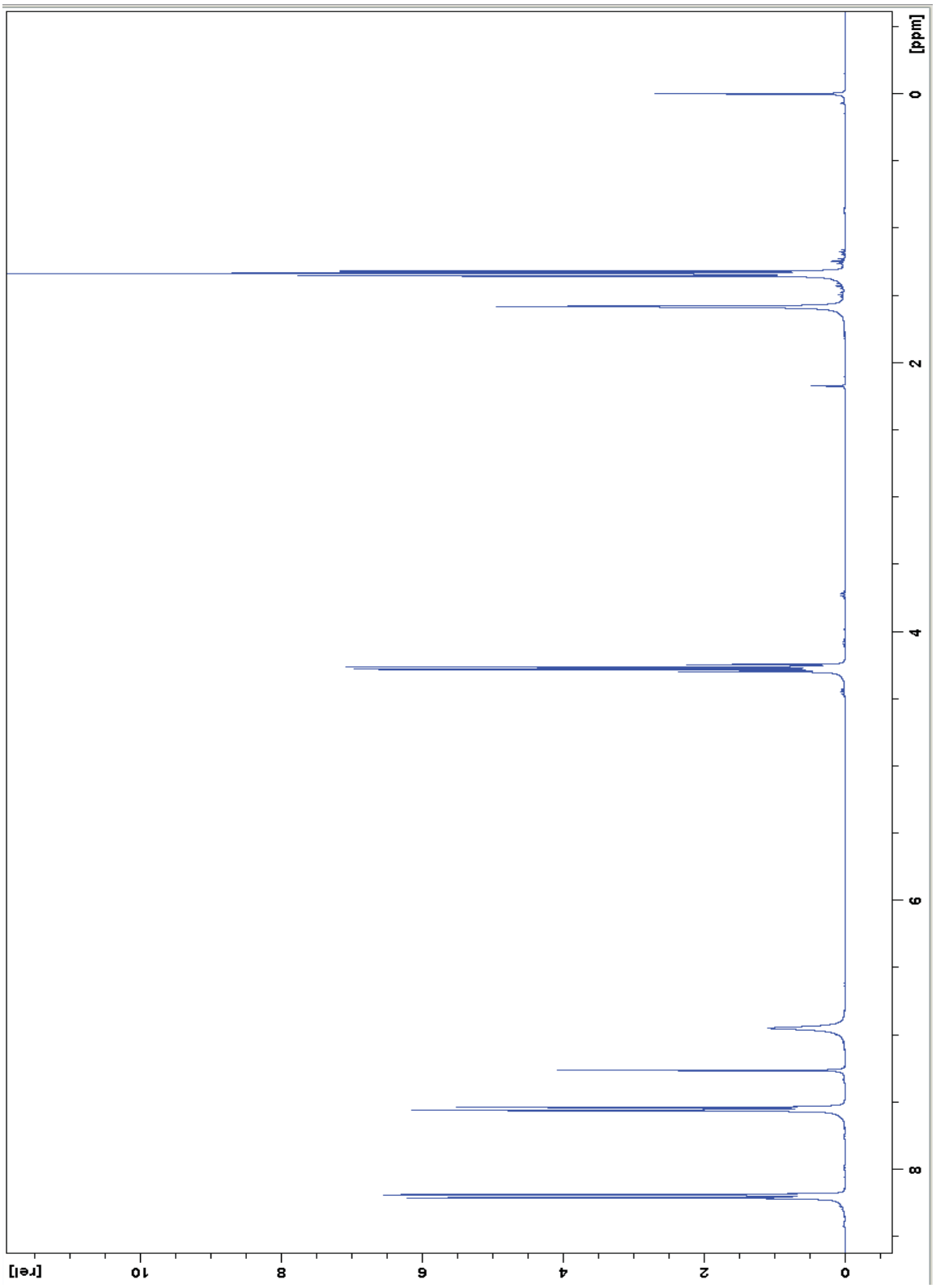


Figure 20: ^{1}H NMR of ethyl (4-nitrophenyl) carbamate (**9**).

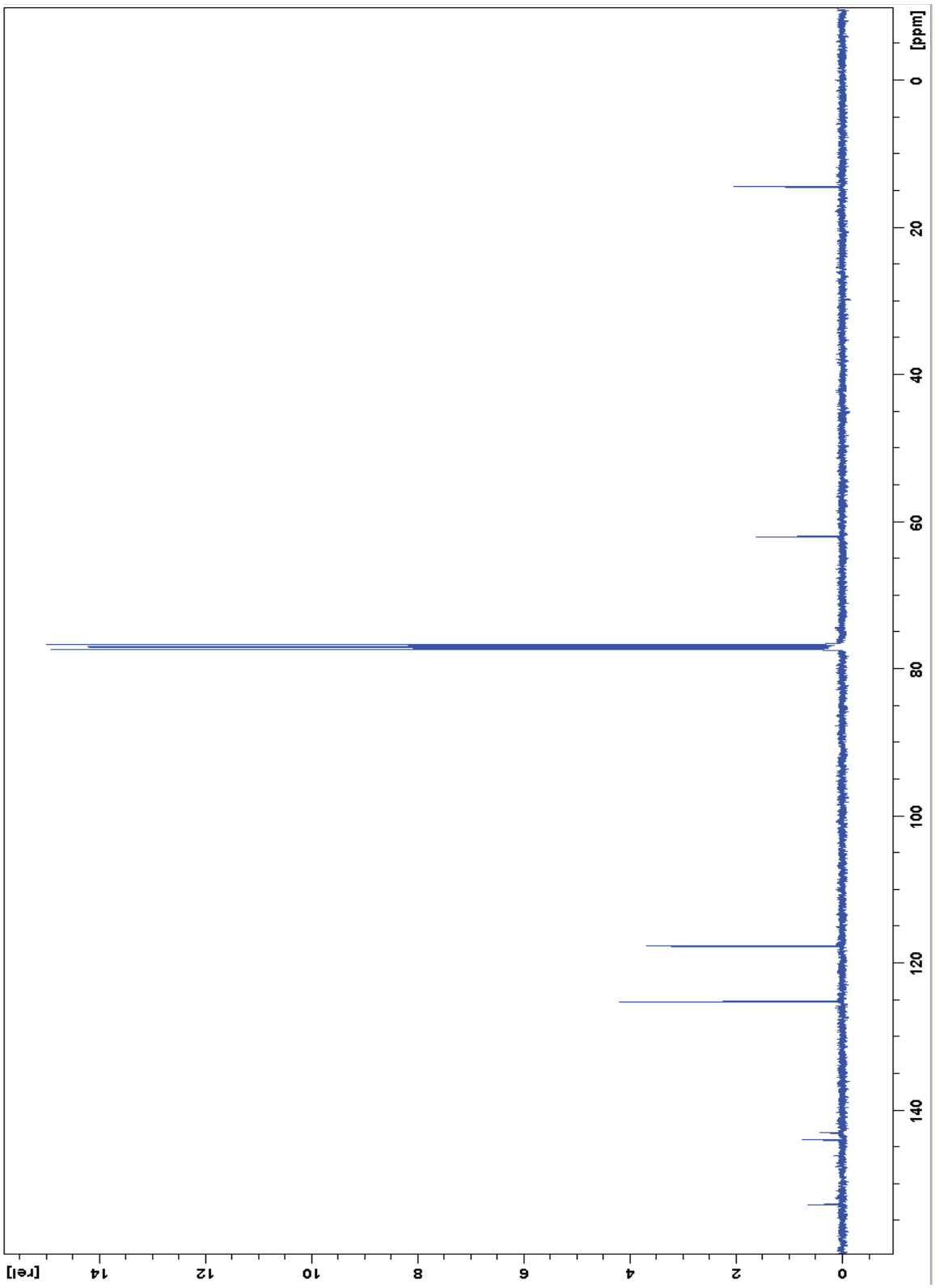


Figure 21: ^{13}C NMR of ethyl (4-nitrophenyl) carbamate (**9**).

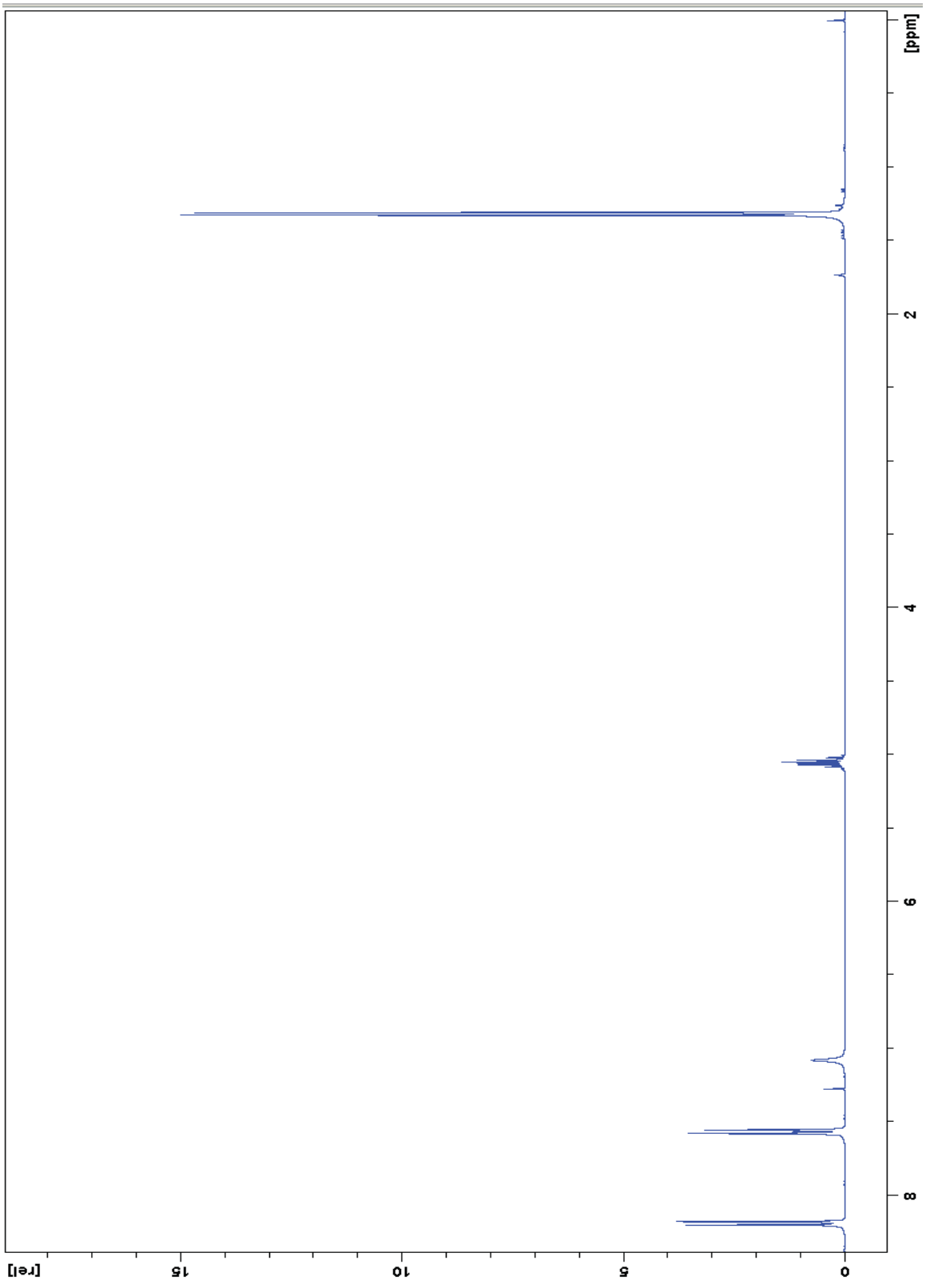


Figure 22: ^{1}H NMR of isopropyl (4-nitrophenyl) carbamate (**10**).

