5-9-2009

Solid Phase Amide Synthesis Using Staudinger-Vilarrasa Coupling and Microwave Irradiation

Ryan Schmidtz
Butler University

BUTLER UNIVERSITY HONORS PROGRAM

Honors Thesis Certification

Applicant Ryan Schmidtz

Thesis title Solid Phase Amide Synthesis Using Staudinger-Vilarrasa Coupling and Microwave Irradiation

Intended date of commencement May 9th, 2009

Read, approved, and signed by:

Thesis adviser(s) _____ 3/20/09 Date

Reader(s) _____ Date _____ 3/3/09 Date

Date

Certified by _____ 6/2/09 Date

Director, Honors Program

Level of Honors conferred: University Magna Cum Laude

Departmental

Acknowledgements

I would like to thank Dr. Morgan for undertaking the difficult task of being my thesis advisor. He was an immense help throughout the entire process and kept me on the right track. I would also like to thank the entire Butler University Chemistry Department for their collective effort in the research opportunities available to students, and to those who provide the funding for such ventures. I would also like to thank Dr. Esteb for his help through the thesis preparation period and Dr. Wilson for her aid throughout the thesis writing process and the use of her laboratory. Finally, I would like to thank Butler University, in particular the Honors Program, and the Holcomb Mini-Grants for giving me the opportunity to do the research and write the thesis for this project.

TABLE OF CONTENTS

Acknowledgements……..1

Table of Contents…….2

Glossary of Terms…….3

List of Tables…….4

List of Figures/Schemes……4

Abstract……5

Introduction……..6

Results and Discussion……10

Conclusion…….....19

General Methods…….....20

Experimental Methods……....20

Appendix A: Spectral Data.....23

References……...31

Glossary of Terms

DMF: N,N-dimethyl formamide

DCM: Dichloromethane

BOP: Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate

PyBOP: benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

^{1}H NMR: Proton Nuclear Magnetic Resonance

ppm: Part per million

IR: Infrared

cm: Centimeters

THF: Tetrahydrofuran

TLC: Thin-Layer Chromatography

MeOH: Methanol

min: Minutes

RT: Room Temperature

h: Hours

μv: Microwave

Δ: Heat

mL: Milliliters

Et_2O: Diethyl ether

GCMS: Gas Chromatography Mass Spectroscopy

List of Tables

Table 1. Microwave Irradiated Vilarrasa Coupling Reaction Conditions and Yields……

List of Figures/Schemes

Figure 1. Examples of Compounds Containing Amide Bonds

Scheme 1. Traditional Method of Creating Amide Bonds

Figure 2. Example of Complex Peptide Coupling Reagents

Scheme 2. Proposed Solid Phase Supported Staudinger-Vilarrasa Amide Formation

Scheme 3. The Vilarrasa Coupling Reaction Mechanism

Scheme 4. S_N2 Reaction for the Production of the Azide Starting Materials

Scheme 5. The Staudinger Reaction

Figure 3. Infrared Spectroscopy Tracking Progression of the Staudinger Reaction

Scheme 6. The Vilarrasa Reaction Using Benzoic Acid

Abstract

Amide bond formation is an already well documented area of organic chemistry, and is very useful in its application in medicine and pharmaceuticals. However, current methods have not been investigated with regards to optimization of reaction times, solvents, and energy sources. In addition, current methods also utilize toxic solvents to cleave the peptide from the solid phase resin. In our study, we combine the Staudinger and Vilarrasa coupling reactions with microwave irradiation to develop and optimize the synthesis of amide bonds through the use of a solid support. Instead of attaching the peptide to the solid support, our amide bond is left in solution, allowing for easier cleanup and the use of less toxic solvents.

Introduction

The formation of amide bonds plays an important role in medicinal and pharmaceutical biochemistry. They are found in peptides, the building blocks of proteins, which are essential to all processes within the human body. Without amide bond formation, immunoglobulin molecules could not form and complex with antigens, halting the immune response, and basic protein receptors in cell membranes could not initiate metabolic and cell-signaling pathways, distorting all physiologic processes of the cell. Amide bonds are also important components of pharmacologic products. β-lactams **1** [Figure 1] are a subset of antibiotics and contain a 4-membered ring with an internal amide bond.[1] These compounds, of which penicillin is an example, contributed to over 55 million prescriptions in 1992.[2] Hydantoins **2** and benzodiazepines **3** [Figure 1], also contain an amide bond within a ring structure, and are a class of psychotropic drugs considered minor tranquilizers and anticonvulsants. Benzodiazepines competitively inhibit the binding site on neurons for the neurotransmitter γ-Aminobutyric acid (GABA), which causes neuron inhibition and creates psychotropic effects.[3] Thus, methods that create amide bonds are essential to many facets of physiology, pharmacology, and immunology.

There are many current methods utilized by chemists to synthesize amide bonds. Most methods create amides **4** from carboxylic acids **5** and amines **6** [Scheme 1].

However, the acid must be “activated” by peptide coupling reagents such as phosphonium class reagents **7** [Figure 2]. These reagents turn the acid portion of the carboxylic acid into a phosphonium leaving group **8** [Scheme 1].[4] A leaving group is denoted as an atom or atoms that are easily lost in a reaction in a way that allows other atoms to be incorporated into the molecule. The use of phosphonium class reagents allows the reaction with the desired amine to occur at room temperature or temperatures not exceeding the boiling point of the solvent.[1,5,6] These peptide coupling reagents are often reacted in toxic and/or halogenated solvents, such as DMF and DCM. Consequently, further methods need to be developed to eliminate some of the use of toxic solvents and side products of peptide coupling reagents.

