DEVELOPMENT OF A SAFE AND EFFICIENT ALKYL AZIDE SYNTHESIS USING ARYLSULFONYL AZIDE

By

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Thesis Abstract

Sodium azide has traditionally been used as the source of azide anion for the synthesis of alkyl azides. Besides difficulties with solubility, sodium azide is toxic, can be absorbed through the skin, and forms potentially explosive compounds with H_2O, Brønsted acids, CH_2Cl_2, and $CHCl_3$. To avoid these dangers, a new azide transfer reagent was developed from the reaction of 4-acetamidobenzenesulfonyl azide (*p*-ABSA) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). It is much safer than sodium azide and was used for the synthesis of alkyl and acyl azides. Alkyl azides thus obtained were employed in an attempted *in situ* generation of 1,2,3-triazoles, which are aromatic five-membered ring heterocycles having two carbon atoms and three nitrogen atoms, and are biologically important. A known one-pot procedure for 1,2,3-triazole synthesis, described by Fokin and colleagues, was repeated and the formation and ease of isolation of the triazole products was compared with the new chemistry described herein.

Acknowledgements

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INTRODUCTION

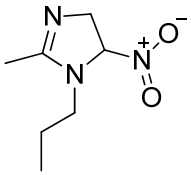
HETEROCYCLIC CHEMISTRY

Heterocyclic rings form part of the structure of most compounds produced by nature, and are key components in many biological systems. More than half of all known organic compounds are heterocyclic compounds. Examples of natural drugs that are heterocycles include quinine, procaine, codeine, morphine, etc. Synthetic drugs that are heterocyclic include metronidazole, azidothymidine, isoniazid, barbiturates, etc. Other compounds that appear as heterocycles include dyes, luminophores, pesticides, and herbicides. These natural and synthetic heterocyclic compounds participate in chemical reactions in the human body.

Heterocyclic compounds are involved in important body functions such as provision of energy, transmission of nerve impulses, sight, metabolism, and the transfer of hereditary information. Examples of such heterocycles are vitamins, enzymes, coenzymes, ATP, DNA, RNA and serotonin.[1]

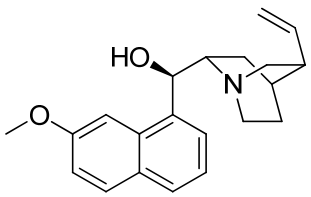
Some of the factors that influence the synthesis of heterocycles include the formation of a stable π-system, the effects of entropy and kinetics, the significance of the carbon-heteroatom bond formed, and ring-closure due to activation by a heteroatom as a carbon-carbon bond is formed.[2]

Structures shown below provide some examples of compounds that are heterocyclic (Figure 1).

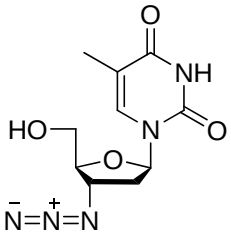


2-methyl-5-nitro-1-propyl-4,5-dihydro-1*H*-imidazole

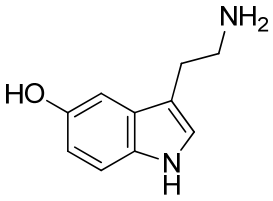
(Metronidazole)



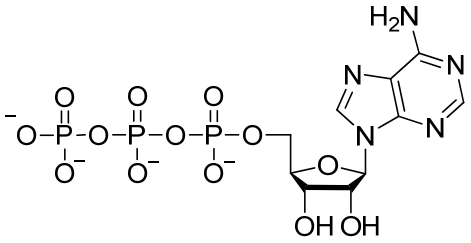
Quinine



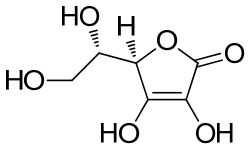
Azidothymidine



Serotonin



Adenosine triphosphate

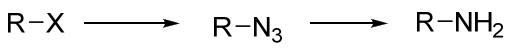


Vitamin C

Figure 1: Examples of heterocycles.[1]

AZIDES

Azides are involved in organic synthesis as a reliable means of introducing a nitrogen substituent to form an azide intermediate which is often immediately reduced to the amine as shown in scheme 1:[3]



Scheme 1: Reduction of azide to amine.

The azide group is the most convenient of the 1,3-dipolar components to introduce, and is probably the only one which is stable toward dimerization and/or hydrolysis. Aside from their significance for their ease of introduction and reduction to primary amino groups, aliphatic azides show a remarkable stability toward a wide variety of other standard organic synthesis conditions.[4]

Synthesis of triazoles and tetrazoles marked the beginning of the industrial interest in organic azides. They were further used as blowing agents (substances capable of producing a cellular structure in a variety of materials) and as functional groups in pharmaceuticals. For instance, the azidonucleosides have been of interest in the treatment of AIDS.[5,6] Most azides, like hydrogen azides, are explosive substances and decompose, releasing nitrogen when external energy is applied. Organic azides serve as important intermediates in organic synthesis in spite of their explosive nature. They have been used in cycloaddition reactions, synthesis of anilines and *N*-substituted anilines, and as precursors for nitrenes.[5,6]

Ionic azides such as sodium azide are relatively stable compared to covalently bound and heavy metal azides which are thermally decomposable. To ensure that organic azides are

not explosive or can be manipulable, the number of nitrogen atoms must not be more than that of carbon atoms.[5]

Although azides are feared for their explosive properties, they are regarded as the most important functional group for "click" chemistry. They have an extraordinary stability toward water, oxygen and most organic synthesis conditions.[3]

SYNTHESIS OF ORGANIC AZIDES

Organic azides have been synthesized through substitution or addition of the N_3 group, diazo transfer reactions involving insertion of N_2, diazotization (a process involving addition of nitrogen atoms), cleavage of triazines (which are heterocyclic rings), and by rearrangement of other azides.[5]

Alkyl Azides

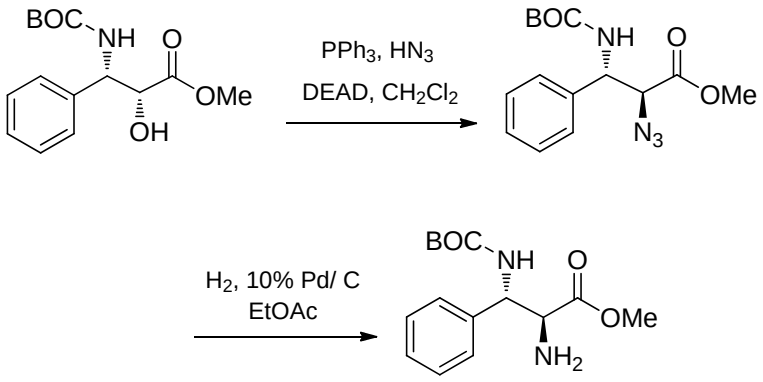
Nucleophilic substitution

Generally alkyl azides are prepared by S_N2 displacement of halides, tosylates, mesylates, nosylates, triflates, imidazylates, and carboxylates. The most commonly used source of the azide is sodium azide. Other useful sources of the azide ion include the tetraalkylammonium azides, polymer-bound azides, or silver azide which is known to be very explosive.[5,6,7]

The Mitsunobu Reaction

The Mitsunobu reaction has been used for the synthesis of azides from alcohols. Synthesis of *N*-containing compounds requires the use of azides prepared from alcohols

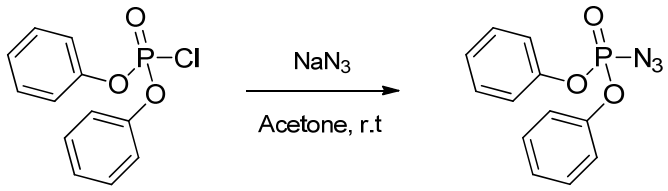
using simple and high-yielding methods. Standard Mitsunobu conditions include the use of triphenylphosphine (PPh_3), dialkylazodicarboxylate (e.g diethyl azodicarboxylate, DEAD), HN_3, $Zn(N_3)_2 \cdot 2Py$, diphenylphosphoryl azide (DPPA), and Me_3SiN_3 (for 1,2-diols).[5,7] Primary and secondary alcohols generally react efficiently with hydrogen azide, triphenyl phosphine, and diethyl azodicarboxylate (DEAD). The Mitsunobu reaction was used by Lee et al. to synthesize 2,3-diamino-3-phenyl propanoic acid derivatives according to Scheme 2 shown below. These derivatives are crucial components of biologically important medicinal compounds such as antibiotics.[5]



Scheme 2: Mitsunobu reaction as used in the synthesis of 2,3-diamino-3-phenylpropanoic acid derivatives.[5]

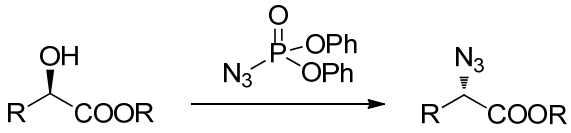
Diphenylphosphoryl azide (DPPA) can be used as an alternative to the explosive hydrogen azide for the Mitsunobu reaction.[5] DPPA is used as an azide-transfer reagent particularly because it is regarded as a non-explosive and nonvolatile material. For this reason it is considered as a non-toxic and therefore safe azide-transfer reagent.[8] DPPA is available commercially at a very high price,[8] but it can be prepared by reaction of

diphenylphosphorochloridate/diphenylphosphorylchloride with a slight excess of sodium azide in acetone at room temperature (Equation 1).[8,9]



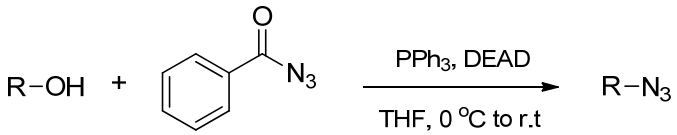
Equation 1: Synthesis of DPPA.[8]

Other reagents that have recently been used as alternatives to DEAD and NaN_3 are DDQ/$Bu_4N^+N_3^-$, and DPPA/DBU or (*p*-NO_2)-DPPA/DBU which displaces esters with azide ions.[7] DPPA has been applied to the 1,3-dipolar cycloaddition to olefinic double bonds and to the activation of carbon-oxygen bonds. Excellent yields have been realized from the conversion of alcohols to azides using DPPA (Equation 2).[8]



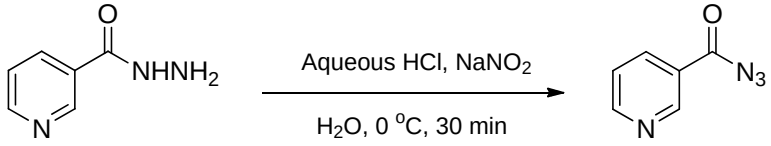
Equation 2: Azide synthesis using diphenylphosphoryl azide.[8]

For the Mitsunobu-type reactions, aroyl azide reagents have been used. Benzoyl azide has been prepared in nearly quantitative yield from benzoyl chloride, and the azide derivative of 3-β-hydroxycholestane was then synthesized in good yield using PPh_3/DEAD, with THF as solvent and a temperature range from 0 °C to room temperature (Equation 3, R = cholestane skeleton).[7]



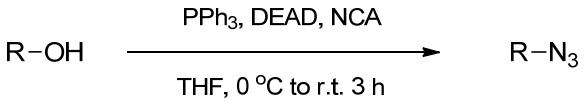
Equation 3: Mitsunobu conversion of alcohol to azide.[7]

Nicotinoyl azide (NCA) has been used in place of benzoyl azide in the conversion of alcohols to azides. It is prepared from the commercially available hydrazide (Equation 4).



Equation 4: Synthesis of nicotinoyl azide (NCA).[7]

Different primary, secondary, and tertiary alcohols have been subjected to the azidation procedure with NCA to yield the aliphatic azides (Equation 5).[7]

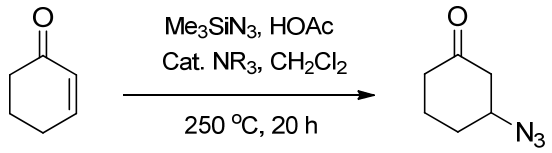


Equation 5: Preparation of alkyl azides using nicotinoyl azide (NCA).[7]

Polar 1,4-Addition Reactions

1,4-Addition of azide ions to α,β-unsaturated carbonyl compounds results in the formation of an organic azide. Trimethylsilyl azide acts as the source of azide ions in a

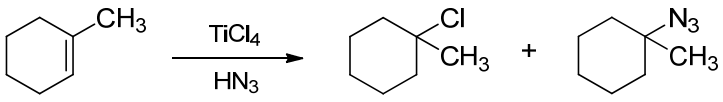
reaction involving an equivalent amount of acetic acid and catalyzed by tertiary amines as Lewis bases (Equation 6).[5]



Equation 6: Conjugate addition of azide ion to cyclohexenone.[5]

Addition to Olefins

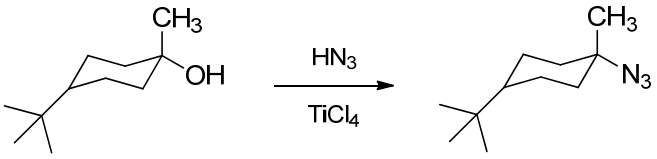
Synthesis of alkyl azides by addition to olefins utilizes halogen azides.[10] The addition of halogen azides to olefins, first described by Hassner and Levy in 1965, brought about access to a variety of vinyl azides.[5] However, reduction of the halide would affect the azide function significantly. Mercuric azides can add to certain olefins, while hydrazoic acid can only add readily to strained cyclopropenes or in Michael additions to unsaturated carbonyl compounds.[10] Both $TiCl_4$ and $AlCl_4$ catalyze HN_3 addition to styrenes, however the Lewis acid catalysts are not needed in the addition of HN_3 to electron-rich alkenes such as enol ethers or silyl enol ethers. Other olefins require the presence of a Lewis acid, preferably $TiCl_4$, but even then substituents that can stabilize a positive charge are required (for example, Equation 7).[10]



Equation 7: $TiCl_4$-catalyzed addition of HN_3 to 1-methylcyclohexene.[10]

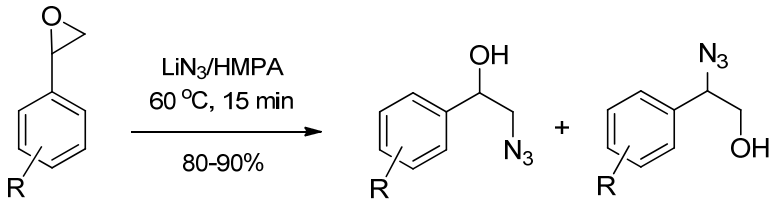
From Alcohols and Epoxides

Azides are also formed from alcohols in reactions catalyzed by $TiCl_4$, however typical primary alcohols appear to be inert toward HN_3-$TiCl_4$. Reaction of benzylic, allylic, or tertiary alcohols with an excess of HN_3 in the presence 0.5 equivalents of $TiCl_4$ produces azides in very good yield (Equation 8). Indeed, the use of a Lewis acid has improved the synthesis of allylic and benzylic azides.[10]



Equation 8: $TiCl_4$-catalyzed formation of azides from alcohols.[10]

Lithium azide in hexamethylphosphoramide (HMPA) has been used for the regio- and stereoselective ring-opening of phenyloxirane at the non-benzylic position. The S_N2 mechanism in the ring-opening was favored (Equation 9). [11]

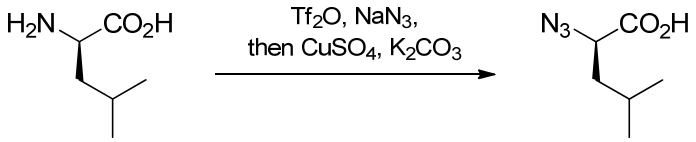


Equation 9: Ring-opening of epoxide by lithium azide in HMPA.[11]

Sodium azide, either zeolite-bound or in the presence of molecular sieves, has also been used for the transformation of epoxides into organic azides.[5]

Diazo Transfer

Diazo transfer involves synthesis of alkyl azides from amines. Triflyl azide is the reagent used for the conversion of primary aliphatic amines to the corresponding azides. Copper is used as a catalyst in this reaction and very good yields of the azide are obtained. Triflyl azide can be prepared *in situ* from trifluoromethanesulfonic anhydride and sodium azide (Equation 10).[5]



Equation 10: Diazo transfer to amines.[5]

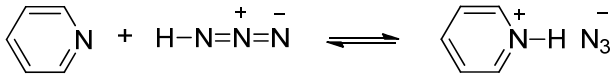
Acyl Azides

The importance of acyl azides in organic chemistry as synthetic intermediates is underlined by their use in the preparation of amides and heterocyclic compounds.[12] Acyl azides are thermally unstable and rearrange to isocyanates on heating, a process known as the Curtius rearrangement.[13] Amines, urethanes, thiourethanes, ketimines, carbodiimides, and ureas are prepared from the isocyanates.[12] They can therefore be synthesized only by those methods which operate at room temperature. Some of the procedures that fulfill this requirement include: reaction of an acyl chloride with sodium azide in an aqueous organic solvent; reaction of an acyl chloride with tetraalkylammonium or guanidinium azide in an organic solvent such as chloroform; or diazotization of an acyl hydrazide with sodium nitrite or alkyl nitrites.[13]

Acid derivatives such as acid halides and acyl hydrazides are the starting materials for the synthesis of acyl azides. Acyl chlorides react with azide ions in a mixture of water and water-miscible organic solvents. Reactions carried out in organic solvents in the absence of water must be done at elevated temperatures. At high temperature, Curtius rearrangement occurs leading to formation of isocyanates.[12] Other conditions in which the reaction has been carried out include the use of sodium azide, lithium azide, hydrazoic acid and tetramethylguanidinium or tetraalkylammonium azides.[12]

Acyl azides have been prepared from different aryl, heteroaryl, alkyl aryl, and alkyl carboxylic acids in reactions with cyanuric chloride, sodium azide and *N*-methyl-morpholine.[5,12] Activators such as ethyl chloroformate, DPPA,[5] phenyldichlorophosphate, $SOCl_2$-DMF, and NCS-Ph_3P have been used to convert carboxylic acids to acyl azides.[12] A combination of chromic anhydride-trimethylsilyl azide and triazidosilane-activated MnO_2 have been used to prepare acyl azides from aldehydes.[12] Azidosilanes are compounds that include one or more azide ligands (N_3) bound to silicon, e.g trimethylsilyl azide.

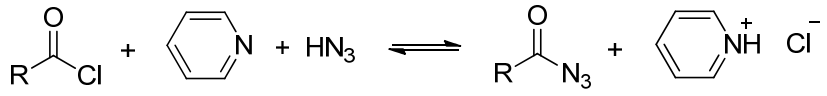
A mixture of equivalent amounts of pyridine and hydrazoic acid in toluene constitutes an organic-soluble source of azide anions (Equation 11).[13]



Equation 11: Azide anions from pyridine and hydrazoic acid.[13]

Addition of the mixture to a solution of acid chloride in toluene at 0 °C resulted in the instant precipitation of pyridinium chloride, and the IR spectrum of the filtered solution indicated

quantitative conversion of the acyl chloride into the acyl azide (Equation 12).[13] The good yields of isocyanates resulting from Curtius rearrangement was a further proof of the structure of the acyl azides.[13]



Equation 12: Synthesis of acyl azide from acyl chloride.[13]

CLICK CHEMISTRY

Click chemistry was introduced by Sharpless and co-workers as a way of categorizing organic reactions.[18] These reactions are required to be modular, highly efficient with good yields, wide in scope, mild and selective, and stereospecific.[18,19] Secondly, the reaction conditions are required to be simple, with simple workup procedures. A key feature of these reactions is that they should be insensitive to oxygen and water, should have readily available starting materials and reagents, use benign or easily removable solvents or no solvent at all and simple product isolation procedures.[4,18] The byproducts generated must be inoffensive and removable by nonchromatographic methods, therefore product purification must be by methods such as distillation or crystallization, and these products are required to be stable under physiological conditions.[4] A general observation is that reactions meeting click chemistry standards proceed better in water than in organic solvent.[4]

Click Chemistry Reaction Types

Three click chemistry procedures have been used in the Sharpless laboratory. The first click reaction type involves the chemistry of three-membered ring heterocyclic electrophiles. The molecules involved in this S_N2 ring-opening procedure include epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions, and episulfonium ions.[4] The second reaction type involves compounds ordinarily used as protecting groups. Acetals, ketals and their aza-analogues represent a rare kind of click chemistry with regard to reversible carbonyl chemistry.[4] Cycloaddition reactions represent the third click chemistry reaction, which includes hetero-Diels-Alder and the 1,3-dipolar cycloadditions. These cycloaddition reactions involve a fusion of two unsaturated starting materials resulting in the formation of a wide variety of five- and six-membered heterocycles.[4]

TRIAZOLES

Triazoles are involved in many biological activities. Examples of these activities include anti-HIV activity, anti-microbial activity against Gram-positive bacteria, selective β_3 adrenergic receptor agonism, anti-allergic, anti-convulsant, β-lactamase inhibitory, anti-fungals, antiviral nucleoside analogues, and many others.[14,15,22,23] They have also found wide use as synthetic intermediates and have been applied in the chemical industry as dyes, corrosion inhibitors, photostabilizers, photographic materials, agrochemicals [14,15] and as halide synthons.[22]

Synthesis of Triazoles

Synthesis of 1,2,3-triazoles has been accomplished using a variety of methods. Among the procedures described have been the 1,3-dipolar cycloaddition of azides to alkynes, the intramolecular cyclization of bishydrazones or mixed hydrazones, and miscellaneous oxidations. Cycloaddition reactions between azides and alkynes have been carried out in refluxing toluene, typically conditions which have not been good for labile molecules. In an attempt to overcome this, sodium, lithium, or magnesium salts of the alkyne, and lower temperatures have been used but with limited success.[15] The reaction has also been carried out in water without a catalyst,[14] and various solvents containing water such as acetone, MeCN, DMF, DMSO, EtOH, MeOH, THF, *t*-BuOH, and 1,4-dioxane.[23]

Huisgen 1,3-Dipolar Cycloaddition

Huisgen 1,3-dipolar cycloadditions involve fusion of two unsaturated reactants resulting in formation of five-membered heterocycles. The most important type of these reactions is the cycloaddition of azides and alkynes to form triazoles.[3] Five-membered rings are generated in a reproducible manner, rapidly and efficiently by the dipolar cycloaddition reactions. A mixture of 1,4- and 1,5-disubstituted triazoles[25] is generated under elevated temperatures, and hence not regiospecific, conditions. This may not be good for preparative work but is advantageous in cases where both regioisomers are needed. For this procedure, the azide appears to be the only three-atom dipole that is nearly devoid of side reactions.[3,15,16]

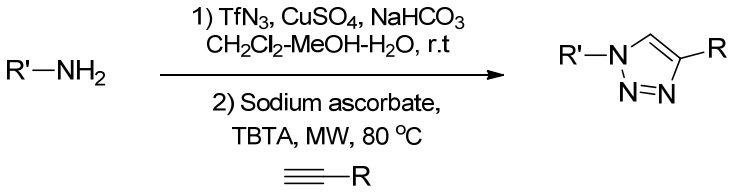
Click Huisgen Reaction

The independent discovery by Sharpless and Meldal, that copper ions accelerate and improve regioselectivity of the reaction of aliphatic azides with terminal alkynes, provided the breakthrough in triazole chemistry. This reaction is biocompatible and works well in aqueous media and also in organic solvents. The reaction is very sensitive toward copper catalysts that even copper wire maintains the required copper ion concentration.[5]

Although the catalytic mechanism has not been elucidated, it is generally known that copper(I) inserts into terminal alkynes in the presence of a base.[25,26] Covalent binding of the copper(I) to the terminal alkyne triple bond causes polarization hence catalyzing the cycloaddition. This probably ends up in a change from concerted to a stepwise reaction.[15] Copper(I) catalysis represents a general and mild approach for the preparation of 1,4-disubstituted-1,2,3-triazole derivatives, and the copper(I)-catalyzed alkyne-azide 1,3-dipolar cycloaddition is selective, efficient, and has a wide scope hence fulfilling the requirements for click chemistry.[16] Cu(I) catalysis increases reaction rates up to 10^7, and the copper(I) can be obtained from Cu(I) salts (mostly copper iodide), *in situ* reduction of Cu(II) salts (mainly copper(II) sulfate), and comproportionation of Cu(0) and Cu(II).[17,26] Copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides on solid-phase has been performed successfully with primary, secondary, and tertiary alkyl azides, aryl azides and azido sugars. 1,4-substituted-1,2,3-triazoles in peptide backbones or side chains have been the products of these reactions.[15]

Synthesis from Primary Amines

1,4-Disubstituted-1,2,3-triazoles have been synthesized from primary amines and terminal acetylenes using the inexpensive, shelf-stable diazotransfer reagent imidazole-1-sulfonyl azide hydrochloride.[20] A procedure developed by Beckman involved generation of azides *in situ* from primary amines. The procedure starts with the formation of azides from primary amines and triflic azide in the presence of copper(II) sulfate and solid sodium bicarbonate. This is followed by the addition of a terminal acetylene along with sodium ascorbate and the copper(I)-stabilizing ligand tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-amine (TBTA). Finally, for the azide-acetylene dipolar cycloaddition, microwave heating is carried out (Equation 13).[20]

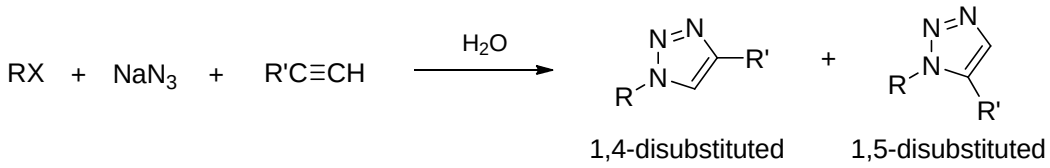


Equation 13: One-pot, two-step procedure for triazole synthesis.[20]

Synthesis of 1,2,3-triazoles in Water under Transition Metal Catalyst-free Reaction Conditions

This is a one-pot reaction involving benzyl and alkyl halides, sodium azide, and alkynes in water to synthesize 1,2,3-triazoles under catalyst-free conditions. Regiospecific 1,4-disubstituted triazoles are generated in good yields in the reaction of terminal aryl-alkynes, sodium azide, and benzyl chlorides or bromides (Equation 14). On the other hand, reactions with terminal aliphatic alkynes were shown to give a mixture of the 1,4- and 1,5-

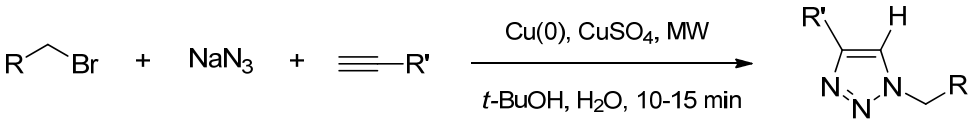
disubstituted regioisomers.[14] Experimental results indicated that substituents attached to the aryl ring of the benzyl halide derivatives affect the cycloaddition reactions with electron-withdrawing groups promoting the reactions and electron-donating groups impeding the reactions.[14]



Equation 14: 1,2,3-triazole synthesis in water.[14]

Microwave-Assisted Click Chemistry

1,4-Disubstituted-1,2,3-triazoles are synthesized *in situ* from various alkyl halides, sodium azide, and alkynes in reactions carried out in the microwave (Equation 15). Microwave-assisted three-component reactions are fast, efficient and regioselective.[21]



Equation 15: Microwave-assisted click reaction.[21]

A one-pot procedure reported by Fokin et al. in 2004 involved the formation of a series of azides using sodium azide and various alkyl halides, which in the presence of a terminal acetylene, copper(II) sulfate, and a reductant underwent azide-acetylene dipolar cycloaddition promoted by microwave irradiation.[20] This method is arguably the most

efficient available currently for the click chemistry synthesis of 1,2,3-triazoles. The reaction conditions and workup are simple and reproducible, and this method will be used in this thesis as the benchmark for us to compare our own methodology.

1,2,3-Triazoles have also been synthesized by cycloaddition of alkyl azides onto enol ethers under solventless conditions. The reaction can access ring-fused triazoles that are unavailable through azide-alkyne cycloadditions, and is also easily scalable. To increase the cycloaddition rate, the azide-enol ether cycloadditions were performed at 200 °C in a sealed tube without solvent.[22]

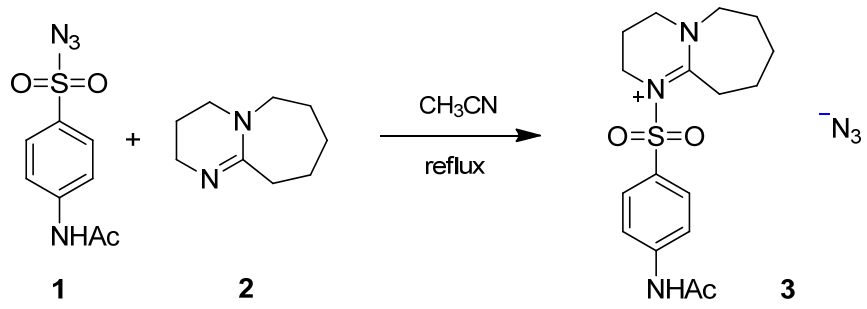
Statement of Problem

Synthesizing heterocycles is one of the key goals of organic chemistry. In this thesis, alkyl halides will be used as the starting materials for the synthesis of alkyl azides, which will serve as the precursors in attempts to form 1,2,3-triazole heterocycles. Traditionally, sodium azide would be used as the source of the azide anion for the formation of the alkyl azides. To guarantee safe synthesis, 4-acetamidobenzenesulfonyl azide (*p*-ABSA) and 1,8-diazabicyclo [5.4.0]-undec-7-ene (DBU) will be used in place of sodium azide as the azide transfer reagent. One-pot synthesis of 1,2,3-triazoles will be attempted under different reaction conditions. TLC and infrared spectroscopy will be used to monitor the reaction progress and NMR spectroscopy will be used to determine the possible product structures.

RESULTS AND DISCUSSION

The major goal of this research was the application of a 4-acetamidobenzenesulfonyl azide (*p*-ABSA)/1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) mixture as an azide transfer reagent, and identification of the correct conditions under which to perform these reactions. Key among these reaction conditions was the identification of the correct solvent system and the optimum temperature for the reaction. These reactions were carried out at room temperature as well as in the microwave for comparison. Microwave irradiation has gained in popularity since the reaction times are shorter, while often promoting selectivity and increased yields.[25] However, our experiments were carried out *in situ* and the azide products were not isolated to calculate the yield.

Sodium azide has traditionally been used in the synthesis of alkyl azides. It is still the main source of azide anion for the substitution of halogens and other leaving groups in organic synthesis. Due to the dangers inherent in the use of sodium azide we came up with an alternative source of the azide anion that is much safer. 4-acetamidobenzene-sulfonyl azide (*p*-ABSA, **1**) is a commercially available reagent which reacts with the organic base 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, **2**) to produce an organic-soluble azide salt (**3**, Equation 16). Formation of the azide anion serves as the backbone of our research.



Equation 16: Synthesis of the organic-soluble azide salt.

Compound **3** (Equation 16) is the organic-soluble salt that serves as the safe source of the azide anion. Synthesis of this compound has been carried out in different solvents and the reaction monitored *in situ* using both Thin Layer Chromatography (TLC) and infrared spectroscopy. The one-pot synthesis and the use of infrared spectroscopy to monitor reactions eliminates the need to isolate the intermediates, especially the low molecular weight organic azides, which are unstable and dangerous. The solvents used for this reaction included acetonitrile, ethanol, deuterated acetonitrile, DMF, DMF-H_2O mixture, *t*-BuOH, *t*-BuOH-H_2O mixture, water, methanol, and acetone. The successful formation of **3** as read from the infrared spectrum was indicated by a change in absorption (Table 1). For instance, reaction in acetonitrile gave an absorption signal for the covalently bound azide group of *p*-ABSA at 2128 cm^{-1}. Upon addition of DBU and subjecting the reaction to the microwave at 70 °C, the IR spectrum shows absorption at 2020 cm^{-1}. In most of these reactions an excess of the DBU was added; for every 1.0 mmol *p*-ABSA used, 1.5 mmol of DBU was added.

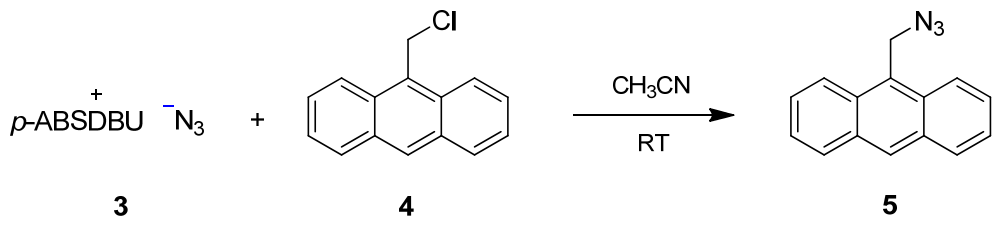
Table 1: Infrared absorptions of **1** and **3** in different solvents.

	p-ABSA (cm^{-1})	*p*-ABSDBU (cm^{-1})	Time (Min)
Acetonitrile	2133.90	2018.95	30
Ethanol	2127.44	2036.46	60
t-BuOH	2126.16	2030.73	30
t-BuOH-H_2O	2126.92	2041.15	30
DMF	2130.43	2012.61	30
CD_3CN	2133.53	2015.79	90

Acetone	2130.17	2005.77	incomplete
DMSO	2128.63	2017.81	incomplete
Methanol	2129.90	2043.28	15

After addition of DBU and subjecting the reaction to microwave conditions at 70-80 °C, a shift in absorption was observed indicating the formation of the ionic azide. In DMSO there was no complete conversion to the azide anion since there was absorption both at 2123.29 and 2005.77 cm^{-1}. In acetone incomplete formation of the azide anion was observed even after addition of 2 mmol of DBU. Absorption was observed at both 2105.13 cm^{-1} and 2017.81 cm^{-1}. *p*-ABSA would not dissolve in *t*-butanol alone; however upon addition of water it dissolved very well after a few minutes and its infrared spectrum taken to determine formation of the azide anion.

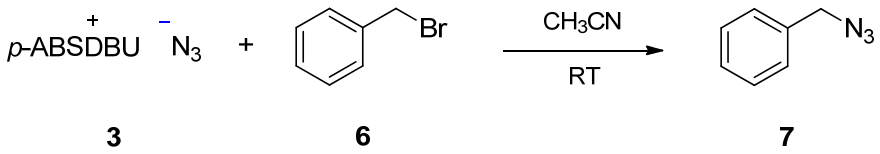
To synthesize the alkyl azides, nucleophilic substitution (S_N2) is commonly used. This uses the highly nucleophilic azide ion, and sodium azide is widely used as the source.[5] The organic salt **3** has been successfully used in the Norris group previously for the synthesis of a limited number of alkyl and acyl azides. The reaction with 9-(chloromethyl)anthracene (**4**) at room temperature was used to synthesize 9-(azidomethyl)anthracene (**5**, Equation 17).



Equation 17: Synthesis of azide **5** from 9-(chloromethyl)anthracene, **4**.

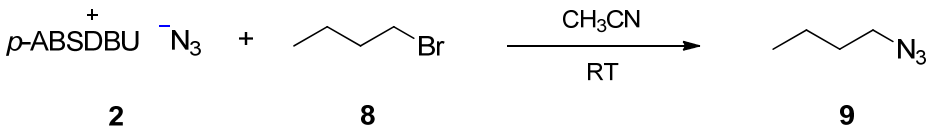
This reaction was carried out successfully in other solvents including *t*-BuOH-H_2O, ethanol, and DMF-H_2O. The reaction was not successful however in acetone. TLC and infrared spectroscopy was used to monitor the reaction progress. In acetonitrile, IR for compound **3** showed absorption at 2018.95 cm^{-1}. The infrared spectrum for compound **5** shows absorption at 2099.86 cm^{-1} which is the typical absorption peak for an alkyl azide. Alkyl azides generally display a strong absorption around 2100 cm^{-1} and this is explained by the polar resonance structures possible within the azide group.[5]

This type of reaction has also been carried out using benzyl bromide (**6**, Equation 18) and 1-bromobutane (**8**, Equation 19) as electrophiles.



Equation 18: Synthesis of azide **7** from benzyl bromide.

The formation of azide **7** (Equation 18) was conveniently monitored using infrared spectroscopy. Compound **7** showed a strong absorption at 2100.12 cm^{-1}, indicating a shift from 2017.81 cm^{-1}, the latter signal being characteristic of the azide anion. Compound **9** was formed appreciably well in DMF as indicated by the infrared spectrum showing absorption at 2098.03 cm^{-1} (Equation 19). The reaction was also attempted in acetone, but the absorption around 2100 cm^{-1} was not prominent enough to suggest that alkyl azide synthesis was actually successful in this particular solvent.



2 **8** **9**

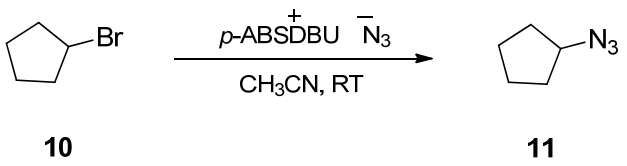
Equation 19: Synthesis of azide **9** from 1-bromobutane.

Aside from using acetonitrile as the solvent for the synthesis of the alkyl azides, other solvents also proved to be useful in the synthesis. Use of *t*-BuOH was limited by the poor dissolution of *p*-ABSA. Microwave irradiation for 15 minutes at 80 °C resulted in dissolution and the IR indicated a strong signal at 2126.16 cm^{-1}. For the reaction in *t*-BuOH at room temperature, upon addition of water the *p*-ABSA dissolved almost instantly. Subsequent addition of the respective alkyl halides resulted in the formation of a product characterized by IR absorption in the region of 2100 cm^{-1}.

DMF was a good solvent for *p*-ABSA; the infrared absorption signal shifted after addition of DBU and subsequent microwave heating. Overall, DMF served as a good solvent for the formation of the alkyl azides.

Dimethyl sulfoxide (DMSO) is the other solvent that was used toward the synthesis of the alkyl azides. However, it does not seem to be a good solvent for the formation of the azide anion. The absorption peak due to the covalently bound azide of *p*-ABSA did not fully disappear as would be expected.

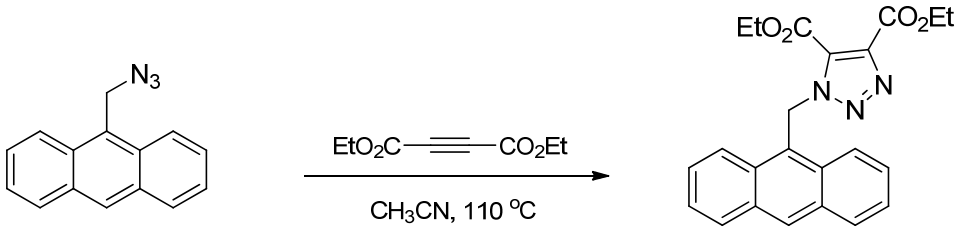
Azide **11** was synthesized from bromocyclopentane (**10**) in acetonitrile (Equation 20). The reaction was monitored using TLC and infrared spectroscopy. The infrared spectrum of the azide **11** indicated absorption at 2101.71 cm^{-1}, a clear sign of successful alkyl azide formation in this case.



10 **11**

Equation 20: Synthesis of azide **11** from bromocyclopentane.