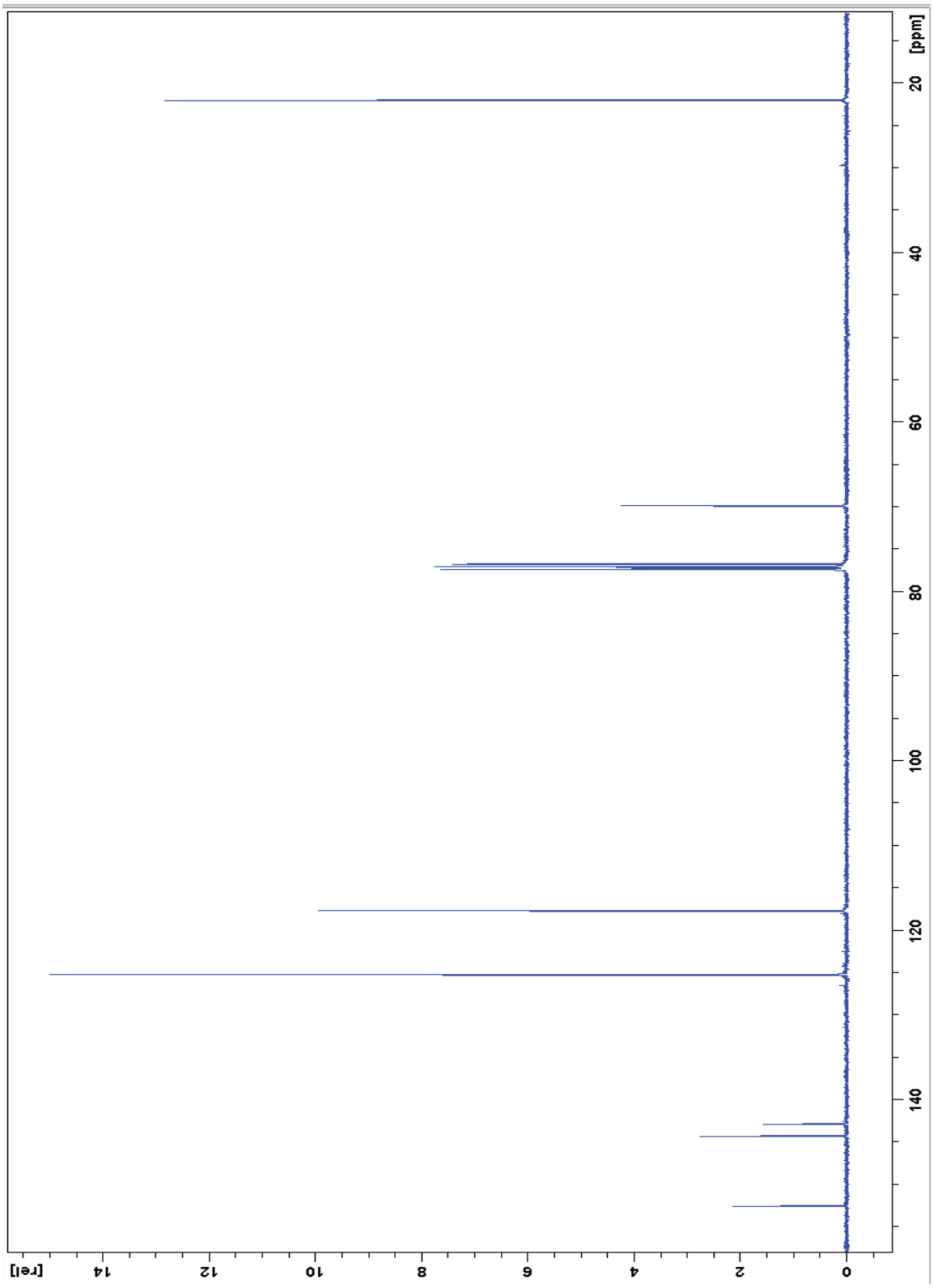


Figure 23: ^{1}H NMR of isopropyl (4-nitrophenyl) carbamate (**10**).

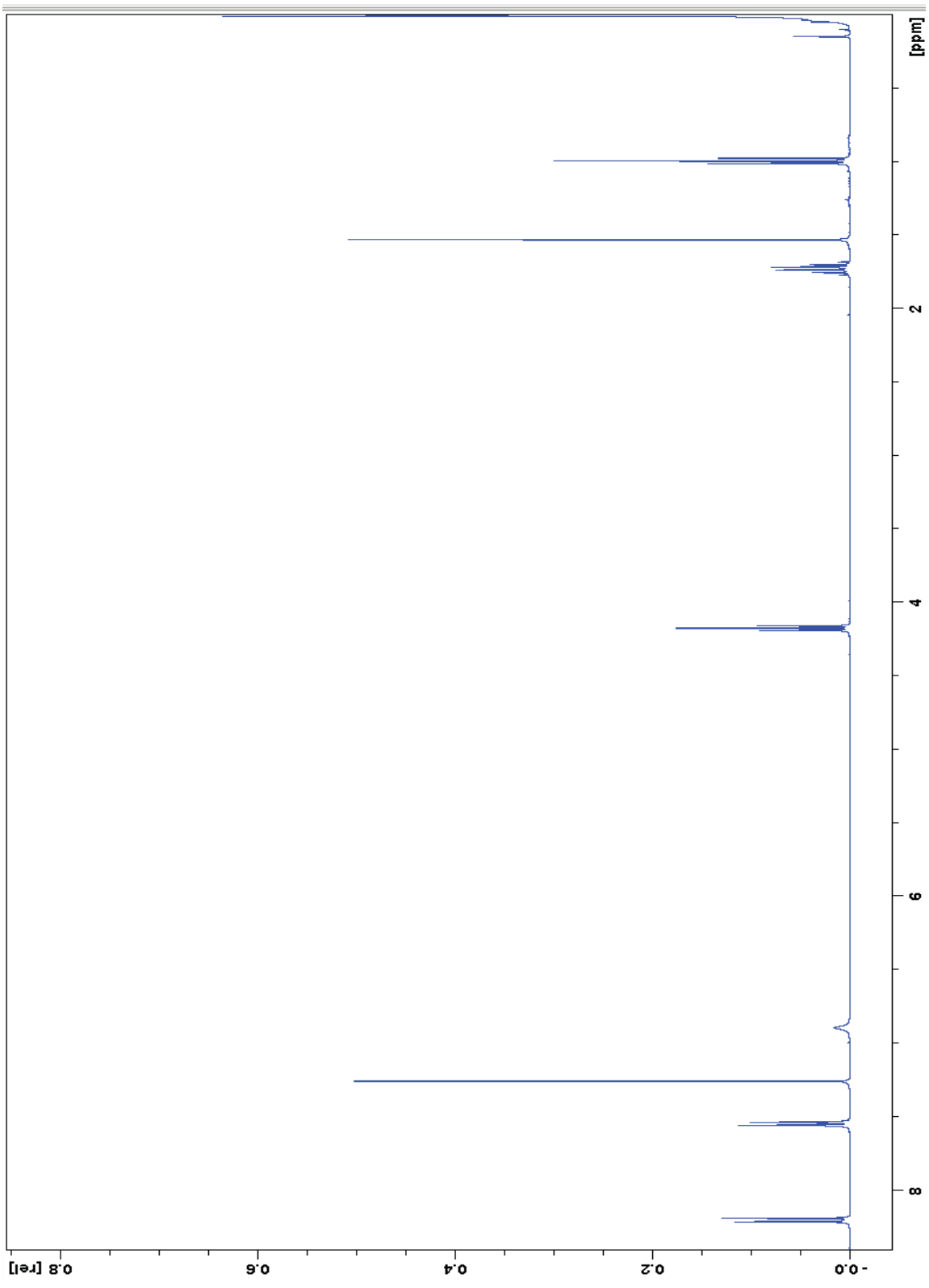


Figure 24: ^{1}H NMR of propyl (4-nitrophenyl) carbamate (**11**).