Solid phase resins are commonly used in the synthesis of amide bonds. This allows for separation of the product from the reaction solution by filtration, as the peptide **4** is bonded to the resin and any impurities from activation remain in solution. Although

this allows for easy product isolation, removal of the peptide from the resin often utilizes excess amounts of acid or other toxic compounds.

In the method proposed in this paper, the amide bond formation occurs with the help of a triphenylphosphine resin. When the reaction is run, the triphenylphosphine oxide leaving group is attached to the resin, and the desired amide product is free in solution [Scheme 2], as opposed to traditional methods, bypassing the steps dealing with removal of the amide from the resin.[7] As a result, not only are less solvents necessary to isolate the product (already filtered from resin), but a greater diversity of solvents can be investigated compared to traditional methods.

The removal of the amide from the resin occurs through the use of the Staudinger-Vilarrasa reaction. The Staudinger portion [Scheme 2] of the proposed reaction results in the reaction of an azide **9** with the triphenylphosphine **10** resin bead. In our reaction, the azide acts as an amino acid methyl ester analog and acts as our “amine” component.[5] The mechanism of the Vilarrasa coupling [Scheme 3] utilizes a carboxylic acid **5** to neutralize the charge on the phosphorazide **15** bound to the resin. The negatively charged acid then acts as a nucleophile and attacks the triphenylphosphonium salt **16**. The nitrogen attached

to the triphenylphosphine **17** then attacks the carbonyl carbon, temporarily breaking the carbon-oxygen π bond. When the carbon-oxygen double bond reforms, the triphenylphosphine oxide **20** serves as the phosphonium leaving group to form the amide **19** in solution.[8]

The proposed reaction will also utilize microwave irradiation as an energy source, as opposed to convectional heating. Microwave irradiation directly heats the reactants or the solvent by interacting with the dielectric polarizations in polar molecules. Molecules that are irradiated align themselves with the applied microwave field as long as a compound is polar. The molecules continually rotate to reposition themselves with the field, thus absorbing the microwave energy. The electromagnetic energy absorbed by the molecule to align itself is converted to heat energy, and the energy is then used to fuel the desired reaction.[6] The use of microwaves is a more efficient energy source compared to convection due primarily to the direct heating of the molecules. In addition, microwave heating in commercial systems (such as the one used in this method), can be adjusted to maintain certain temperatures and pressures. This allows certain solvents, when heated with microwaves, to be heated above their boiling points, leading to a sort of

superheating that tends to lead to increased reactions rates in various reactions.[6,8]

Results and Discussion

The production of the α-azido substituted methyl ester **22** resulted from the reaction of 2-bromo-acetic acid methyl ester **21** and sodium azide [Scheme 4]. In order to increase the solubility of sodium azide in acetone, 18-crown-6 was added to the reaction mixture. After the reaction, ^{1}H NMR of 2-azido-acetic acid methyl ester **22** revealed a singlet peak at 3.90 ppm of integration 2 corresponding to the two hydrogens attached to the alpha carbon. It also showed a singlet peak at 3.81 ppm of integration 3, signifying the three hydrogens attached to the ester carbon. Infrared spectroscopy revealed a strong, narrow peak at 2108 cm^{-1}, signifying the attachment of the azide in place of the bromide. Another two peaks occurred at 1748 cm^{-1} and 2950 cm^{-1}, signifying the presence of the carbonyl and sp^3 hybridized carbon-hydrogen bonds, respectively. These all correspond to literature values.[9] Given this information, it is inferred that the azide did in fact replace the bromide, and product **22** was created as intended. Since this reaction is a simple S_N2 reaction, 98% yields were reached given the ability of the azide to act as a nucleophile and the leaving group ability of the bromine atom.

The production of α-azido substituted methyl ester **24** also occurred between α-bromo-phenylacetic acid **23** and sodium azide [Scheme 4]. After the reaction, ^{1}H NMR of α-azido-phenylacetic acid methyl ester **24** revealed peaks at 7.37, 4.9, and 3.81 ppm. The set of peaks at 7.37 ppm indicated the aromatic phenyl ring on the alpha carbon as an