Synthesis of the 1,2,3-triazole system is one of the major objective of this research. The successful synthesis of the alkyl azides was key to the next step towards the synthesis of the triazoles. In synthesizing the triazoles, click chemistry conditions and ideas were applied. Firstly, diethylacetylene dicarboxylate was used for the attempted synthesis of a triazole in acetonitrile. This reaction did not involve copper catalysis, since the alkyne is symmetrical and not terminal, and was carried out in the microwave at 110 °C for 1 hour (Equation 21).



5 **12**

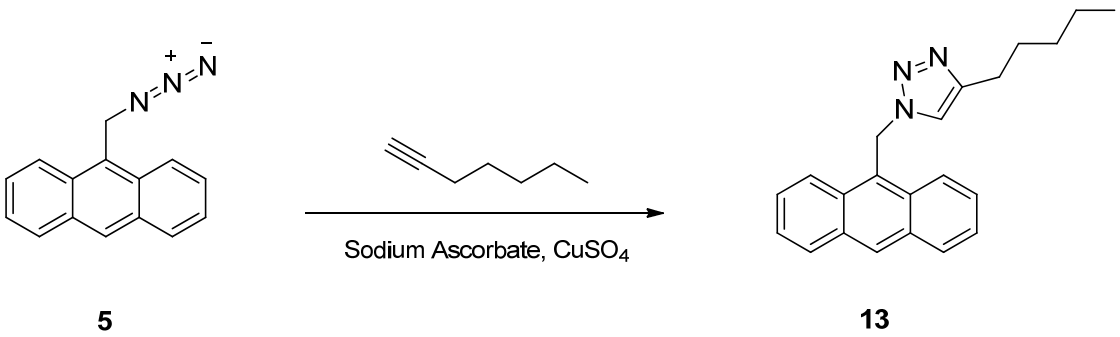
Equation 21: Attempted reaction of azide **5** with diethylacetylene dicarboxylate.

The potential formation of **12** was monitored using infrared spectroscopy and TLC. Infrared spectroscopy was used to monitor the reaction for 8 days. After 5 days extra diethylacetylene dicarboxylate (1 mmol) was added to test the possibility of eliminating the absorption at 2099 cm^{-1} which is due to the azide starting material. This reaction was subjected to microwave heating at 70 °C for 15 minutes. The absorption peak remained

intact leading to the conclusion that triazole formation was not satisfactory. The reaction was repeated again with a total of 3 mmol of diethylacetylene dicarboxylate and temperature of 110 °C for 30 minutes. There was a marked improvement in the infrared spectrum since the absorption at 2100 was greatly reduced and this was a good sign towards formation of the triazole. TLC for **12** (R_f 0.44) was different from that of the azide **5** mixture (R_f 0.13, 0.3, 0.44) with new spots appearing with different R_f values. NMR spectroscopy was used in an attempt to characterize the product. After evaporating the solvent on the rotovap, an NMR sample was prepared using d_6-DMSO and both the ^{1}H and ^{13}C spectra were obtained. ^{13}C NMR was more important for the determination of the product since it indicates the number of types of carbon atoms in the final product. $CDCl_3$ did not dissolve the sample well and was not useful here. Ultimately, however, both ^{1}H and ^{13}C spectra were not clear and hence could not provide adequate information for product characterization. Purification was then attempted using flash column chromatography with a Hexanes: Ethyl acetate 4:1 solvent system. The NMR data for the purified product prepared in d_6-DMSO were not clear either and hence could not provide sufficient evidence for product formation.

The reaction toward the formation of **12** was also tried using copper (II) sulfate and ascorbic acid, however the infrared spectrum still had a strong absorption at 2099.92 cm^{-1} even after 6 days of the reaction.

Click chemistry reaction conditions were next applied to a reaction involving 1-heptyne, a terminal alkyne (Equation 22). The reaction was carried out at room temperature and was monitored periodically by infrared spectroscopy. Characterization of the product was attempted using NMR spectroscopy.

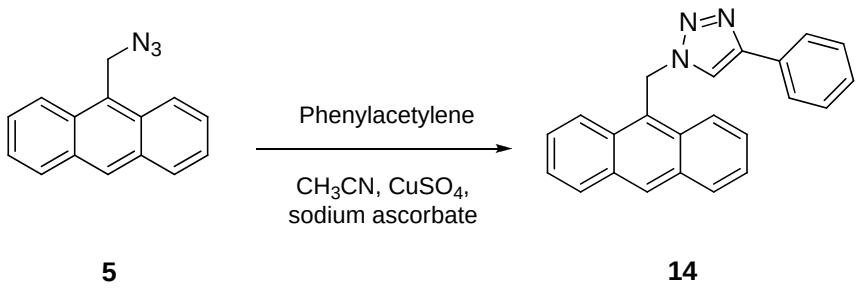


5 **13**

Equation 22: Attempted reaction of azide **5** with 1-heptyne.

Compound **13** was the expected product from this reaction. The infrared spectrum of **5** shows the characteristic azide absorption at 2099.62 cm^{-1} and, after performing a click chemistry reaction with 1-heptyne, the absorption still remained at 2099.97 cm^{-1} indicating no reaction. Addition of 1mL methanol appears to alter the reaction markedly since a weak absorption at 2043.84 cm^{-1} was now observed. Apparently methanol enhances the solubility of the copper catalyst thus promoting the reaction. After evaporating the solvent, an NMR sample was prepared in d_6-DMSO for determination of both ^{1}H and ^{13}C NMR spectra. The NMR spectra were not clean enough to provide adequate information about the product. Further purification was carried out using flash column chromatography with hexanes: ethyl acetate 5:1 as the solvent system. ^{1}H and ^{13}C NMR spectra of the purified sample were obtained in d_6-DMSO. The ^{1}H NMR spectrum of the residue showed a singlet at 7.53 ppm, which could correspond to the expected triazole proton, a singlet at 6.6 ppm, which could belong to the benzylic CH_2 group, and a triplet at 4.2 ppm that could belong to the *N*-CH_2 group of the alkyl chain. Although this evidence points towards triazole formation, the fundamental requirements of click chemistry have not been met in this reaction.

Phenylacetylene was also used for an attempted click reaction involving compound **5** in the presence of sodium ascorbate and copper(II)sulfate (Equation 23).



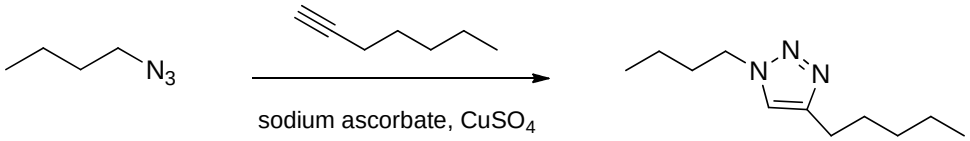
5 **14**

Equation 23: Attempted reaction of azide **5** with phenylacetylene.

The reaction was followed by infrared spectroscopy; compound **5** absorbed at 2099.54 cm^{-1}. The reaction was continued for 8 hours, and the infrared spectrum obtained indicating the disappearance of this peak. The product from this reaction was light green syrup, and instead of the strong absorption at 2099.54 cm^{-1}, a very weak absorption was observed at 2069.46 cm^{-1} (Figure 5, Appendix).

When the same reaction was carried out with ascorbic acid instead of sodium ascorbate, the results were unsatisfactory since the peak at 2099.54 cm^{-1} remained intact. Addition of water to this solution to enhance solubility did not help since water and acetonitrile could not mix adequately. An NMR sample was prepared in $CDCl_3$ and d_6-DMSO since it dissolved well in both solvents. ^{1}H and ^{13}C NMR were obtained and provided preliminary evidence of 1,2,3-triazole formation; a singlet at 6.6 ppm could belong to the benzylic CH_2 group with the triazole proton being buried in the complex group of signals that represent the protons on the aromatic rings. Again purification here was problematic and not within the constraints of click chemistry.

The click reaction was next carried out using 1-bromobutane in place of 9-(chloromethyl)anthracene. Reaction with the *p*-ABSA/DBU mixture was carried out at room temperature with the formation of azide **9**. After the successful synthesis of the 1-azidobutane, observed from infrared absorption spectra, click chemistry was attempted using 1-heptyne in the presence of sodium ascorbate and copper sulfate (Equation 24).

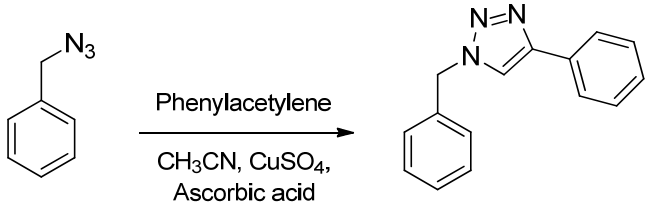


9 **15**

Equation 24: Attempted reaction of azide **9** with 1-heptyne.

From the infrared spectra, the azide **9** absorbs at 2099.94 cm^{-1}, and after click chemistry was performed the absorption peak was observed at 2100.19 cm^{-1}. This was not the change expected and it was attributed to the poor solubility of sodium ascorbate and copper sulfate. To increase the solubility and enhance the reaction 1 mL of methanol was added and reaction allowed to proceed overnight. The infrared spectrum showed the elimination of the absorption signal at 2100 cm^{-1} and this was a good indication of the possible formation of the expected product. Although no precipitate was observed, one of the basic goals of click chemistry, the ^{1}H NMR spectrum of the residue remaining after evaporation of the solvents showed evidence for triazole formation. A singlet at 7.3 ppm likely belongs to H-5 of the triazole ring, and the triplet at 4.3 ppm could indicate the *N*-CH_2 group of the butyl chain.

Benzyl bromide was also used for the click chemistry reactions. Reaction of benzyl bromide with the *p*-ABSA/DBU mixture in acetonitrile was monitored with infrared spectroscopy, which indicated the formation of benzyl azide (**7**, Equation 18 above). Synthesis of triazole **16** was then attempted in different solvents with varying results. Among the solvents used for this reaction were DMF, acetonitrile, ethanol, and *t*-BuOH-H_2O. When the click reaction was performed using phenylacetylene in DMF, ascorbic acid and copper sulfate were used. In acetonitrile, sodium ascorbate and copper sulfate were used to catalyze the reaction. Reaction of compound **7** was monitored by infrared spectroscopy. For the reaction in acetonitrile a strong absorption is observed at 2099.73 cm^{-1} and, after addition of 1 mL of methanol, the infrared showed a weak absorption at 2100.11 cm^{-1}. Addition of methanol seemed to promote dissolution of the catalyst mixture, hence enhancing reaction, potentially toward formation of **16** (Equation 25).



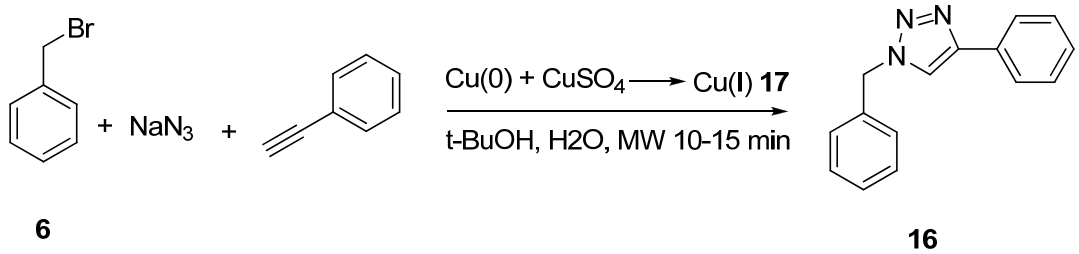
7 **16**

Equation 25: Attempted reaction of azide **7** with phenylacetylene.

Further studies were carried out using ethanol as the solvent and the overall reaction procedure was the same as with the other solvents. *p*-ABSA solution in ethanol absorbed very strongly at 2127.46 cm^{-1} which was for the covalently bound azide. DBU (1.5 mmol) was added and it required extended heating for the reaction to go to completion. After initial heating at 70 °C for 30 minutes, it had to be taken back to the microwave for an additional 15

minutes. The reaction was repeated with the same amount of reagents but at 80 °C for 60 minutes, which eventually gave satisfactory absorption for the azide anion. *p*-ABSA in ethanol absorbed at 2127.41 cm^{-1}, but shifted to 2036.93 cm^{-1} after addition of DBU and subsequent microwave heating. Thin Layer Chromatography (with 1:1 hexanes: ethyl acetate) showed completion of the reaction; observed R_f value for *p*-ABSA was 0.28, whereas that for *p*-ABSDBU was 0.15. Benzyl bromide was added to the azide anion solution and allowed to stir overnight at room temperature (Equation 18 above). The infrared spectrum indicated a shift in absorption from the ionic azide to the covalently bound azide which now absorbed at 2100.49 cm^{-1}. Thin Layer Chromatography in 1:1 hexanes: ethyl acetate gave an R_f value of 0.18. After formation of the benzyl azide, click chemistry was attempted with phenylacetylene in the presence of 1.5 mL of water (Equation 25). Extraction was carried out three times with 1.5 mL portions of ethyl acetate. The infrared spectrum of the organic solution showed a weak absorption at 2099.23 cm^{-1}. NMR analysis carried on the product residue did not give clean spectra to prove the formation of triazole **16**.

Two similar reactions with **7** and phenylacetylene were then run at the same time, one in the microwave and one at room temperature. The microwave reaction was observed to be faster than the room temperature reaction based on the rate of formation of the azide anion as observed from the infrared spectra.

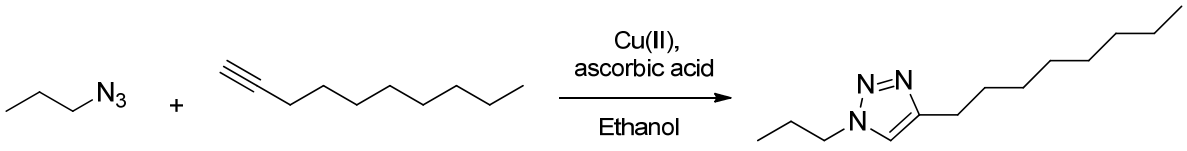


6 **16**

Equation 26: Attempted reaction of azide **7** under Fokin conditions to produce **16**.

^{1}H NMR spectrum,from the attempted synthesis of **16,** showed a singlet at 5.58 ppm which could indicate the benzylic CH_2 group and a singlet at 7.76 ppm probably due to H-5 of the triazole. Attempted synthesis under Fokin conditions (Equation 26) gave a much cleaner NMR spectrum (Figure 44); ^{1}H NMR showed a singlet at 5.57 ppm which could be attributed to the benzylic CH_2 group, a singlet at 7.65 ppm for the H-5 of the triazole. The actual work by Fokin et al.[14] showed a ^{1}H NMR with a singlet (2H) at 5.46 ppm, and a singlet (1H) at 7.67 ppm. These results are positive indicators for the attempted formation of triazole **16**.

Reaction of azide **9** with 1-decyne in ethanol was expected to yield triazole **18** (Equation 27). From the infrared spectrum the absorption at 2103.26 cm^{-1} due to the azide **9** completely disappeared after the click reaction in an attempt to synthesize **18**. Ethanol proved to be a difficult solvent to work with especially when synthesizing **9.** Both peaks due to the azide anion and the alkyl azide are visible in the spectrum at 2037.67 cm^{-1} and 2103.26 cm^{-1}, indicating incomplete conversion. The microwave reaction, however, appears to be faster than the room temperature reaction.

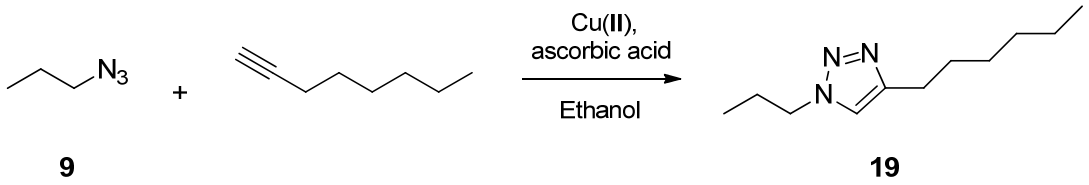


9 **18**

Equation 27: Attempted reaction of azide **9** with 1-decyne.

Attempted reaction of azide **9** with 1-octyne in ethanol in the presence of copper(II) acetylacetonate and ascorbic acid was expected to yield triazole **19** (Equation 28). Infrared

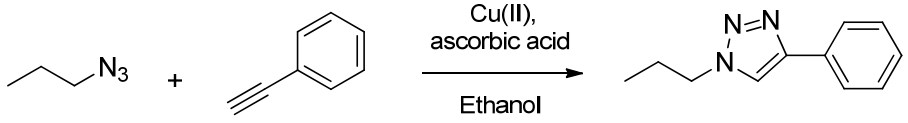
spectrum after the click reaction showed the disappearance of the absorption signals at 2125.24 cm^{-1} and 2037.85 cm^{-1}. After evaporation of the solvent, the ^1H NMR spectrum of the residue in $CDCl_3$ did not show anything promising in terms of a triazole structure.



9 **19**

Equation 28: Attempted reaction of azide **9** with 1-octyne.

Phenylacetylene was next used in the reaction with **9** with the expected formation of triazole **20** (Equation 29). Once again infrared spectroscopy was used to monitor the reaction and it showed a remarkable difference between the IR spectrum of **9** and the resulting reaction mixture. Despite the disappearance of the azide signal, evaporation of the solvent provided a residue whose ^1H NMR spectrum gave no indication of the usual signals associated with 1,2,3-triazole.

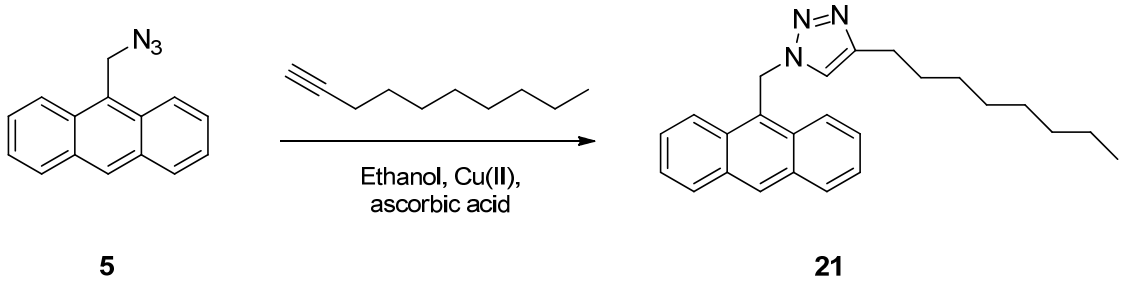


9 **20**

Equation 29: Attempted reaction of azide **9** with phenylacetylene.

The azide anion from *p*-ABSA/DBU mixture generated in ethanol was reacted with 9-(chloromethyl)anthracene to generate the covalently-bound azide **5**. The infrared spectrum

showed that the azide anion does not react so well under these conditions considering the presence of absorption signal for azide anion at 2037.09 cm^{-1}, along with the signal for alkyl azide product at 2100.90 cm^{-1}. Addition of the 9-(chloromethyl)anthracene results in the relatively slow formation of the covalently bound azide **5** showing azide absorption at 2100.03 cm^{-1}. However, when a click reaction was carried out with the addition of 1-decyne (Equation 30), there was no change in the infrared spectrum, and an absorption at 2108.61 cm^{-1} was observed. Ideally, absorption for the azide functionality at 2108.61 cm^{-1} should not be there after performing the click reaction.

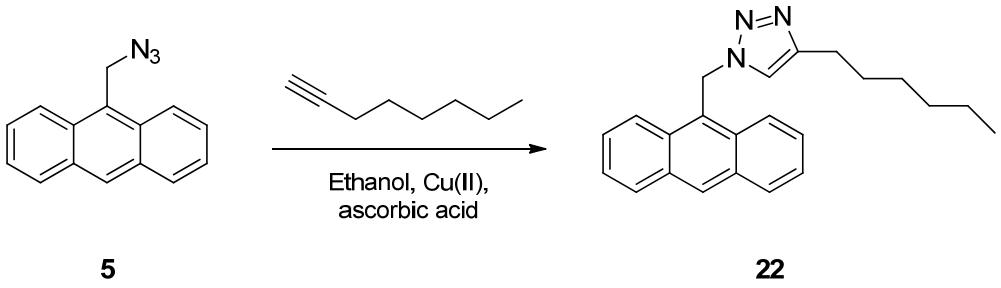


5 **21**

Equation 30: Attempted reaction of azide **5** with 1-decyne in ethanol.

Attempted reaction of the azide **5** with 1-decyne in ethanol was expected to give the triazole **21** (Equation 30). The reaction was monitored by infrared spectroscopy and the indications were that ethanol may not be the best solvent for this synthesis. Even after changing the reaction conditions by conducting the reaction in the microwave, formation of **21** was not conclusive. Evaporation of the solvent and ^{1}H NMR analysis of the residue gave no indication of 1,2,3-triazole formation. The same reaction was repeated using 1-heptyne and 1-octyne and it yielded the same results. The infrared spectra could not absolutely point to the formation of the triazoles **13** (equation 22) and **22** (Equation 31). Thin Layer

Chromatography of the azide **5** against the reaction solution was further evidence that there was no change in the product formation even after the click reaction. Both azide **5** and the major component of the reaction mixture gave an R_f value of 0.41 in 7:1 Hexanes: Ethyl acetate. This observation led to the conclusion that ethanol does not serve as a good solvent for triazole synthesis using 9-(chloromethyl)anthracene as the starting material.

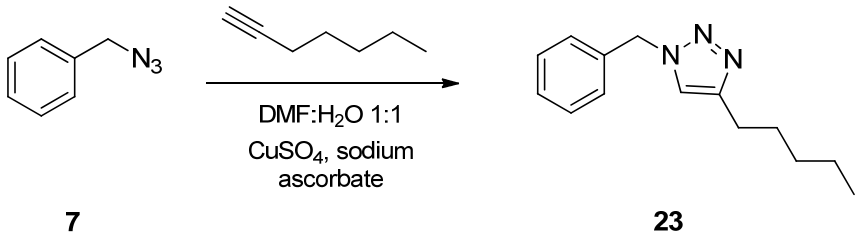


Equation 31: Attempted reaction of azide **5** with 1-octyne.

Synthesis of alkyl azides and triazoles was also carried out with dimethylformamide (DMF) as solvent. The reaction of 1mmol of *p*-ABSA and 1.5 mmol of DBU proceeded in the microwave at 70 °C for 30 minutes and was monitored by infrared spectroscopy to verify whether reaction was complete. Two different conditions were explored upon the addition of the alkyl halide. 1.0 mmol of benzyl bromide was added with one reaction proceeding at room temperature and another in the microwave at 70 °C for 30 minutes (compare to Equation 18). Infrared spectra of both reactions showed the complete formation of the azide anion. The click reaction was performed for both sets of reactions with one taking place in the microwave and the other at room temperature. Phenylacetylene was the alkyne used for the reaction (compare to Equation 25). The major component in the click reaction absorbed at 2098.39 cm^{-1}, representing no change hence triazole **16** may not have formed as was

expected. Addition of 1 mol% water to the reaction mixture did not change the results of the reaction since the infrared absorption spectrum remained the same.

The reaction was repeated with a 1:1 solution of DMF:H_2O and with 1-heptyne as the alkyne (Equation 32). After the click reaction was performed, the infrared spectra obtained indicated complete elimination of absorption at 2100 cm^{-1}. This was a positive sign and was an indication of potential formation of the triazole **23**. In light of this, NMR spectroscopy was used in an attempt to characterize the product.



7 **23**

Equation 32: Reaction of azide **7** with heptyne.

The solution potentially containing compound **23** was filtered, the filtrate evaporated under reduced pressure, and the NMR spectra of both residue and the filtrate were taken using $CDCl_3$ as solvent. The NMR spectra obtained did not provide convincing evidence for 1,2,3-triazole formation.

1-Bromobutane was also used as the starting material in DMF in a reaction with azide anion generated from *p*-ABSA and DBU (compare to Equation 19). 1-Azidobutane forms very well and its infrared spectrum shows absorption at 2097.43 cm^{-1}. Addition of 1-heptyne to the azidobutane in the presence of sodium ascorbate and copper(II) sulfate (compare to Equation 24) did not yield any change in the infrared spectrum, which continued to show a

strong absorption at 2097.82 cm^{-1}. The conclusion drawn out of this was that DMF on its own is not a good solvent for the formation of the triazole under the reaction conditions used. However, DMF is a good solvent for the formation of the alkyl azides.

Tertiary butyl alcohol and water mixture was also used as the solvent for the attempted synthesis of the alkyl azide and triazole. This reaction was prepared along with that of *t*-butyl alcohol on its own. *p*-ABSA would not easily dissolve in *t*-butyl alcohol at room temperature. After heating *p*-ABSA in *t*-BuOH for 15 minutes at 80 °C it dissolved very well and its infrared spectrum showed an absorption at 2126.16 cm^{-1}. Addition of 2 mmol of DBU followed by microwave heating at 80 °C for 30 minutes resulted in an infrared absorption at 2029.87 cm^{-1}, an indication of complete formation of the azide anion (compare to Equation 16). Addition of 1 mmol of 1-bromobutane in a room temperature reaction resulted in the formation of the alkyl azide **9** (compare to Equation 19) as indicated from the appropriate absorbances in the infrared spectra.

Click chemistry was attempted in *t*-BuOH with the addition of 1-heptyne, with the reaction being run at room temperature. However, infrared spectrum showed no change in absorption suggesting no product formation. As a result, 1.5 mL of deionized water was added possibly to enhance dissolution of the catalyst. Infrared spectra showed a visible change in the absorption with the peak at 2115.12 cm^{-1} much broader than previously. The conclusion is that *t*-BuOH is not a good solvent on its own for triazole synthesis, but water added improves dissolution hence enhancing the chance for product formation. *t*-BuOH-H_2O solvent mixture was viewed as a big improvement compared to *t*-BuOH alone. *p*-ABSA dissolved quite easily on this solvent mixture giving an infrared absorption at 2126.70 cm^{-1}. Addition of 1.5 mmol of DBU with subsequent microwave heating resulted in absorption at

2040.93 cm^{-1} indicating the formation of the azide anion (compare to Equation 16). When 1-bromobutane was added, the reaction was allowed to continue stirring at room temperature overnight and the reaction monitored using infrared, which indicated a strong absorption at 2097.95 cm^{-1} (compare to Equation 19). The alkyl azide in *t*-BuOH alone absorbed strongly at 2097.75 cm^{-1}. The strong infrared absorption was an indication of successful alkyl azide formation, and TLC with 1:1 hexanes: ethyl acetate gave an R_f of 0.33 for **9**.

Attempted click reaction (compare equation 24), carried out using 1 mmol of 1-heptyne in the presence of 20 mol% of sodium ascorbate and 20 mol% of copper(II) sulfate, gave infrared spectra that were different in the two solvent systems. Reaction in *t*-BuOH gave a strong absorption at 2098.47 cm^{-1}, whereas the reaction in *t*-BuOH-H_2O showed a weak but broad absorption at 2116.49 cm^{-1}. The aqueous alcohol mixture was adjudged to be a better potential solvent for triazole synthesis than *t*-BuOH alone. To verify the structure of any product synthesized in *t*-BuOH-H_2O, an extraction was carried out using ethyl acetate and de-ionized water. The organic layer was dried over magnesium sulfate and evaporated, then an NMR sample was prepared in $CDCl_3$. ^1H NMR of **15** (equation 24) showed a singlet at 7.27 ppm probably for the H-5 triazole, triplet at 4.33 ppm for the *N*-CH_2 of the butyl chain, and triplet at 2.73 likely of CH_2 group of side chain (Figure 47). Purification was done by flash column chromatography using 5:1 chloroform: methanol as the solvent in an attempt to get cleaner NMR spectra. The NMR sample of the residue was then prepared in d_6-DMSO, however neither the ^1H nor the ^{13}C NMR spectra could conclusively verify the formation of the triazole **15**.

t-BuOH-H_2O was again used as the solvent in the synthesis of benzyl azide (**7**, compare to Equation 18). The infrared spectrum obtained absorption at 2099.46 cm^{-1}, a very

good indicator for the benzyl azide. Attempted click reaction with phenylacetylene resulted in a weak infrared absorption at 2098.56 cm^{-1}. Once again to verify the structure obtained an aqueous workup was performed with 1.5 mL de-ionized water and extracted three times with 1.5 mL portions of ethyl acetate. After drying and evaporating, NMR samples were prepared in both d_6-DMSO and $CDCl_3$, however these spectra did not provide any evidence of triazole formation. Finally, *t*-BuOH-H_2O was used in the synthesis of 9-(azidomethyl)anthracene (**5**). This reaction did not proceed well due to the fact that 9-(chloromethyl)anthracene could not dissolve adequately in the solvent mixture. Microwave heating could not improve the solubility either.

Acetone and DMSO were the other solvents used for these studies. The infrared spectrum of *p*-ABSA in acetone showed a strong absorption at 2130.30 cm^{-1}. However, upon addition of DBU there occurs only a slight change in the absorption spectrum indicating an incomplete formation of the azide anion. DMSO did not perform any better in the synthesis of both the alkyl azide and triazole for there was still incomplete formation of the azide anion as indicated by infrared spectra of the reaction mixtures.

Kinetic studies using CD_3CN

Kinetic studies on the reaction of *p*-ABSA and DBU in deuterated acetonitrile were attempted. These reactions were performed at room temperature and the NMR spectra were obtained after every 30 minutes to see how the reaction progressed with time. The NMR spectra read after 1 minute of the reaction was markedly different from the rest. It appeared that after 30 minutes the reaction was largely complete since the spectra taken after that time showed only minor signal differences with that read after 3 hours. There were slight signal

shifts as the reaction progresses. The ^{1}H NMR spectrum for *p*-ABSA alone shows a singlet at 2.03 ppm, and after 1 minute of the reaction with DBU, the singlet is seen at 2.04 ppm, then at 1.90 ppm after 30 minutes, 2.14 ppm after 90 minutes, 1.91 ppm after 2 hours, and finally at 2.14 ppm after 3.5 hours of the reaction. These spectral changes provide an indication of an ongoing reaction as time changes. Most importantly, the spectra show that the reactions are largely complete in 30 minutes with the formation of the azide anion. The fluctuations that occur subsequently could be due to changes in concentration.

CONCLUSION

The mixture of *p*-ABSA and DBU was successfully used to produce the soluble organic salt that served as a safe source of the azide anion. It proved to be a good azide transfer reagent for the S_N2 synthesis of alkyl azides in a variety of different solvent systems. However, the subsequent attempted synthesis of triazoles may need further studies to prove its viability. While some infrared and ^{1}H NMR spectra gave good indications for the synthesis of the triazole, further investigation into the experimental conditions may lead to the realization of better results.

EXPERIMENTAL

General Procedures

Reagents used for the reactions were obtained commercially; 4-acetamido-benzylsulfonyl azide (*p*-ABSA) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), the two compounds used for the preparation of the soluble-organic salt that serves as the azide transfer reagent, were all obtained from Sigma-Aldrich. All the reactions were monitored using Thin Layer Chromatography (TLC) and ultraviolet light detection. A Thermo Electron Corporation IR 200 Infrared spectrometer was also used to monitor the progress of the reaction *in situ.* A CEM (Discover) Corporation microwave was used for sample irradiation at different temperatures to improve reaction rate. Bruker Avance 400 Ultrashield and Bruker Avance 400 NMR instruments were used for ^{1}H and ^{13}C spectroscopy using $CDCl_3$ and d_6-DMSO as solvent.

Azide Synthesis Using Different Solvents

1. Acetonitrile

Preparation of Azide anion

4-Acetamidobenzenesulfonyl azide (*p*-ABSA, 1.0 mmoles (0.24 g)) was put in a 10 mL microwave tube and dissolved in 1.5 mL of acetonitrile. An infrared spectrum of the mixture was run to monitor the reaction. 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 1.5 mmol (0.22 mL)) was added and the reaction heated in the microwave for 30 minutes at 70 °C. Thin Layer Chromatography (TLC) was carried out. A duplicate reaction was prepared to run at room temperature and IR spectra were taken periodically.

p-ABSA IR = 2134.11 cm^{-1}

p-ABSDBU = 2018.23 cm^{-1}

TLC in 1:1 Hexanes: Ethyl acetate: *p*-ABSA R_f = 0.29; *p*-ABSDBU R_f = 0.16

Preparation of Alkyl Azide

9-(Chloromethyl)anthracene (1.0 mmol (0.226 g) was added to the reaction mixture containing azide anion (above). The mixture was stirred to dissolve material and put into the microwave at 110 °C for 30 minutes. TLC and infrared spectrum were taken to monitor and determine whether the reaction was complete.

9-(azidomethyl)anthracene IR = 2099.95 cm^{-1}

TLC in 5:1 Hexanes: Ethyl acetate: R_f = 0.43

Attempted synthesis of Triazole Using Diethylacetylene Dicarboxylate

Diethyl acetylene dicarboxylate (DEAD, 2.0 mmol (0.32 mL)) was added to the reaction (above) and the mixture was stirred to dissolve, and then placed in the microwave for 60 minutes at 110 °C. Infrared spectra of the sample were taken periodically. The mixture was then transferred into a round bottom flask and reduced under vacuum. An NMR spectrum was taken in d_6-DMSO. Purification was carried out using flash column chromatography with 4:1 Hexanes: ethyl acetate as solvent. Fractions were transferred into a round bottom flask and reduced under vacuum.

TLC in 4:1 Hexanes: Ethyl acetate: 9-(azidomethyl)anthracene R_f = 0.44; 9-(azido-methyl)anthracene-DEAD R_f = 0.13, 0.3, 0.44

Infrared = 2099.97 cm^{-1}

^{1}H and ^{13}C NMR – No conclusive data for triazole formation.

Attempted Synthesis of Triazole using 1-Heptyne

1-Heptyne (1 mmol (0.13 mL) was added to the acetonitrile solution of azide **5**. This was followed by the addition of 20 mol% (0.039 g) sodium ascorbate and 20 mol% (0.032 g) copper (II) sulfate, and the mixture was allowed to stir overnight at room temperature. An infrared spectrum of sample was taken, which still showed azide to be present. 1.0 mL of methanol was added and reaction left stirring overnight. An infrared spectrum of the sample was obtained and the solution was transferred into a round bottom flask and reduced under vacuum. NMR spectra were taken in d_6-DMSO.

TLC, Hexanes: Ethyl acetate 1:1 $R_f = 0.415$

Infrared = 2099.97 cm^{-1}

Infrared after addition of 1 ml MeOH = 2043.84 cm^{-1}

^{1}NMR = δ 7.53 ppm (s, 1H), 6.6 ppm (s, 2H), 4.2 ppm (t, 2H)

Attempted Triazole Synthesis Using Phenyl acetylene

Phenylacetylene (1.0 mmol (0.11 mL) was added to a solution of azide **5** followed by addition of 20 mol% (0.04 g) sodium ascorbate and 20 mol% (0.032 g) copper sulfate. The reaction was allowed to proceed at room temperature with continued stirring for 12 hours. Infrared spectra were taken to monitor the reaction progress. A syrupy solution, green in color, was formed.

TLC Hexanes: Ethyl acetate 2: 1: Product mixture $R_f = 0.21, 0.4, 0.66$

Infrared : 9-(azidomethyl)anthracene (**5**) = 2099.54 cm^{-1}

Infrared : Product mixture = weak absorption at 2069.46 cm^{-1}

^{1}H NMR = δ 6.6 ppm (s, 2H)

Reactions Involving 1-Bromobutane in Acetonitrile

4-Acetamidobenzenesulfonyl azide (*p*-ABSA, 1.0 mmol (0.241 g)) was added to a microwave tube and dissolved in 1.5 mL of acetonitrile. An infrared spectrum of the mixture was run, then 1.5 mmol (0.22 mL) of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was added and the reaction was heated in the microwave for 30 minutes at 70 °C. Thin Layer Chromatography (TLC) was carried out, and an infrared spectrum was obtained to monitor the formation of the azide anion. 1.0 mmol (0.11 mL) of 1-bromobutane was added and reaction was allowed to continue overnight with stirring. The IR spectrum of the reaction was obtained, then 1.0 mmol (0.031 mL) of 1-heptyne was added followed by 20 mol% (0.039 g) sodium ascorbate and 20 mol% (0.0319 g) copper (II) sulfate. The reaction was left to stir overnight, and then an infrared spectrum was obtained. 1.0 mL of methanol was added and then the reaction was left to stir overnight. An infrared spectrum was obtained, the solution was reduced under vacuum, and the NMR spectrum of the residue was taken in d_6-DMSO.

Infrared data :

p-ABSA = 2133.90 cm^{-1} ; *p*-ABSDBU = 2019.40 cm^{-1}

1-Azidobutane (**9**) = 2099.69 cm^{-1}

Reaction mixture without MeOH = 2100.19 cm^{-1}

Reaction mixture with MeOH = No azide absorption signal.

^{1}H NMR = 4.3 ppm (t, 2H), 7.3 ppm (s, 1H)

Reactions Using Benzyl Bromide

4-Acetamidobenzenesulfonyl azide (*p*-ABSA, 1.0 mmoles (0.241 g)) was put in a microwave tube and dissolved in 1.5 mL of acetonitrile. An Infrared spectrum of the mixture was taken, then 1.5 mmol (0.22 mL) of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was added and the reaction continued in the microwave for 30 minutes at 70 °C. Thin Layer Chromatography (TLC) was carried out, and an infrared spectrum obtained to monitor the formation of the azide anion. 1.0 mmol (0.12 mL) of benzyl bromide was added and the mixture was allowed to stir at room temperature overnight. An infrared spectrum of the reaction was taken; then 1.0 mmol (0.11 mL) of phenylacetylene was added, followed by addition of 20 mol% (0.039 g) sodium ascorbate and 20 mol% (0.032 g) copper sulfate. The reaction was allowed to stir at room temperature with infrared spectra being taken to monitor the reaction. 1.0 mL of methanol was added and the reaction stirred overnight. Infrared spectra were again taken.

TLC 1: 1 hexanes: ethyl acetate

1-Azidobutane (**7**) R_f = 0.7

Product mixture, R_f = 0.3

Infrared data:

p-ABSA = 2133.90 cm^{-1}

p-ABSDBU = 2018.95 cm^{-1}

1-Azidobutane (**7**) = 2099.94 cm^{-1}

Product mixture without MeOH = Strong absorption at 2099.73 cm^{-1}

Product mixture with MeOH = Weak absorption at 2100.11 cm^{-1}

^1H NMR = δ 5.59 ppm (s, 2H), 7.76 (s, 1H)

2. ETHANOL

Preparation of the Azide anion

4-Acetamidobenzenesulfonyl azide (*p*-ABSA, 1.0 mmol (0.24 g)) was dissolved in 1.5 mL of ethanol and its infrared spectrum taken. 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU, 1.5 mmoles (0.22 mL)) was added followed by heating in the microwave at 80 °C for 60 minutes. A duplicate reaction was also carried out at room temperature for comparison.

TLC with hexanes: ethyl acetate 1:1

p-ABSA $R_f = 0.28$

p-ABSDBU $R_f = 0.15$

Infrared, *p*-ABSA = 2127 cm^{-1}

p-ABSDBU = 2036.93 cm^{-1}

Preparation of Alkyl Azide in Ethanol

9-(Chloromethyl)anthracene (1 mmol (0.226 g) was added to the sample (above). The mixture was stirred to dissolve and put in the microwave at 70 °C for 30 minutes. A duplicate reaction was carried out at room temperature. TLC (with chloroform: methanol 3:1), and an infrared spectrum were taken to monitor and determine whether reaction was complete.