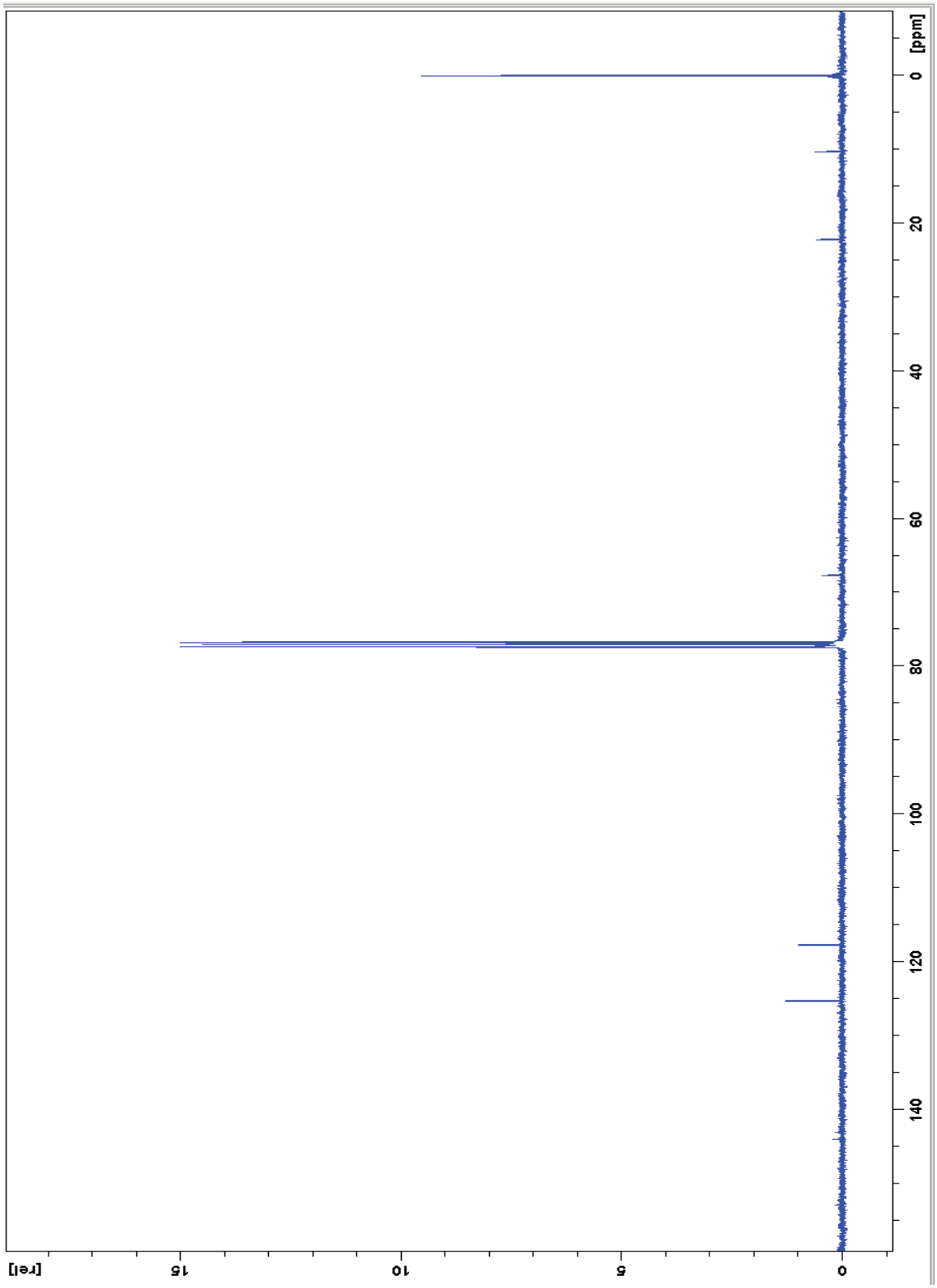


Figure 25: ^{13}C NMR of propyl (4-nitrophenyl) carbamate (**11**).

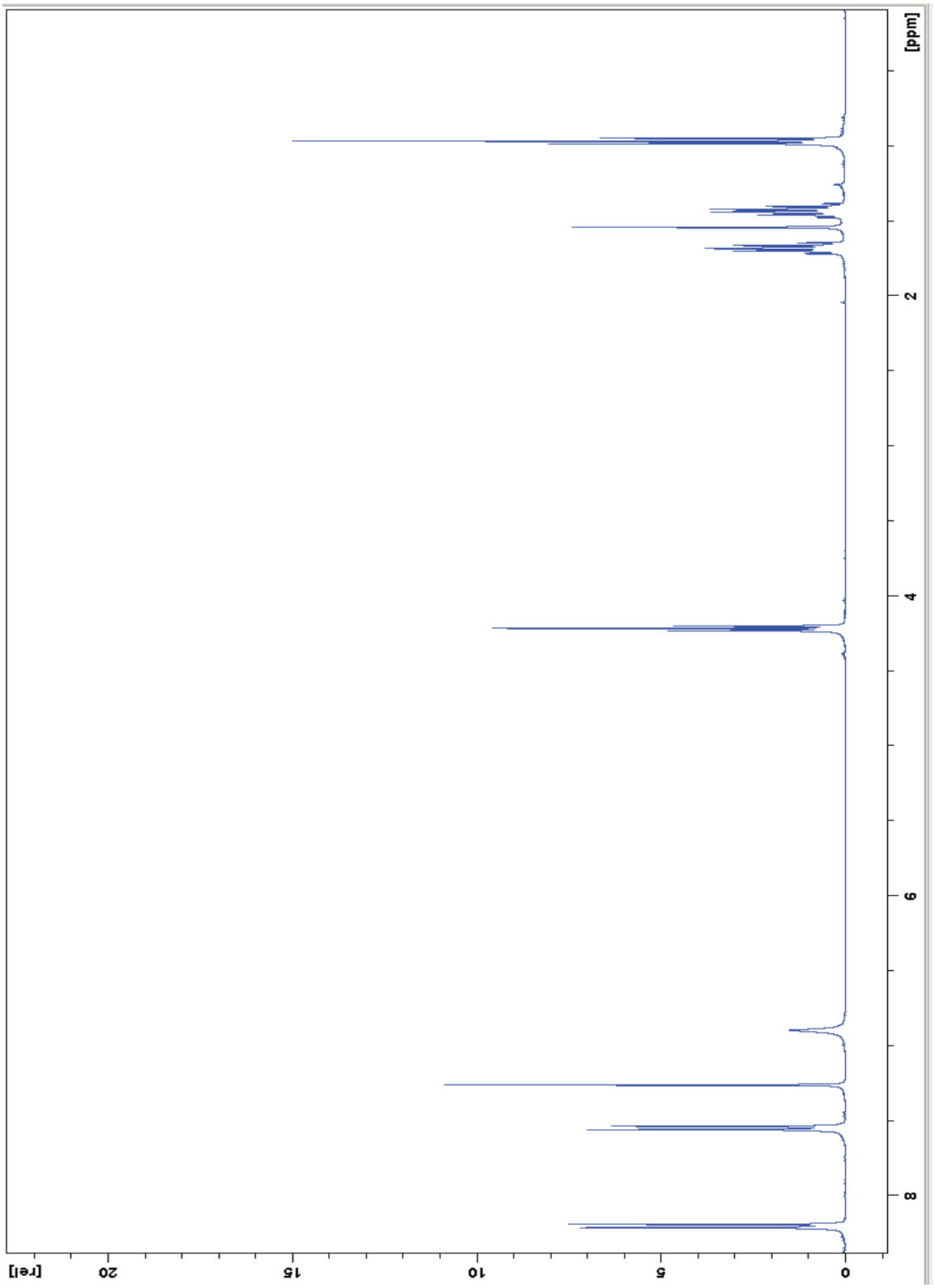


Figure 26: ^{1}H NMR of butyl (4-nitrophenyl) carbamate (**12**).

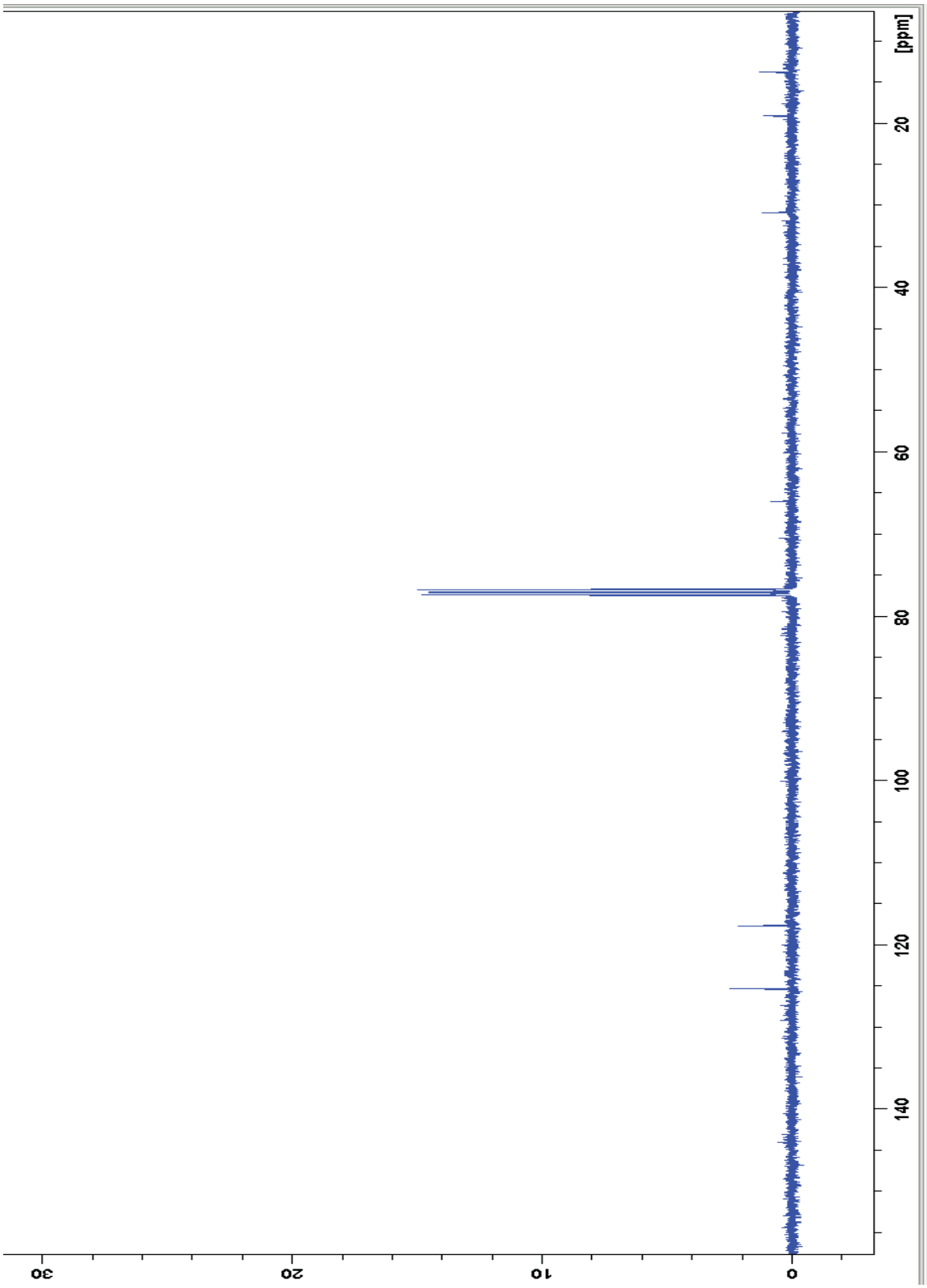


Figure 27: ^{13}C NMR of butyl (4-nitrophenyl) carbamate (**12**).