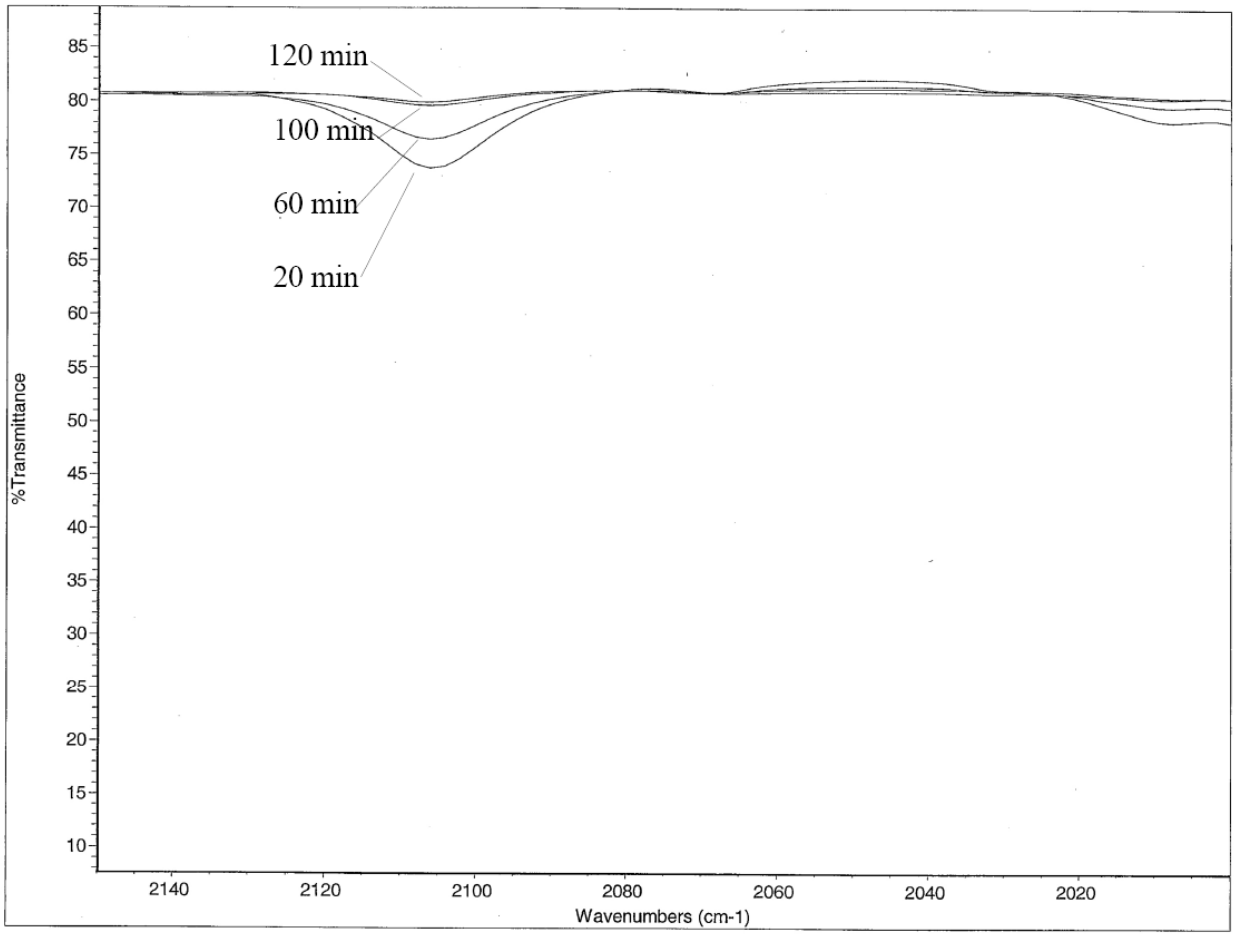
integration 5 multiplet. The 4.9 ppm singlet of integration one corresponds to the lone H atom on the α carbon. Finally, the 3.74 ppm triplet of integration 3 represents the 3 hydrogen molecules attached to the ester carbon. All of these, again, correspond to literature values.[9] Infrared spectra shows peaks at 3025, 2950, 2112, and 1740 cm^{-1}. Similar to compound **22**, the strong narrow peak at 2112 cm^{-1} signifies the azide absorption. Also, the peaks at 1740 cm^{-1} and 2950 cm^{-1} occurred, signifying a carbon-oxygen π bond and sp^3 carbon atoms bonded to hydrogens, respectively. The addition of a 3025 cm^{-1} peak in comparison to compound **22** represents the presence of the aromatic sp^2 carbons bonded to hydrogens atoms of the phenyl group. Thus, given the spectral data, our desired product of α-azido-phenylacetic acid methyl ester **24** was created with a yield of 78%.

The second reaction in the sequence, the Staudinger reaction, represents the attachment of the azide compound to the resin forming a phosphazide [Scheme 5]. The lone pair of electrons from the triphenyl phosphine resin attacks the azide, creating a resonance-stabilized, charged nitrogen-phosphorus bond **11** with the release of nitrogen gas. When using 2-azido-acetic acid methyl ester **22**, THF or toluene was the solvent used. When done initially, the 2-azido-acetic acid methyl ester **22** was only added to the resin for 5 min, and the subsequent microwave irradiated Vilarrasa reaction did not

produce a noticeable reaction. The Staudinger reaction was performed again and monitored by TLC. A TLC was performed on the reaction mixture in every 1 minute for the first 10 minutes then at the 15 minute mark on a subsequent reaction using 5% MeOH in DCM as the elution solvent. The TLC was then stained with phosphomolybdic acid to determine the disappearance of the α-azido methyl ester from solution. Only at the 15 minute mark was a reaction noted by TLC. This indicated the initial conditions (5 min, RT) did not allow the Staudinger reaction to occur on such a short time scale. Thus, the reaction was set for 2 hours, allowing for it to run for a longer time period. Infrared spectroscopy was taken of the reaction solution, and loss of the azide peak at around 2100 cm^{-1} was noted. Loss of absorption was used as an indication of the attachment of the methyl ester to the resin, and release of N_2 gas was also noted to occur during the reaction.

In the Staudinger reaction of α-azido-phenylacetic acid methyl ester **24**, toluene was used as the solvent. This change was necessary as the Vilarrasa reaction was to be performed in toluene. Previous literature used toluene as a solvent for these reactions as it is able to be heated to twice the temperature of THF based on their known boiling points. It was hypothesized that the higher temperature may help with regards to the microwave irradiated reaction by increasing the rate.[7] When switching over to compound **24**, optimization of the Staudinger reaction was necessary, as it was found previously that the Staudinger reaction was not completing in the short amount of time used, and at 2 hours

it seemed to be completed. Thus, the Staudinger reaction of **24** was allowed to run for 2 h, with samples of the reaction solution taken at the 20, 60, 100, and 120 min marks for IR spectroscopy to determine loss of the α-azido-phenylacetic acid methyl ester **24** from solution, indicating attachment to the resin. Figure 2 shows the absorbance at 2106 cm^{-1} of the four IR spectra transposed [Figure 3]. From the spectra the azide reaction completed by 100 min, and only miniscule amounts remained at 120 min. Thus, the optimal time for allowing the Staudinger reaction to complete was found to be 100 min.



The last step in the reaction series is the microwave irradiated Vilarrasa reaction [Scheme 6], utilizing benzoic acid to create the amide bonded product free in solution while leaving the triphenyl phosphine oxide compound attached to the resin. Multiple

combinations of reaction times, temperatures, solvents, and reactants were used [Table 1].