TLC with 7:1 hexanes: ethyl acetate: 9-(azidomethyl)anthracene $R_f = 0.41$; 9-(chloromethyl)anthracene, $R_f = 0.28$

Infrared data :

Azide **5** Microwave = 2106.48 cm^{-1}

Azide **5** Room Temp. = 2102.37 cm^{-1}

Attempted Triazole Synthesis in Ethanol

The triazole synthesis was attempted using 1.0 mmol of different alkynes including 1-heptyne, 1-decyne, phenylacetylene, and 1-octyne. In each of the reactions involving the alkynes, 20 mol% of ascorbic acid and 20 mol% of copper (II) acetylacetonate or copper (II) sulfate was added. The reactions were let to stir overnight at room temperature.

IR data:

Attempted synthesis of **13** Microwave = 2108.34 cm^{-1}

Attempted synthesis of **13** Room Temp. = 2105.50 cm^{-1}

Attempted synthesis of **21**Microwave = 2108.61 cm^{-1}

Attempted synthesis of **21** Room Temp. = 2100.51 cm^{-1}

Attempted synthesis of **14** Microwave = 2109.38 cm^{-1}

Attempted synthesis of **14** Room Temp. = 2101.75 cm^{-1}

Attempted synthesis of **22** Microwave = 2110.73 cm^{-1}

Attempted synthesis of **22** Room Temp. = 2124.41 cm^{-1}

TLC 1: 1 Hexanes: Ethyl acetate : Product **22** R_f = 0.41 ; Azide **5** R_f = 0.41

Reaction with Benzyl Bromide

Benzyl bromide (1.0 mmol (0.12 mL) was added to the azide anion (above) and the reaction continued overnight stirring at room temperature. Infrared spectra were taken.

Infrared = 2100.48 cm^{-1}

TLC, 1:1 Hexanes: Ethyl acetate $R_f = 0.18$

1:2 Hexanes: Ethyl acetate $R_f = 0.3$

Attempted Triazole synthesis using Benzyl azide and Phenylacetylene

De-ionized water (1.5 mL) was added to the azide solution and stirred. Then 1.0 mmol (0.11 mL) of phenylacetylene was added followed by 10 mol% (0.02 g) $CuSO_4$ and 20 mol% (0.035 g) ascorbic acid. Reaction continued stirring overnight at room temperature. Infrared spectra were obtained.

Infrared = 2111.26 cm^{-1}

3. *t*-BuOH

p-ABSA (1.0 mmol) was dissolved in 1.5 mL of *t*-BuOH. The sample was heated in the microwave for 15 minutes at 80 °C, then the infrared spectrum of the solution was collected. DBU (2 mmol (0.30 mL) was added and reaction continued in the microwave at 80°C for 30 minutes. The infrared spectrum of the sample was taken.

Infrared *p*-ABSA = 2126.16 cm^{-1}

p-ABSADBU = 2029.87 cm^{-1}

4. *t*-BuOH-H_2O

Preparation of Azide Anion

4-Acetamidobenzenesulfonyl azide (*p*-ABSA, 1.0 mmol (0.24 g)) was dissolved in 1.5 mL of *t*-butanol. This was followed by addition of 1.5 mL water and the reaction was allowed to stir until the reagents dissolved. An infrared spectrum of the solution was then taken. 1,8-Diazabicyclo-[5.4.0]-undec-7-ene (DBU, 1.5 mmol (0.22 mL)) was added and the reaction continued in the microwave at 80 °C for 30 minutes. An infrared spectrum was taken to monitor the progress of the reaction.

Infrared, *p*-ABSA = 2126.70 cm^{-1}

p-ABSADBU = 2040.93 cm^{-1}

Preparation of Alkyl Azide

Reaction with 9-(Chloromethyl)anthracene

9-(Chloromethyl)anthracene (1.0 mmol (0.226 g) was added to the azide anion and the solution allowed to stir. The reaction was put in microwave at 80 °C for 30 minutes to enhance dissolution.

Data = 9-(Chloromethyl anthracene did not dissolve under these conditions.

Reaction with 1-bromobutane

1-Bromobutane (1.0 mmol (0.11 mL) was added to the azide anion and the reaction allowed to proceed at room temperature with stirring. Infrared spectra were taken.

Infrared data : Alkyl azide **9** in *t*-BuOH-H_2O = 2097.95 cm^{-1}

Alkyl azide **9** in *t*-BuOH = 2097.75 cm^{-1}

Attempted Triazole Synthesis Using 1-Heptyne in *t*-BuOH-H_2O

1-Heptyne (1.0 mmol (0.13 mL) was added, followed by 20 mol% (0.039 g) sodium ascorbate and 20 mol% (0.032 g) copper (II) sulfate. The reaction left to stir at room temperature, with infrared spectra being collected periodically. An aqueous work-up was performed; 1.5 mL of deionised water was added, followed by 1.5 mL of ethyl acetate. The organic layer was transferred into an Erlenmeyer flask and the aqueous layer was extracted with ethyl acetate (2 x 1.5 mL). The organic layers were combined into an Erlenmeyer flask and dried over magnesium sulfate, filtered into a round bottom flask and reduced under vacuum. NMR spectra of the residue were collected in $CDCl_3$.

TLC 1: 1 Hexanes: Ethyl acetate, R_f = 0.33

Infrared data: Product solution = Weak absorption at 2116.49 cm^{-1}

^1H NMR = δ 7.27 ppm (s, 1H), 4.33 ppm (t, 2H), 2.73 (t, 2H)

Attempted Triazole Synthesis Using 1-Heptyne in *t*-BuOH

1-Heptyne (1 mmol (0.13 mL) was added to the 1-azidobutane, followed by 20 mol% (0.039 g) sodium ascorbate and 20 mol% (0.032g) copper (II) sulfate. The reaction was left to stir at room temperature, followed by collection of an infrared spectrum.

Infrared data : Product mixture = Strong absorption at 2098 cm^{-1}

Dimethylformamide (DMF)

p-ABSA (1.0 mmol (0.24 g) was dissolved in 1.5 mL of DMF. An infrared spectrum was taken, followed by addition of 1.5 mmol (0.22 mL) of DBU. The reaction was heated in the microwave at 70 °C for 30 minutes. An infrared spectrum of the solution was taken.

Infrared data : Product mixture = 2098.39 cm^{-1}

Synthesis of Alkyl Azide in DMF

1-Bromobutane (1 mmol (0.11 mL) was added to the azide anion generated from the *p*-ABSA and DBU, and then the mixture was left to stir at room temperature overnight and its infrared spectrum taken.

Infrared 1-azidobutane (**9**) = 2097.68 cm^{-1}

The same reaction was repeated with 1 mmol (0.12 mL) of benzyl bromide and left to stir overnight at room temperature. An infrared spectrum was taken to ascertain formation of the benzyl azide.

Infrared benzyl azide (**7**) = 2097.95 cm^{-1}

Attempted Triazole Synthesis in DMF Using Phenylacetylene

Phenylacetylene (1.5 mmol (0.16 mL) was added to the solution of benzyl azide (1.0 mmol), followed by 20 mol% (0.035 g) of ascorbic acid and 20 mol% (0.032 g) of copper (II) sulfate. The reaction proceeded at room temperature with stirring and infrared spectra were obtained.

Infrared : Product mixture = 2099.75 cm^{-1}

Attempted Triazole Synthesis in DMF Using 1-Heptyne

1-Heptyne (1 mmol (0.13 mL) was added to the 1-azidobutane (1.0 mmol) solution, followed by addition of 20 mol% (0.04 g) sodium ascorbate and 20 mol% (0.032 g) copper(II) sulfate. The reaction was left to stir at room temperature and infrared spectra were taken.

Infrared : Product mixture = 2097.82 cm^{-1}

5. DMF-H_2O

1-Bromobutane (1.0 mmol (0.11 mL) was added to azide anion in DMF and allowed to stir at room temperature. This was followed by addition of 1.5 mL of deionized water with continued stirring. 1-Heptyne (1.0 mmol (0.13 mL) was then added, followed by 20 mol% (0.039 g) sodium ascorbate and 20 mole% (0.032 g) copper (II) sulfate. The mixture was left to stir at room temperature and infrared spectra were taken.

Infrared data :

p-ABSA in DMF = 2130.25 cm^{-1}

p-ABSDBU in DMF = 2012.56 cm^{-1}

1-Azidobutane (**9**) = 2097.54 cm^{-1}

Click reaction with 1-heptyne = No azide absorption

Kinetic Studies in Deuterated Acetonitrile (CD_3CN)

Proton NMR kinetic studies of the *p*-ABSDBU formation in CD_3CN were carried out for reactions in the microwave, and at room temperature. 1.0 mmol (0.24 g) of *p*-ABSA were dissolved in CD_3CN. 1.2 mmol (0.18 mL) of DBU were added with continued stirring,

and an NMR spectrum of an aliquot was taken immediately. ^{1}H NMR spectra were then subsequently taken after every 30 minutes. Infrared spectra were also taken at intervals of 30 minutes. An NMR spectrum of *p*-ABSA was also obtained from a solution of 10 mg of *p*-ABSA in CD_3CN for comparison. 4 drops of DBU were dissolved in 1.0 mL of CD_3CN and the proton NMR was obtained.

For *p*-ABSA :

^{1}H NMR: δ 7.75, 7.77, 7.80, 7.83 (4H), 2.03 (s, 3H)

For DBU :

^{1}H NMR: δ 3.04 (t, 2H), 3.09 (t, 2H), 2.20 (t, 2H), 2.47 (t, 2H), 1.62 (quintet, 2H)

p-ABSDBU after 1 minute of reaction:

^{1}H NMR: δ 7.75, 7.79, 7.81, 7.83 (4H), 2.04 (s, 3H), 2.22 (t, 2H), 3.06 (t, 2H), 3.10 (t, 2H), 1.64 (quintet, 2H), 1.44-1.56 (m, not resolved)

p-ABSDBU after 3 hours:

^{1}H NMR: δ 7.91 (s), 7.54-7.76 (m), 2.14 (s, 1H), 2.39 (t, 2H), 3.18 (t, 2H), 3.26 (t, 2H) 1.79 (quintet, 2H), 1.97 (quintet), 1.56-1.69 (m, not resolved)

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Appendix

IR and NMR Spectra

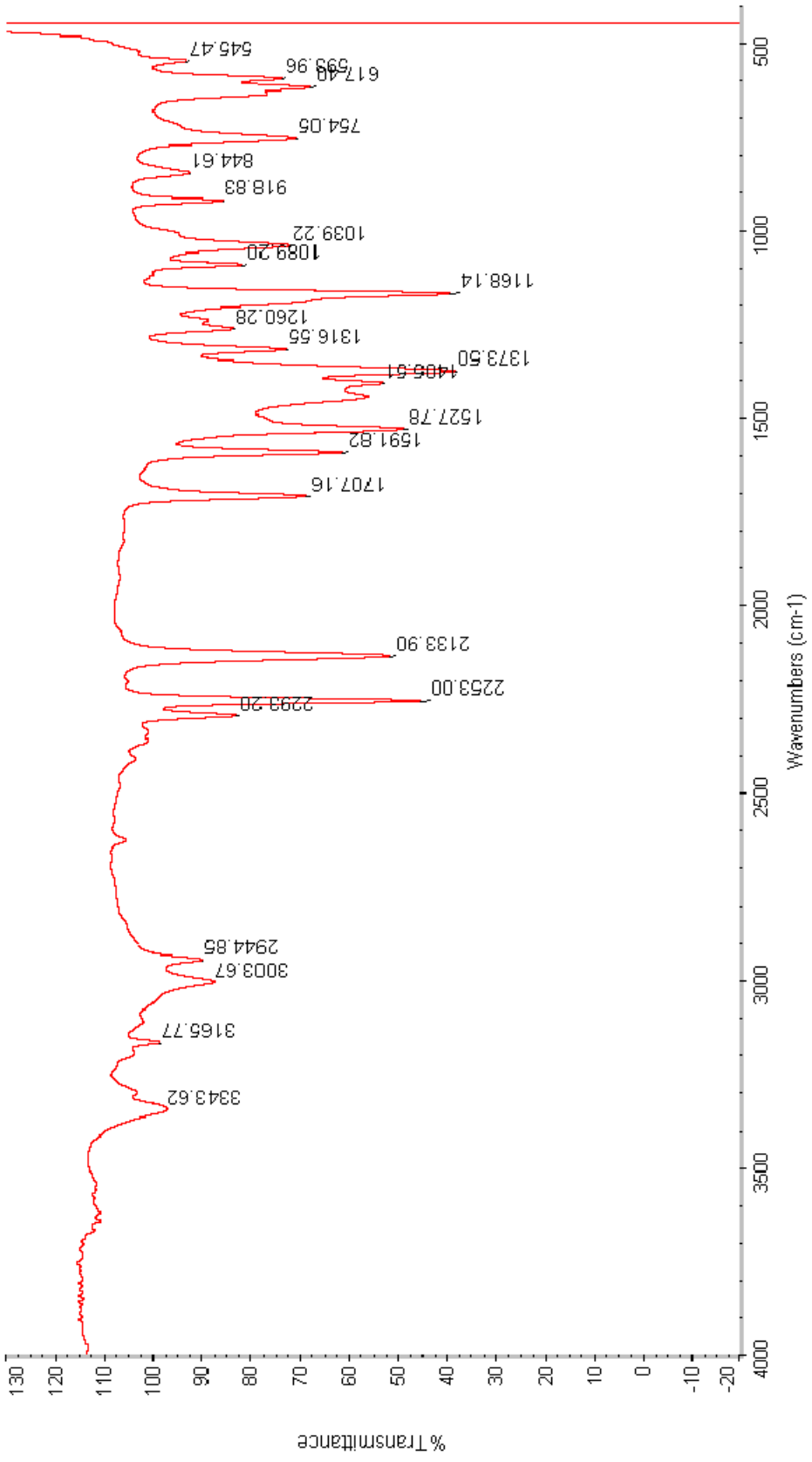

Figure 2: Infrared spectrum of *p*-ABSA in acetonitrile.

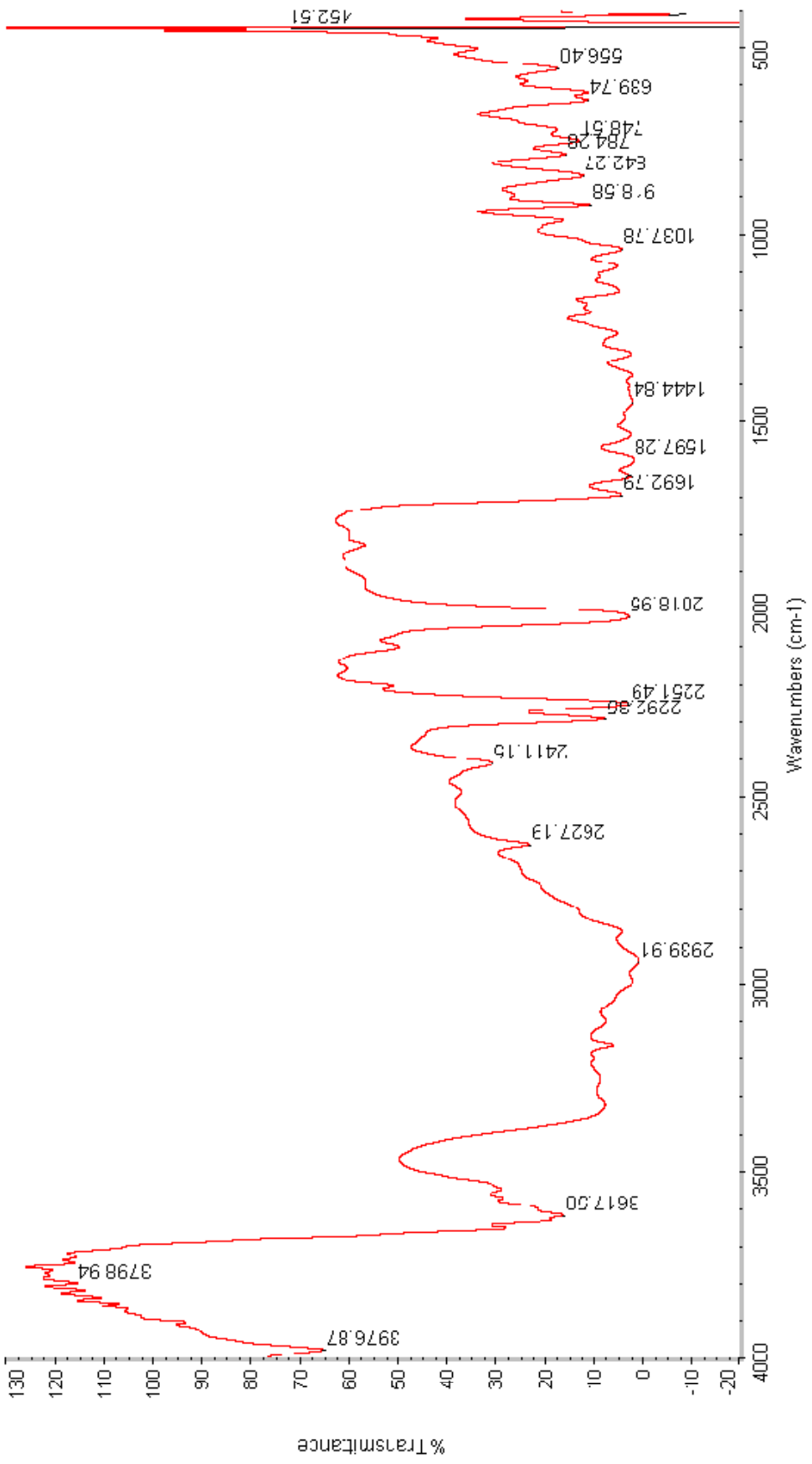

Figure 3: Infrared spectrum of *p*-ABSDBU (**3**) in acetonitrile.

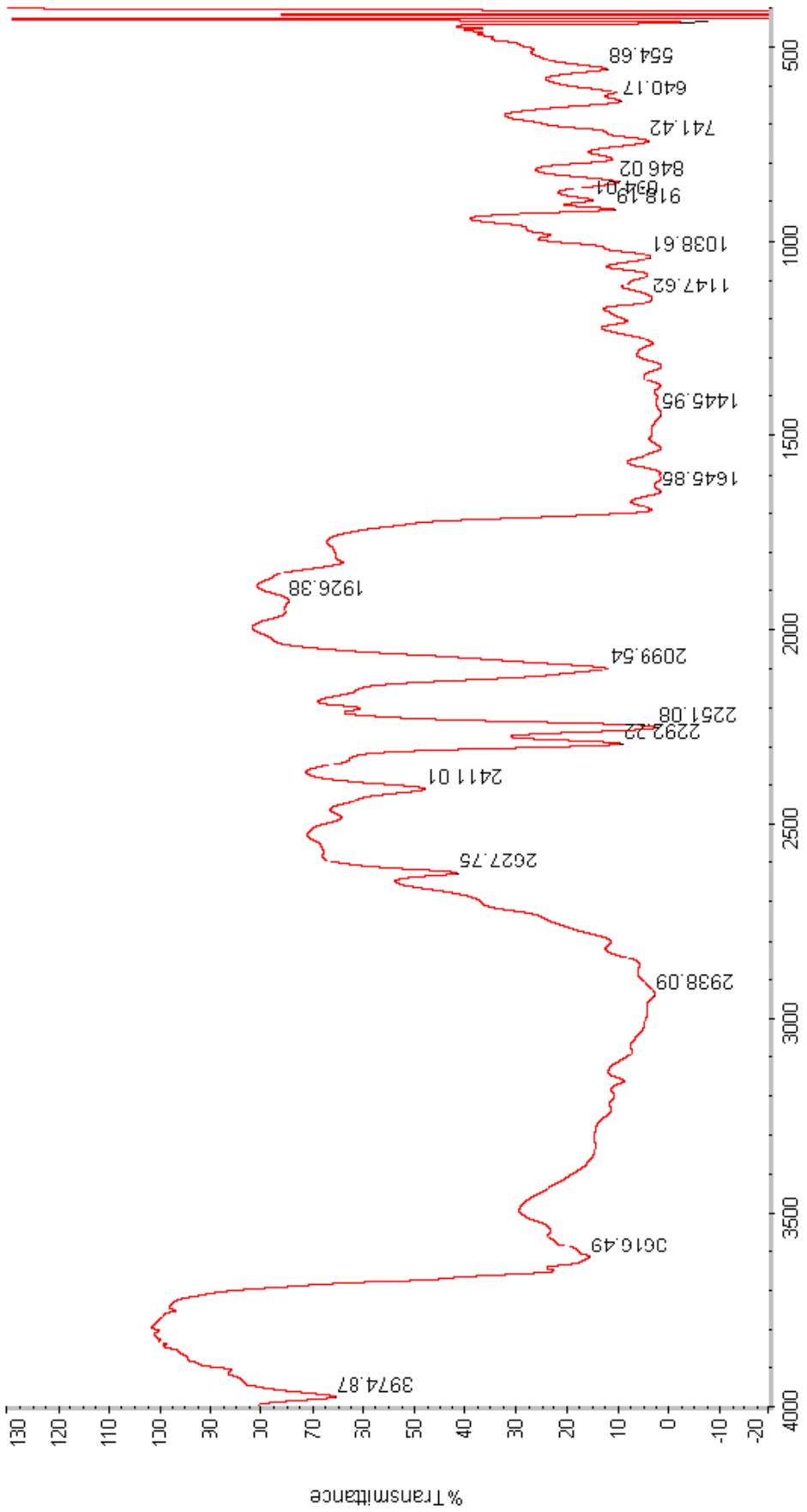

Figure 4: Infrared spectrum of **5** in acetonitrile.

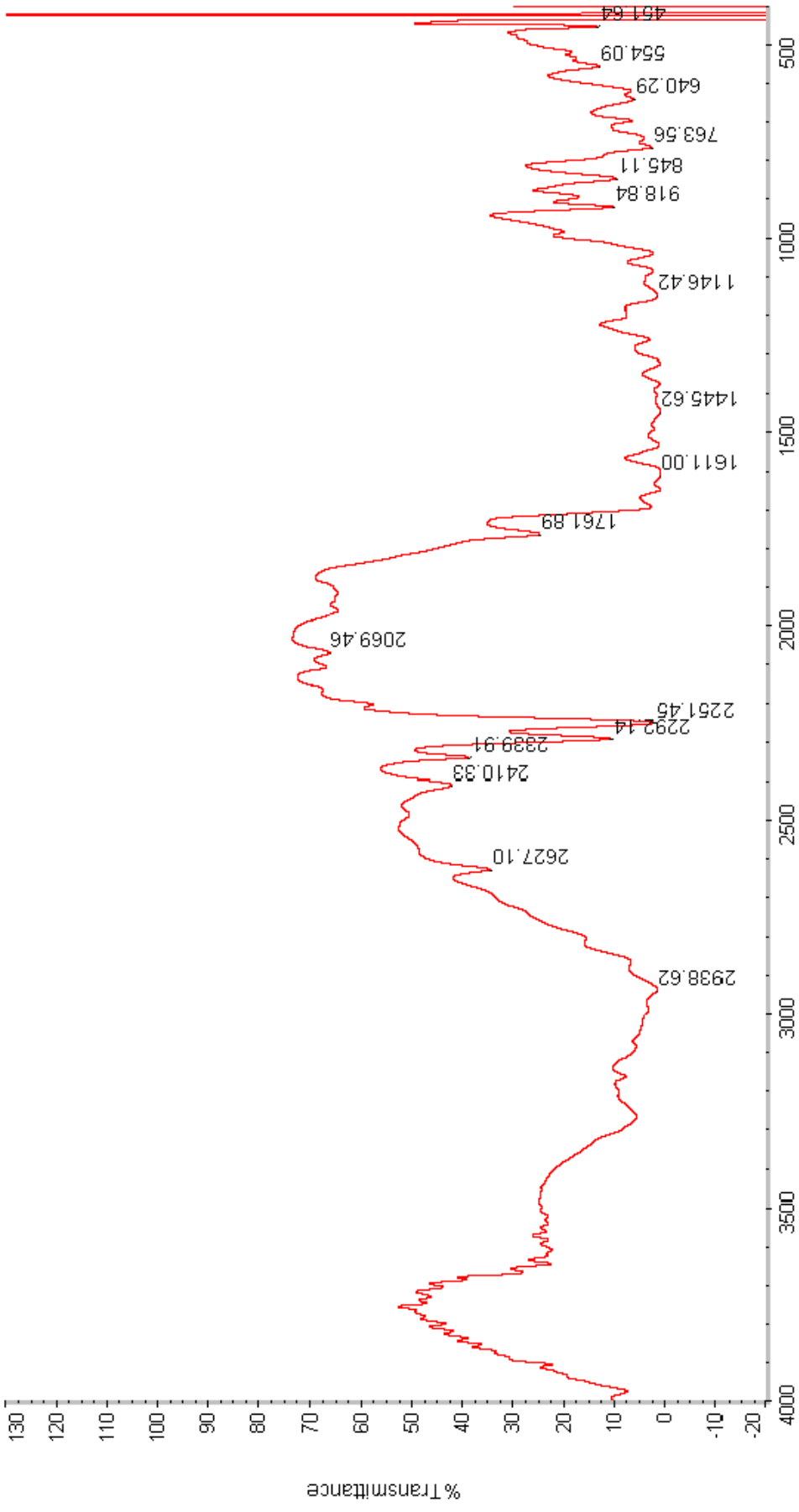

Figure 5: Infrared spectrum of attempted synthesis of **14** in acetonitrile.

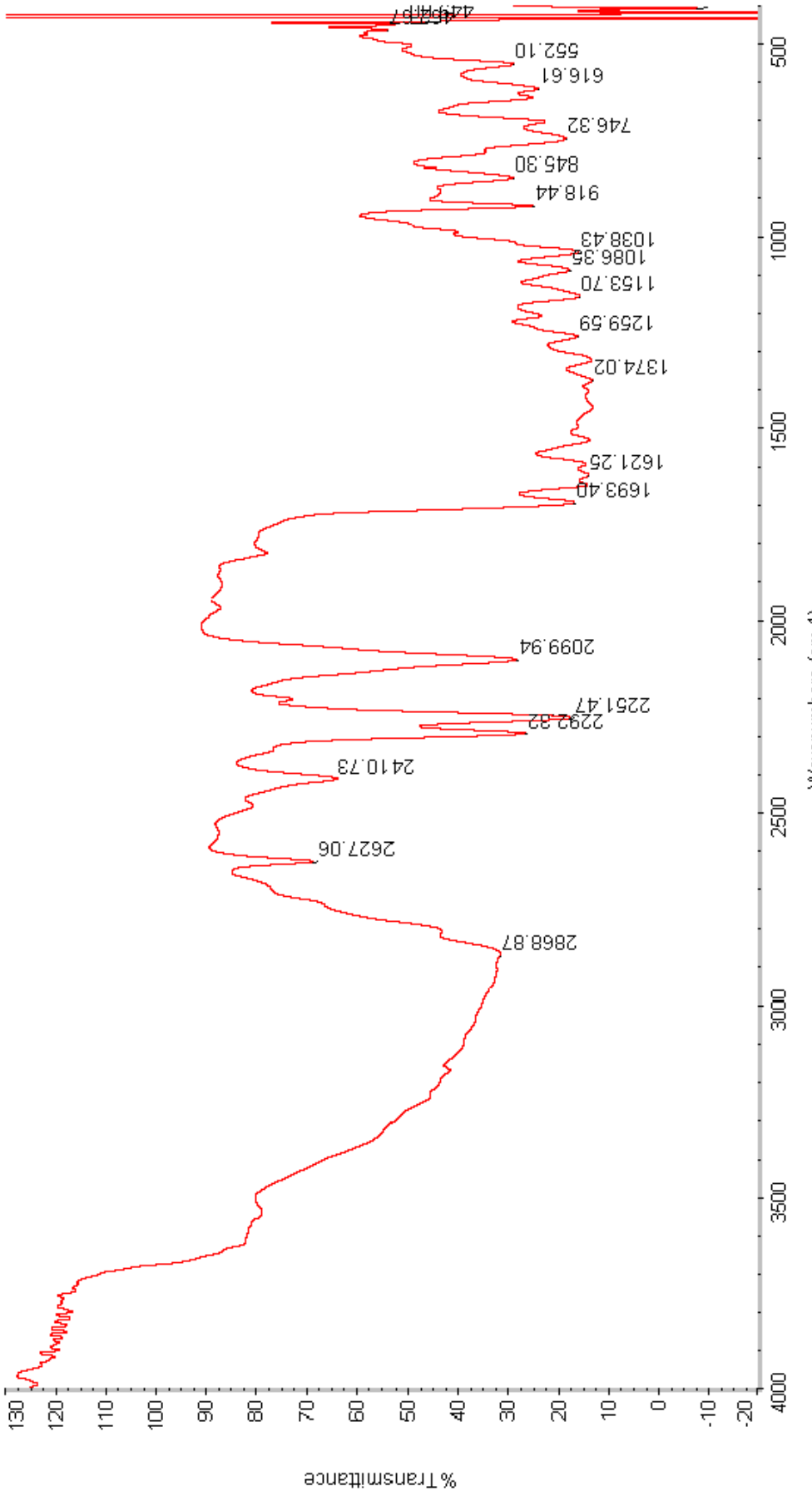

Figure 6: Infrared spectrum of **7** in acetonitrile.

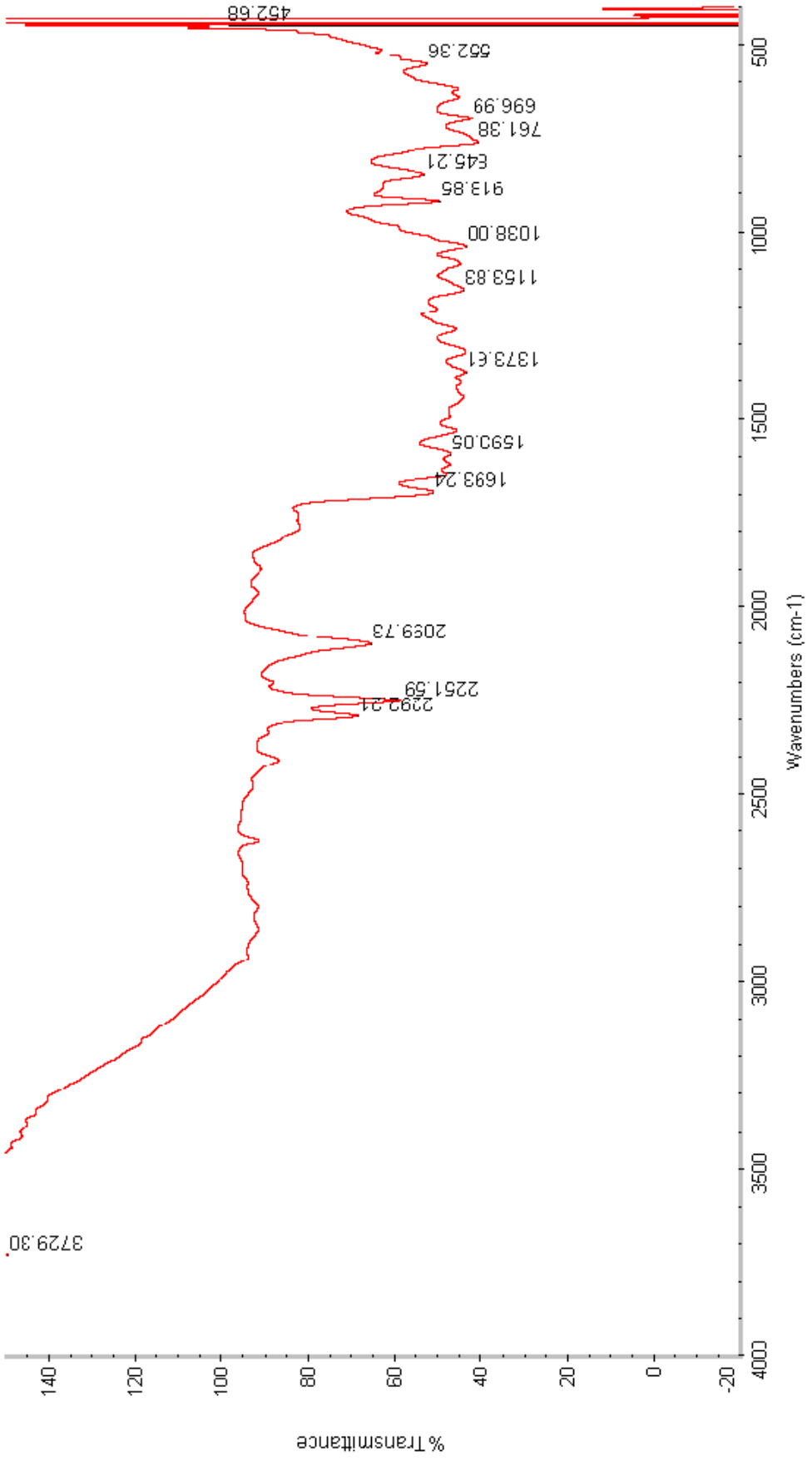

Figure 7: Infrared spectrum of attempted synthesis of **16** in acetonitrile.

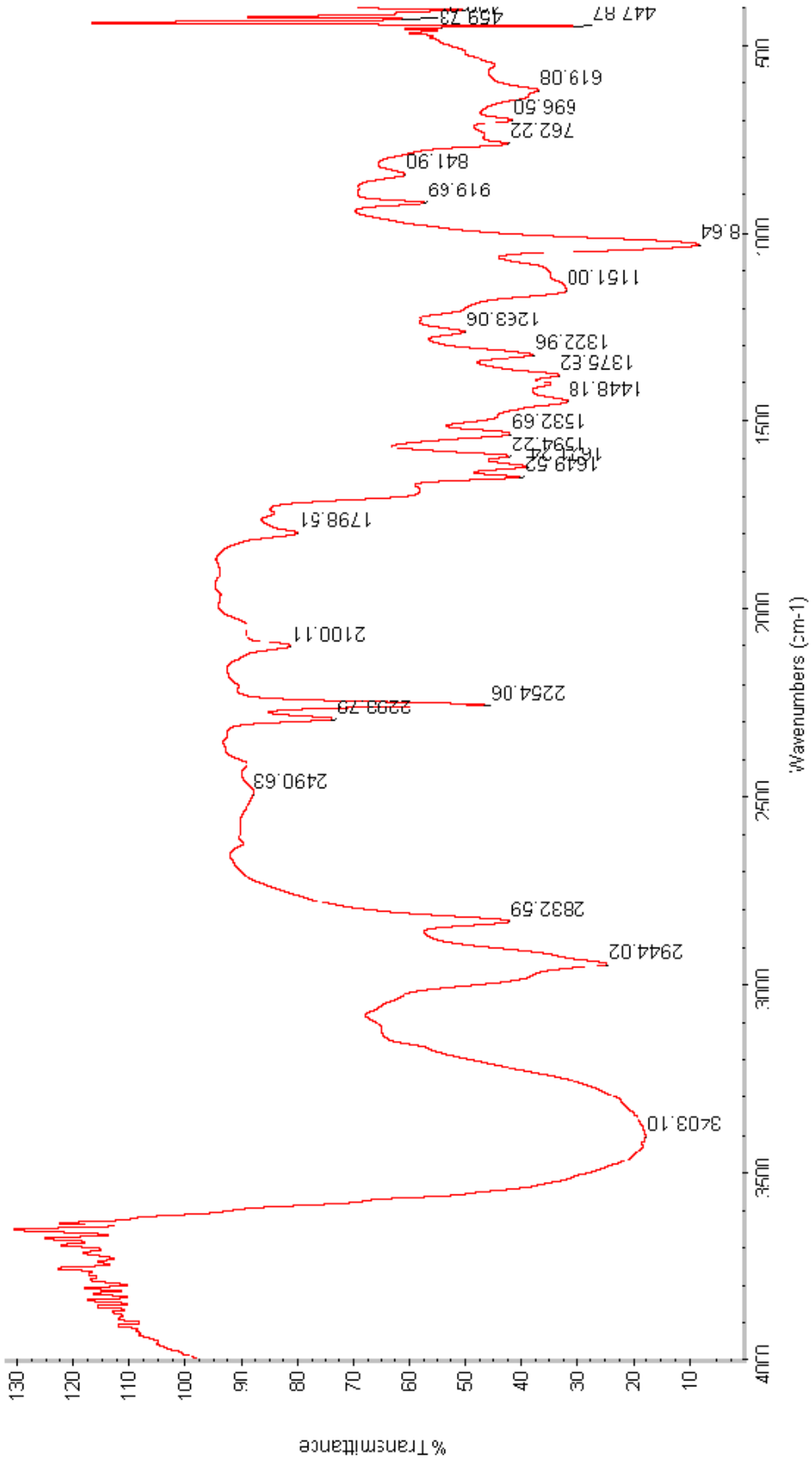

Figure 8: Infrared spectrum of attempted synthesis of **16** in acetonitrile-methanol.

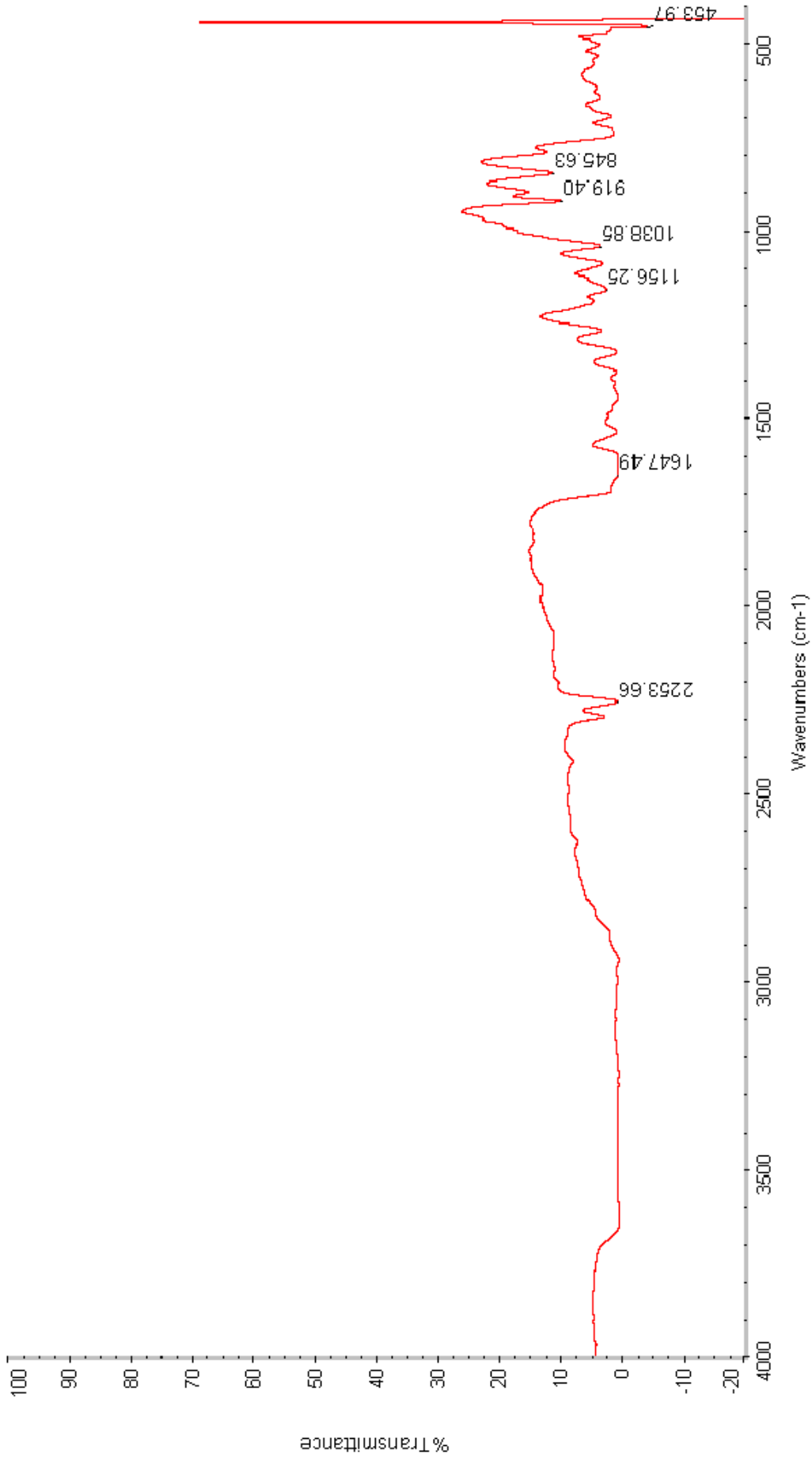

Figure 9: Infrared spectrum of attempted synthesis of **17** in acetonitrile.