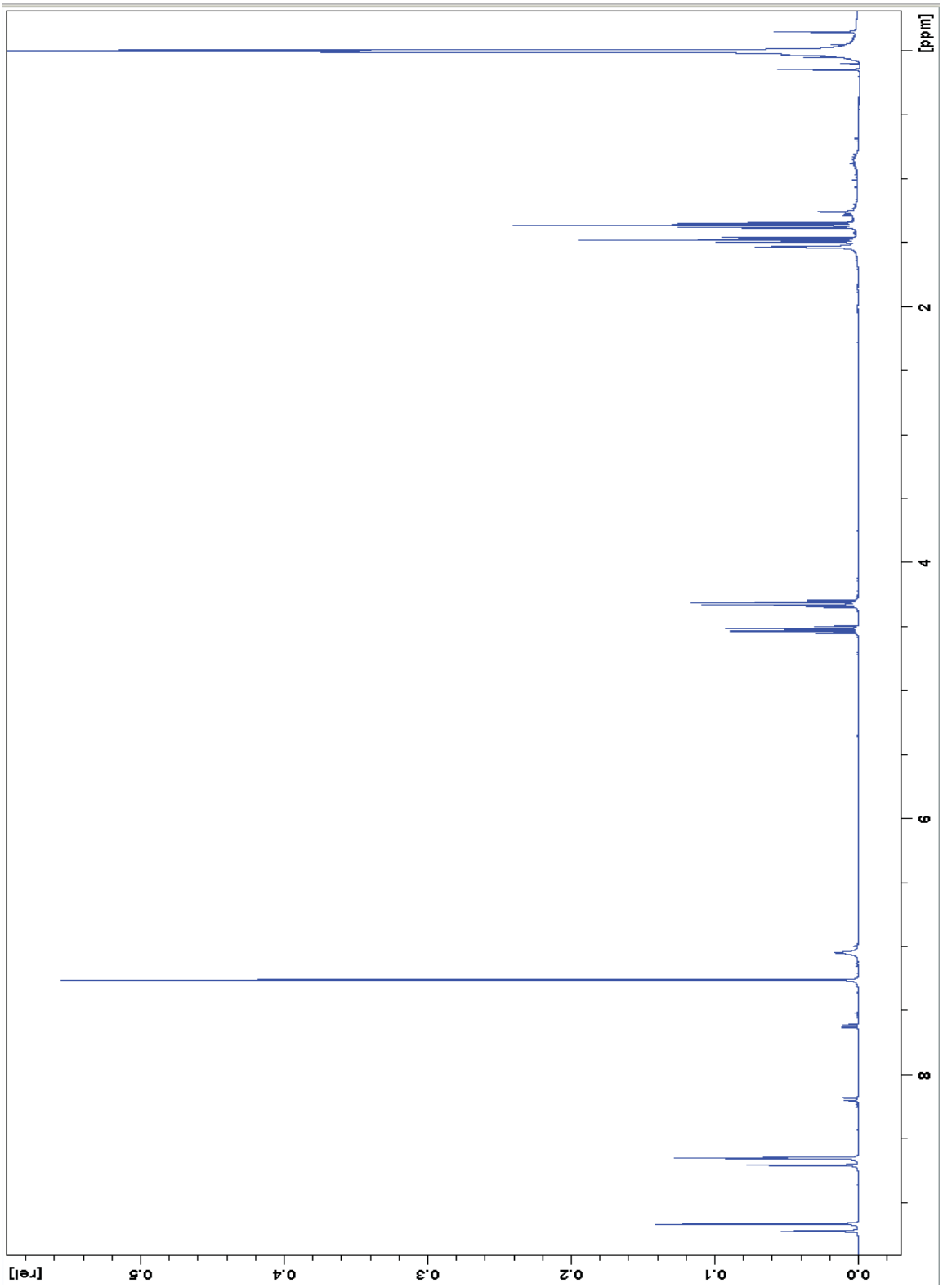


Figure 28: ^{1}H NMR of ethyl (3,5-dinitrophenyl) carbamate (**13**).

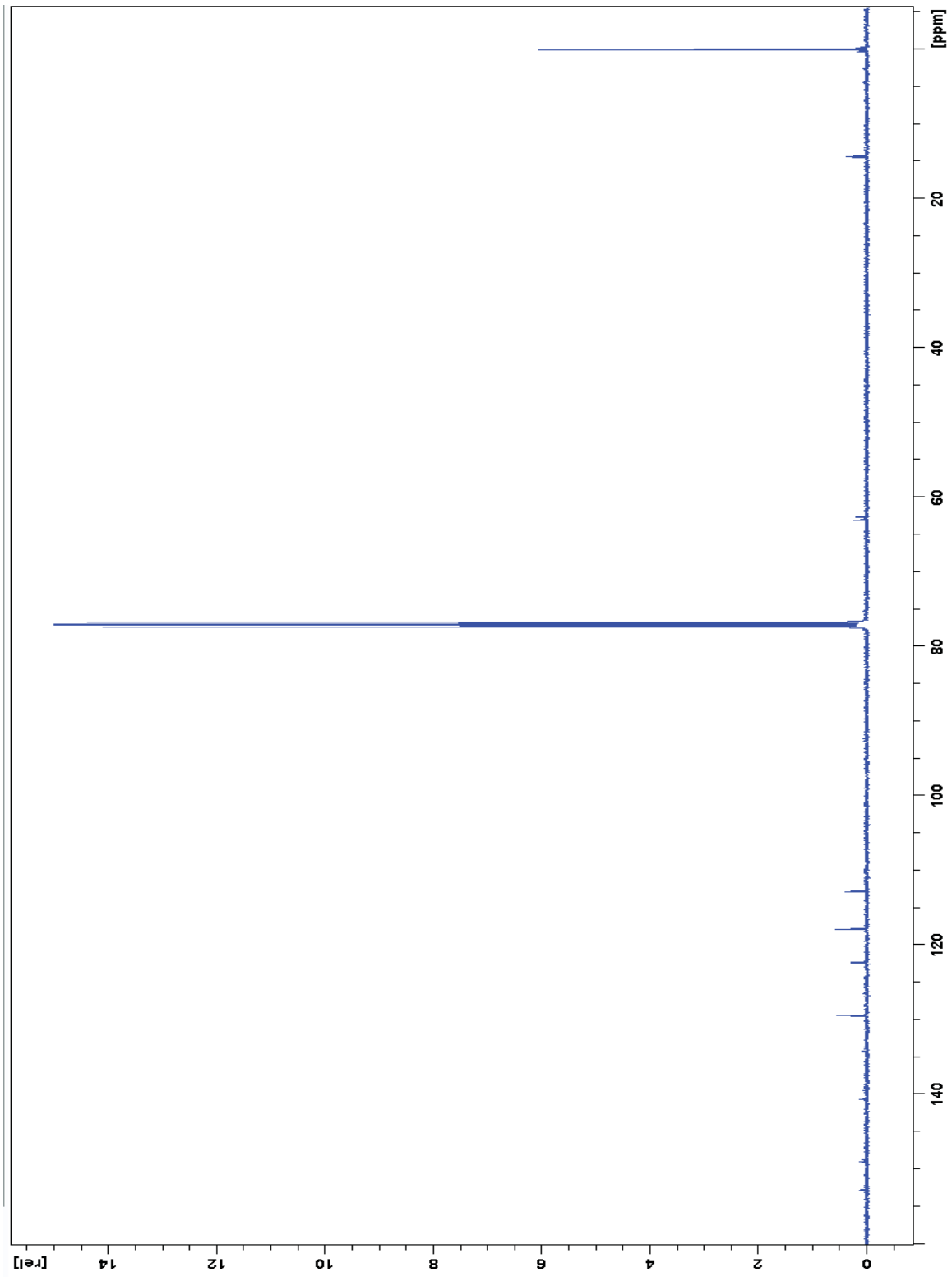


Figure 29: ^{13}C NMR of ethyl (3,5-dinitrophenyl) carbamate (**13**).