Reactant	[Benzoic Acid]	Solvent	Time	(°C)	% Yield
2-azido-acetic acid methyl ester **22**	1.5 equiv	THF	90 min	55	0
2-azido-acetic acid methyl ester **22**	1.5 equiv	THF	90 min	55	0
2-azido-acetic acid methyl ester **22**	1.0 equiv	Toluene	2 h	60	0
α-azido-phenylacetic acid methyl ester **24**	1.0 equiv	Toluene	2 h	100	0
α-azido-phenylacetic acid methyl ester **24**	1.0 equiv	Toluene	2 h	110	trace
α-azido-phenylacetic acid methyl ester **24**	1.0 equiv	Toluene	4 h	110	7%

Table 1. Microwave irradiated Vilarrasa coupling reaction conditions, in chronological order.

This phase of the study was performed on both azide compounds **22** and **24**. Initially, 2-azido-acetic acid methyl ester **22** was added to benzoic acid **12** to form the compound N-benzoyl-glycine methyl ester **25** [Scheme 6]. After the reaction was run for 90 min, the product was washed with NaOH to remove the excess benzoic acid. GCMS was then taken, but there were no compounds detected that corresponded to expected molecular weights. The reaction was thus run again using the same conditions. Thin-layer chromatography was performed on the reaction solution and co-spotted with benzoic acid and a sample of the organic layer after subsequent NaOH washes. The TLC was developed and R_f values of the mixture compounds were 0.85, 0.45, and 0.30. The compound corresponding to the R_f of 0.85 existed in every sample except the benzoic acid, and is believed to be an impurity from the resin. The 0.45 compound corresponded to benzoic acid, and the 0.30 R_f compound appeared only in the post-microwave solution.

This compound was assumed to be a product of interest. This compound's concentration faded until it no longer appeared in the TLC of the organic layer after subsequent washes. Thus, it was concluded that the product of the reaction, possibly N-benzoyl-glycine methyl ester **25**, was being lost during the aqueous wash due to its polarity. The microwave reaction was then run with toluene as the solvent at 60 ^{o}C to ensure similar reactivity in that solvent. A TLC developed in 5% MeOH in DCM was used to separate and identify the components of the reaction mixture. There were two compounds that were present after the reaction that were not there before – one with an R_f value of 0.47 and another with R_f equal to 0.34. These two compounds correspond to the benzoic acid and a possible product, respectively. Since the R_f of the product in toluene matched that of the product produced in THF, it was assumed that the reactions were performing similarly despite the solvent change.

At this point, the α-azido substituted methyl ester component was modified to make a product that would be more hydrophobic and thus more likely to remain in the organic layer for isolation. The starting material chosen was α-bromo-phenylacetic acid methyl ester **23**, which after reacting with the sodium azide, became α-azido-phenylacetic acid methyl ester **24.** The solvent utilized for study of the Staudinger and Vilarrasa reactions of **24** was toluene as previous work showed increased reactivity at higher temperatures.[7] For the creation of α-(benzoylamino)-phenylacetic acid methyl ester **26**, the microwave was heated to 100 ^{o}C for 1 hour. A TLC was performed on the

reaction mixture after heating the reaction in the microwave. Co-spotting was performed to determine the solution components. A compound assumed to be a product of the reaction was noted at an R_f of 0.44 (5% MeOH in DCM). Two other compounds of R_f values 0.50 and 0.53, because they appear in the reaction mixture before benzoic acid is added but after the Staudinger reaction, these compounds are hypothesized to be unintended side products. A possible side reaction may occur if water gets into the flask, which then may protonate the nitrogen of the resin bound methyl ester instead of benzoic acid, producing α-amino phenylacetic acid methyl ester **27** in solution, replacing the intended amide bond forming reaction.

All compounds from the product reaction mixture remained visible on the TLC throughout the successive washes, concluding that the product remained in the organic layer after subsequent washes. When the solvent was removed from the washed reaction mixture, both a solid and a liquid remained. The ^{1}H NMR spectral data was taken of both phases, and both revealed a large number of small peaks or impurities in the solution. Due to the large number of impurities in both ^{1}H NMR spectra of the solid and liquid phases, the identification of any one compound was not possible.

The microwave irradiated reaction was executed again in toluene, but at 110 ^{o}C in an attempt to form a larger amount of product for identification. The reaction produced both solid and liquid products again, which were analyzed by TLC to determine the compounds contained in the solid and liquid, and to establish the best way to isolate the

components. The developing solutions were 1% MeOH in DCM and 5% MeOH in DCM. In the 1% MeOH solution, the compound assumed to be the product **26** did not move at all, and remained on the baseline, and several other products showed up off of the baseline, with R_f values from 0.78 to 0.24 in samples of both the solid and liquid. In the 5% MeOH solution, a majority of the impurities had an R_f value of around 0.70 and the assumed product had an R_f value of 0.23 in samples of both solid and liquid. Both TLC plates were stained with ninhydrin, and both showed very deep brown staining of one compound of the product mixture (R_f approx. 0.0 in 1% MeOH, R_f of 0.23 in 5% MeOH), a likely indication of an amide bond. Ninhydrin also stained an area corresponding to impurities thought to come from the resin, possibly indicating the solution which contains the product is not fully devoid of triphenyl phosphine residue, leading to some purification issues. This being said, based on the above TLC data, there seemed to be no significant differences in content between the solid and liquid when looking at the TLC.