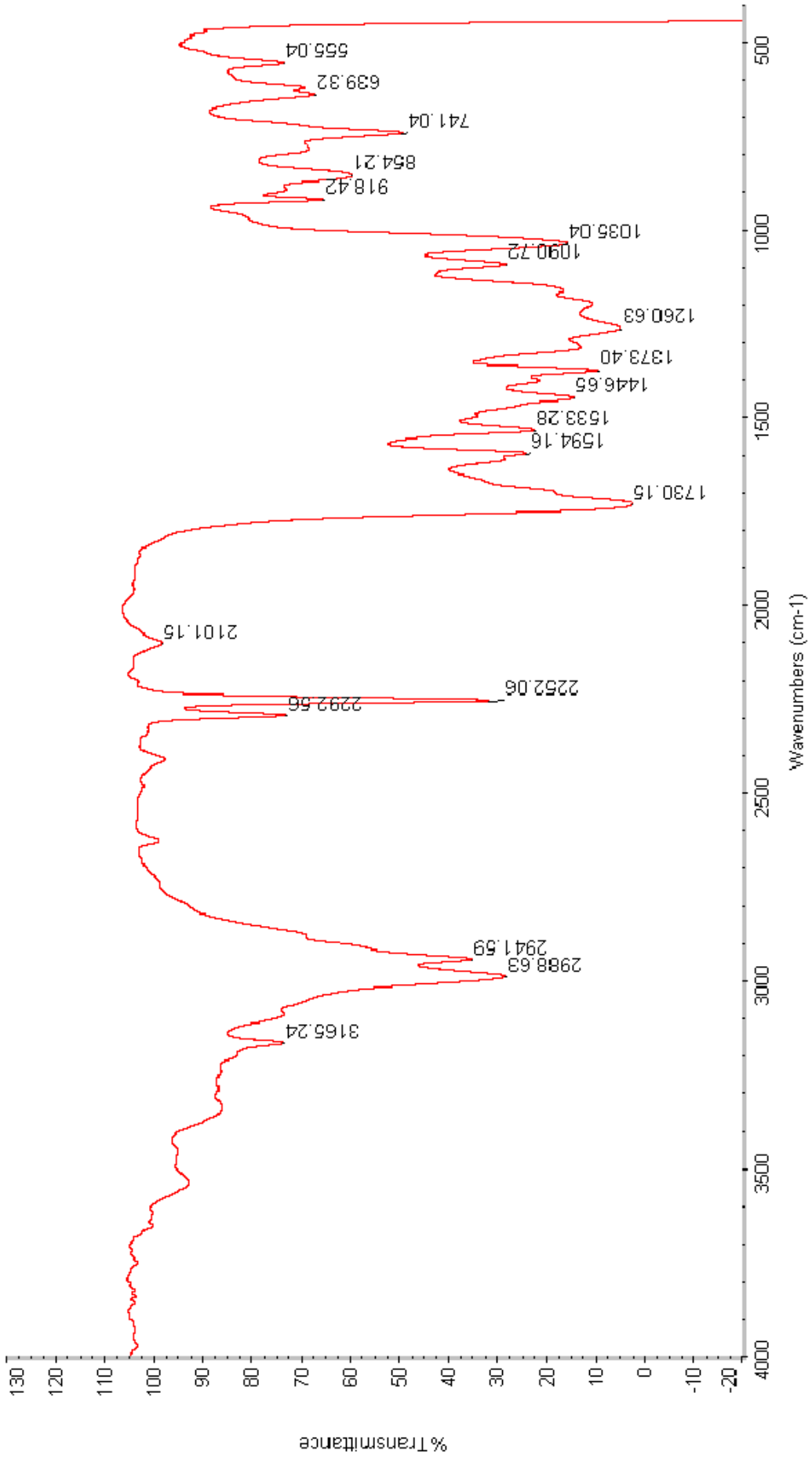

Figure 10: Infrared spectrum of attempted synthesis of **12** in acetonitrile.

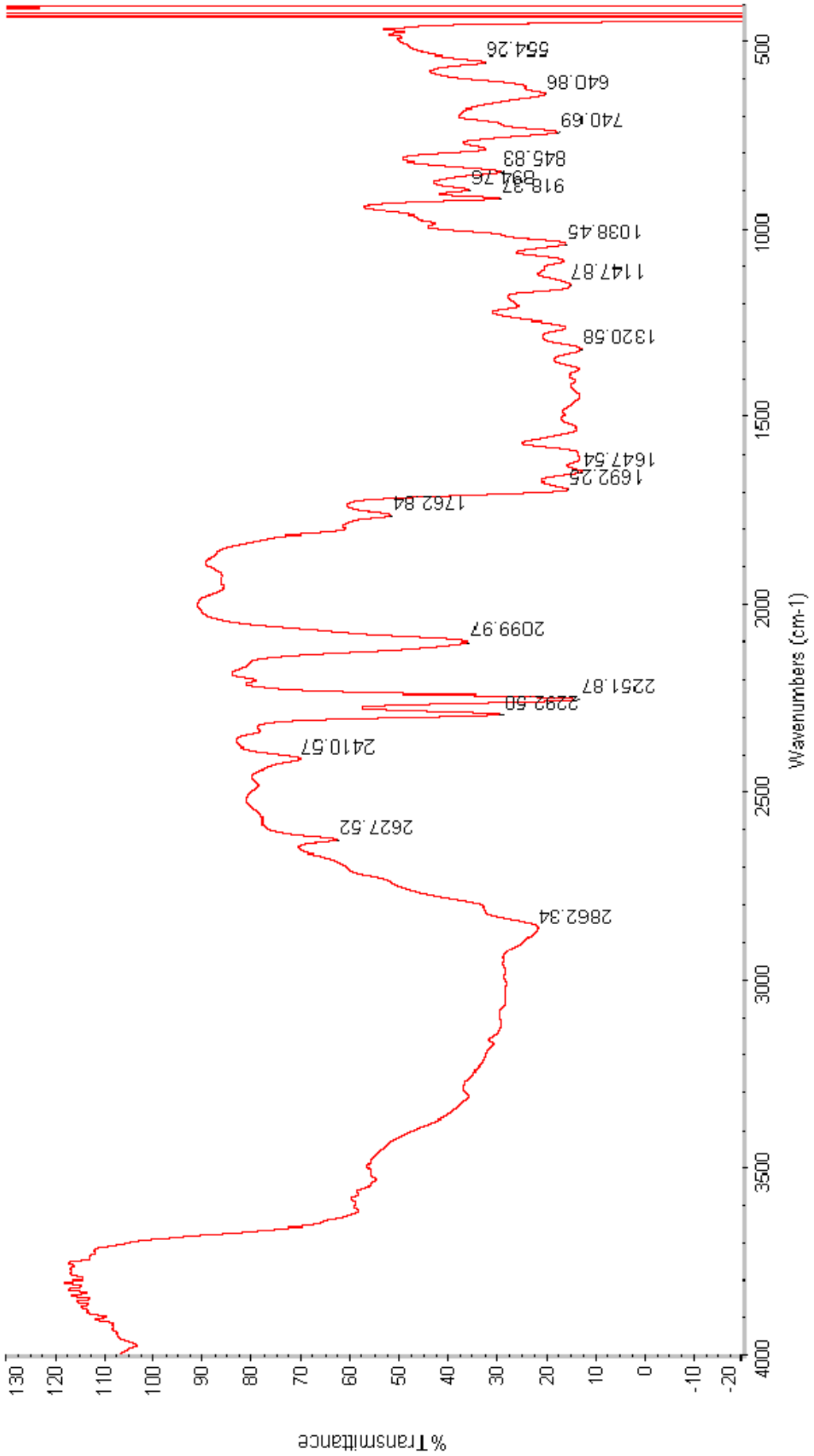

Figure 11: Infrared spectrum of attempted synthesis of **13** in acetonitrile.

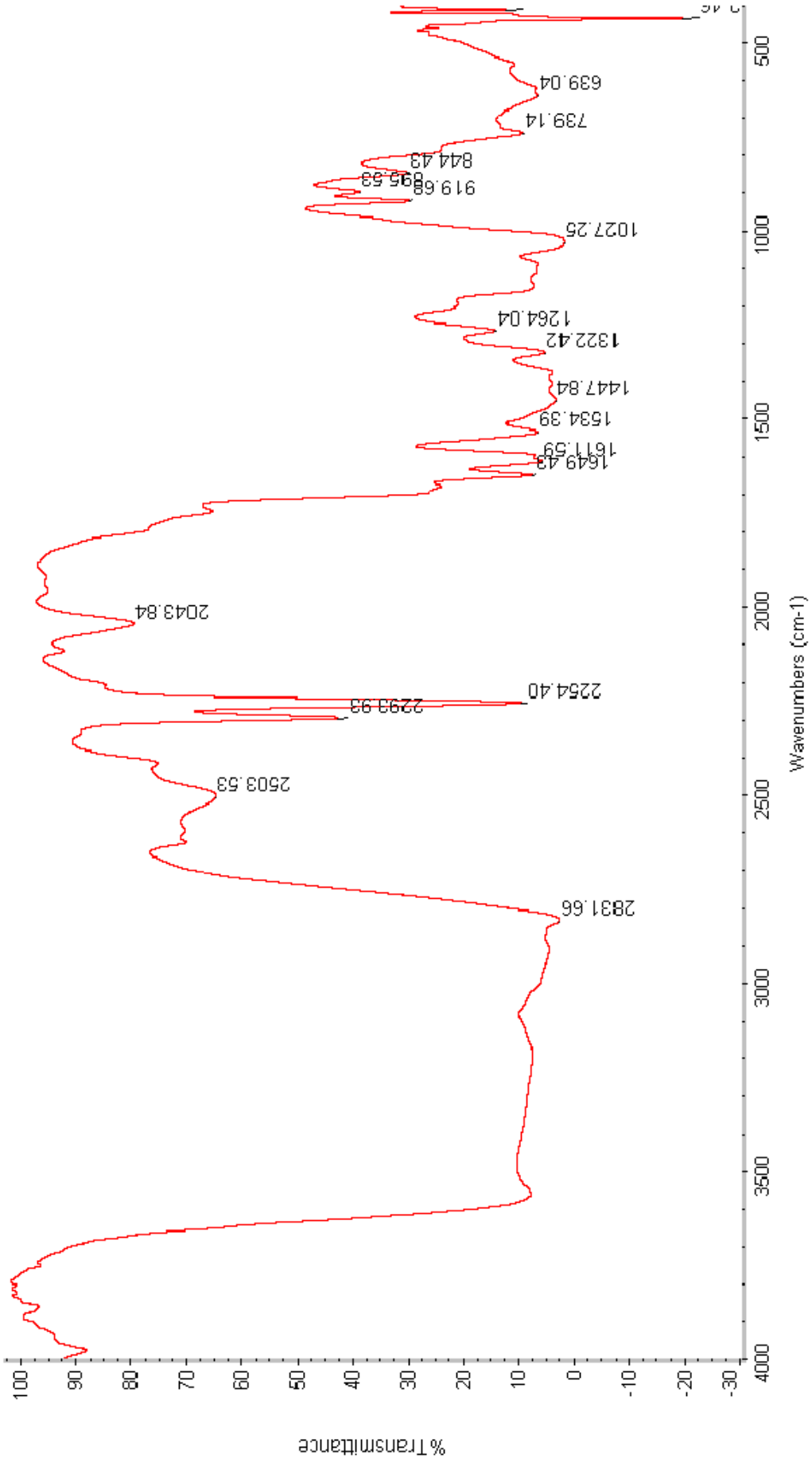

Figure 12: Infrared spectrum of attempted synthesis of **13** in acetonitrile-methanol.

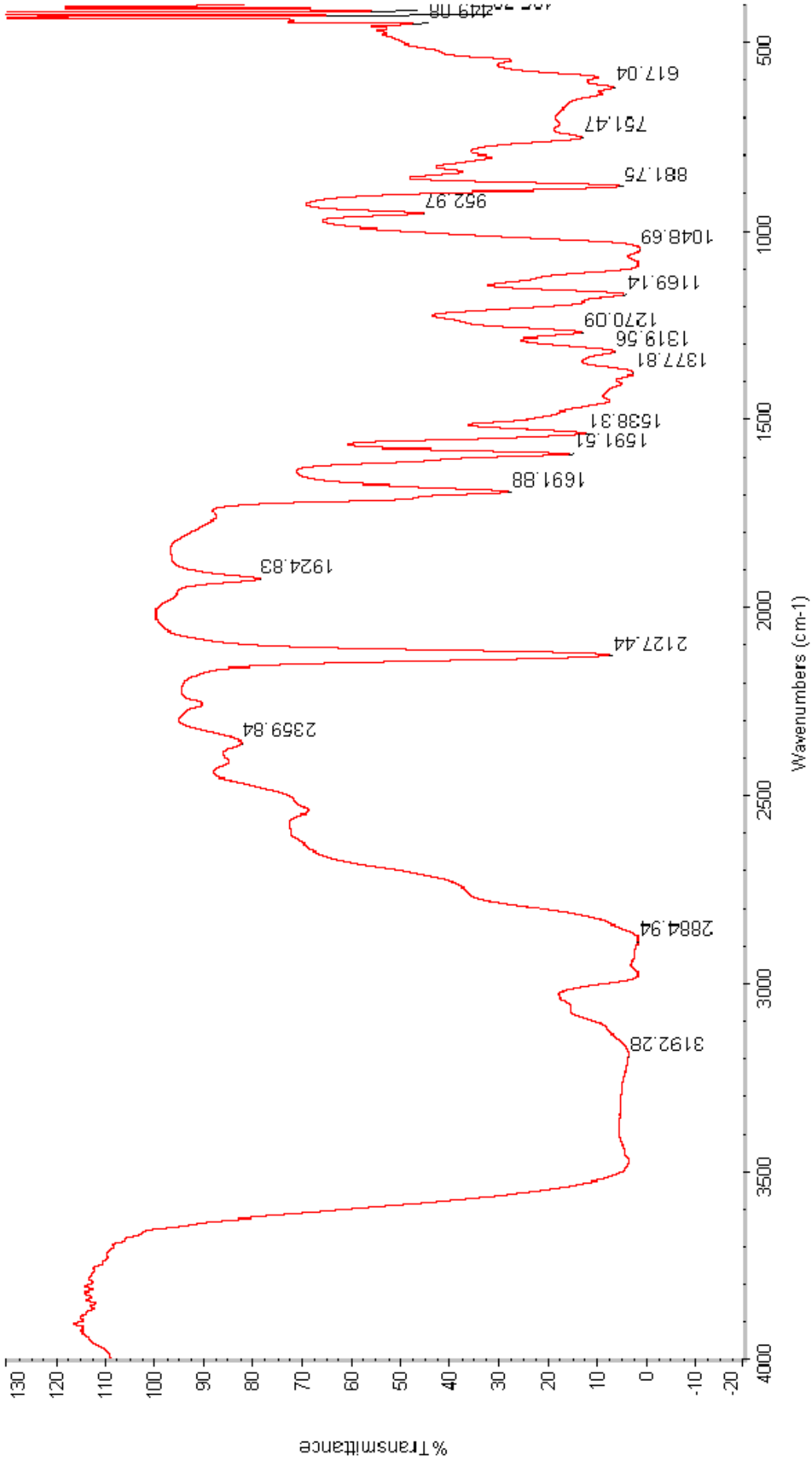

Figure 13: Infrared spectrum of *p*-ABSA in ethanol.

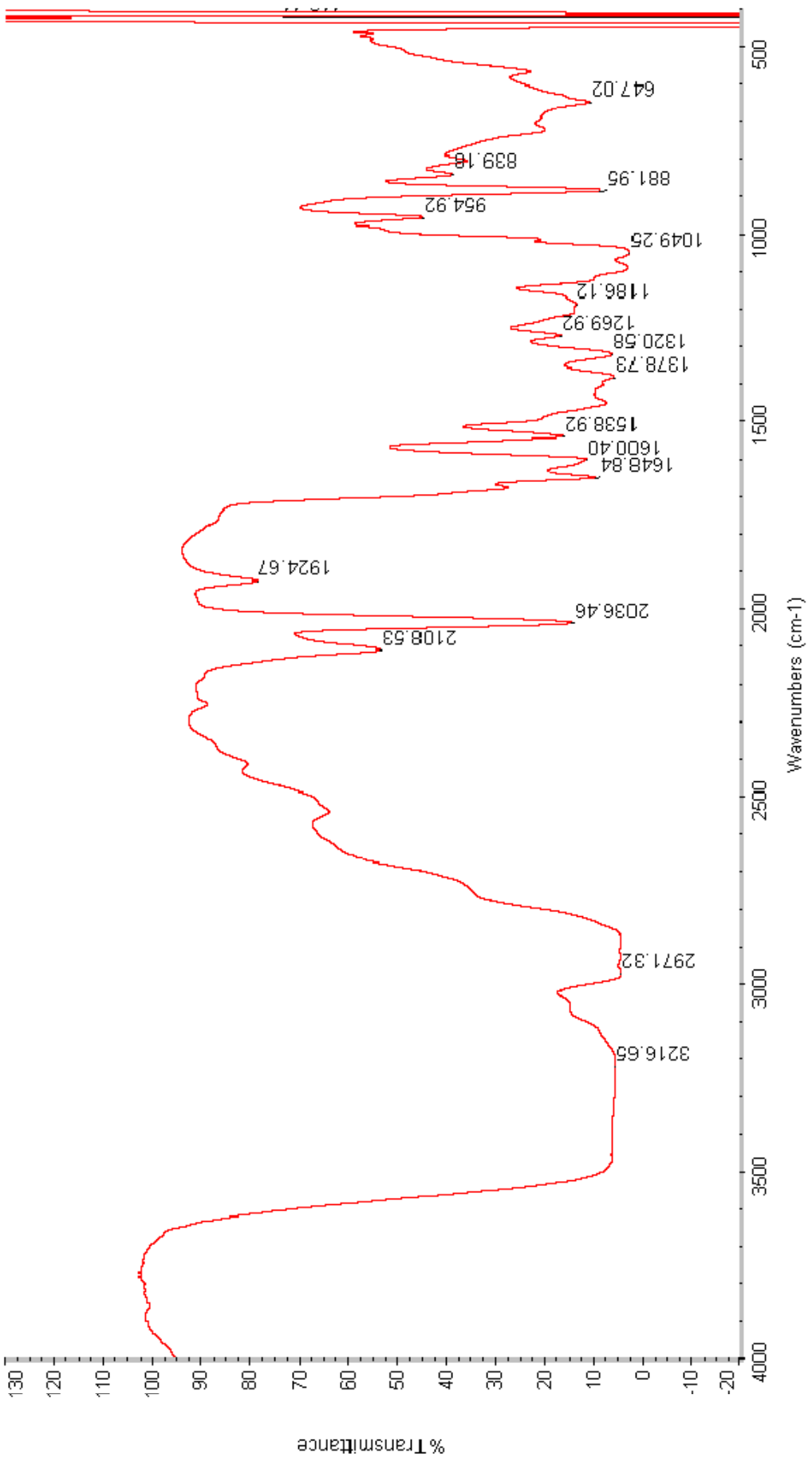

Figure 14: Infrared spectrum of *p*-ABSDBU in ethanol.

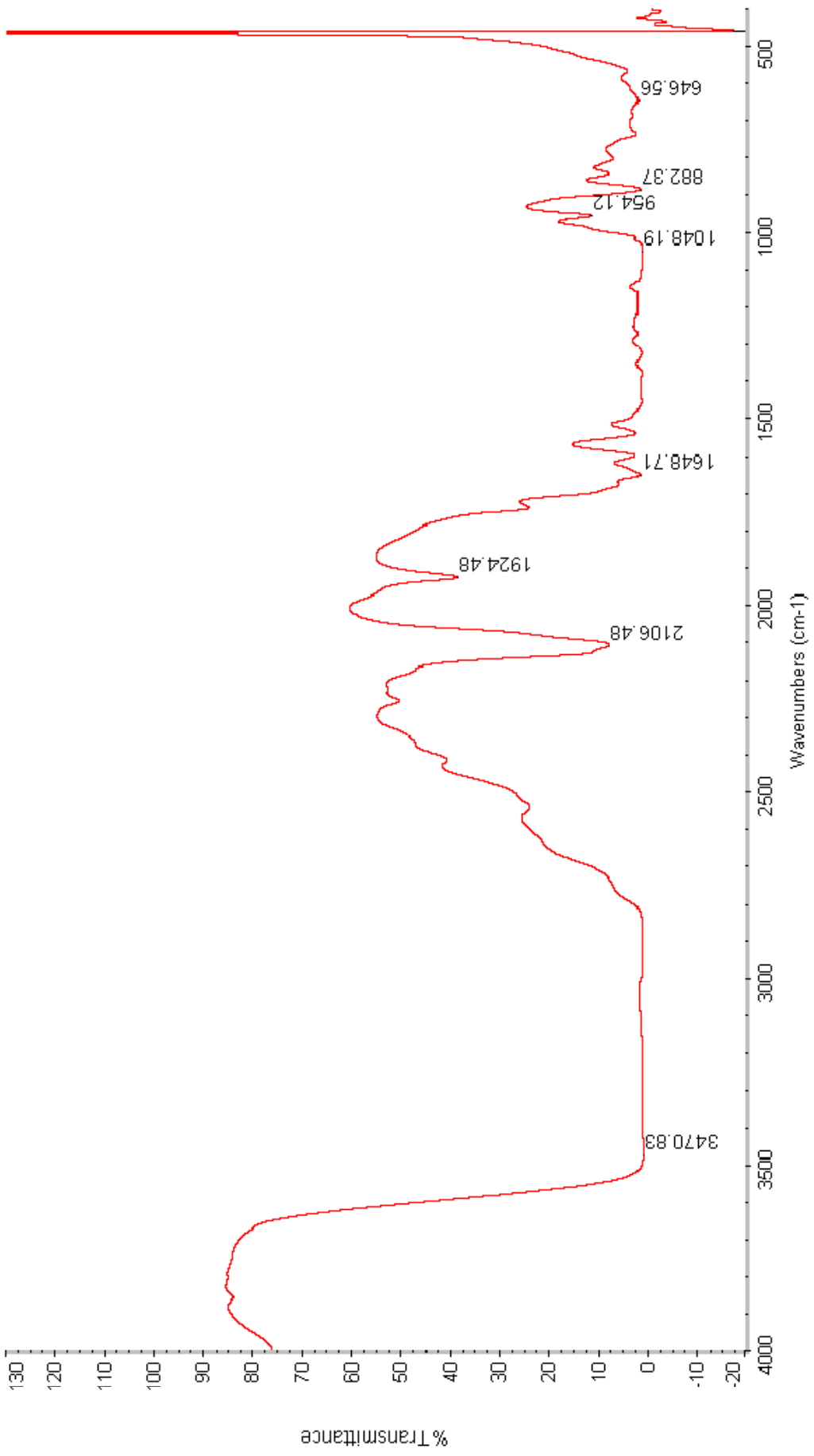

Figure 15: Infrared spectrum of **5** in ethanol under microwave heating.

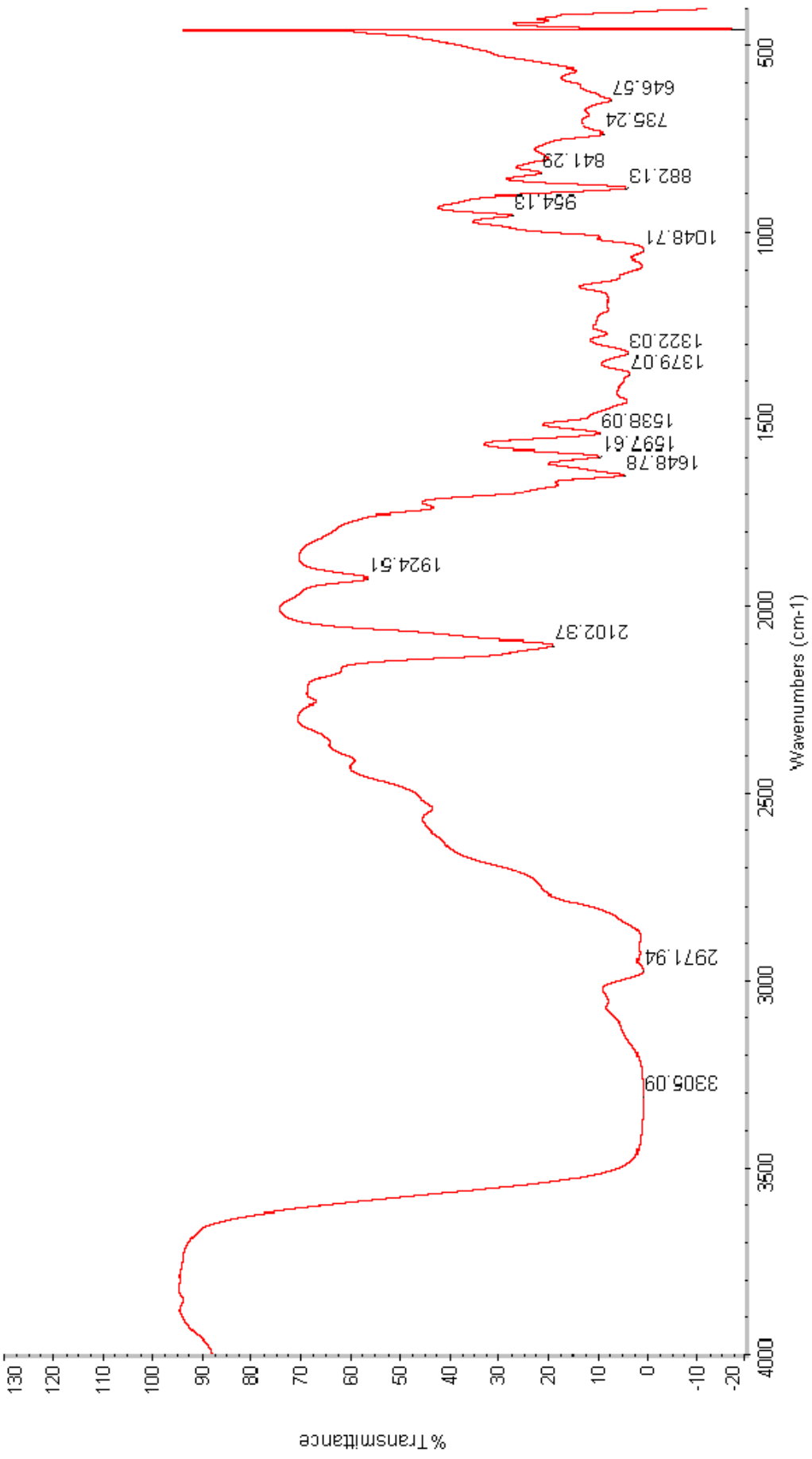

Figure 16: Infrared spectrum of **5** in ethanol at room temperature.

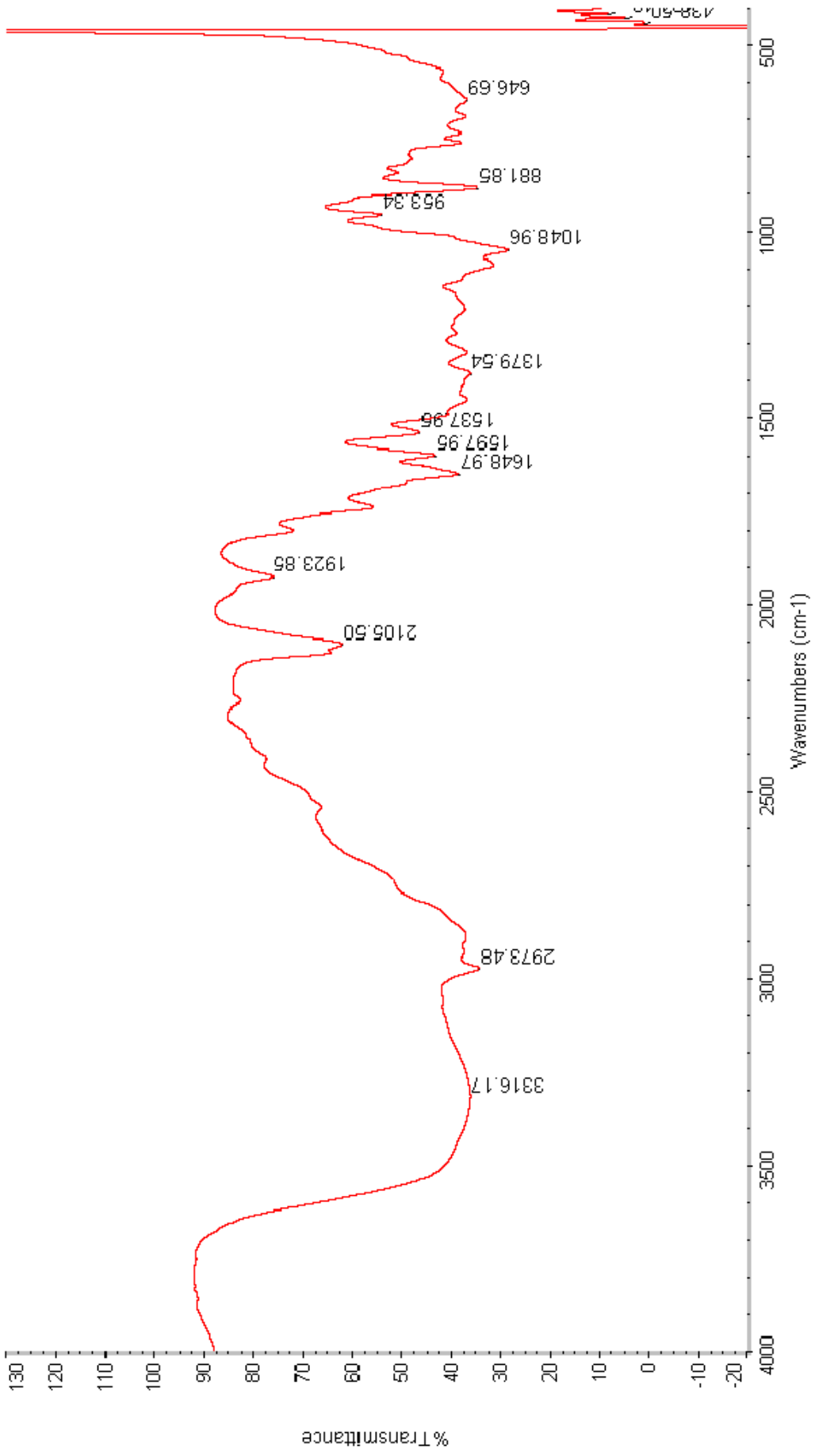

Figure 17: Infrared spectrum of attempted synthesis of **14** in ethanol at room temperature.

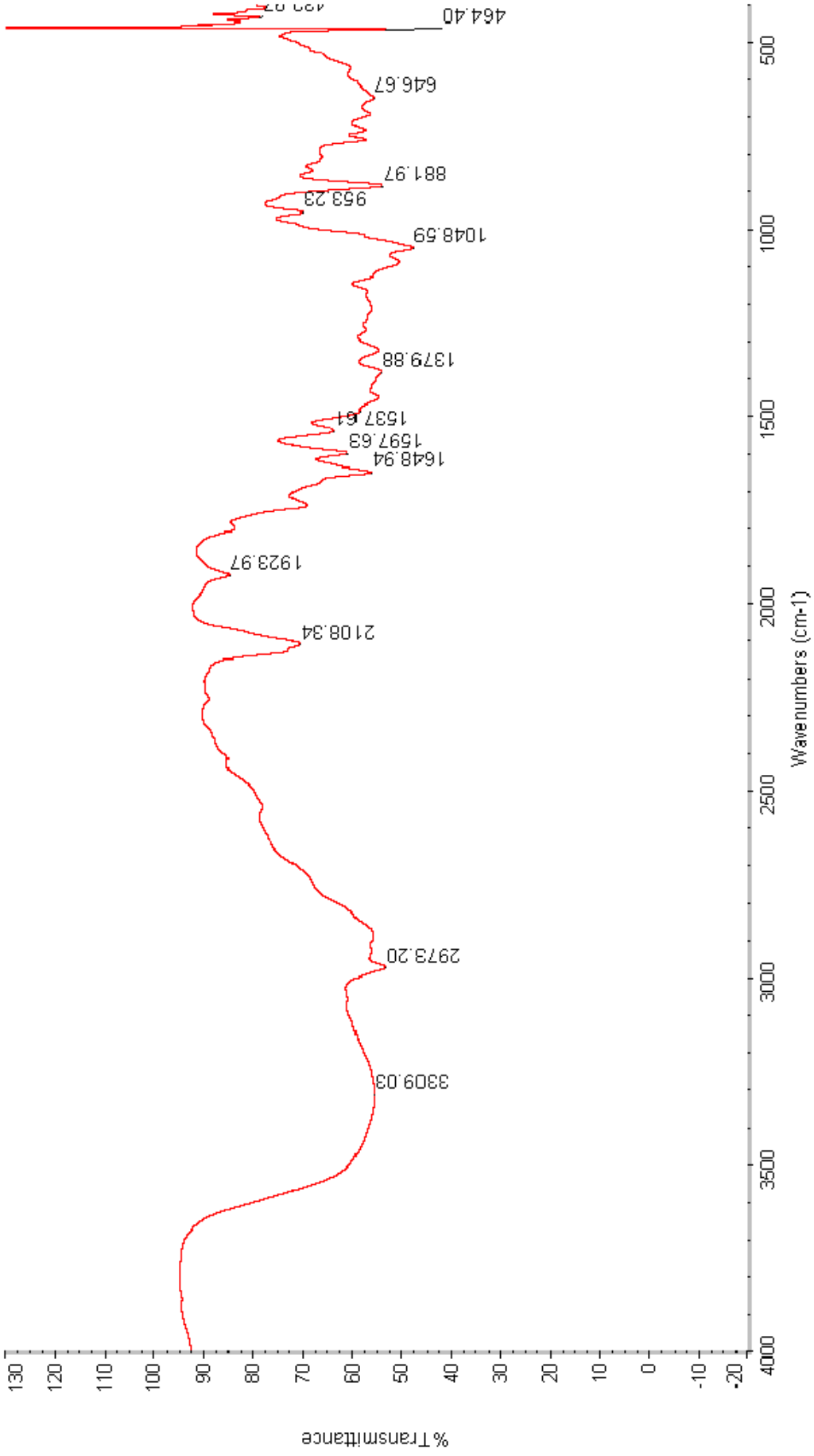

Figure 18: Infrared spectrum of attempted synthesis of **14** in ethanol under microwave heating.

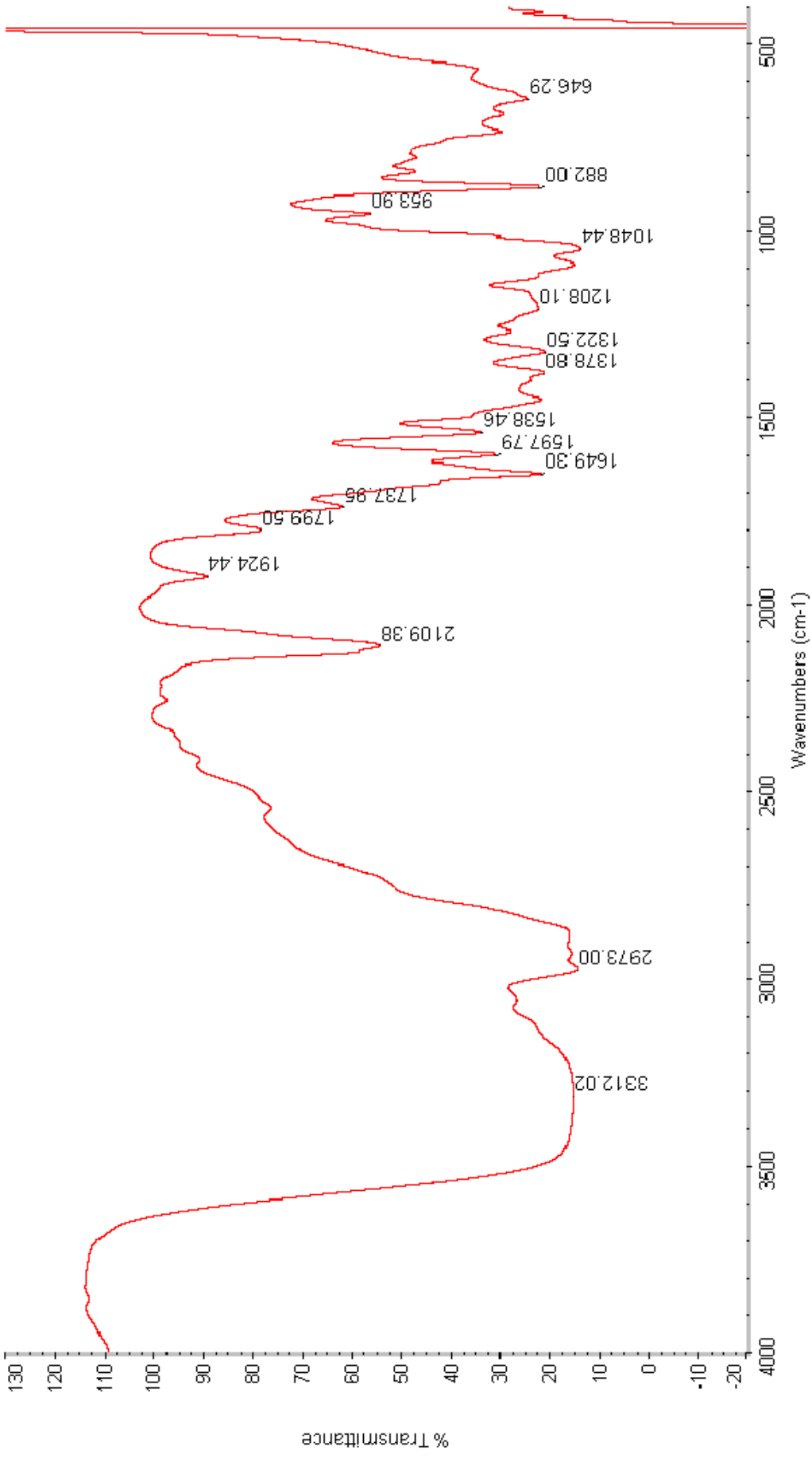

Figure 19: Infrared spectrum of attempted synthesis of **13** in ethanol under microwave heating.