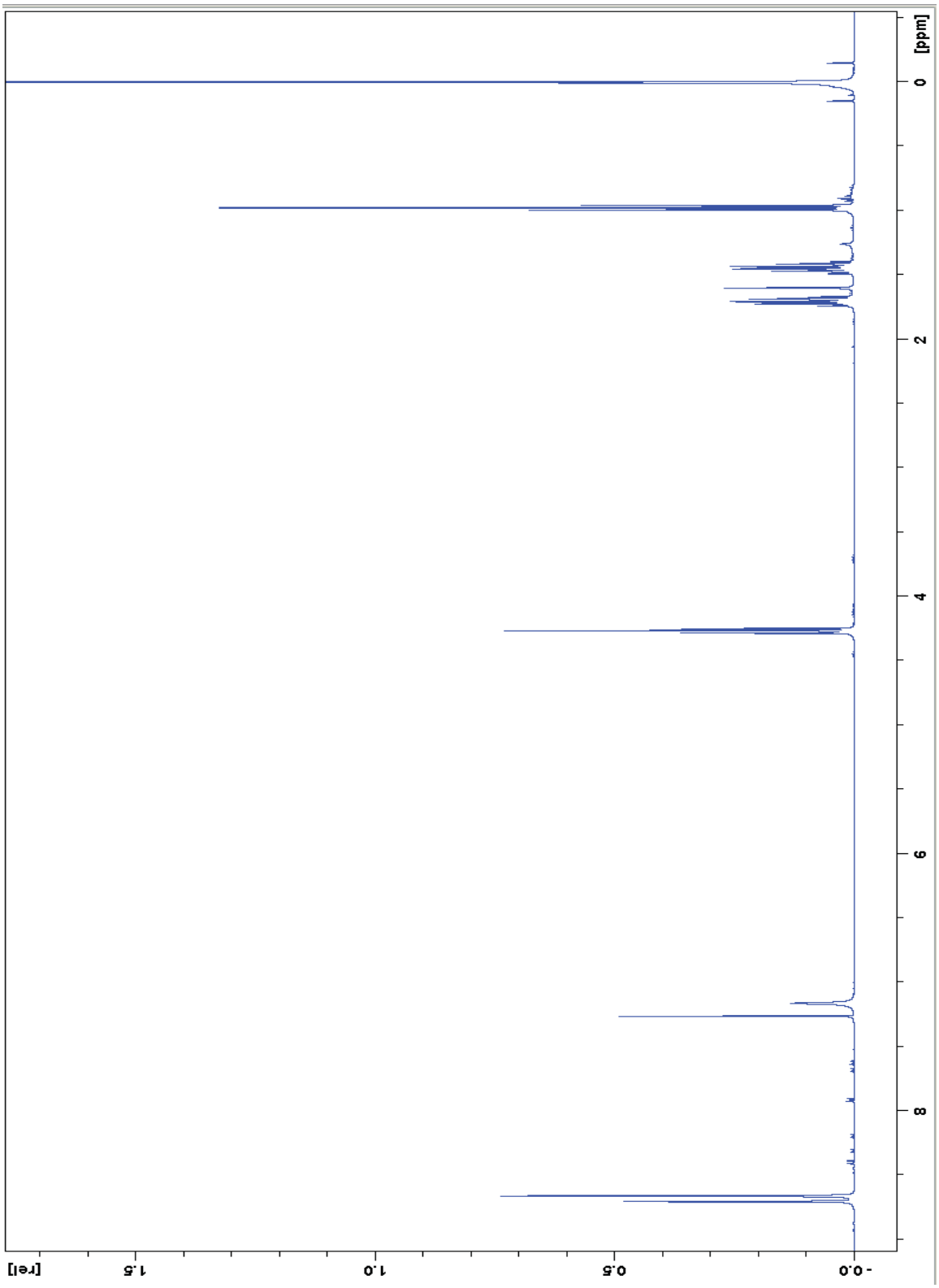


Figure 30: ^{1}H NMR of butylyl (3,5-dinitrophenyl) carbamate (**14**).

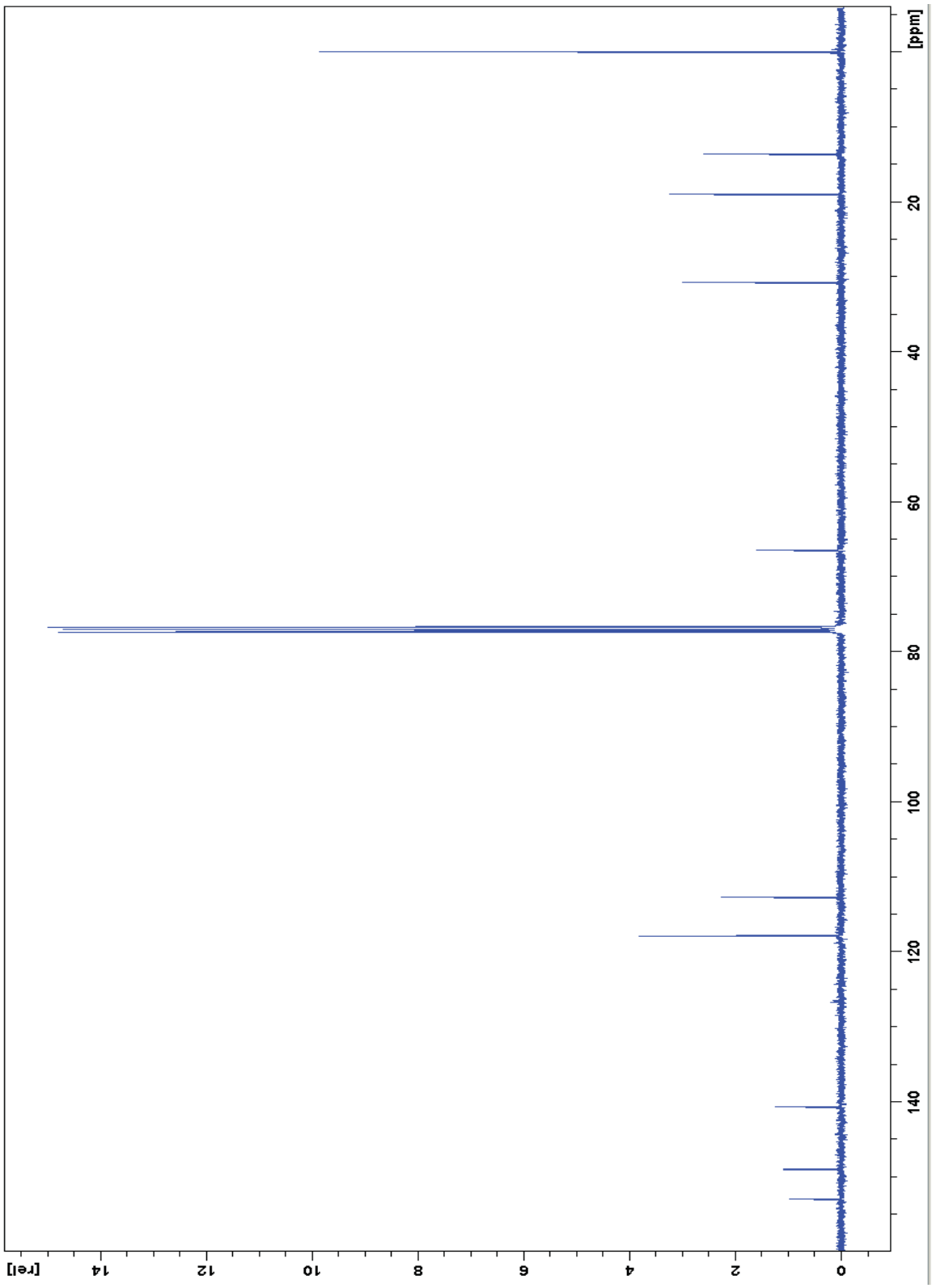


Figure 31: ^{13}C NMR of butyl (3,5-dinitrophenyl) carbamate (**14**).

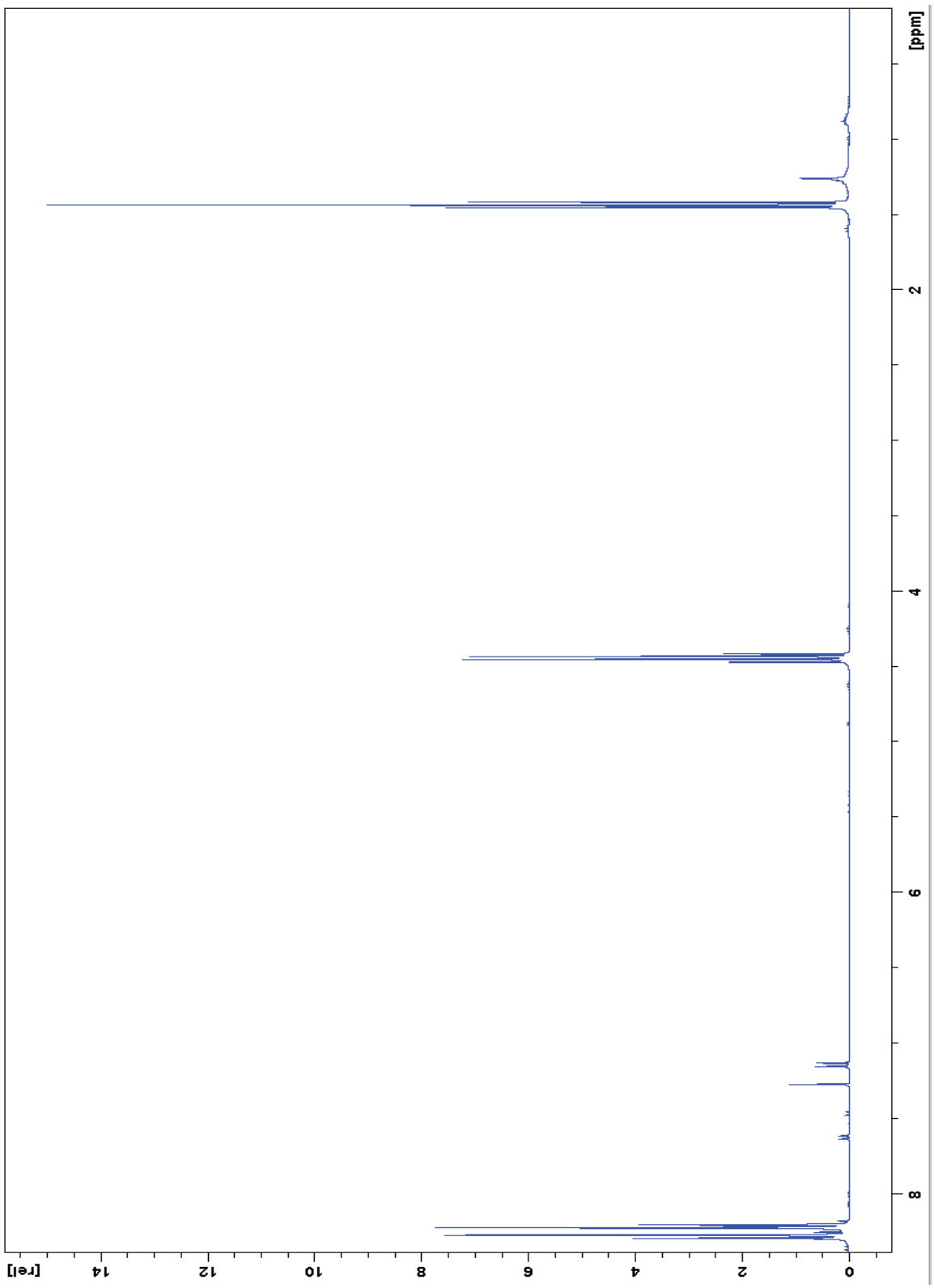


Figure 32: ^{1}H NMR of ethyl 4-nitrobenzoate (**15**).