So, in order to separate the possible product from the rest of the components, column chromatography was carried out, with 1% MeOH in DCM as the first elution solvent, and then 5% MeOH in DCM as the second elution solvent. Twenty-eight 0.5 mL portions were separated, and all underwent TLC in 5% MeOH in DCM and stained with ninhydrin to identify the components. The first few fractions contained the resin residue, and were thus discarded. In the 10th-12th fractions, the ninhydrin deeply stained spots of R_f 0.25. Fractions 13-28 showed no significant staining at all. The 10th-12th fractions were then combined, an IR and ^{1}H NMR spectra were taken. Infrared spectroscopy revealed peaks at 1739, 2950, and 3050 cm^{-1}, which indicate a carbonyl (slightly off the range of

an amide), sp^3 hybridized carbons attached to hydrogen atoms, and sp^2 carbons linked to hydrogen atoms, respectively. The ^{1}H NMR spectra were taken, and a few impurity peaks were more noticeable in comparison to the previously taken ^{1}H NMR spectra of the solid and liquid portions previously examined. The spectra revealed a singlet peak at 3.70 and 5.3 ppm, and a multiplet at 7.37 ppm, corresponding to the hydrogens attached to the ester carbon, the alpha hydrogen of the carbonyl, and the aromatic rings, respectively. However other peaks were observed indicating the presence of an impurity. Based on this, it seems as though the intended product α-(benzoylamino)-phenylacetic acid methyl ester **26** was being formed in approximately 7% yield, but the side product α-amino phenylacetic acid methyl ester **27** might also be produced as well, most likely due to the presence of ambient water in the reaction. The sample of product isolated here was consumed in IR and ^{1}H NMR analysis and further identification or purification was not possible.

Previous literature on the subject of the Vilarrasa reaction use reaction times of around 24 hours in refluxing toluene, as this was found to increase yield of the reaction.[7] Thus, it was decided to execute the microwave reaction at 110 ^{o}C, but this time for 4 h to determine if yield would be increased, and show a correlation between reaction time and yield. If any correlation between reaction time and yield was observed, it can be assumed that increasing the reaction to even greater amounts of time shown in previous literature would further enhance the production of yield. A TLC was then performed on the

reaction mixture. A compound at R_f of 0.80 appeared, corresponding to impurities associated with the resin. A mixture with R_f of 0.34, which stained dark brown when placed in ninhydrin is presumably the amide bonded product **26**. At the time this thesis was being written, however, purification of the product was not complete.

Conclusion

In the S_N2 formation of the α-azido substituted methyl esters **21** and **23**, a significant decrease in yield was observed when moving from 2-bromo-acetic acid methyl ester **21** to α-bromo-phenylacetic acid **23** as the reagent. This difference in yield can be attributed to the presence of the benzene ring, which causes a much greater steric setback for the reaction, as the sodium azide has a much harder time attacking the brominated carbon at the correct angle for the S_N2 mechanism. One could hypothesize that this same steric hindrance can be carried over to the Vilarrasa portion of the reaction, but that data was not able to be utilized in this experiment due to the solubility of product **25** in the aqueous wash layer.

Thus, it can be inferred that the use of microwave irradiation with regards to the Staudinger-Vilarrasa reaction is creating the intended product based on the spectral data. However, because the product is in solution rather than on the resin, the product must be fairly hydrophobic so that it is not lost in the aqueous layer when washing with NaOH.

The impurities in the final product may be related to the resin impurities and the presence of ambient water in the reaction solution. The presence of water in the reaction may lead to amine formation rather than creating the desired amide bond. Since the reaction is normally done on the 24 h time scale, our low yields may be attributed to the fact that our time scale for the microwave-irradiated Staudinger-Vilarrasa coupling is 1 to

4 h, and not yet optimized. This being said, more research utilizing microwave irradiation with the use of a solid-phase in this area of peptide synthesis is necessary, as the intended product was believed to be in our final solution utilizing an easier and less toxic procedure. Optimization of the reaction is possible, and just needs to be more thoroughly investigated under longer time periods and under more controlled conditions.

General Methods

All reagents were purchased from Sigma-Aldrich or Acros and used without further purification. The resin was purchased from Nova Biochem. All Infrared spectral data were taken using Nicolet Avatar 300-FT-IR. All ^{1}H NMR spectroscopy was taken on a 250 MHz Bruker AVANCE DMX Spectrometer. The Vilarrasa coupling reactions were irradiated using a Discover® CEM Microwave. All TLC plates used were of Polygram® silica gel, made by Macherey-Nagel.

Experimental Methods

Preparation of Azide Compounds 22 and 24 for Staudinger reaction. 2-Bromo-acetic acid methyl ester **21** or α-bromo-phenylacetic acid methyl ester **23** (10 mmol) and 18-Crown-6 (1 mmol) were added to sodium azide (25 mmol) in acetone (5 mL). The mixture was stirred for 4 h at room temperature. Reaction was diluted with water (5 mL) and extracted three times with ether (5 mL), then dried with $MgSO_4$, and then filtered through suction filtration. The solvent was removed in vacuo. Reaction isolated a yellow, oily liquid **22** and a brown, oily liquid **24**.

2-azido-acetic acid methyl ester (22): (from 2-bromo-acetic acid methyl ester **21**) 98% yield. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 3.90 (s, 2H, N_3-CH_2-C-), 3.81 (s, 3H, -O-CH_3) ; IR (cm^{-1}): 2950, 2108, 1748.

α-azido-phenylacetic acid methyl ester (24): (from α-bromo-phenylacetic acid methyl ester **23**) 74% yield. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 7.37 (m, 5H, Ar), 4.9 (s, 1H, N_3-*CH*-C-), 3.74 (s, 3H, -O-CH_3); IR (cm^{-1}): 3025, 2950, 2112, 1740.