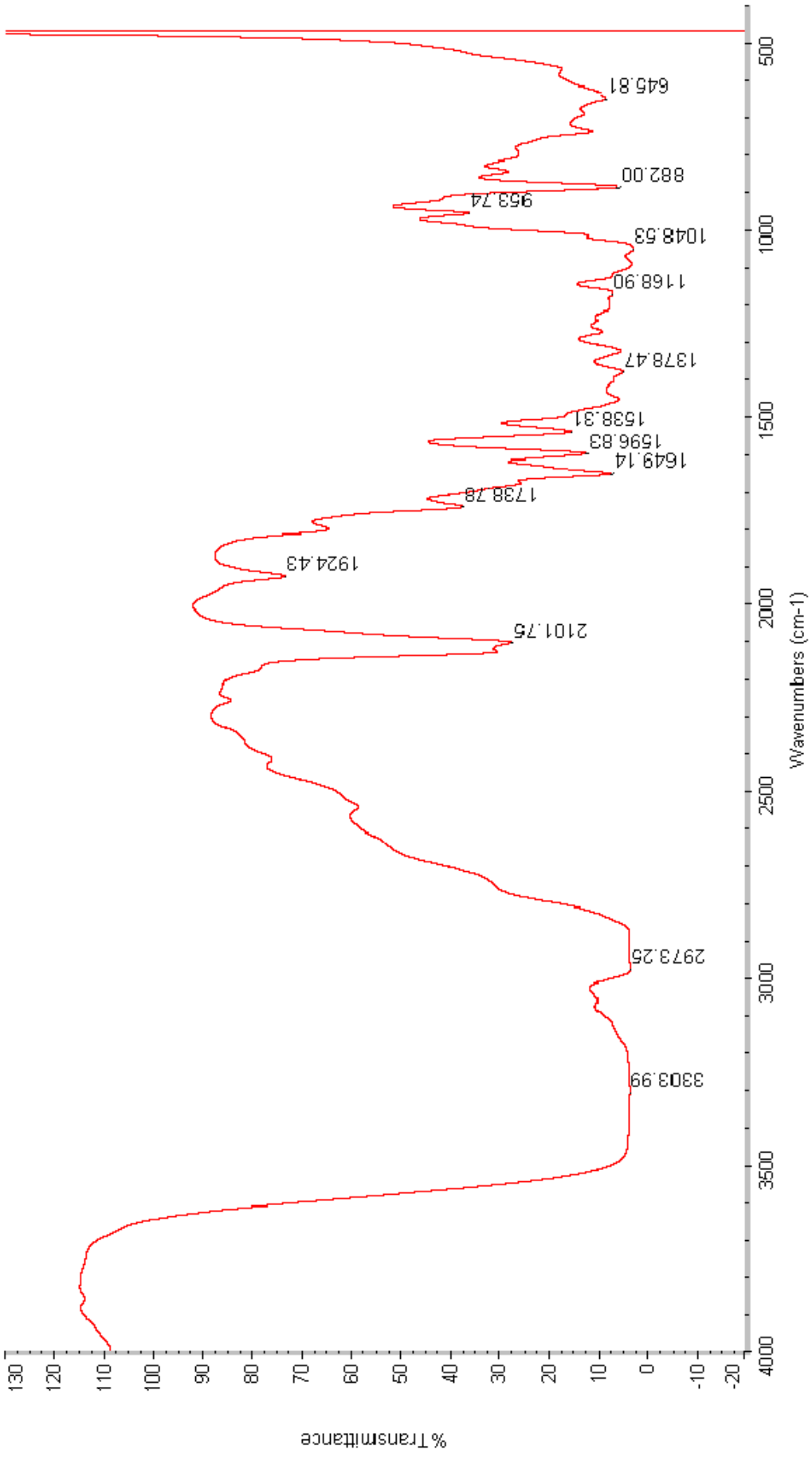

Figure 20: Infrared spectrum of attempted synthesis of **13** in ethanol at room temperature.

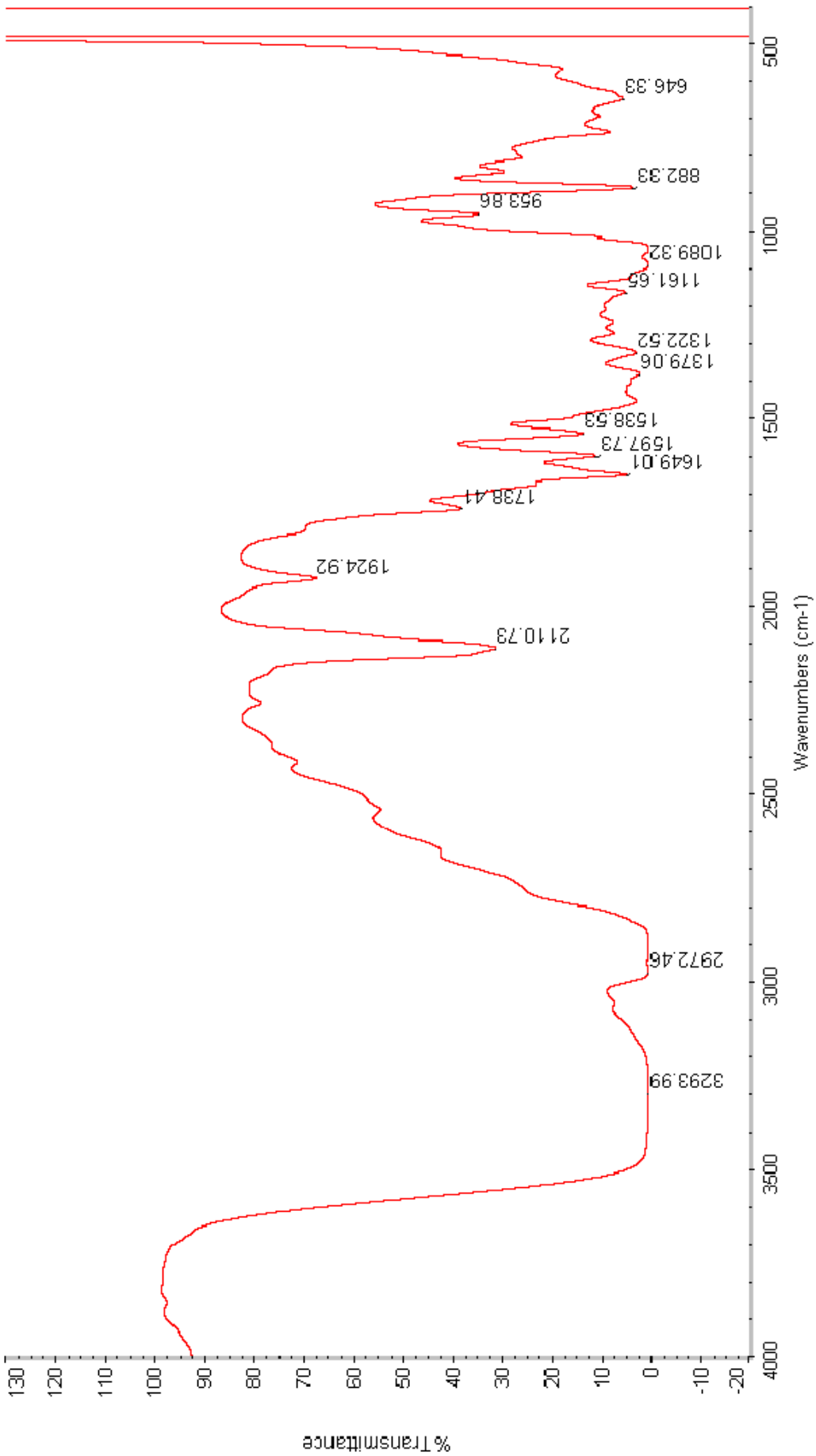

Figure 21: Infrared spectrum of attempted synthesis of **22** in ethanol under microwave heating.

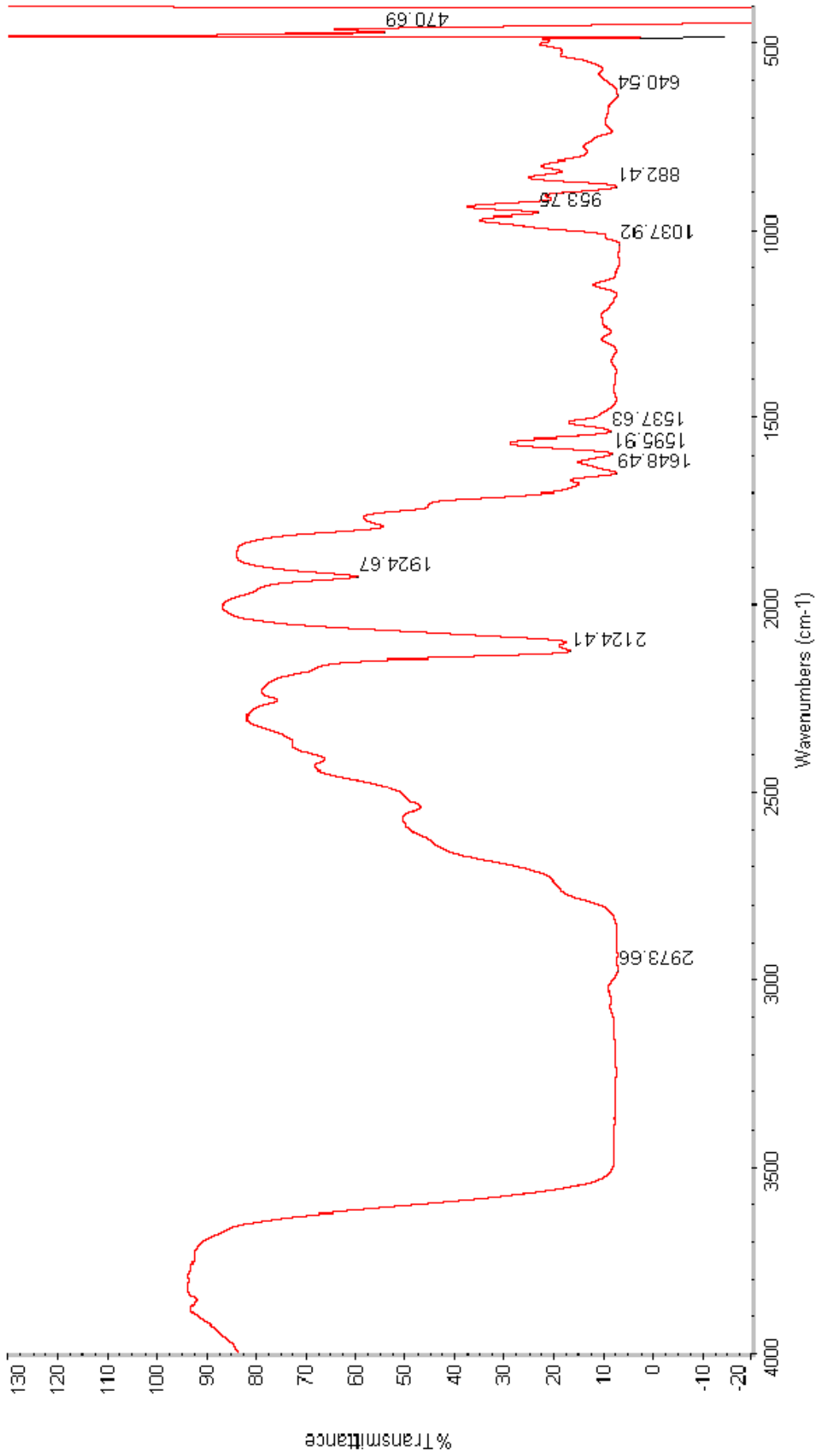

Figure 22: Infrared spectrum of attempted synthesis of **22** in ethanol at room temperature.

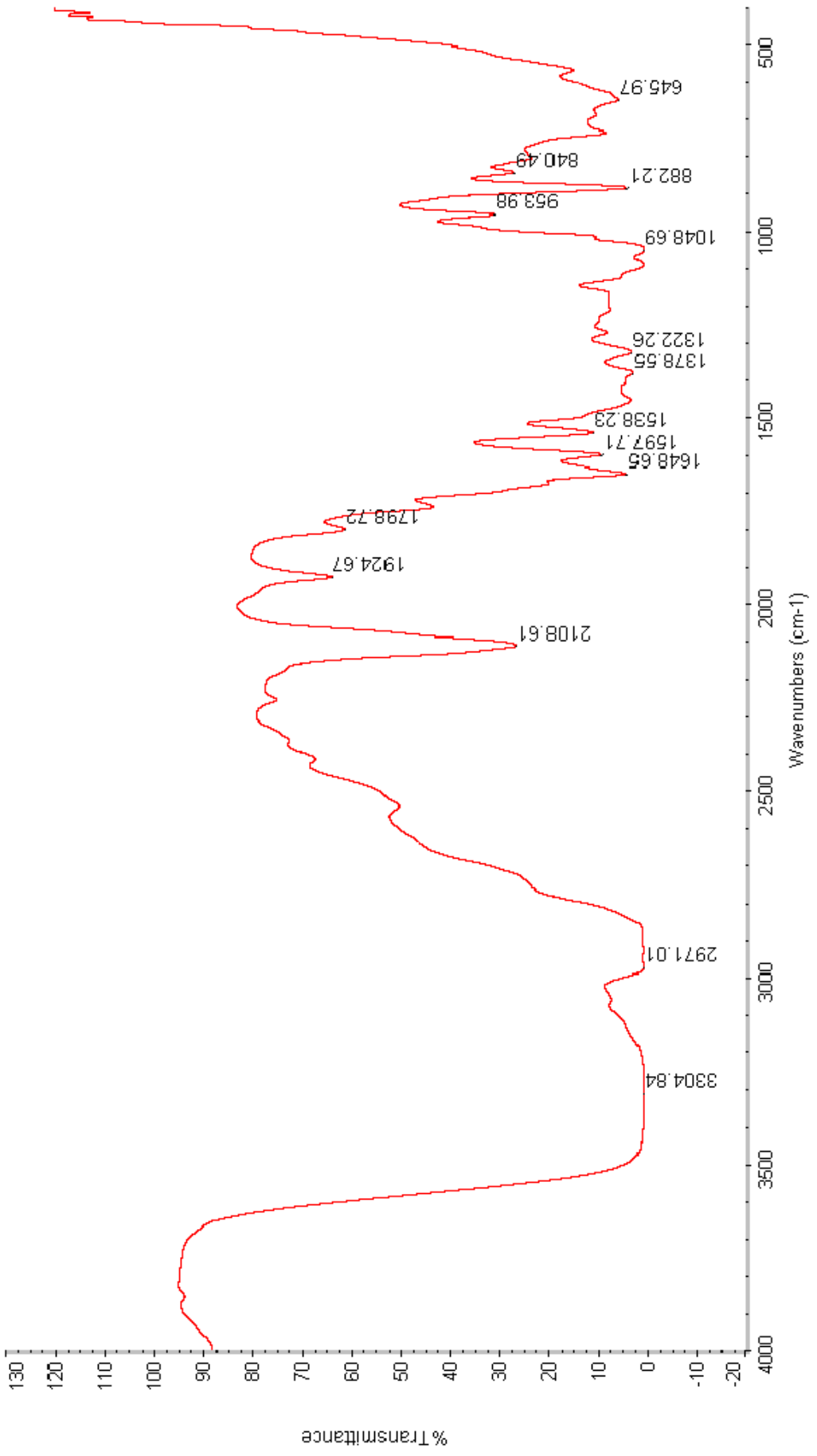

Figure 23: Infrared spectrum of attempted synthesis of **21** in ethanol under microwave heating.

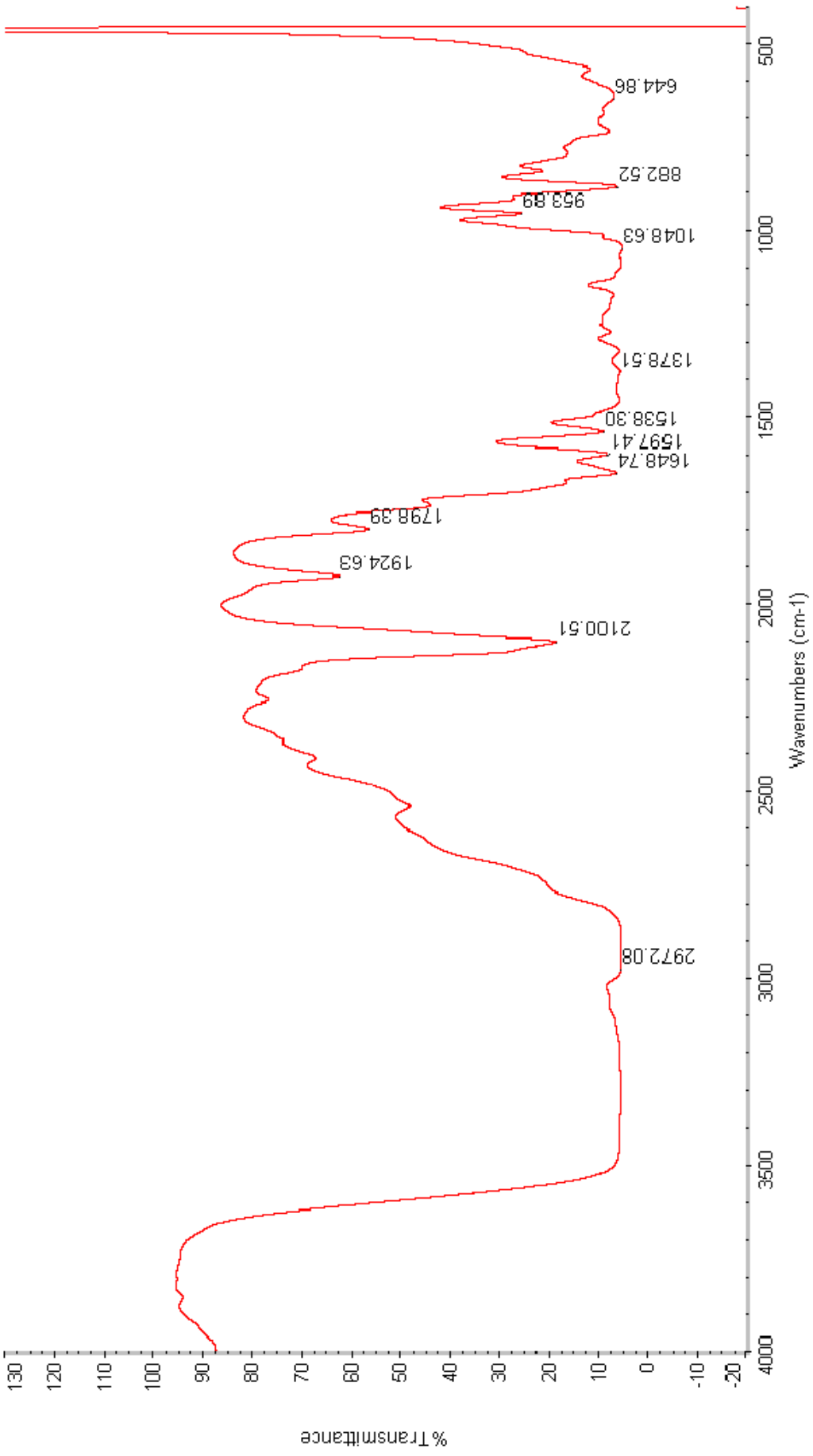

Figure 24: Infrared spectrum of attempted synthesis of **22** in ethanol at room temperature.

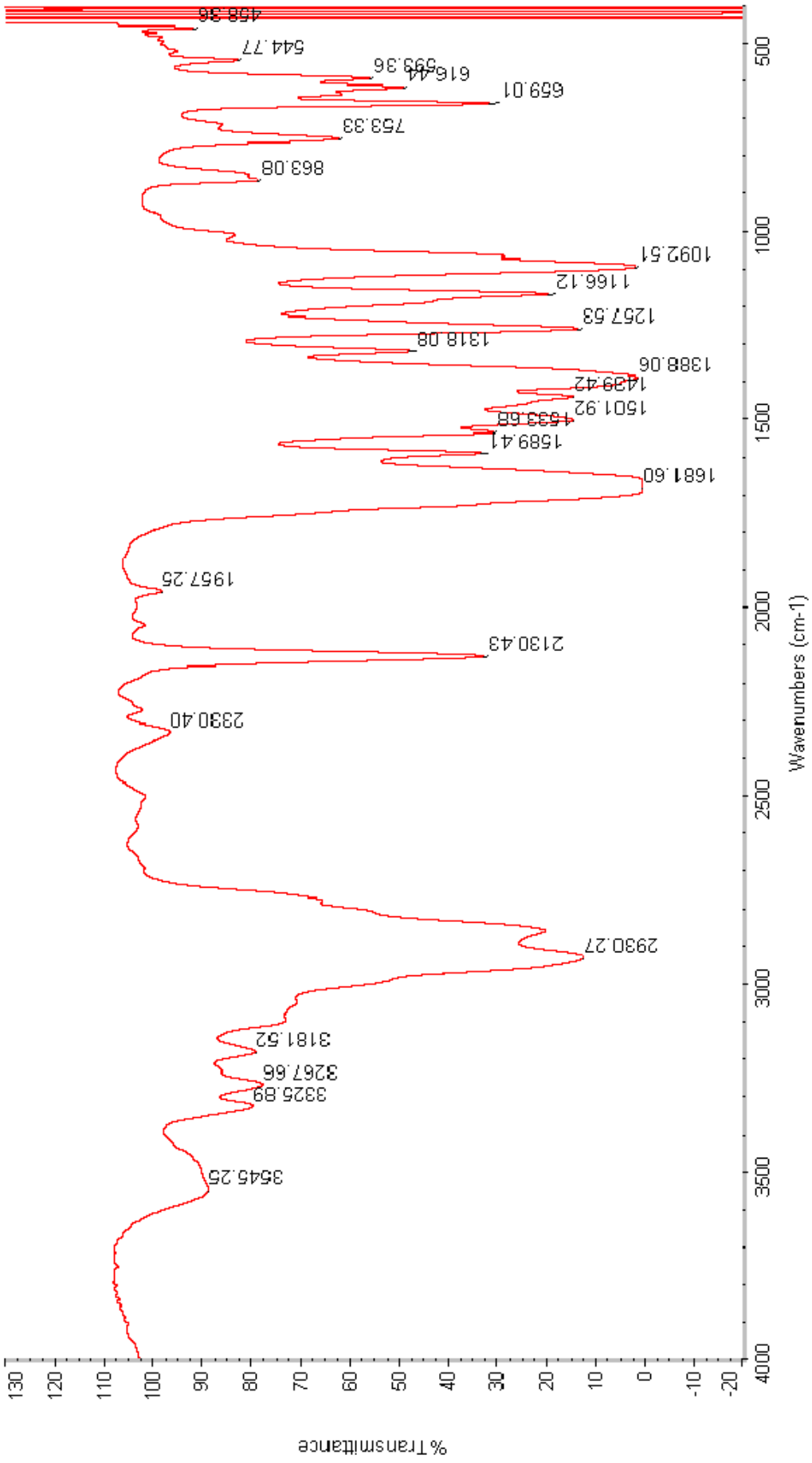

Figure 25: Infrared spectrum of *p*-ABSA in DMF.

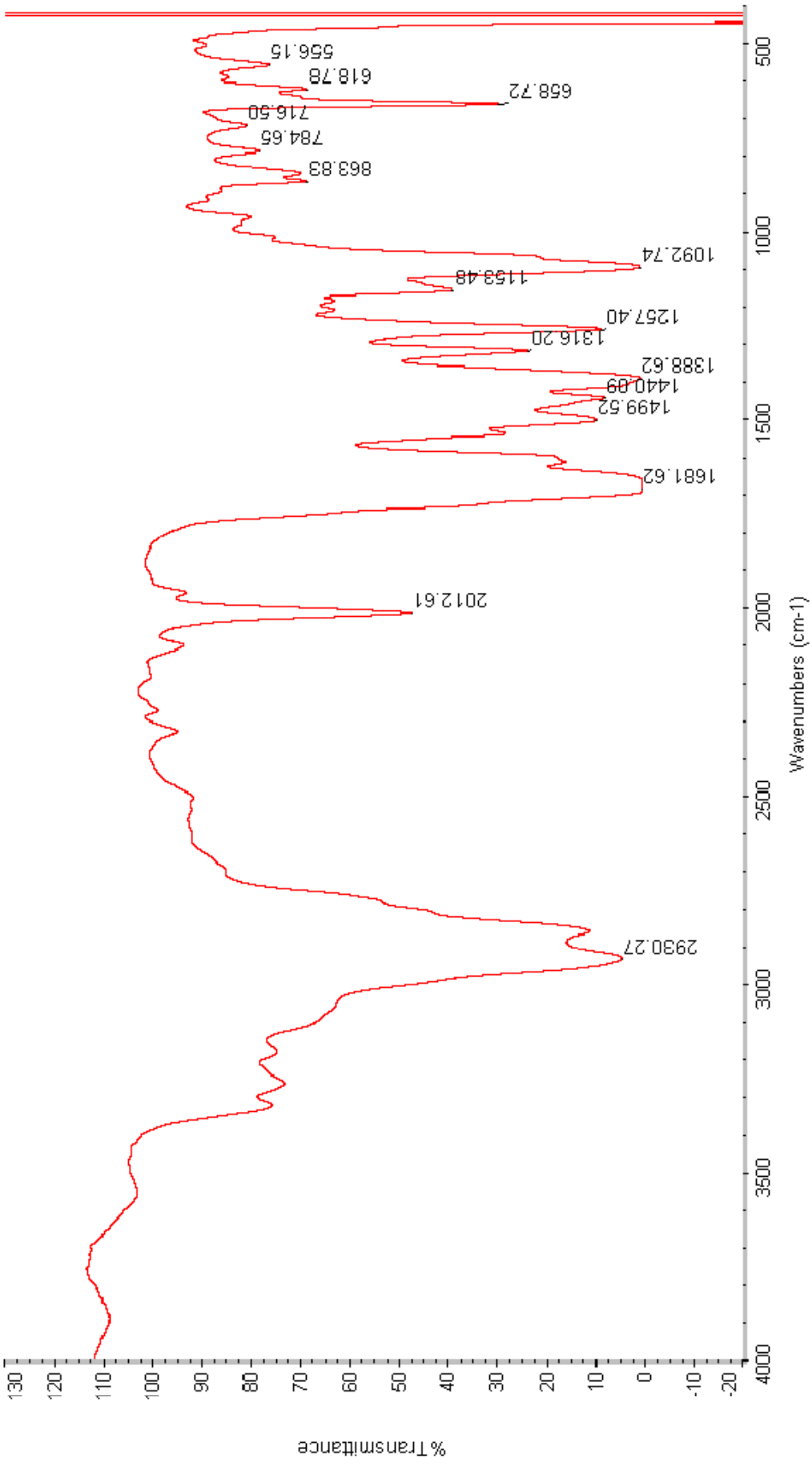

Figure 26: Infrared spectrum of *p*-ABSDBU in DMF.

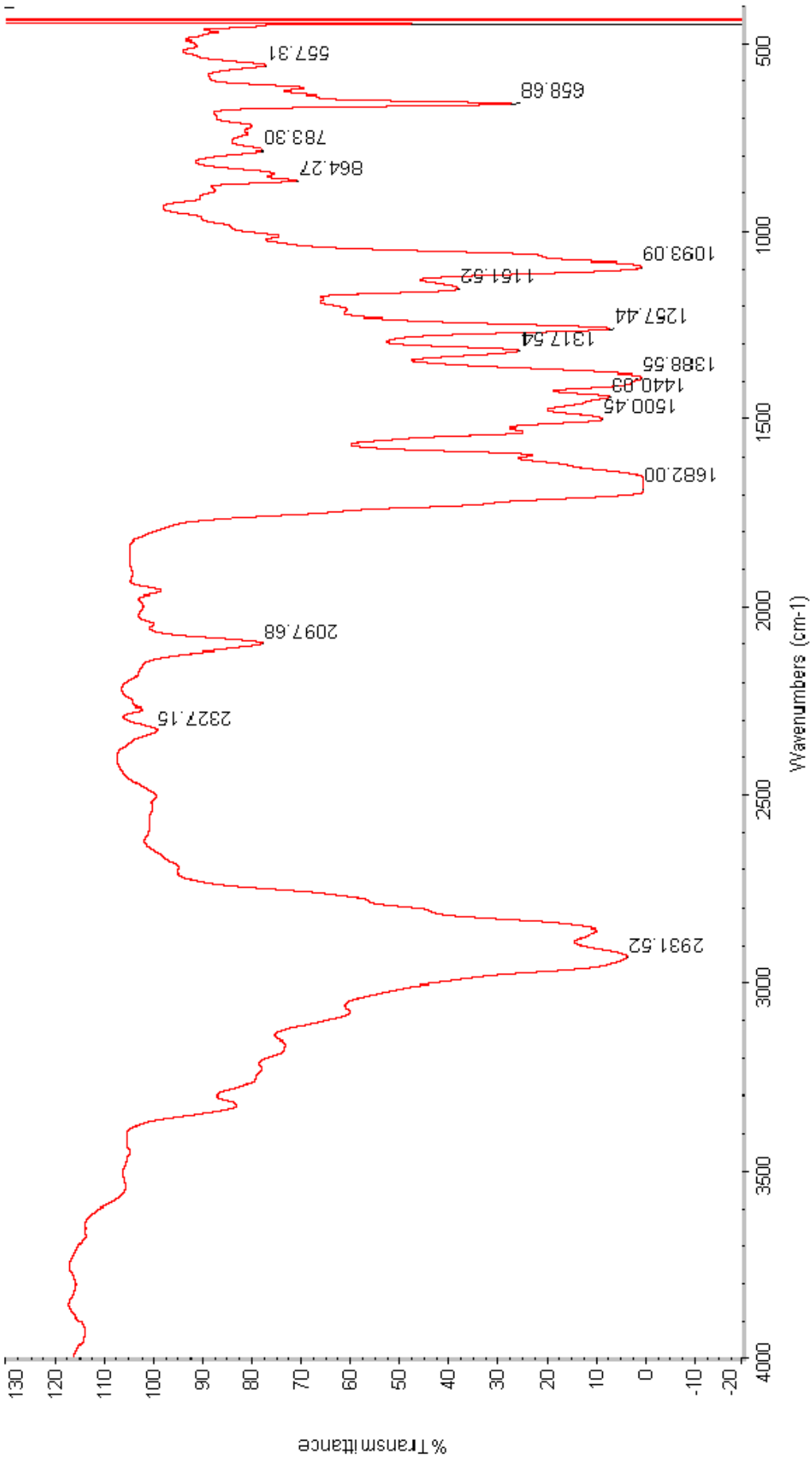

Figure 27: Infrared spectrum of **9** in DMF.

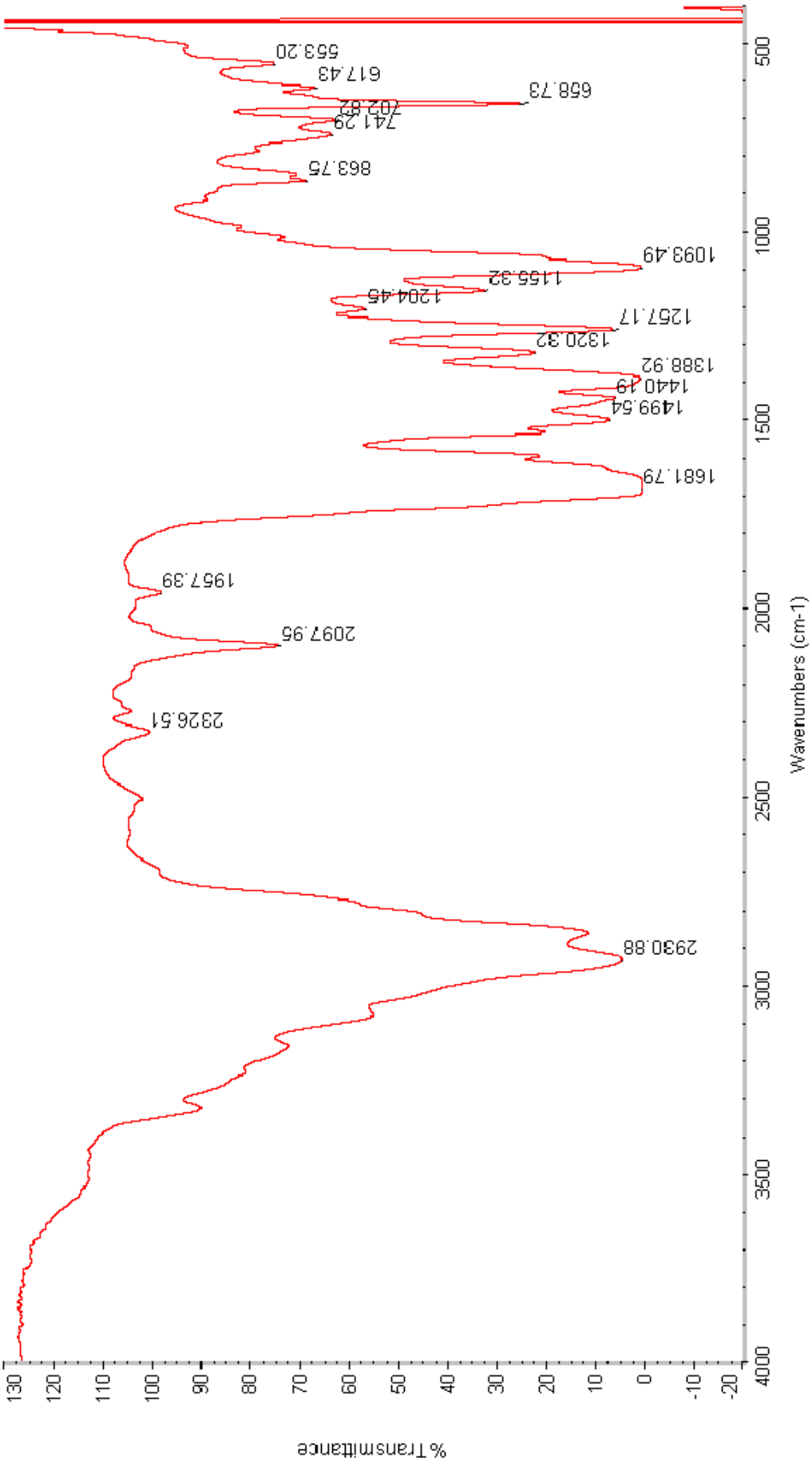

Figure 28: Infrared spectrum of **7** in DMF.

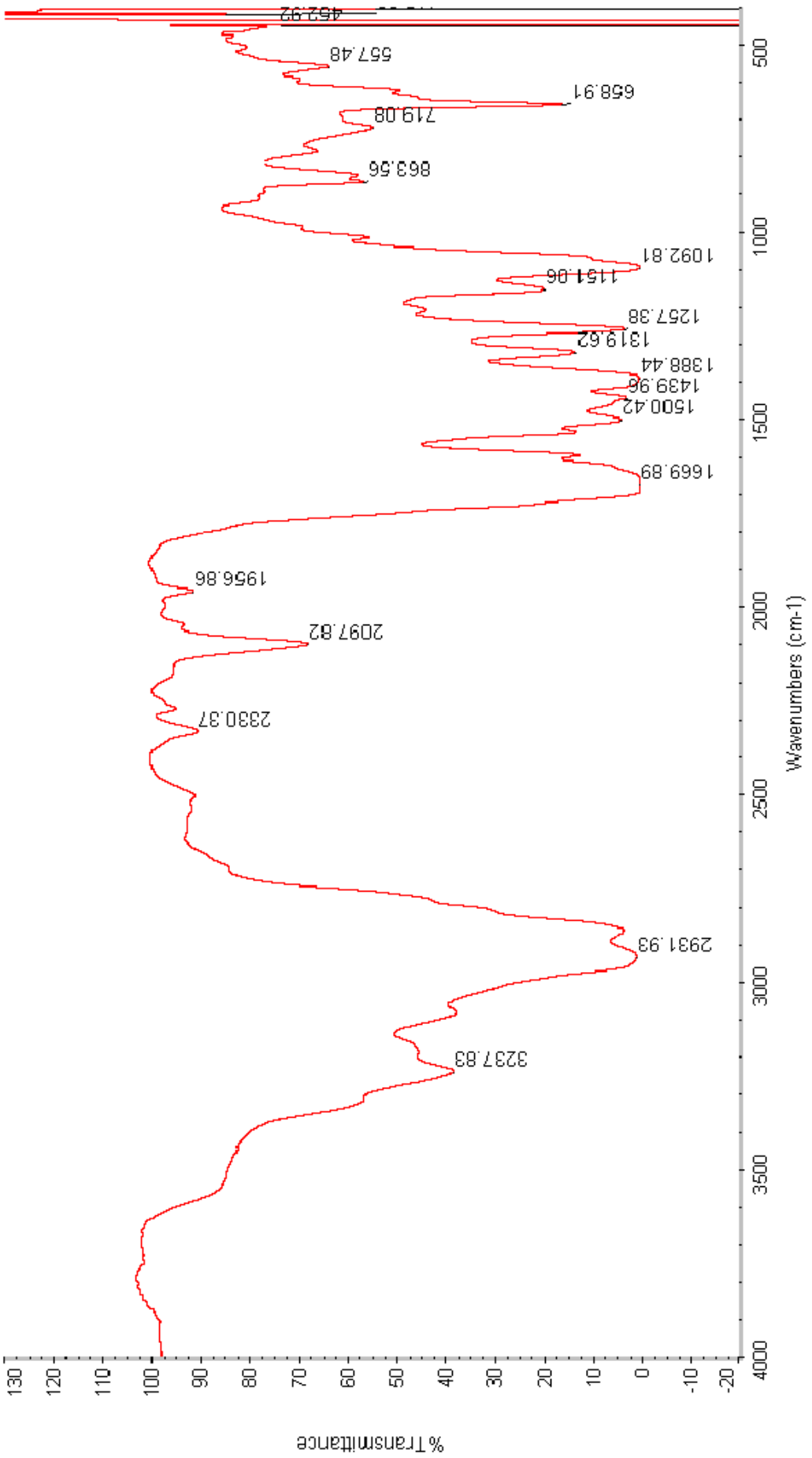

Figure 29: Infrared spectrum of attempted synthesis of **23** in DMF.