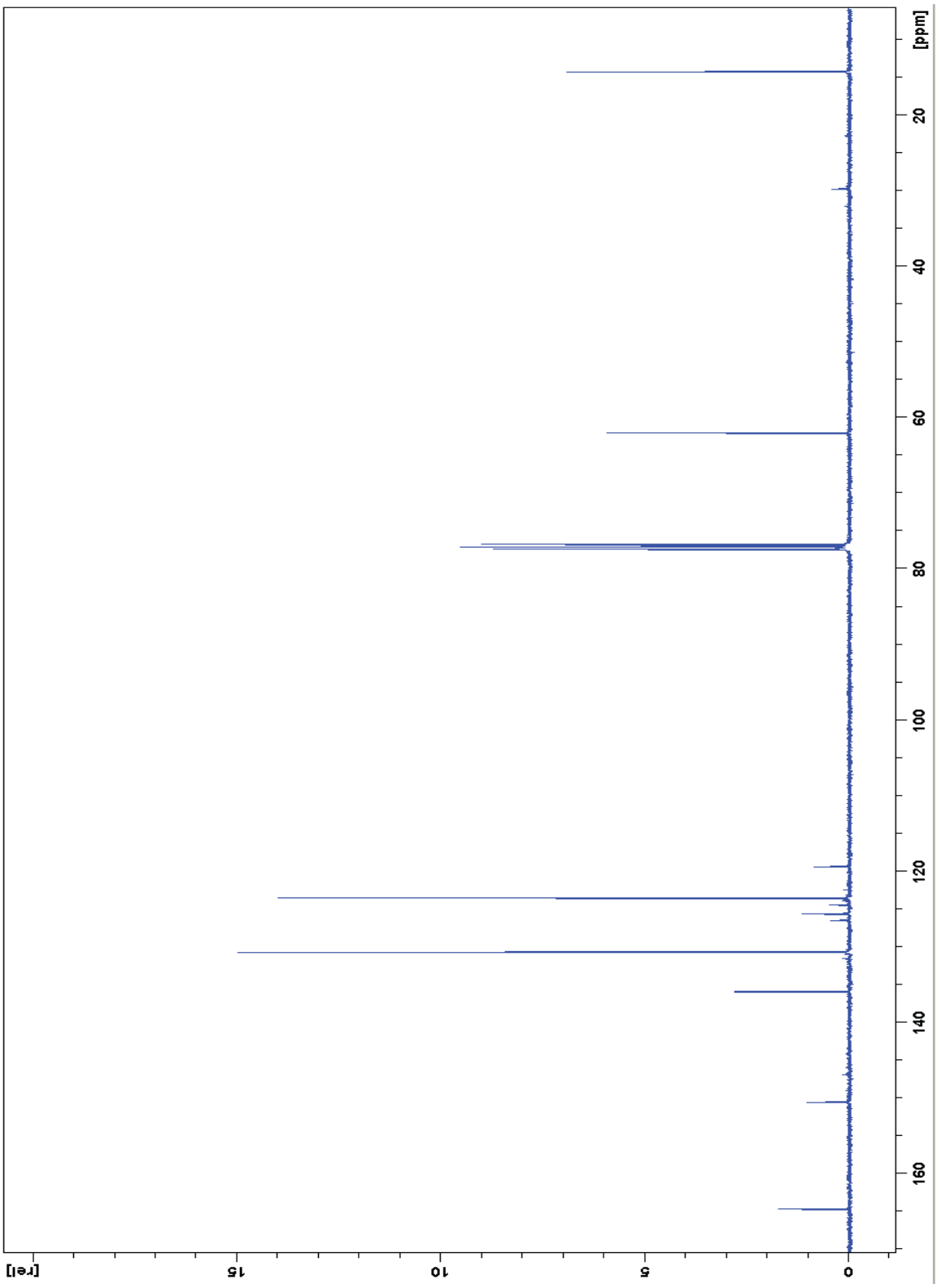


Figure 33: ^{13}C NMR of ethyl 4-nitrobenzoate (**15**).

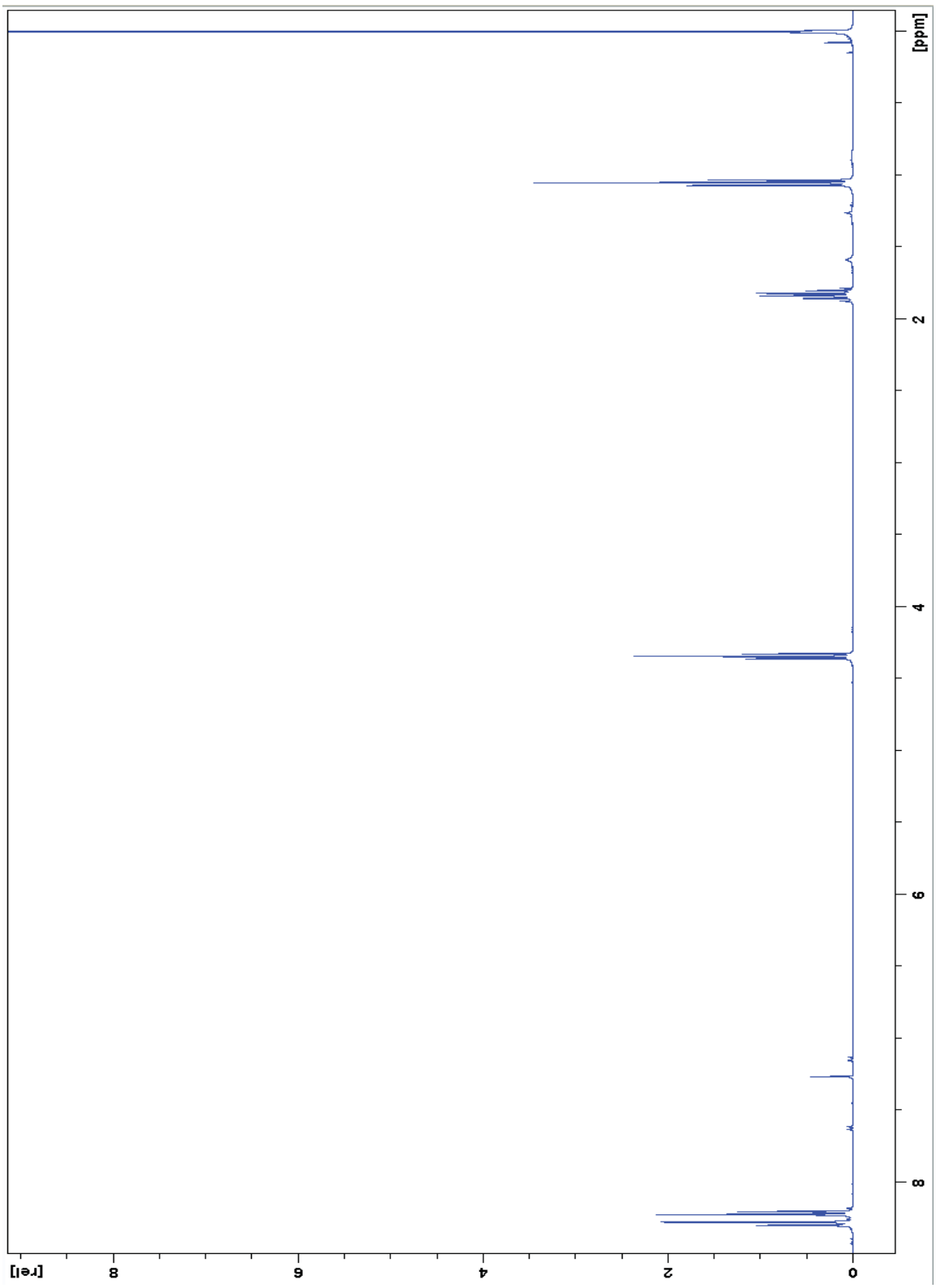


Figure 34: ^{1}H NMR of propyl 4-nitrobenzoate (**16**).

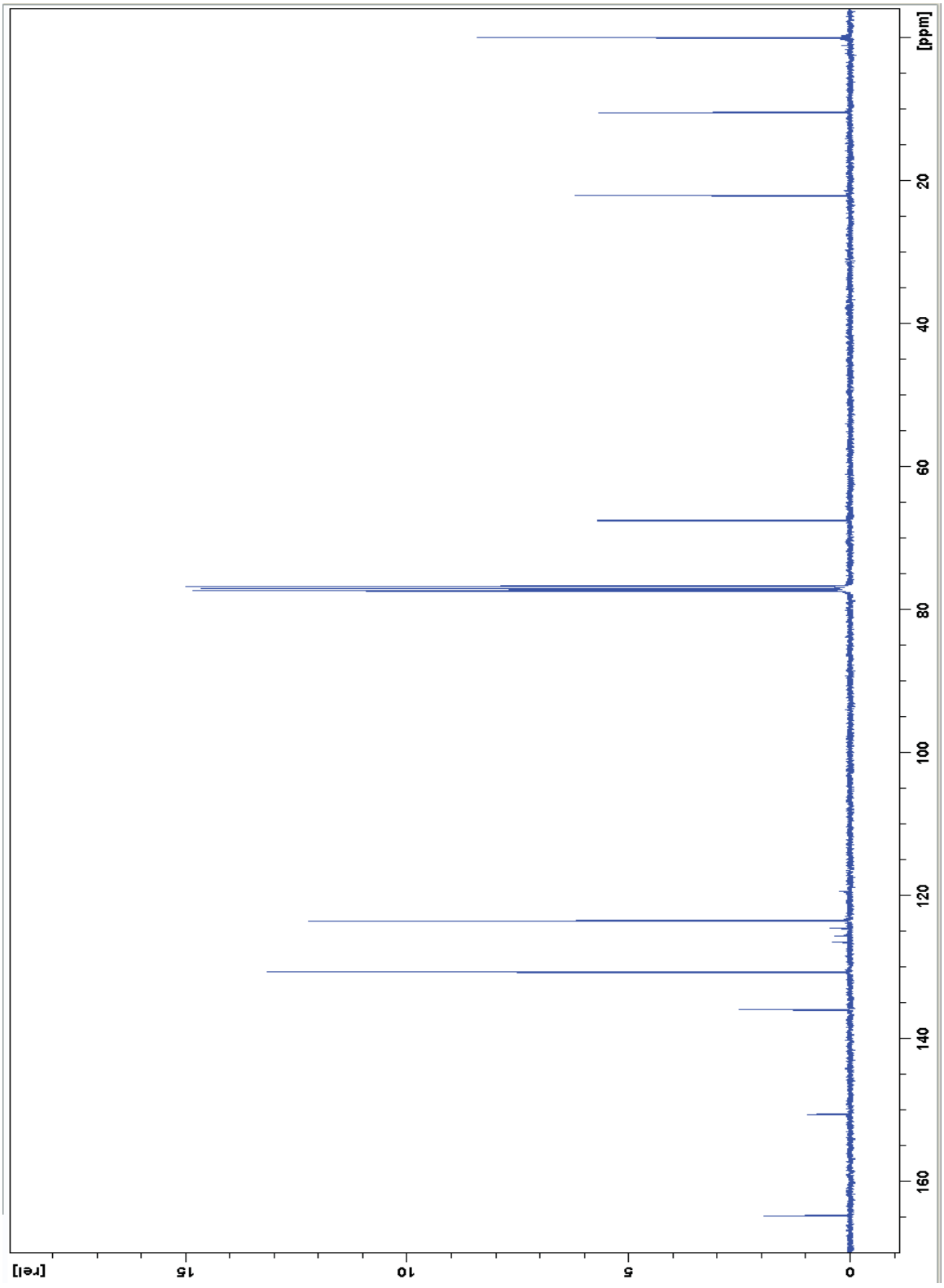


Figure 35: ^{1}H NMR of propyl 4-nitrobenzoate (**16**).