Optimization of Staudinger Reaction: The triphenylphosphine resin **10** (1.1 equiv. per resin loading) was suspended in 5 mL of THF or toluene for 5 min. Compound **22** or **24** (0.5 mmol) was added and stirred for 100 min at room temperature. Thin-layer chromatography and IR spectroscopy was used to measure the progress of the reaction. The elution conditions were 5% MeOH in DCM. The TLC plates were stained with ninhydrin or phosphomolybdic acid to characterize reaction progression.

Combined Staudinger-Vilarrasa Reaction: Compound **22** or **24** (0.5 mmol) was added to a triphenylphosphine resin **10** (1.1 equiv. per resin loading), which was soaked in solvent (5 mL) for 5 min and then stirred for 100 min at room temperature. Benzoic acid (0.5 mmol) was then added and the reaction placed in a microwave reactor (times and temperatures vary, see results section). Thin-layer chromatography was then performed on the product and developed in 5% MeOH in DCM. The reaction solution was then washed four times with 1 M NaOH (5 mL each wash) to remove excess benzoic acid. Product then washed with Et_2O (10 mL) and dried. ^{1}H NMR was then taken.

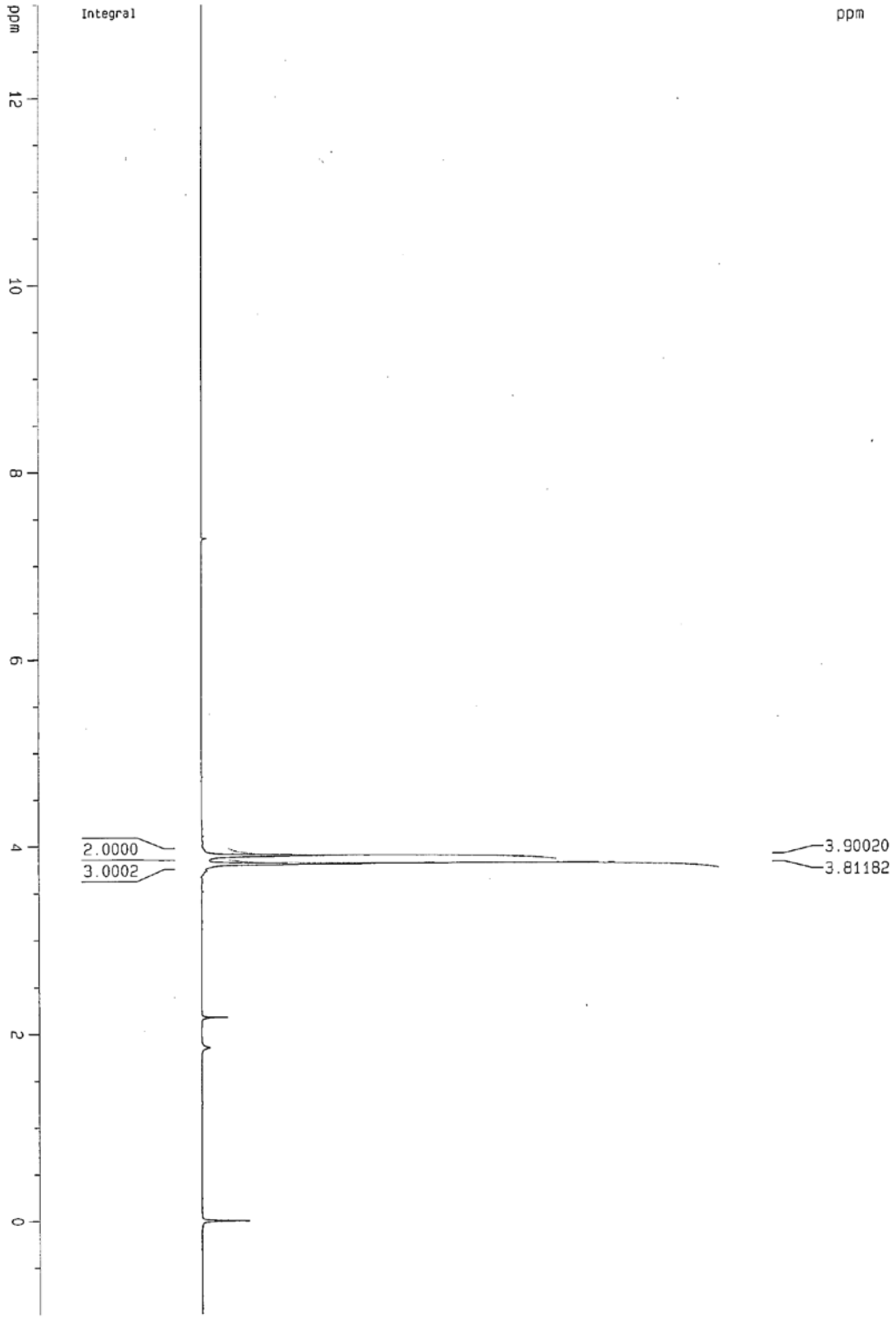
N-benzoyl-glycine methyl ester (25): GCMS revealed no peaks corresponding to possible product molecular weights. ^{1}H NMR revealed no relevant peaks in their spectra.