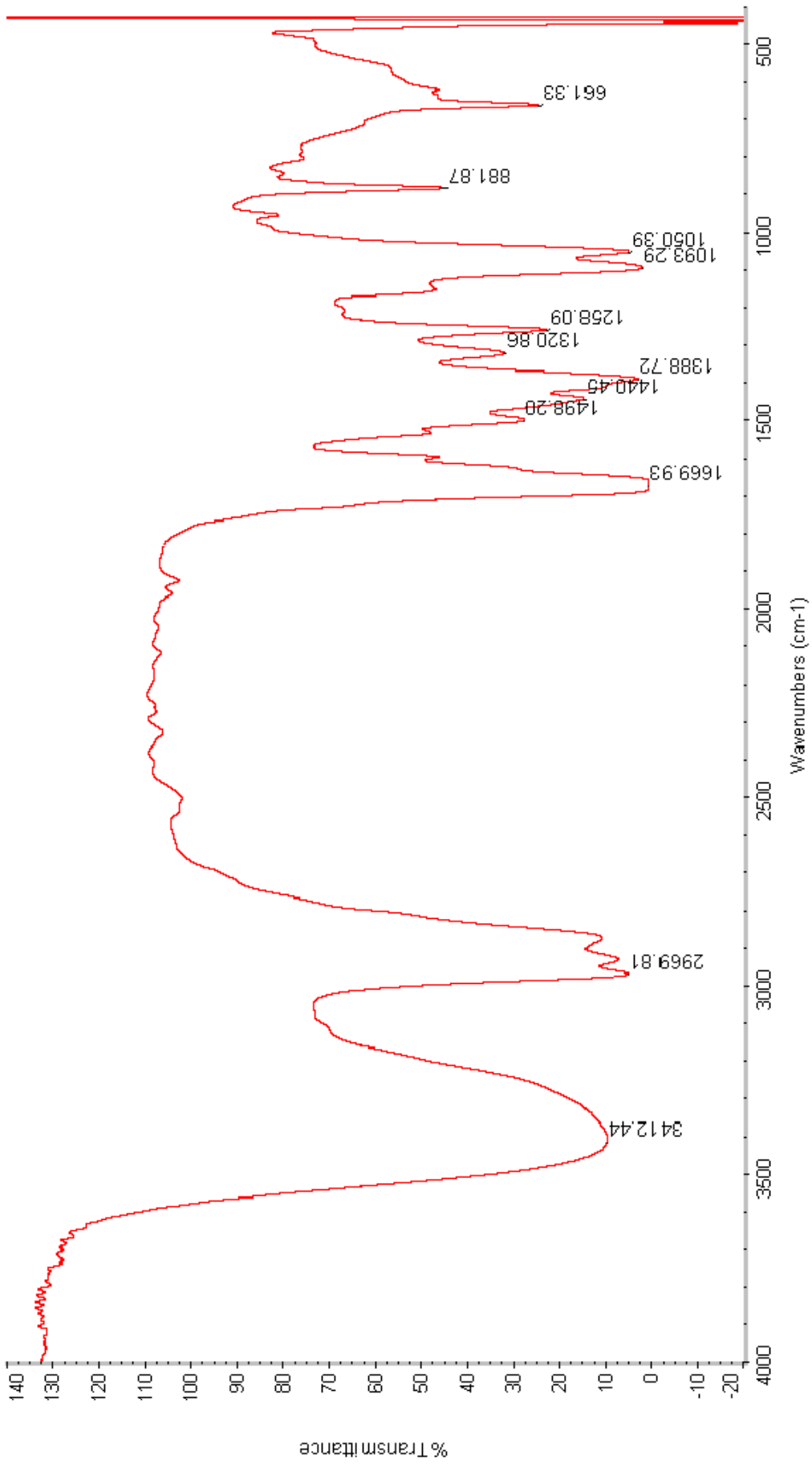

Figure 30: Infrared spectrum of attempted synthesis of **23** in DMF-H_2O.

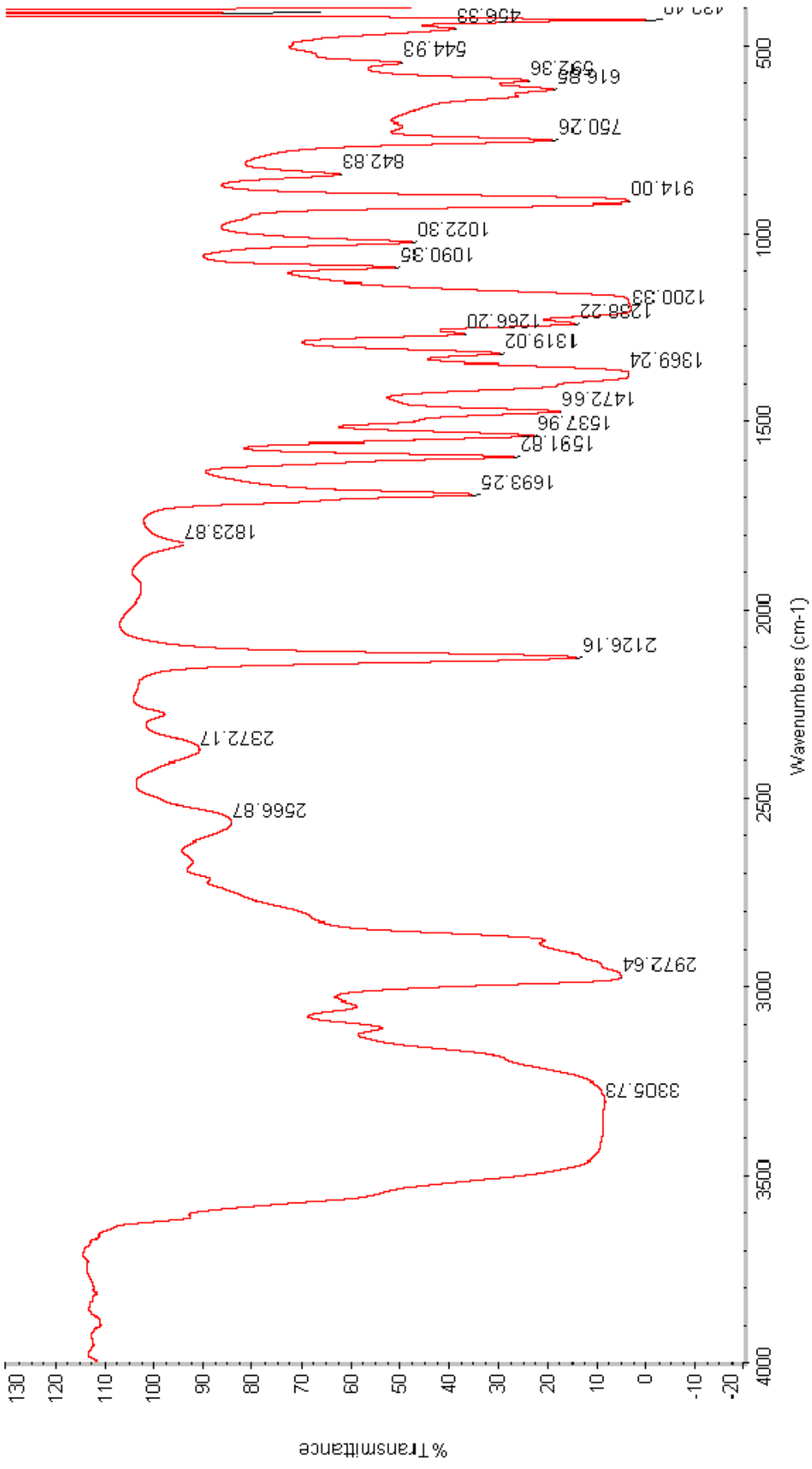

Figure 31: Infrared spectrum of *p*-ABSA in *t*-BuOH.

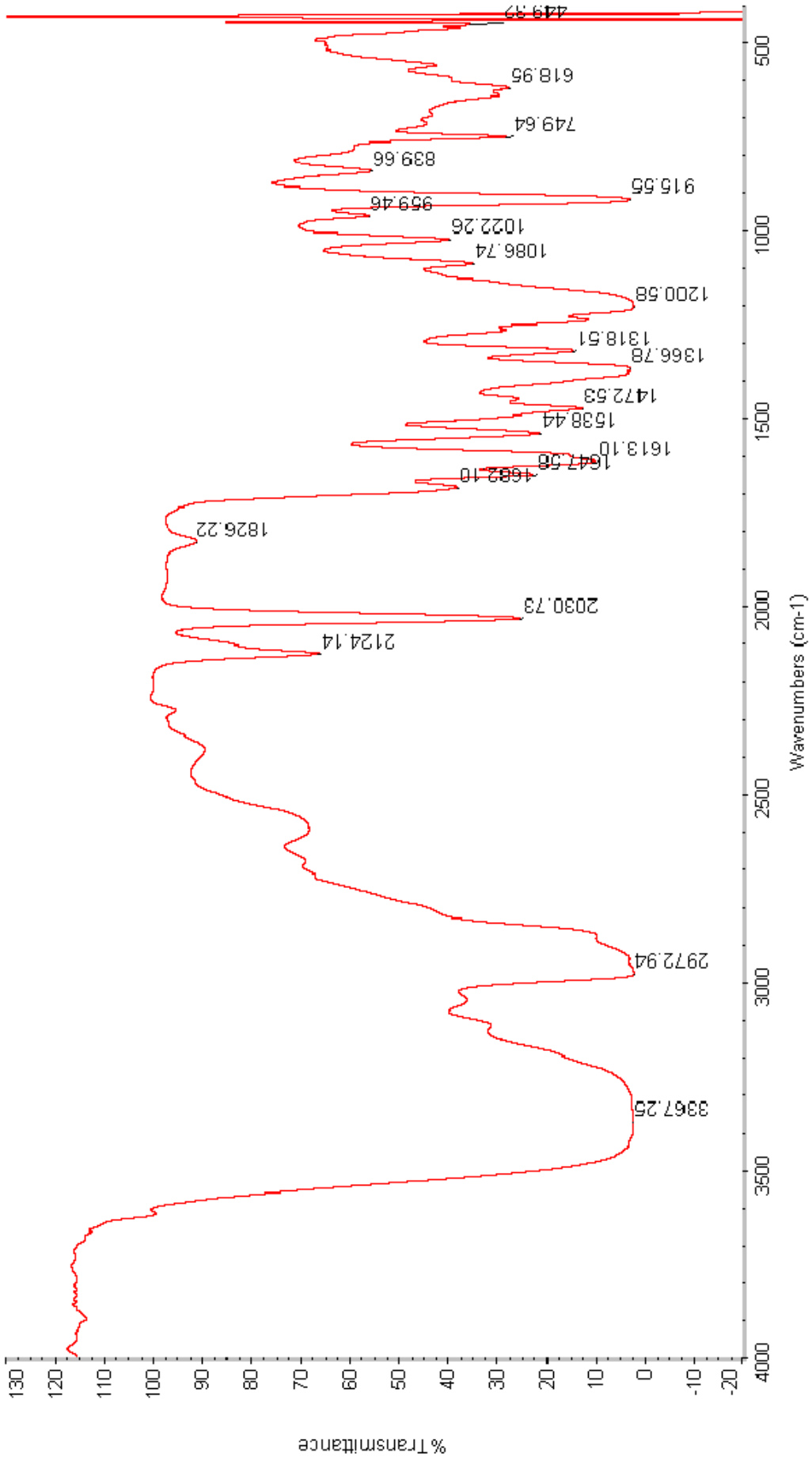

Figure 32: Infrared spectrum of *p*-ABSDBU in *t*-BuOH.

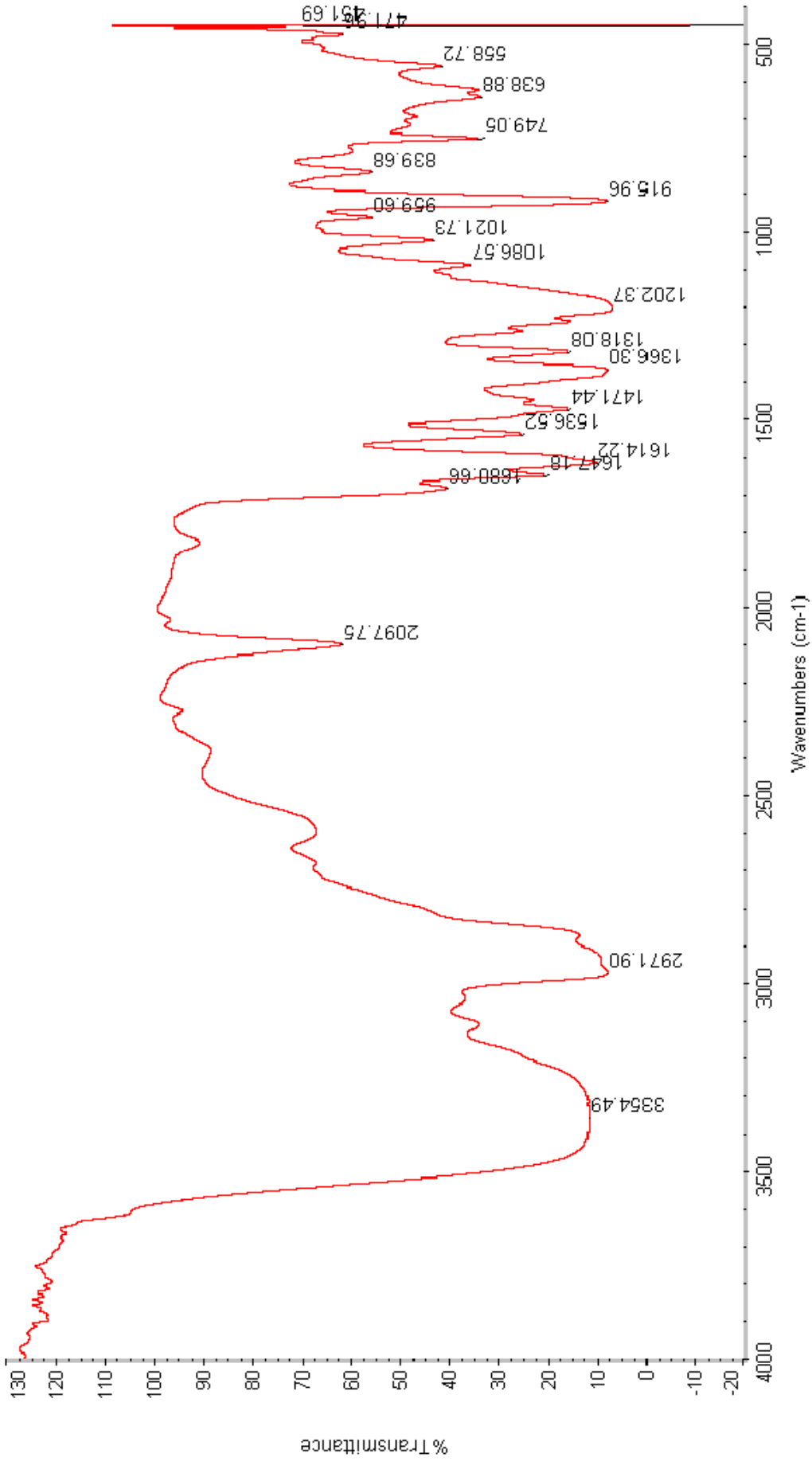

Figure 33: Infrared spectrum of **9** in *t*-BuOH.

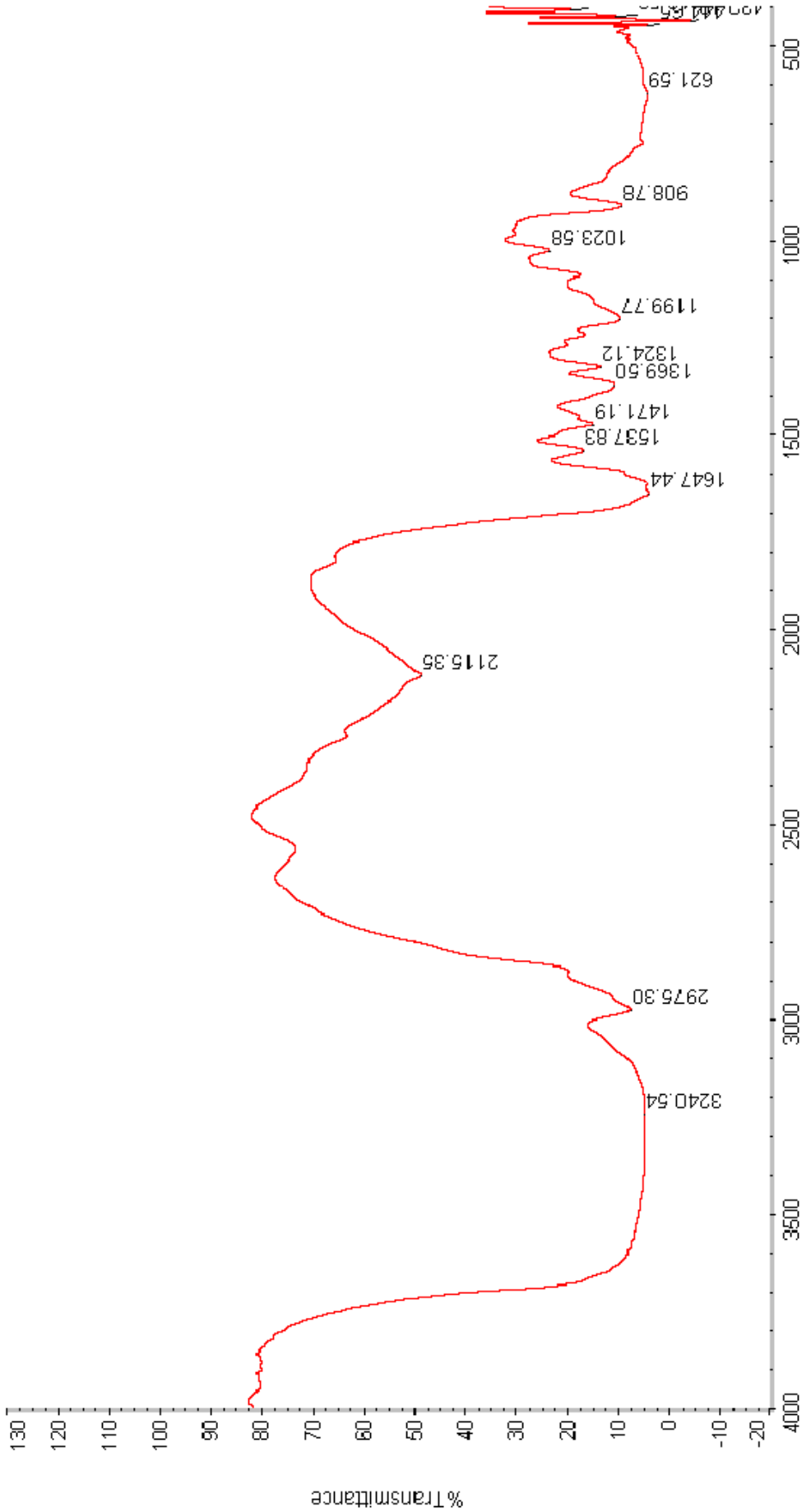

Figure 34: Infrared spectrum of attempted synthesis of **15** in *t*-BuOH.

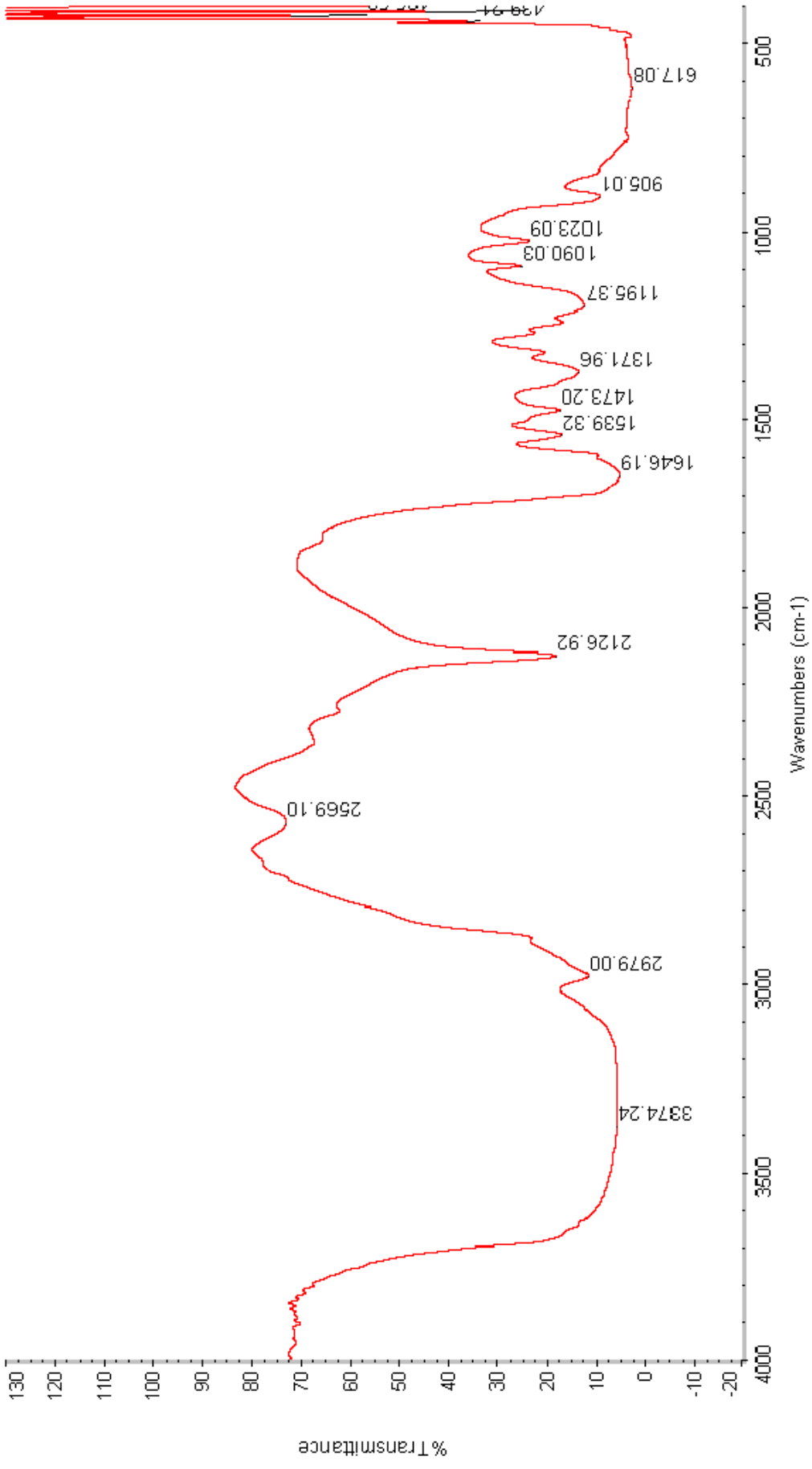

Figure 35: Infrared spectrum of *p*-ABSA in *t*-BuOH-H_2O.

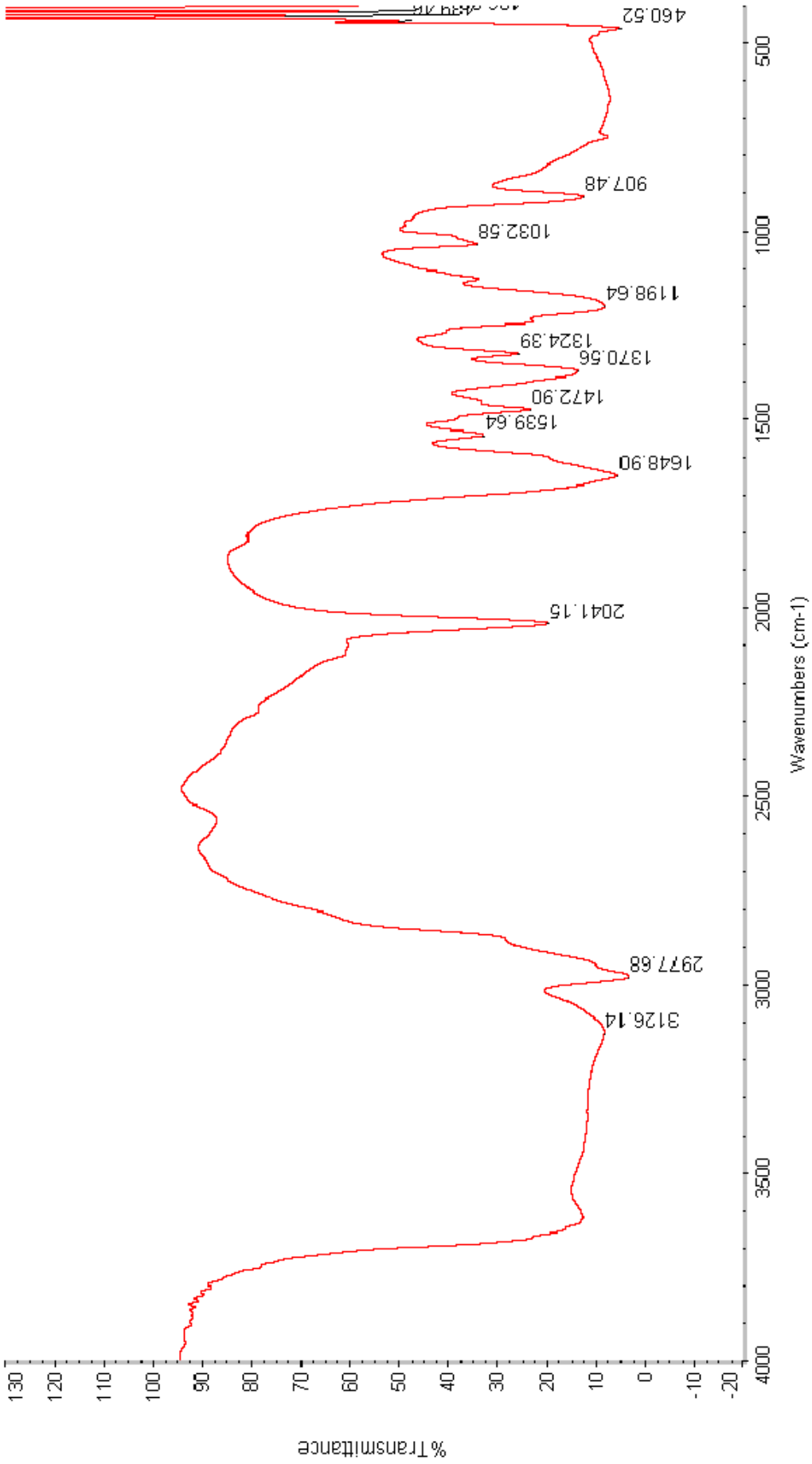

Figure 36: Infrared spectrum of *p*-ABSDBU in *t*-BuOH-H_2O.

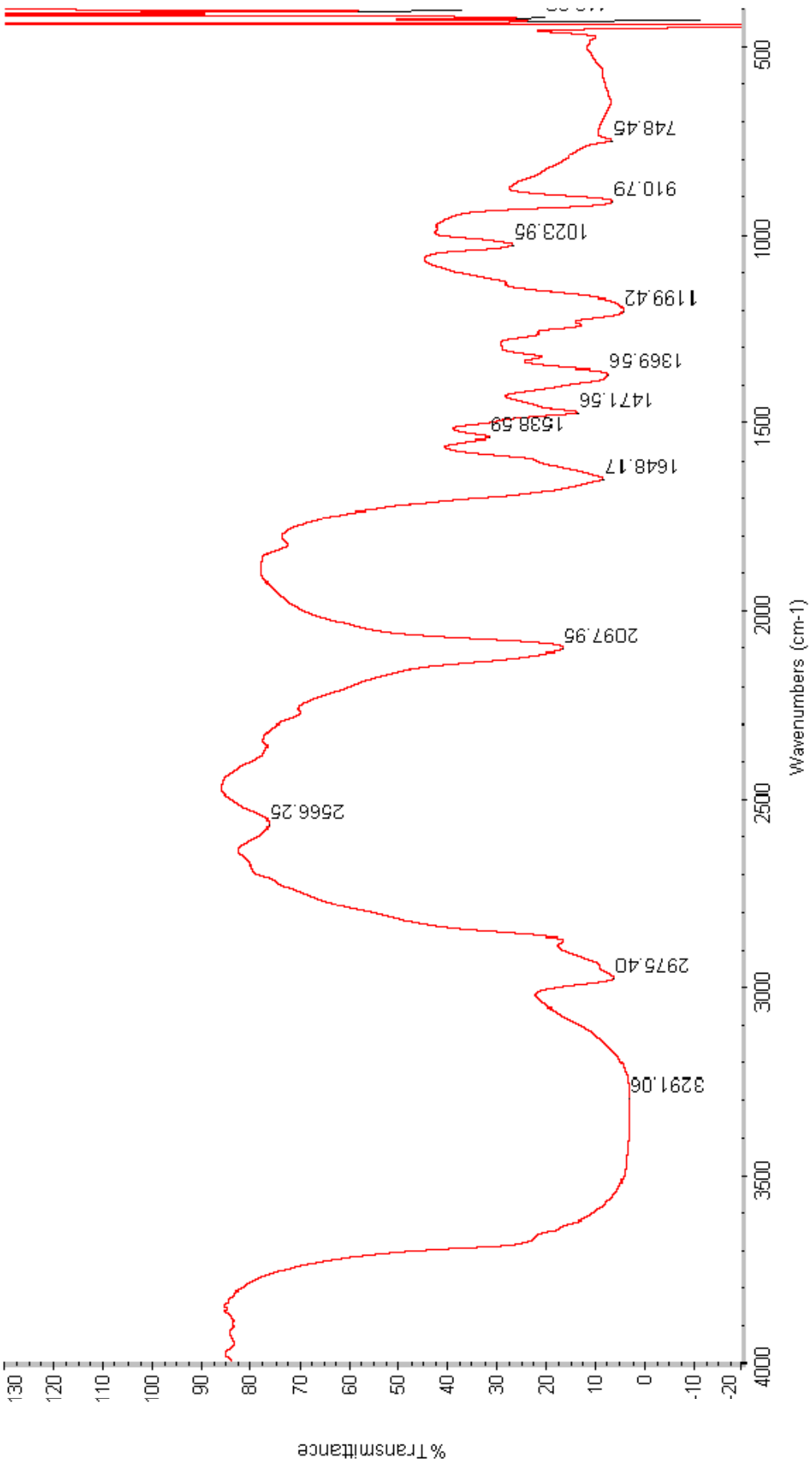

Figure 37: Infrared spectrum of **9** in *t*-BuOH-H_2O.

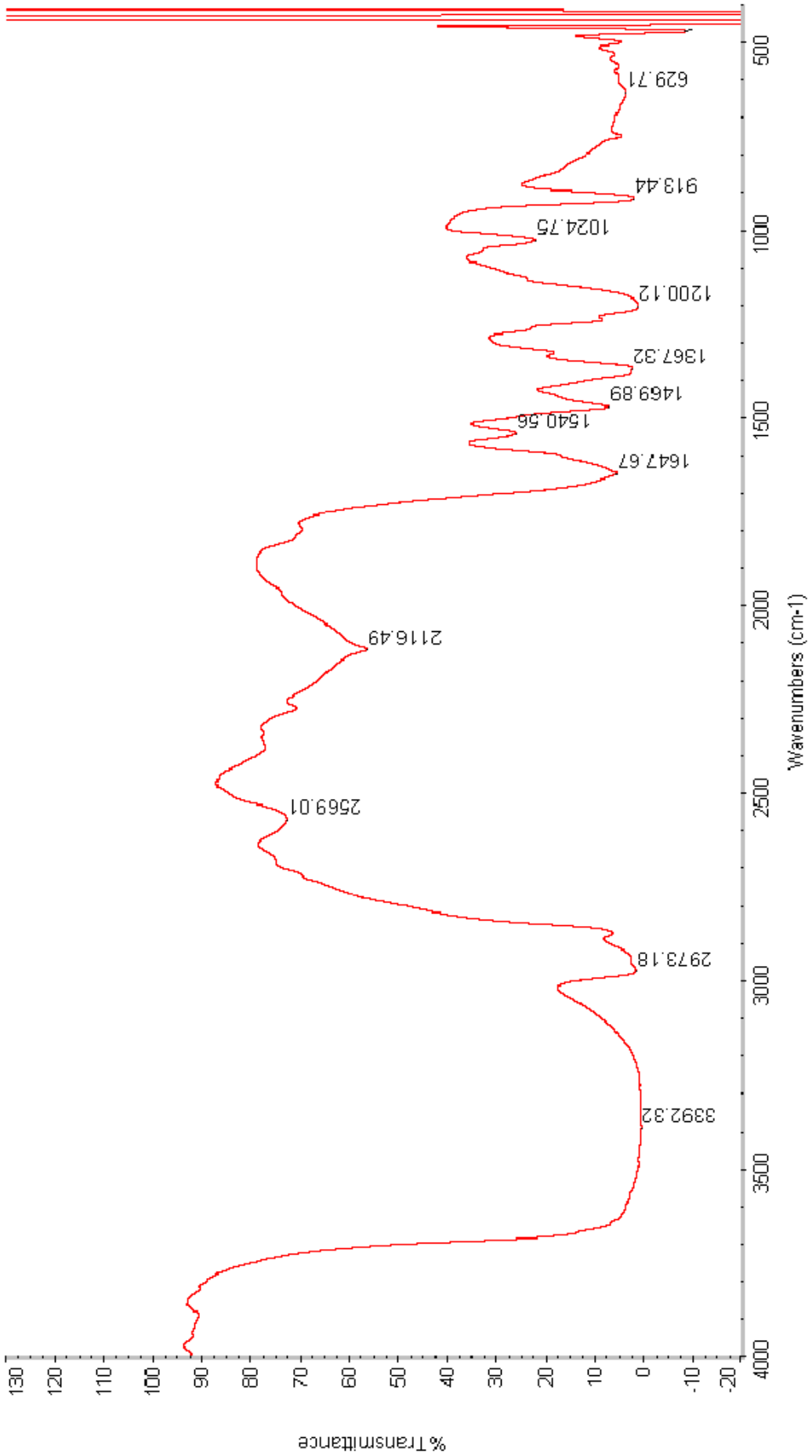

Figure 38: Infrared spectrum of 15 in t-BuOH-H_2O

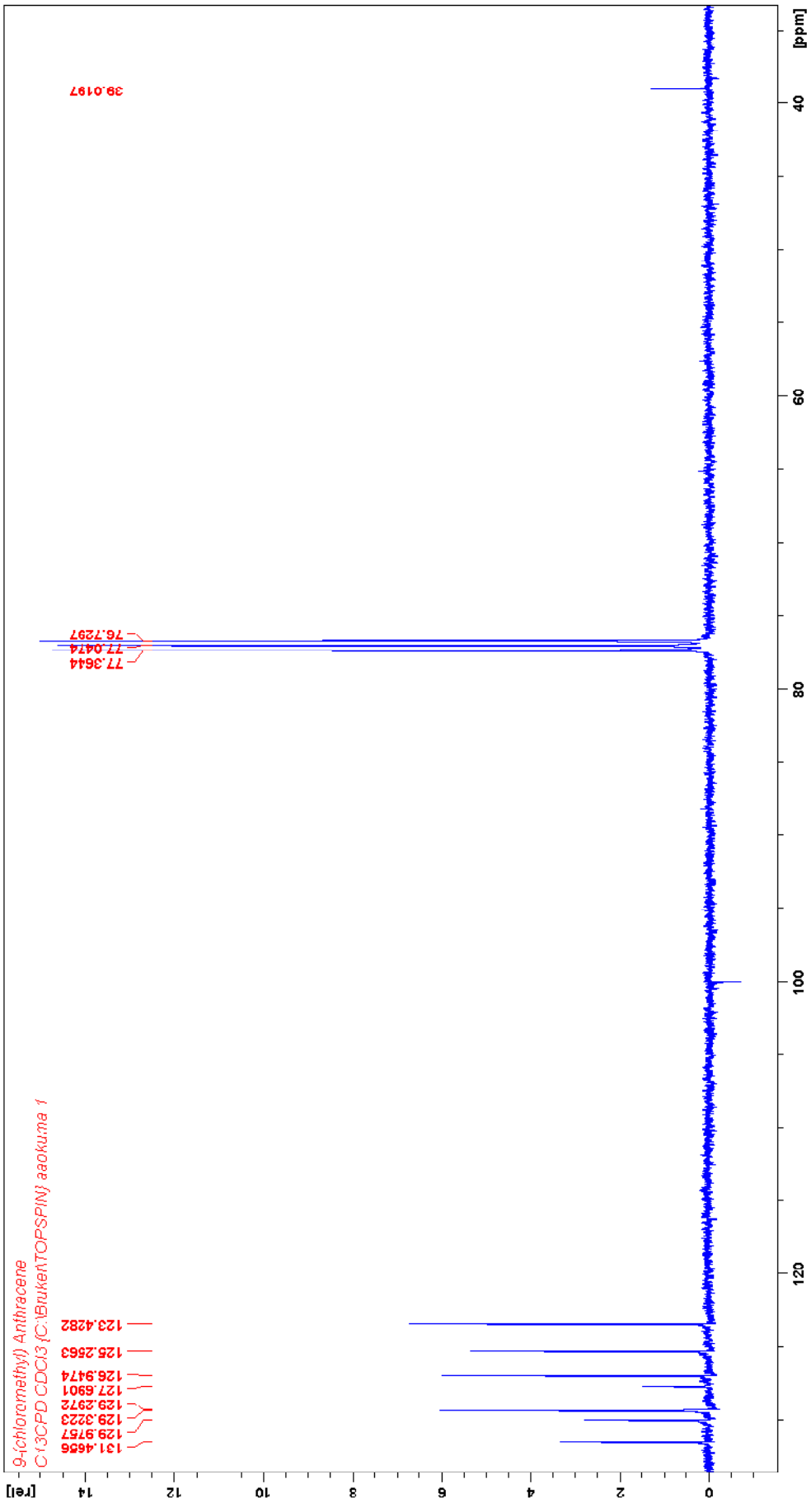

Figure 39: ^{13}C NMR spectrum of 9-(chloromethyl)anthracene.

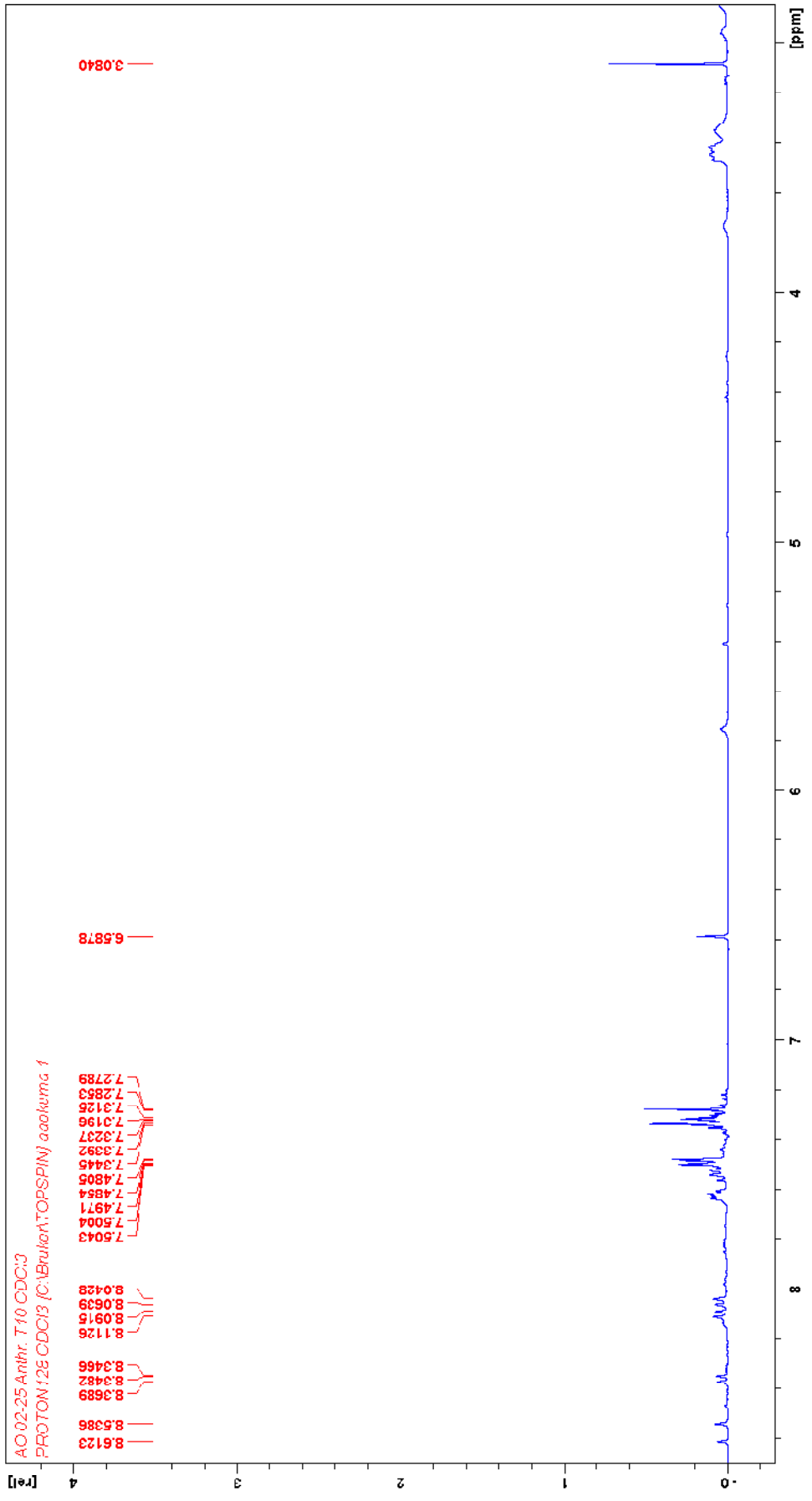

Figure 40: ^{1}H NMR spectrum of attempted synthesis of **14** in acetonitrile.