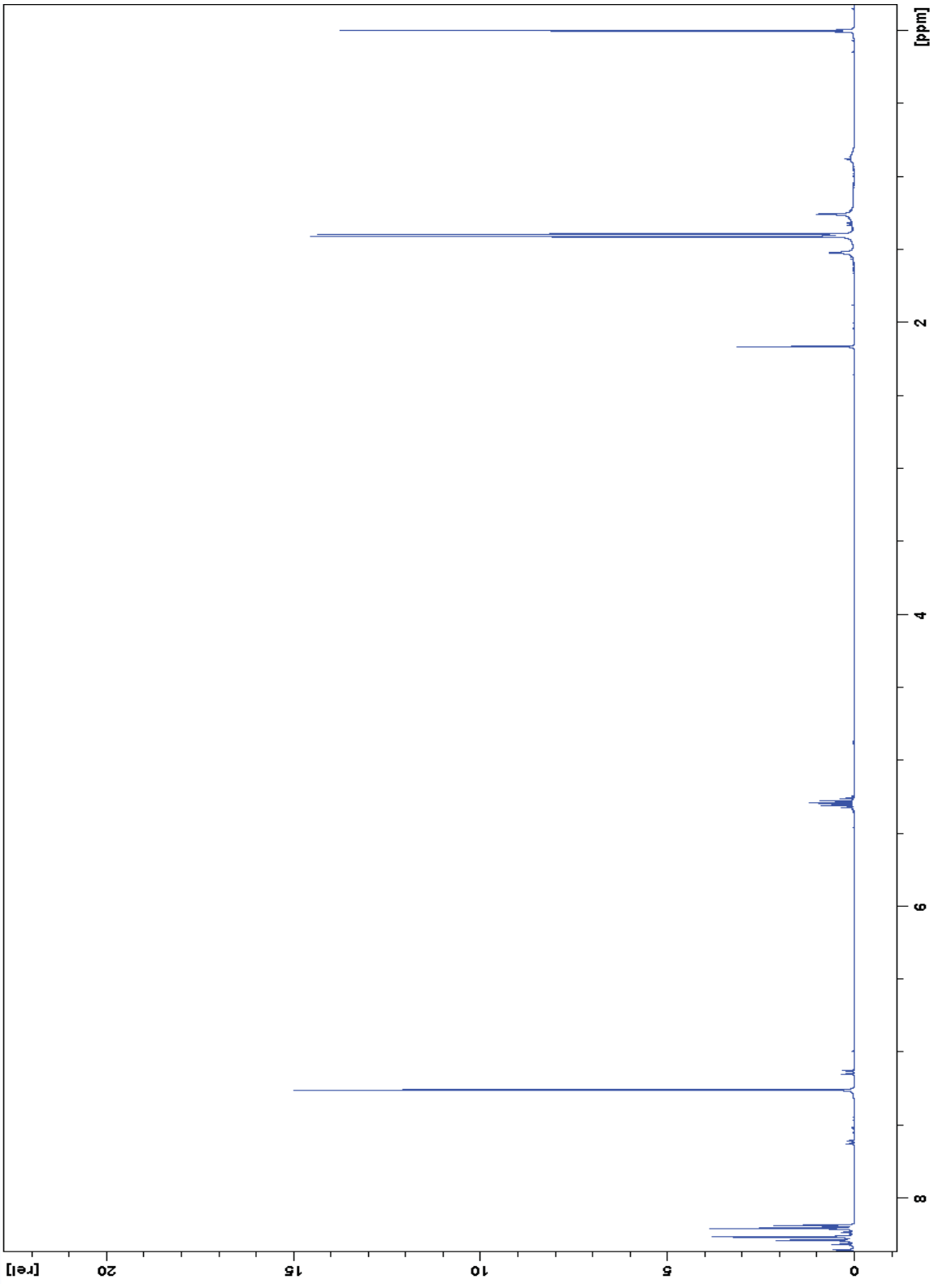


Figure 36: ^{1}H NMR of isopropyl 4-nitrobenzoate (**17**).

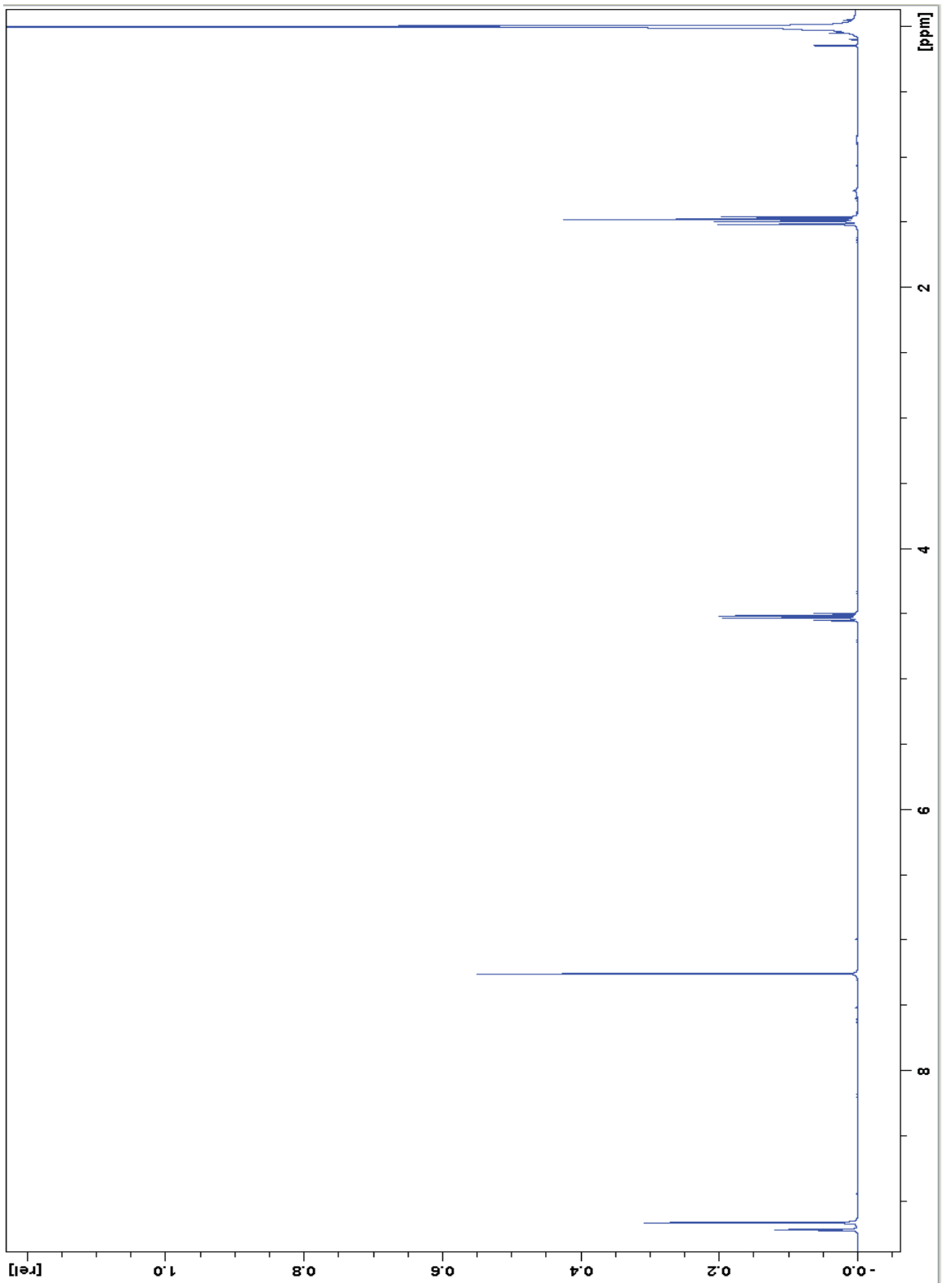


Figure 37: ^{1}H NMR of ethyl 3,5-dinitrobenzoate (**18**).