α-(benzoylamino)-phenylacetic acid methyl ester (26): 7.9% yield. ^{1}H NMR (250

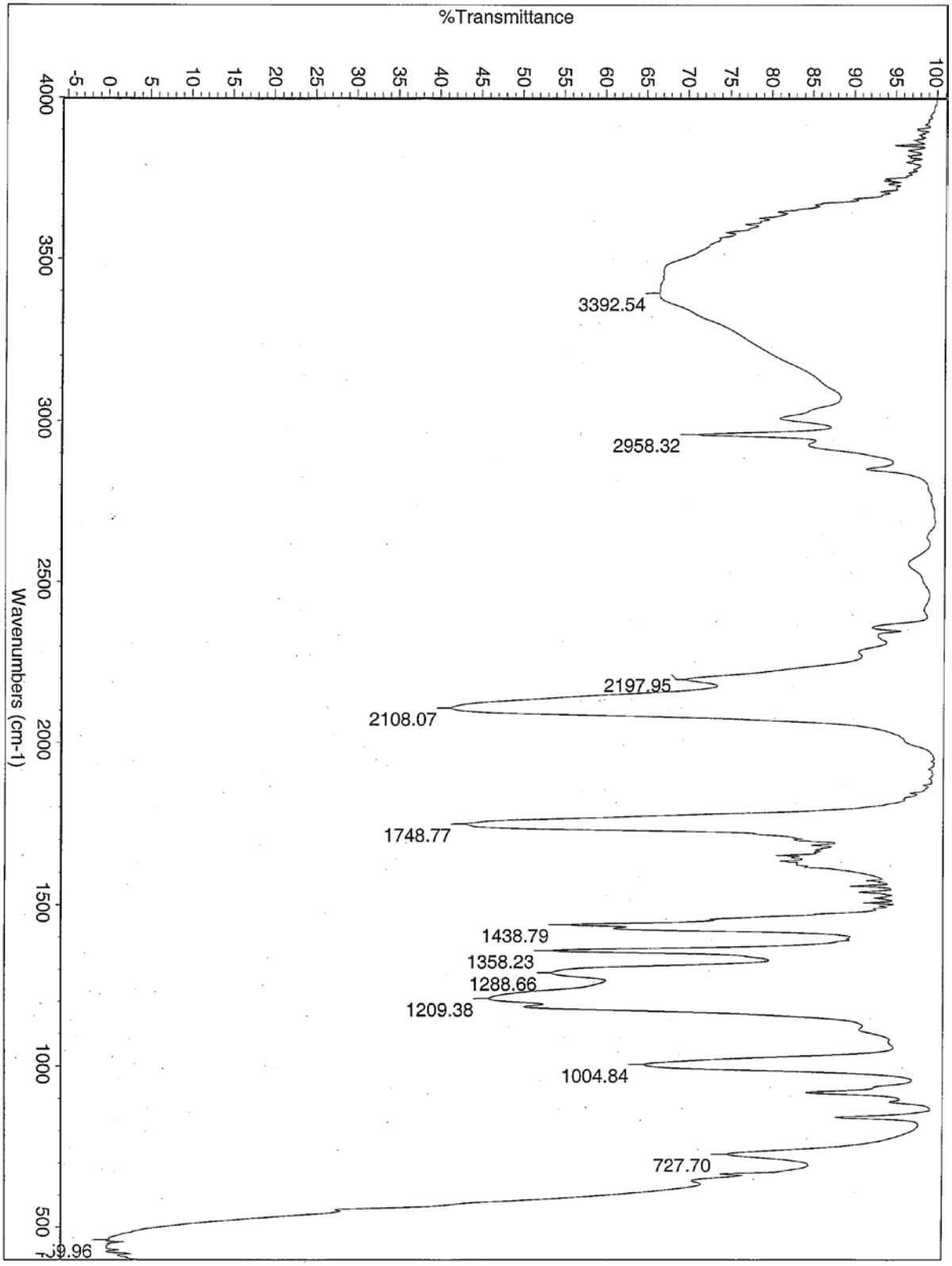
MHz, $CDCl_3$, δ): 7.37 (m, 5H, Ar), 5.3 (s, 1H, NH-CH-C-), 3.70 (s, 3H, -O-CH_3), Hexane and unidentified impurities; IR (cm^{-1}): 3050, 2950, 1739.