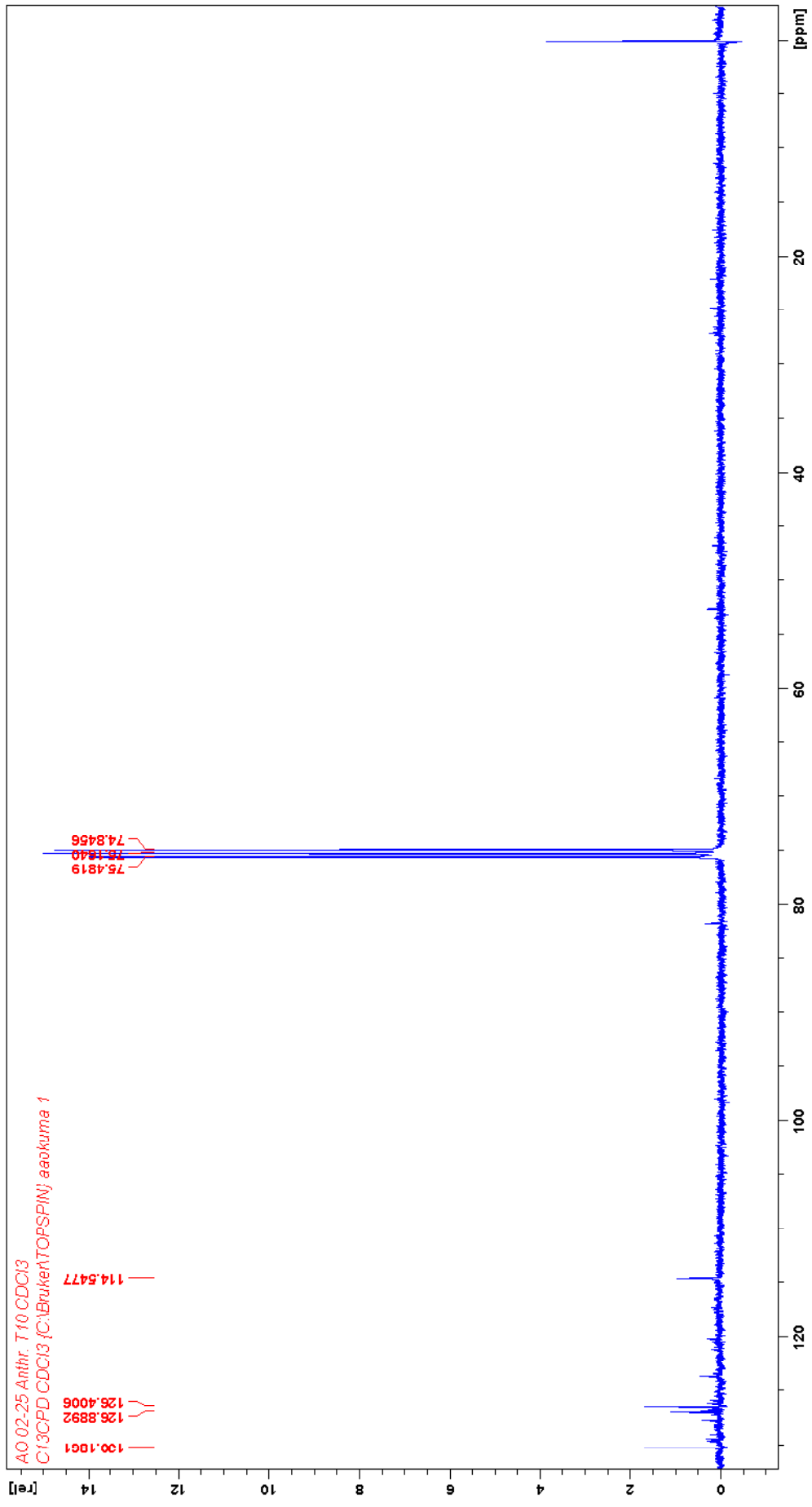

Figure 41: ^{13}C NMR spectrum of attempted synthesis of **14** in acetonitrile

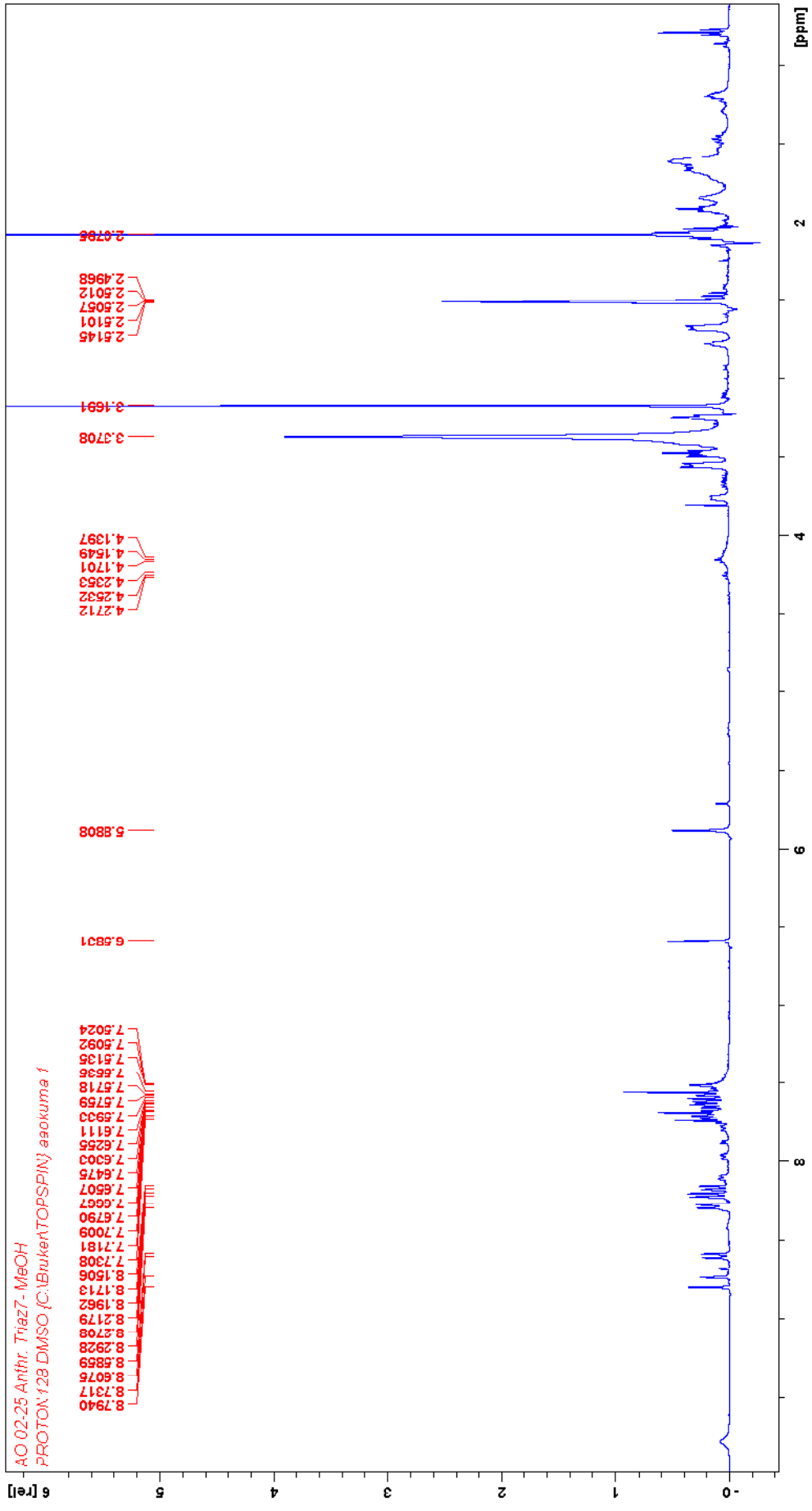

Figure 42: ^{1}H NMR spectrum of attempted synthesis of **13** in acetonitrile.

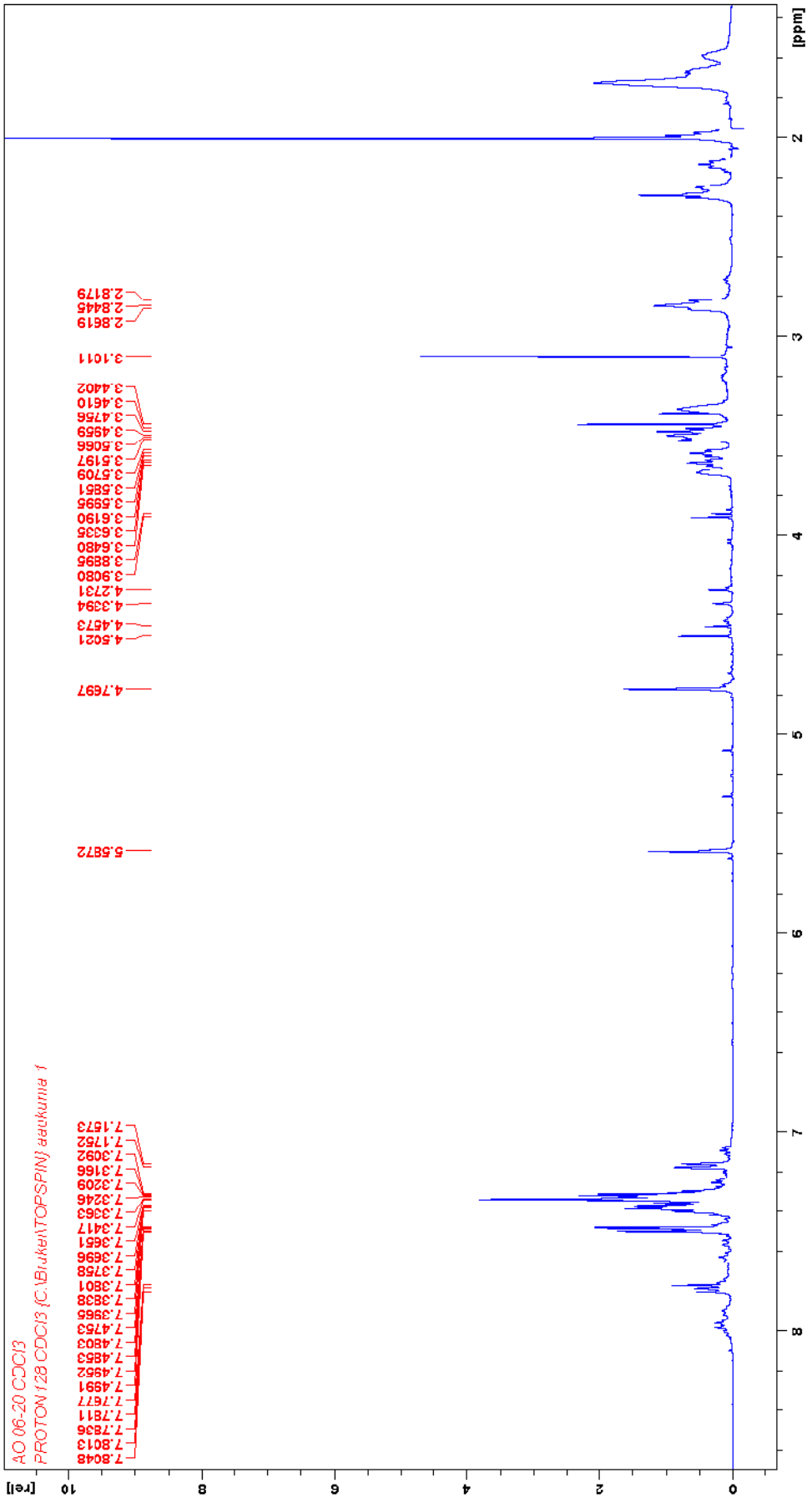

Figure 43: ^{1}H NMR spectrum of attempted synthesis of **16** in acetonitrile.

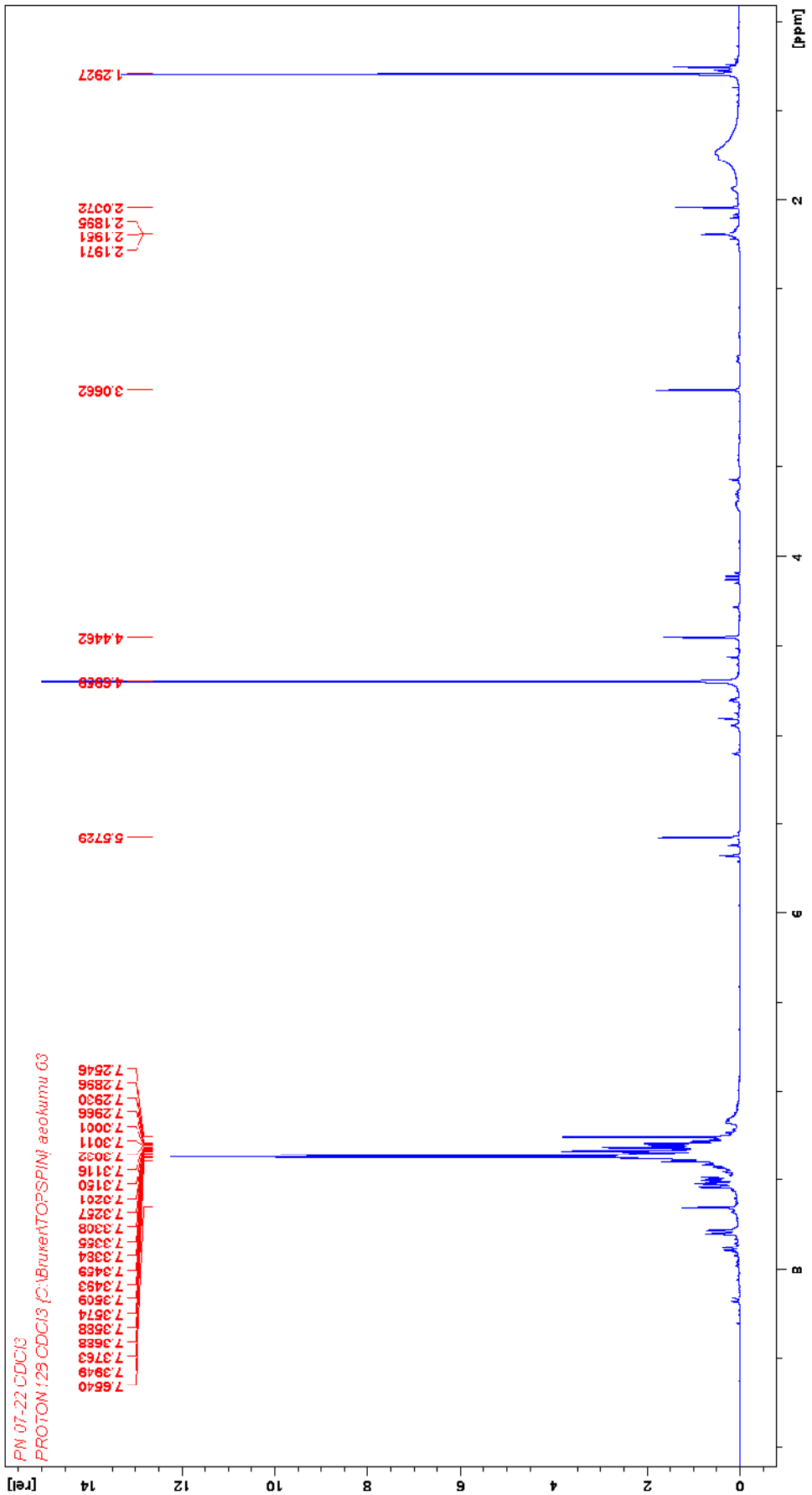

Figure 44: Attempted synthesis of **16** under Fokin conditions.

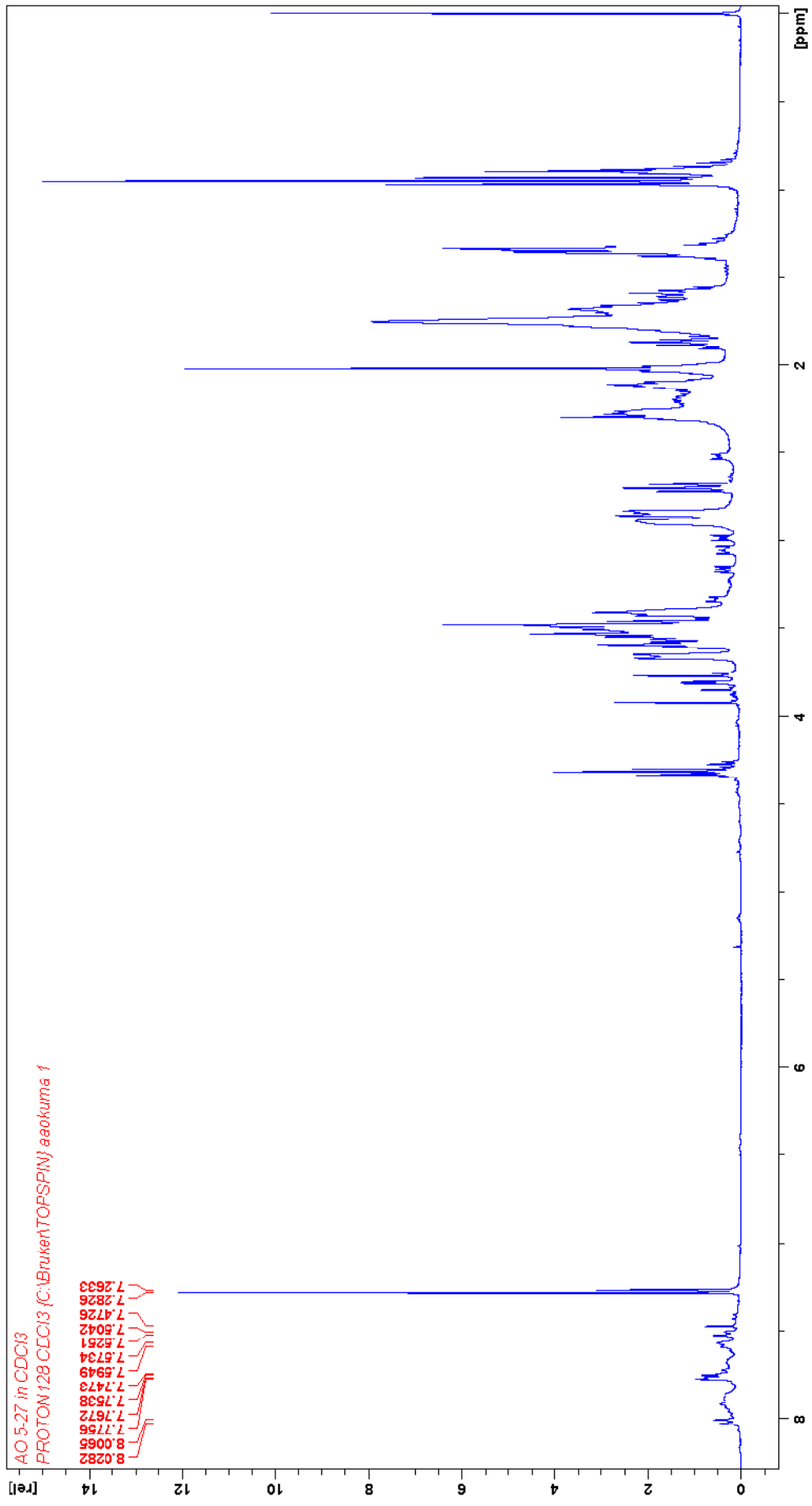

Figure 45: ^{1}H NMR spectrum of attempted synthesis of **15** in CH_3CN-MeOH.

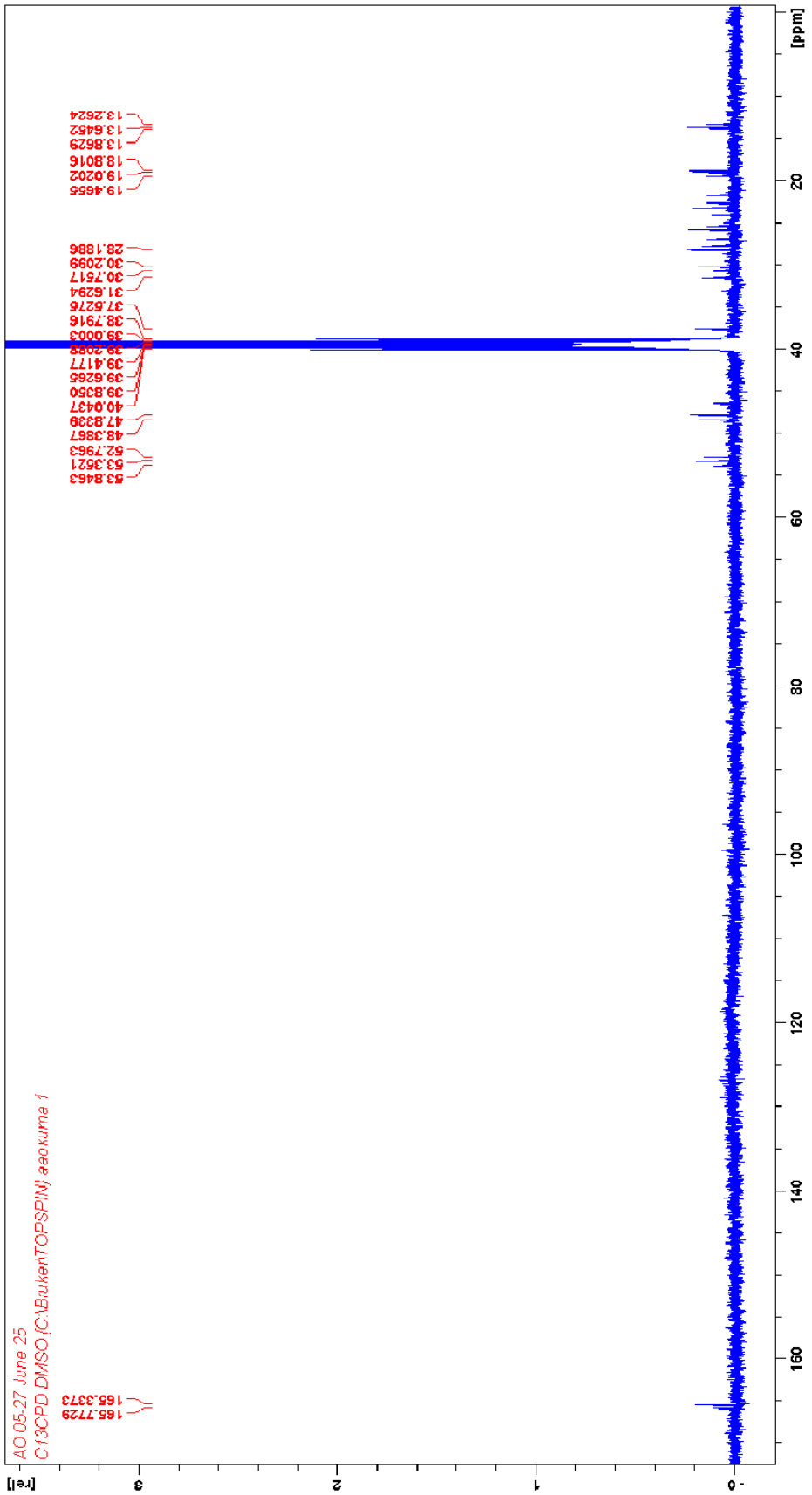

Figure 46: ^{13}C NMR spectrum of attempted synthesis of **15** in CH_3CN-MeOH.

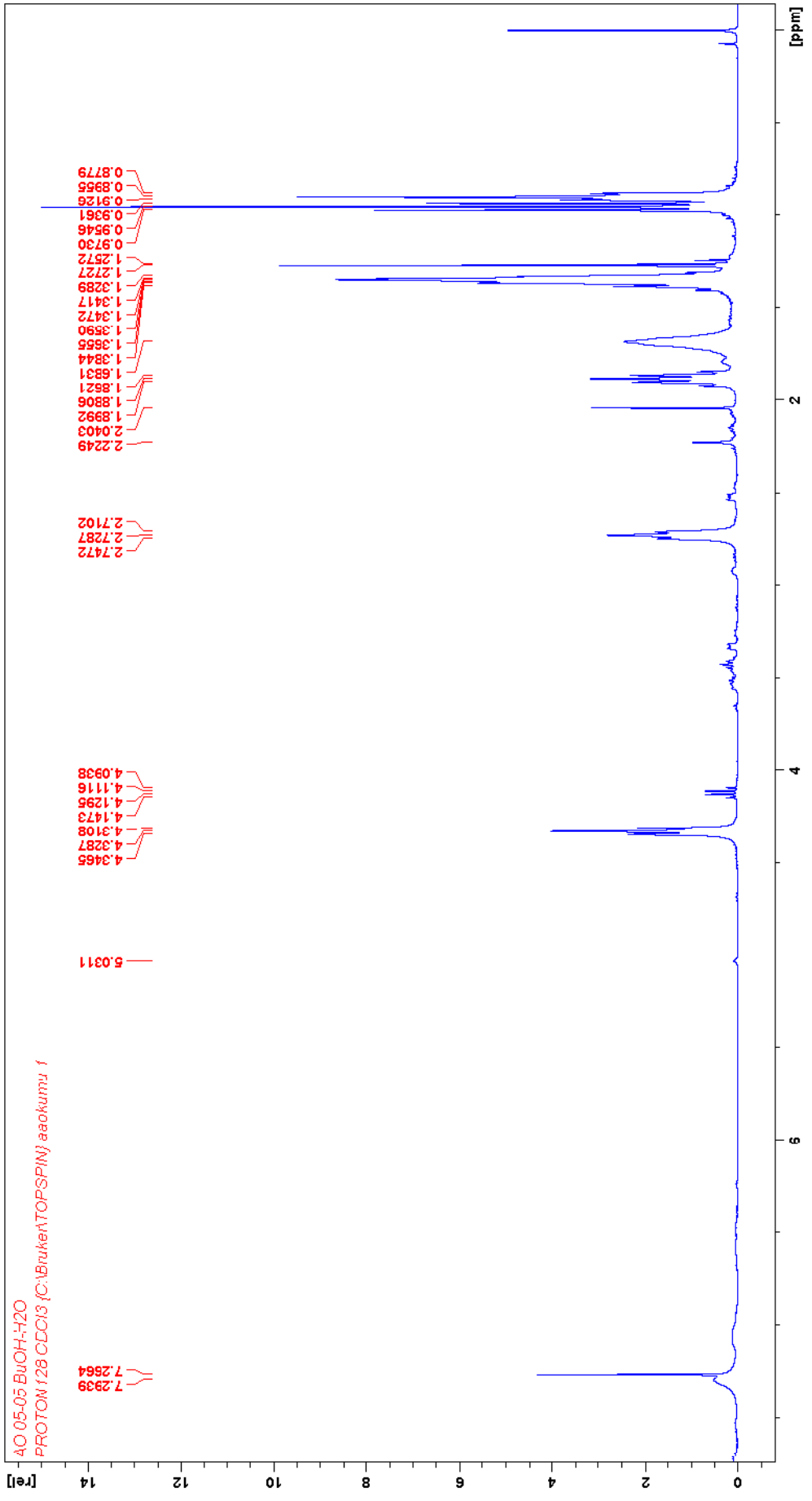

Figure 47: ^{1}H NMR spectrum of of **15** in t-BuOH-H_2O.

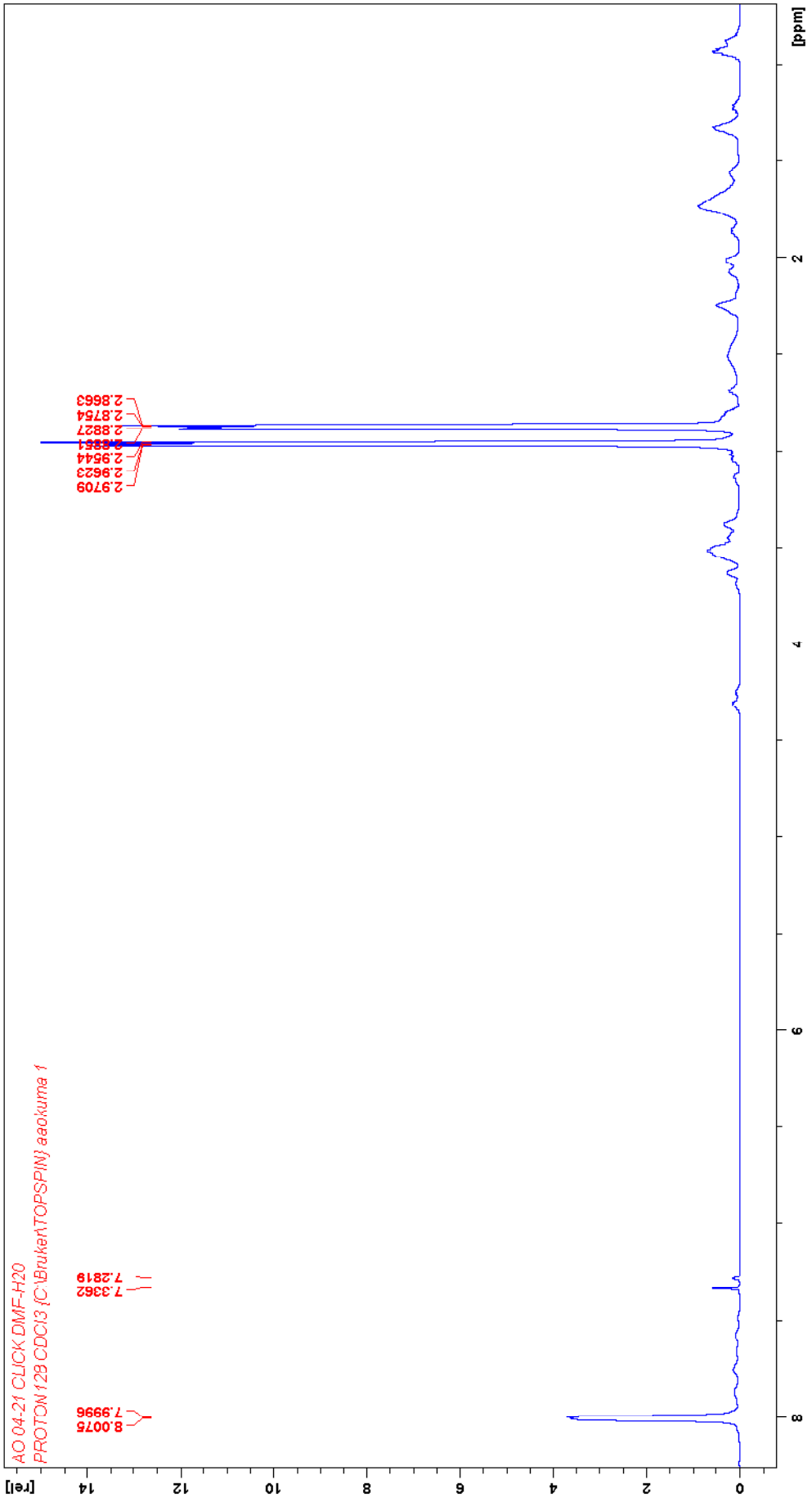

Figure 48: ^{1}H NMR spectrum of attempted synthesis of **15** in DMF-H_2O.

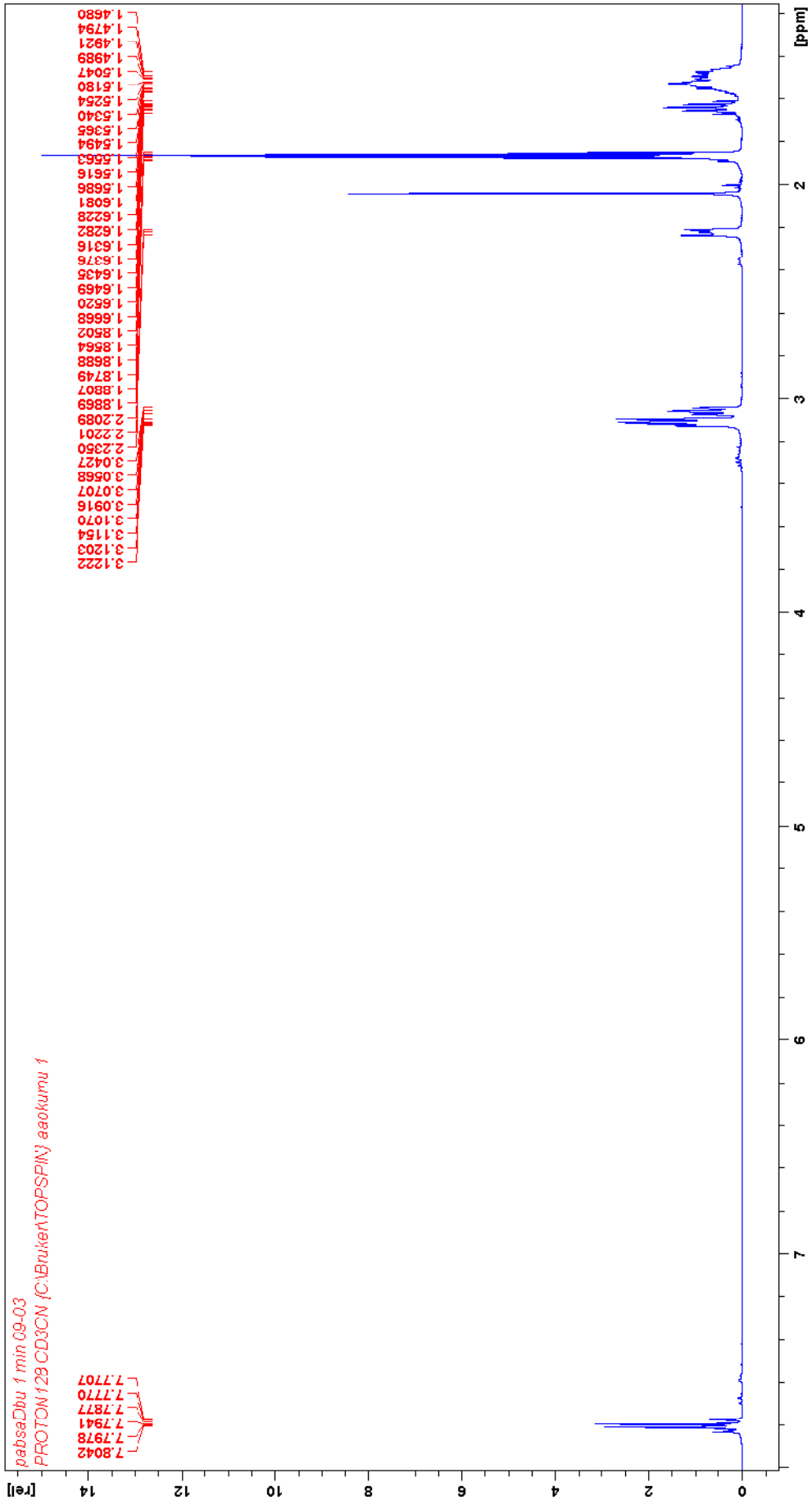

Figure 49: Kinetic studies in CD_3CN - After 1 minute.

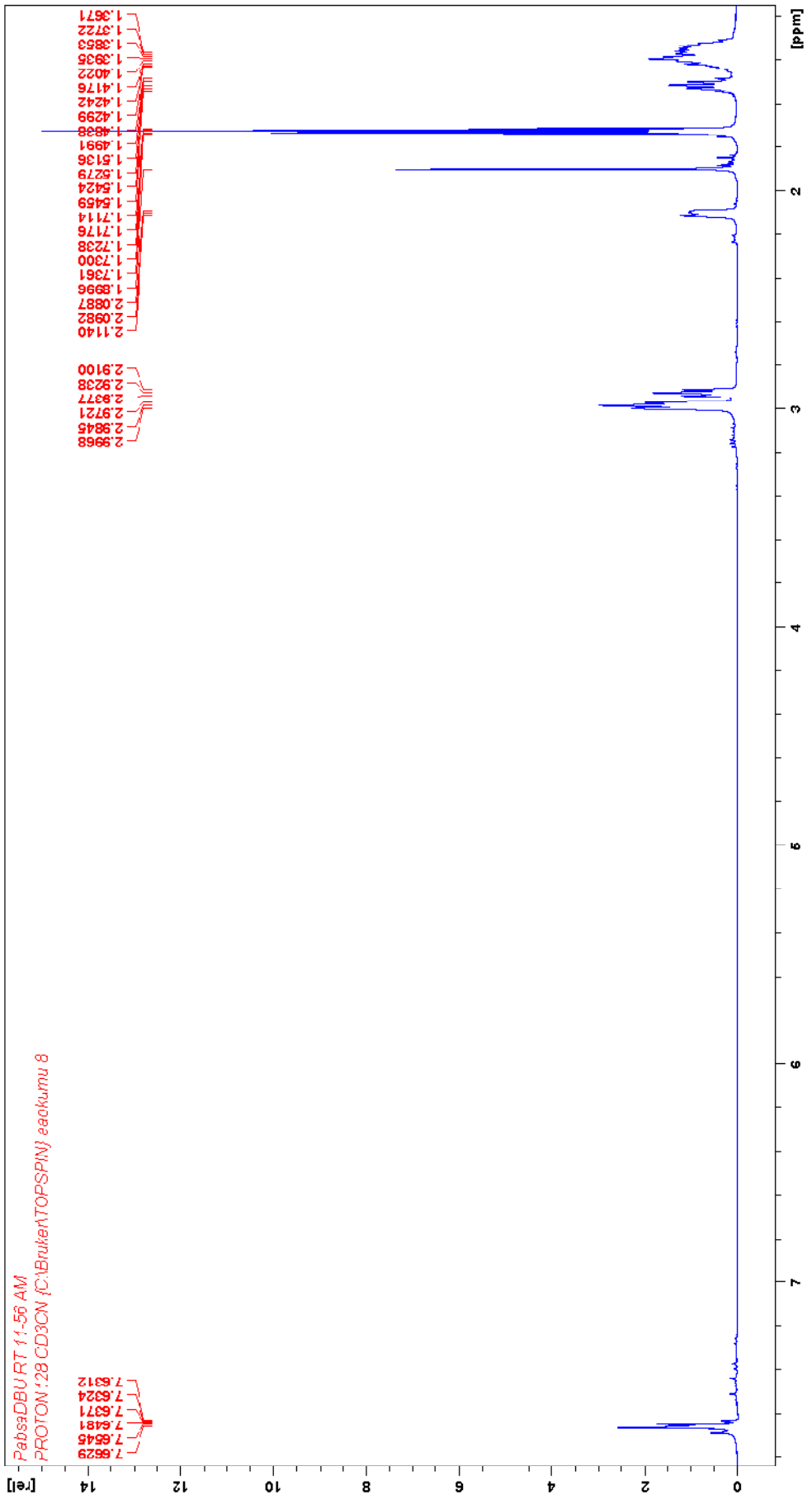

Figure 50: Kinetic studies in CD_3CN - After 30 minutes.