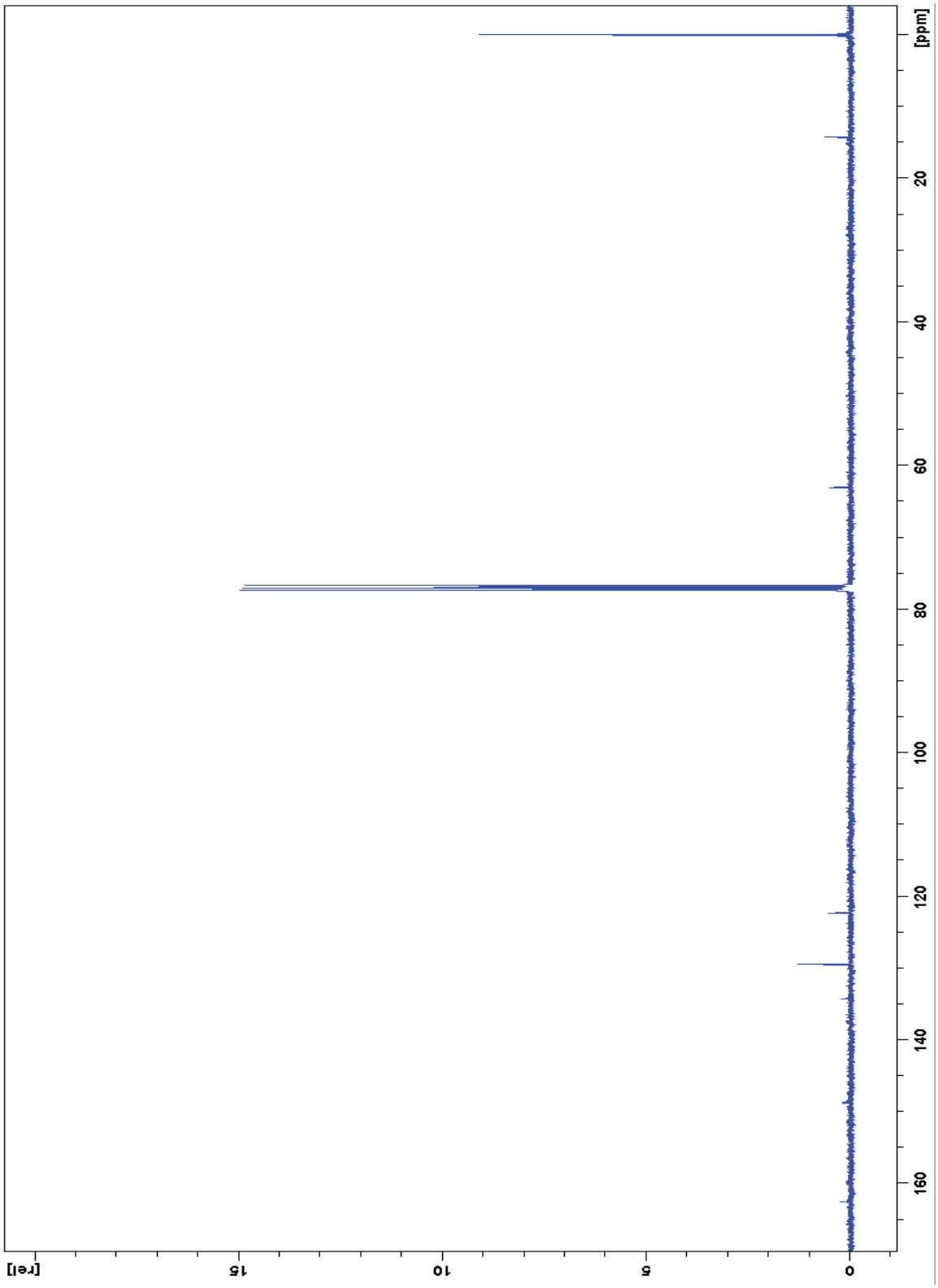


Figure 38: ^{13}C NMR of ethyl 3,5-dinitrobenzoate (**18**).

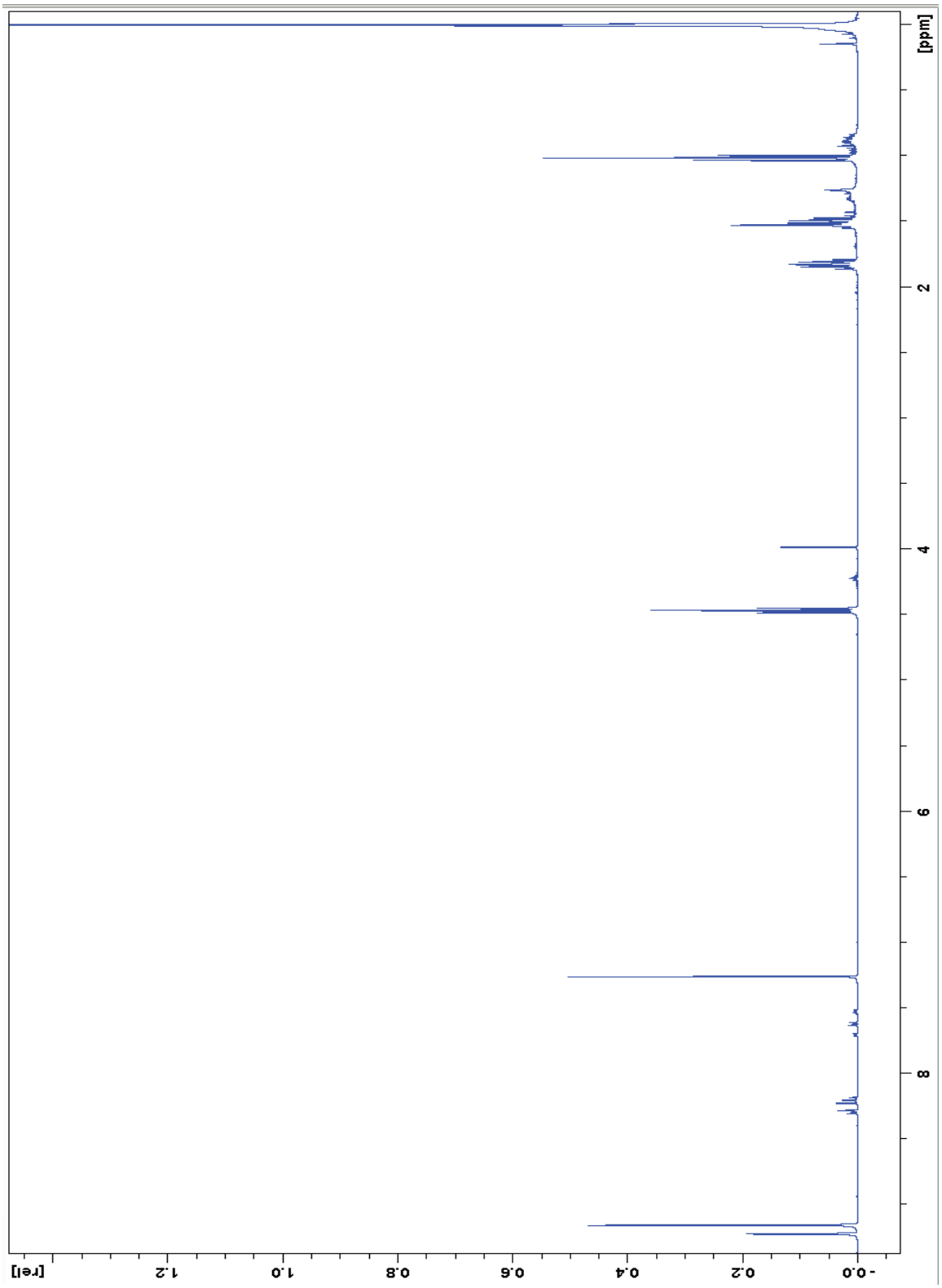


Figure 39: ^{1}H NMR of butyl 3,5-dinitrobenzoate (**19**).

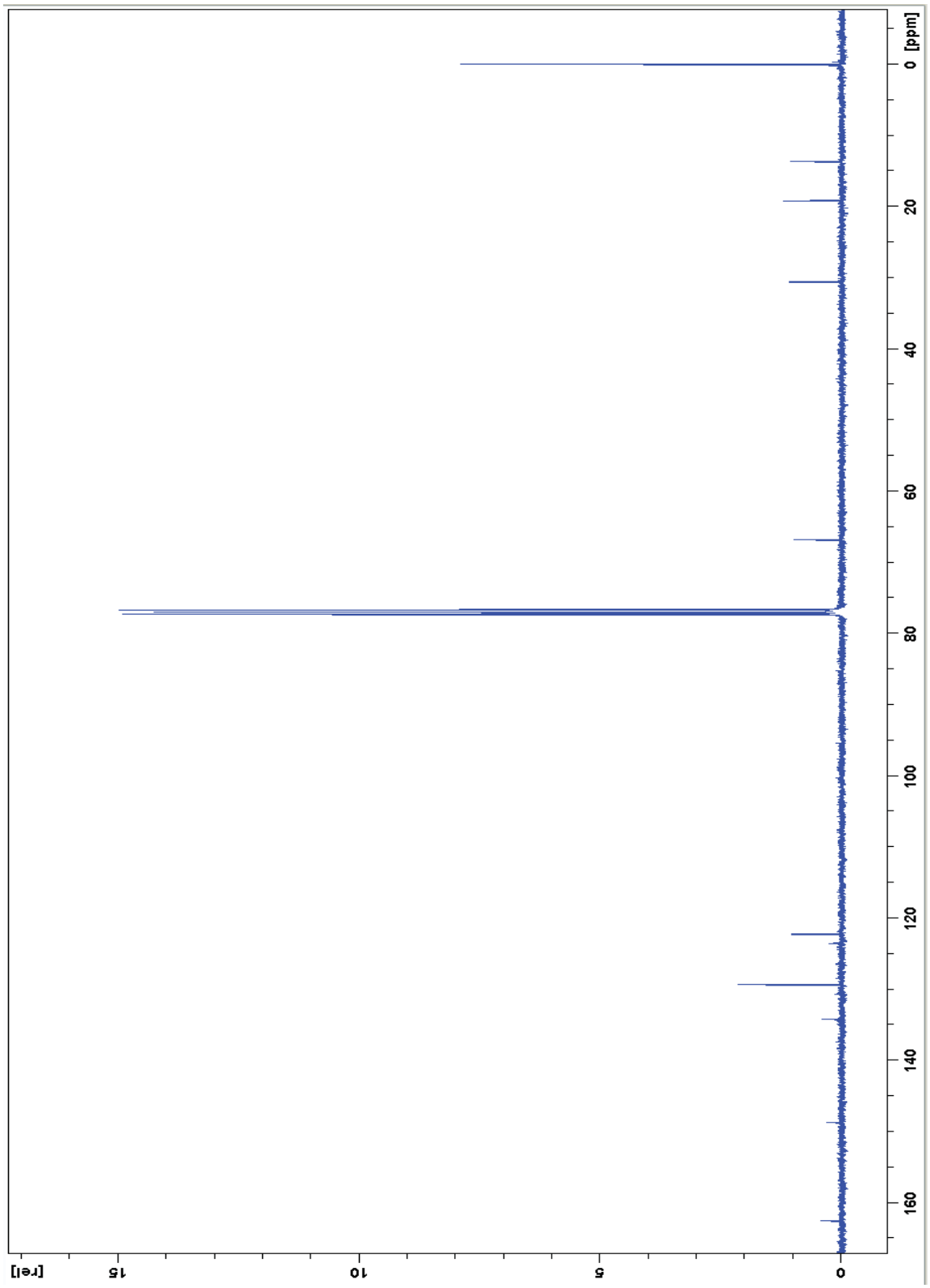


Figure 40: ^{13}C NMR of butyl 3,5-dinitrobenzoate (**20**).