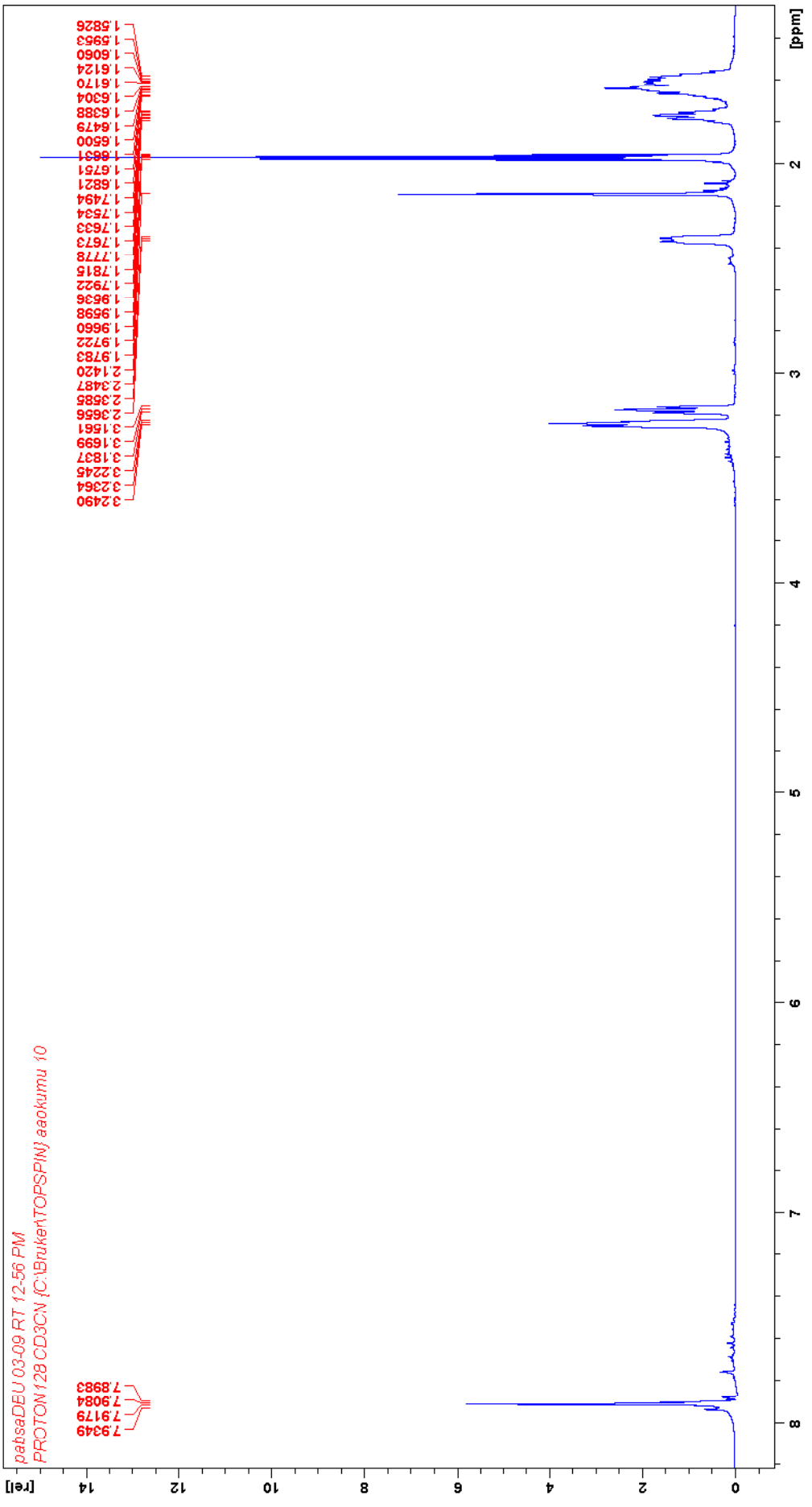

Figure 51: Kinetic studies in CD_3CN - after 1 hour.

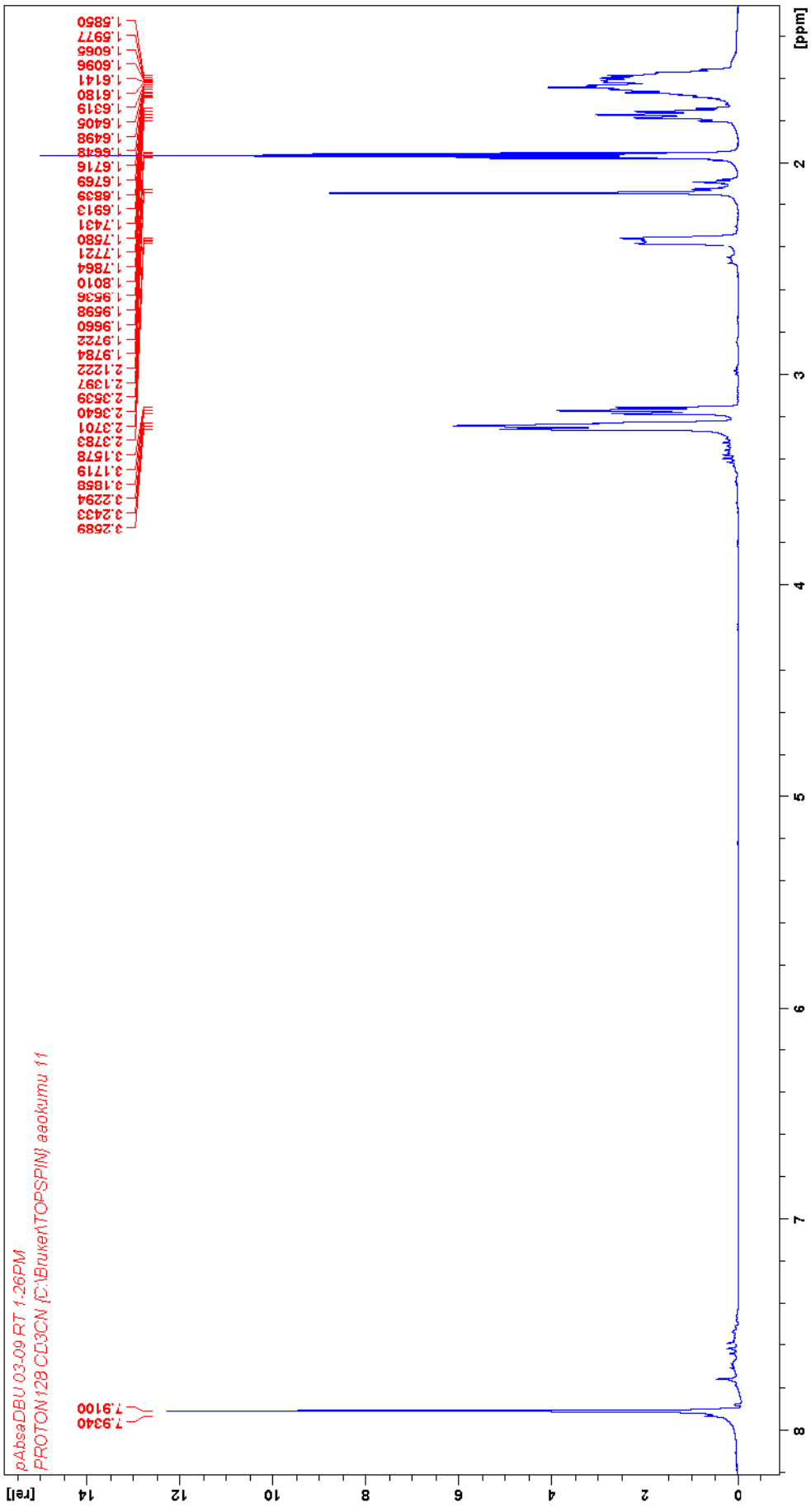

Figure 52: Kinetic studies in CD_3CN - after 1.5 hours.

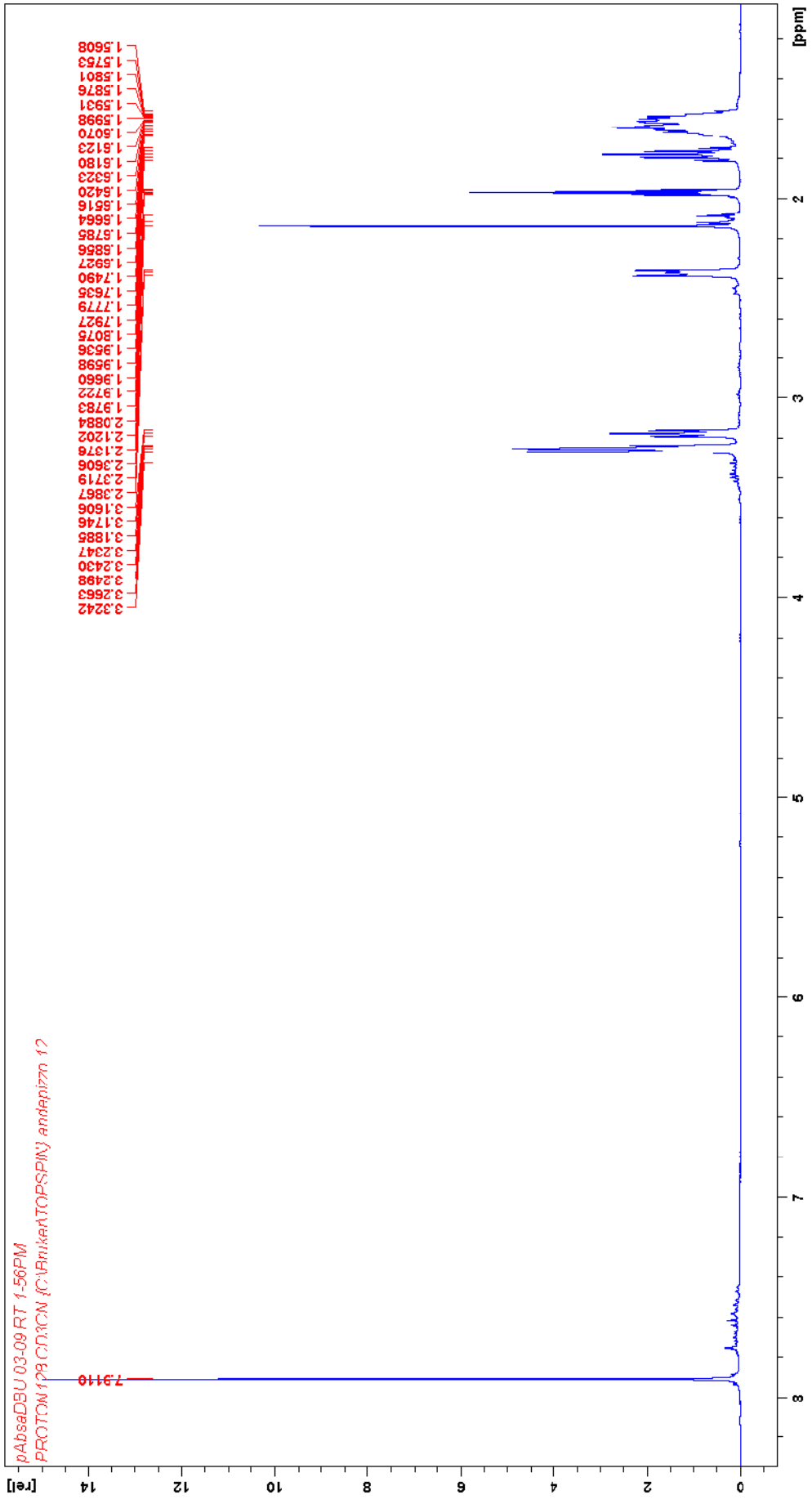

Figure 53: Kinetic studies in CD_3CN - after 2 hours.

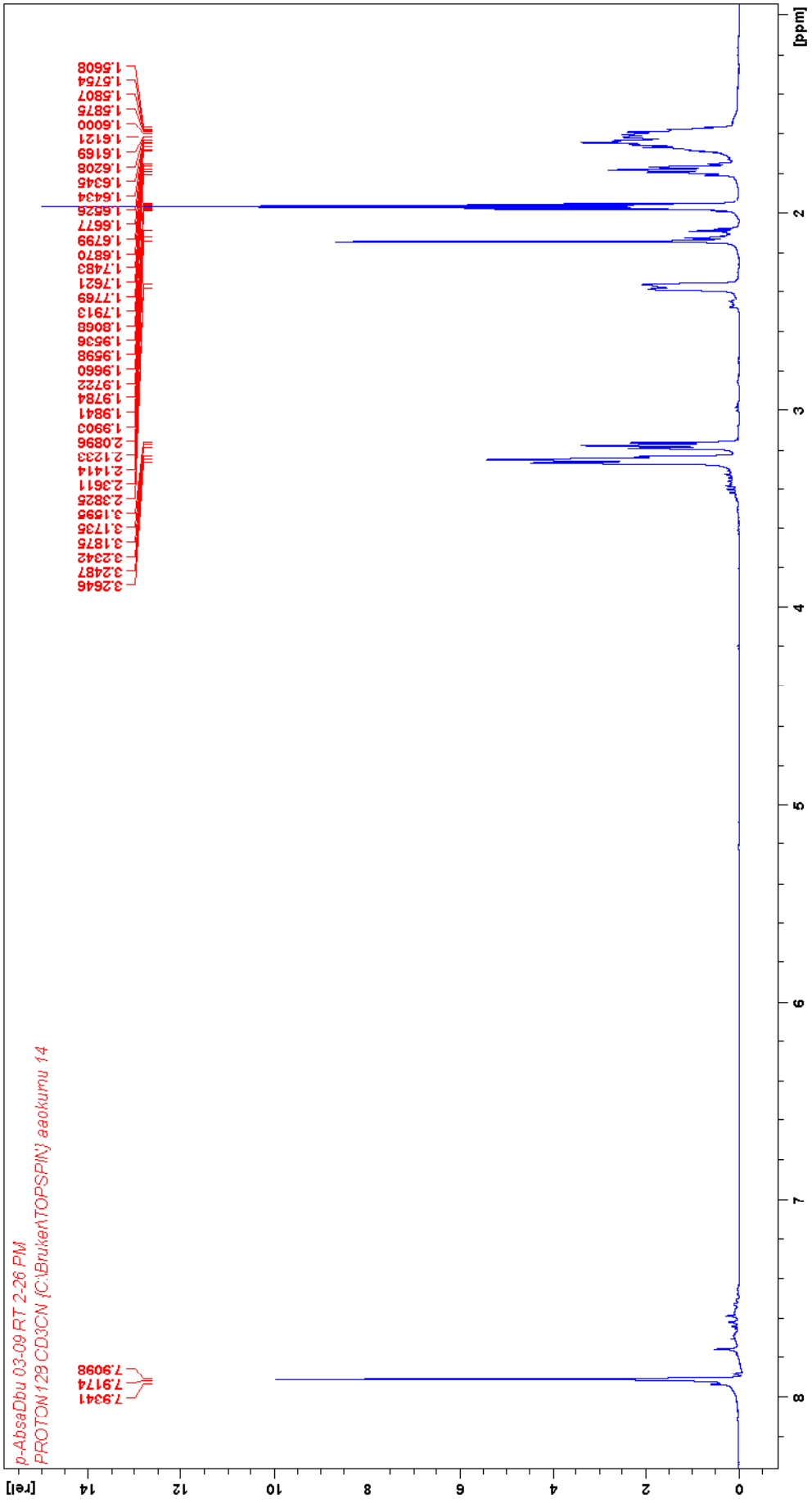

Figure 54: Kinetic studies in CD_3CN - after 2.5 hours.

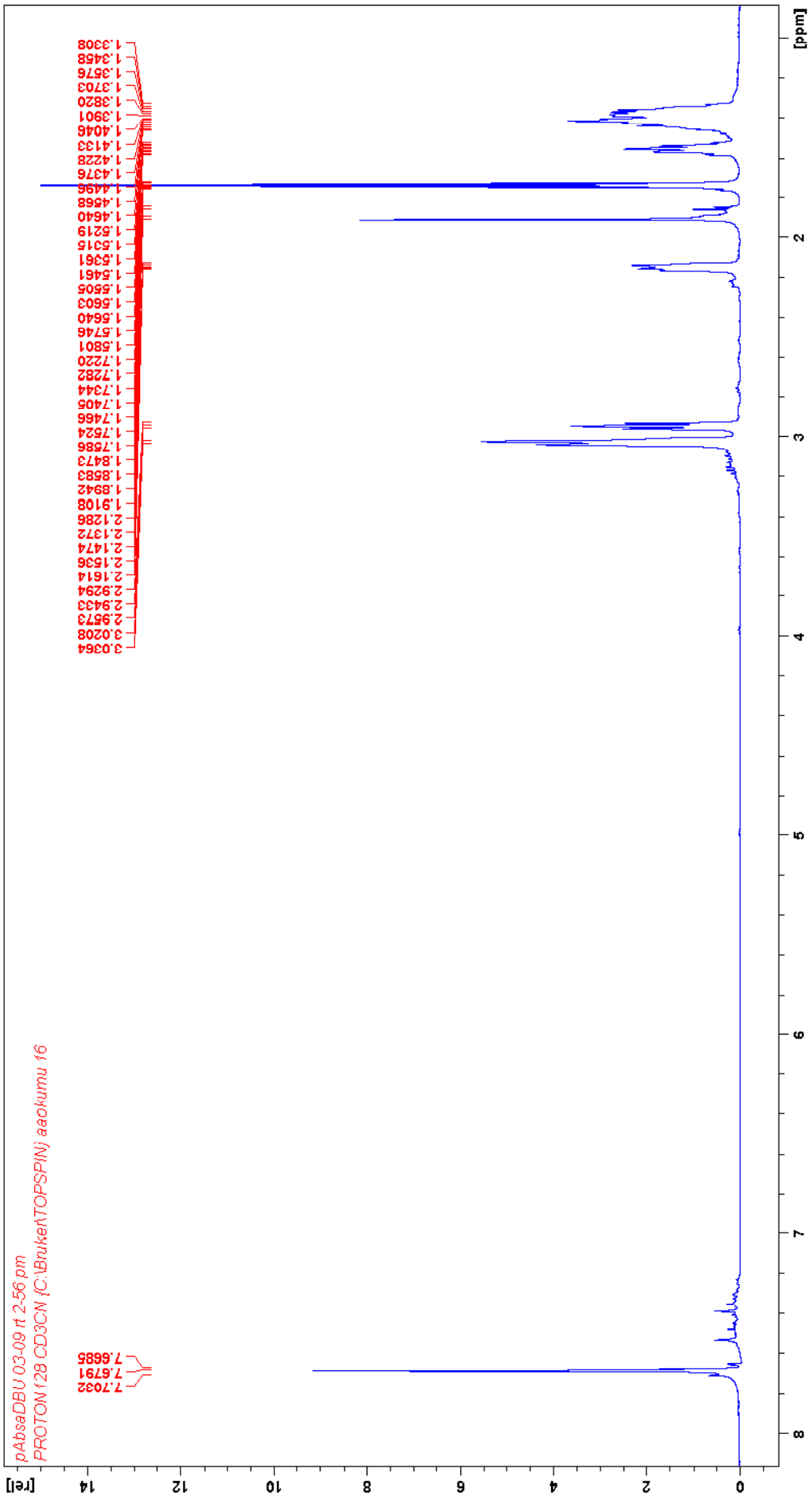

Figure 55: Kinetic studies in CD_3CN - after 3 hours.

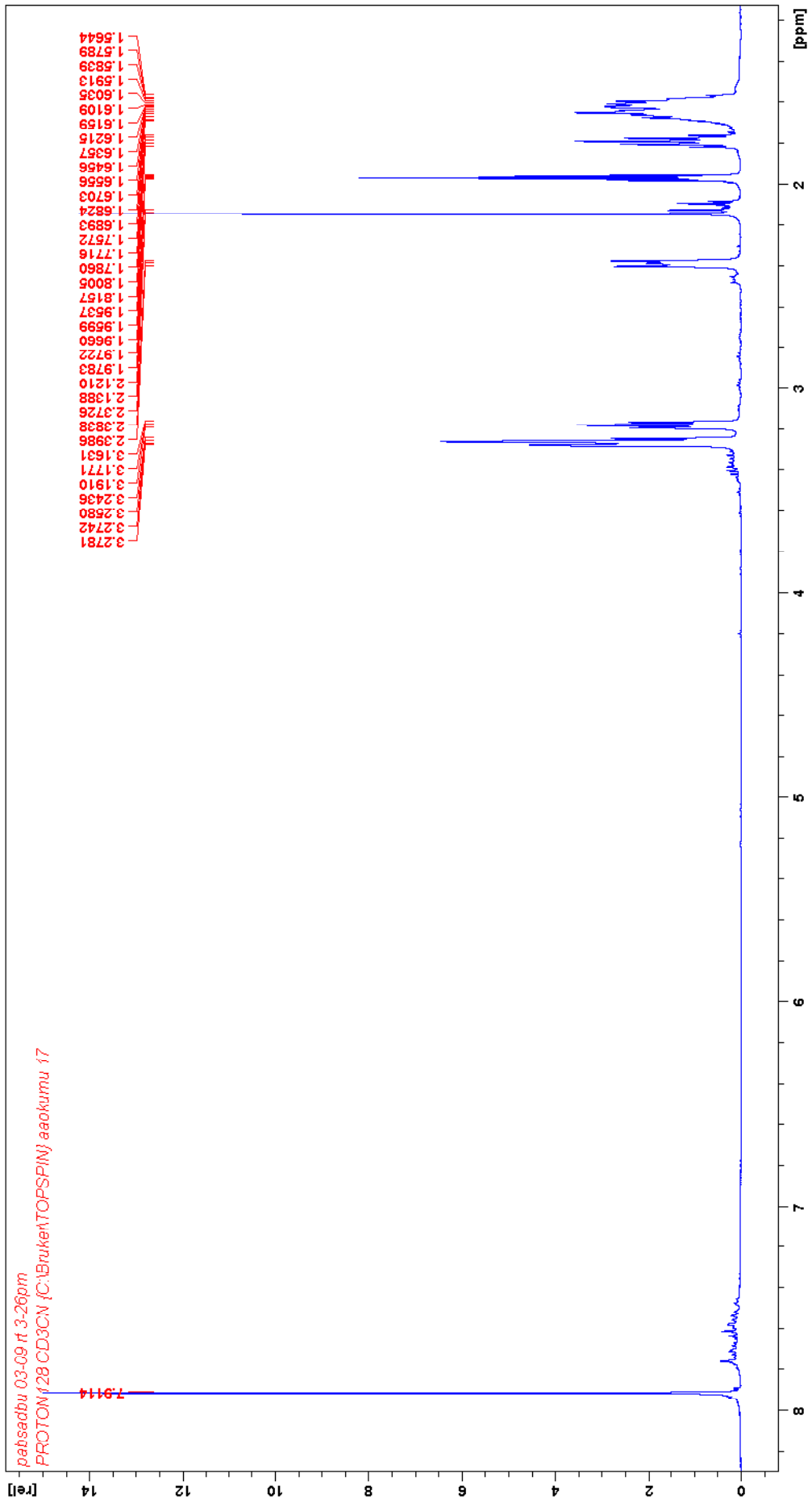

Figure 56: Kinetic studies in CD_3CN - after 3.5 hours.

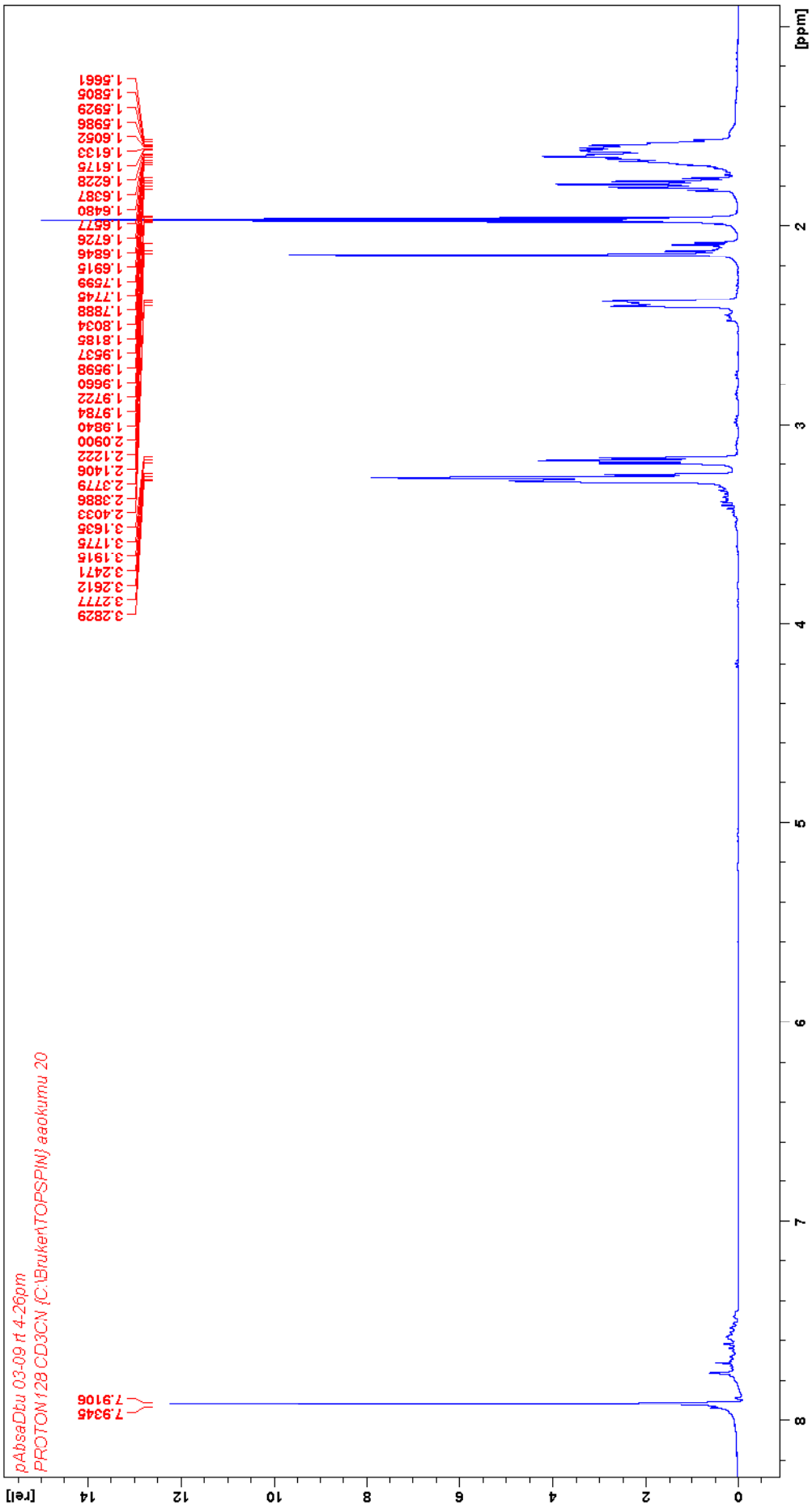

Figure 57: Kinetic studies in CD_3CN - after 4.5 hours.

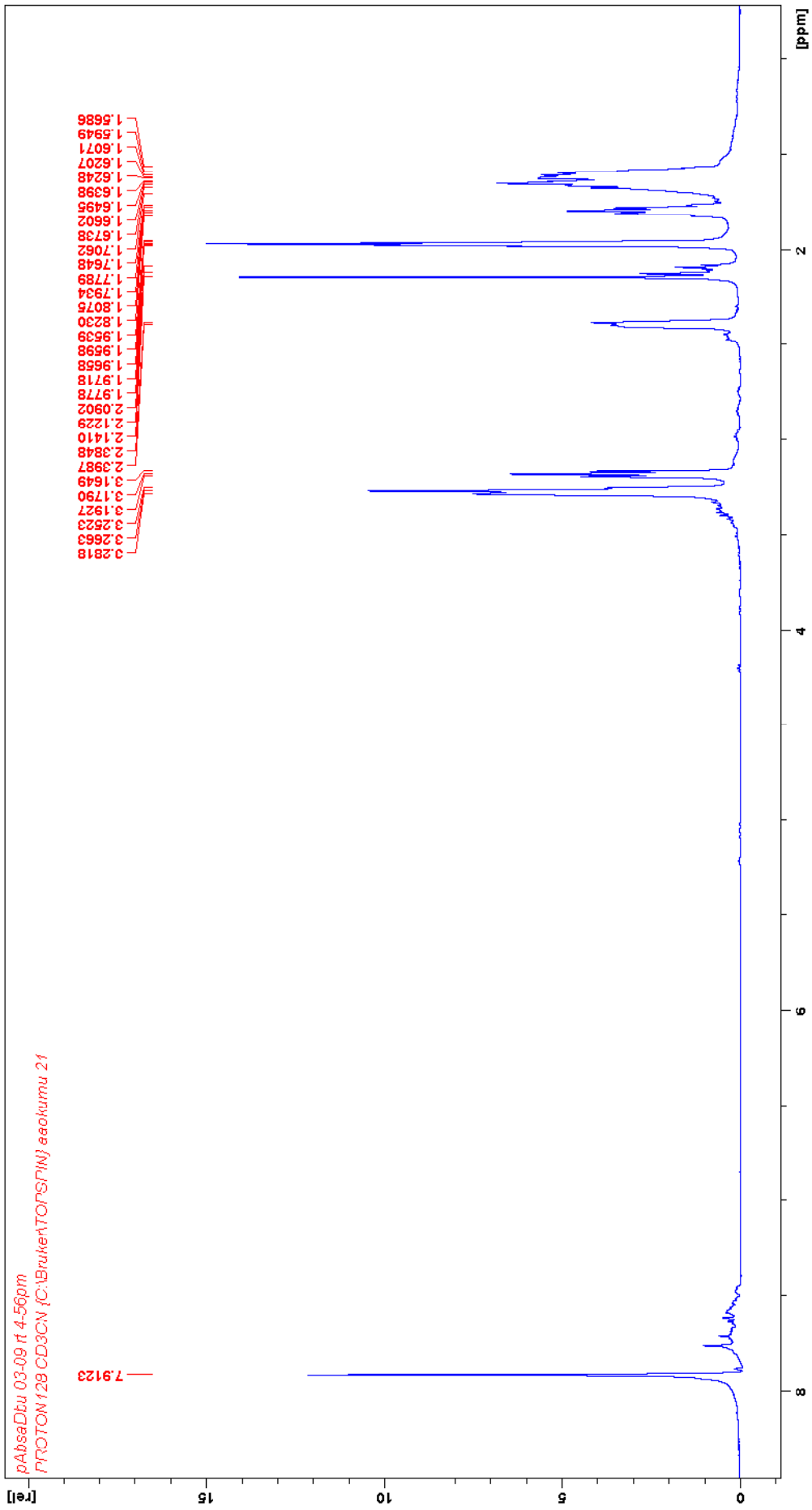

Figure 58: Kinetic studies in CD_3CN - after 5 hours.

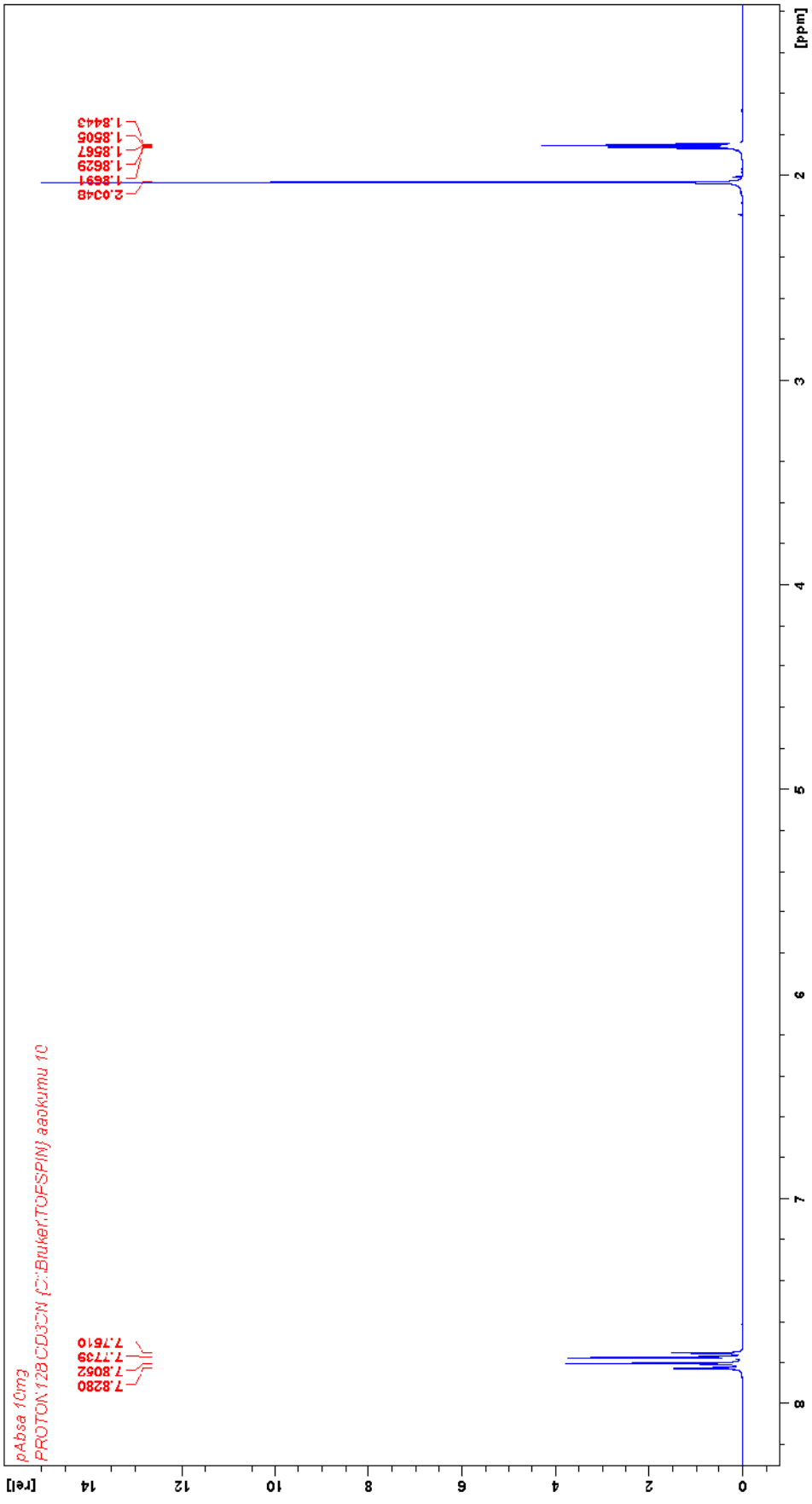

Figure 59: ^{1}H NMR spectrum of *p*-ABSA in CD_3CN.

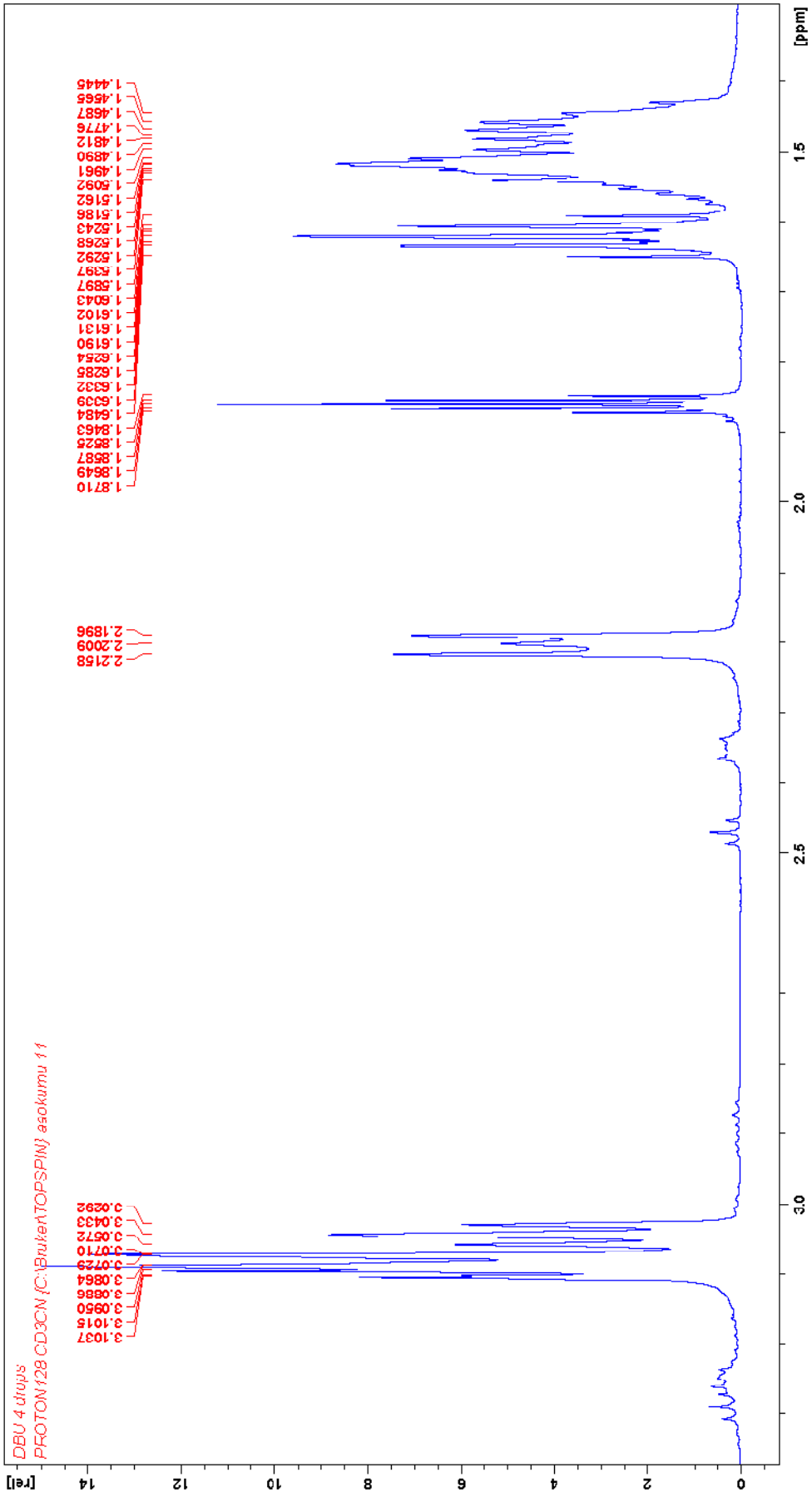

Figure 60: ^{1}H NMR spectrum of DBU in CD_3CN.