Appendix A: Spectral Data

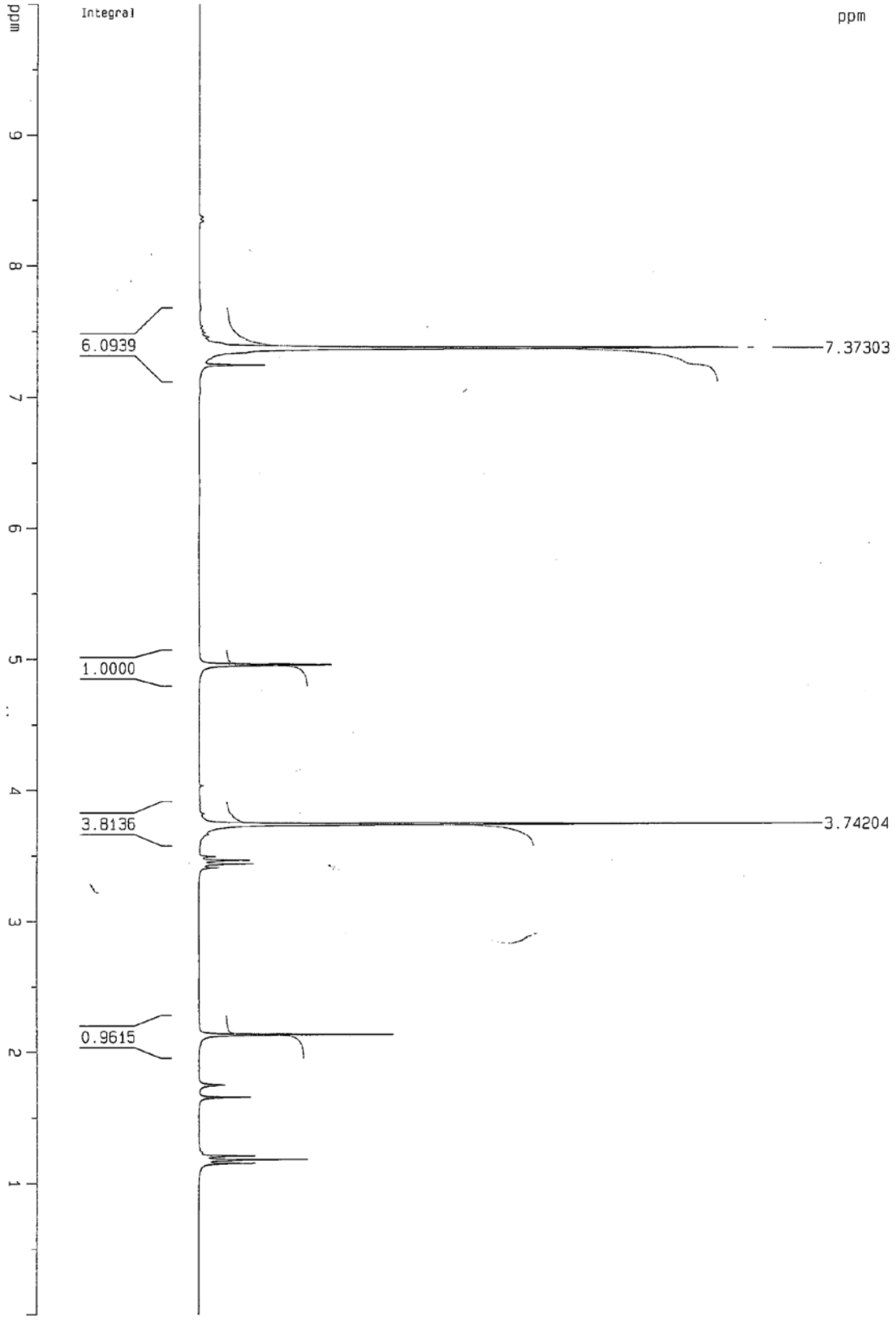
22 ^{1}H NMR



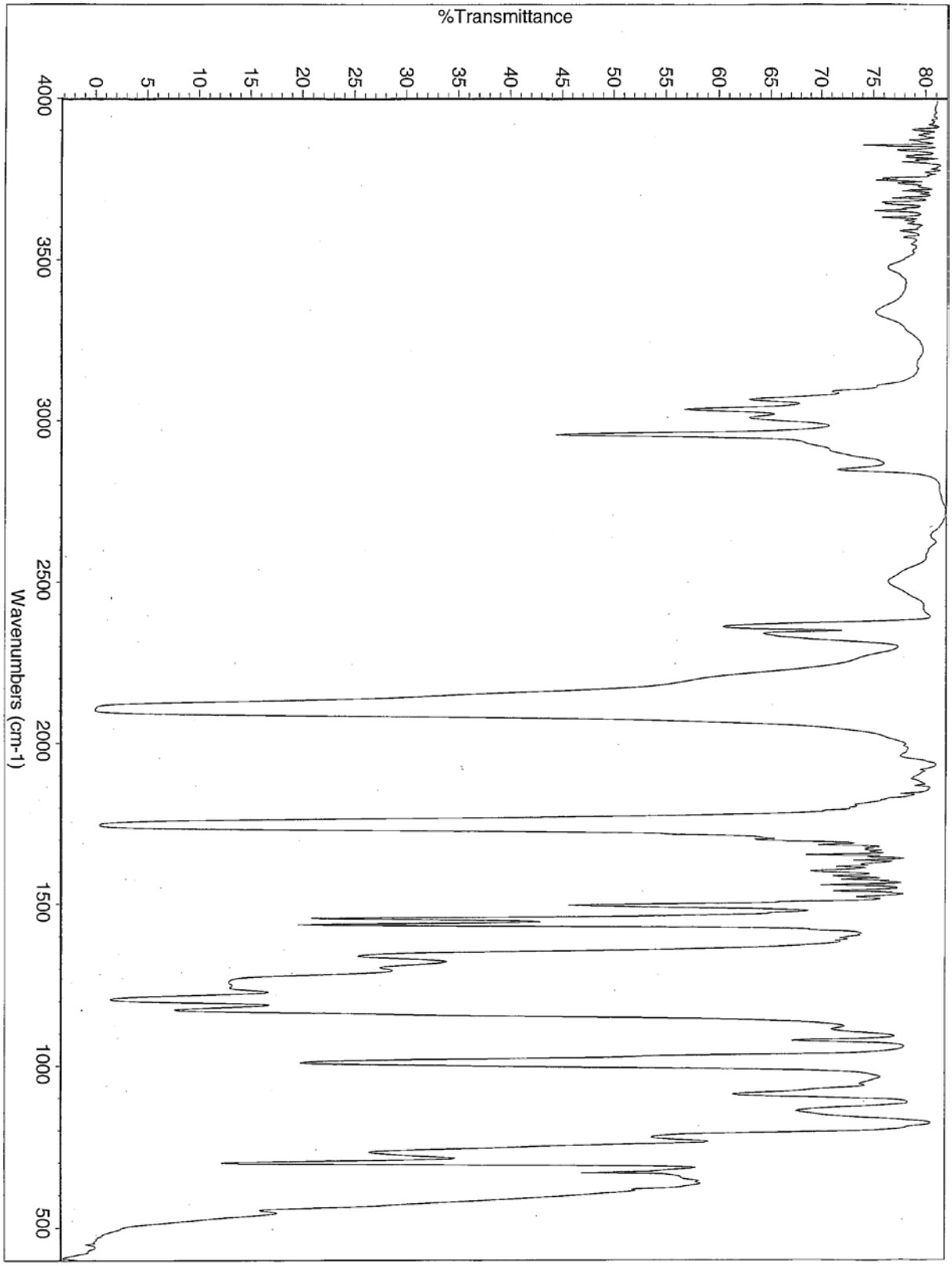
22 IR Spectroscopy with Residual H_2O



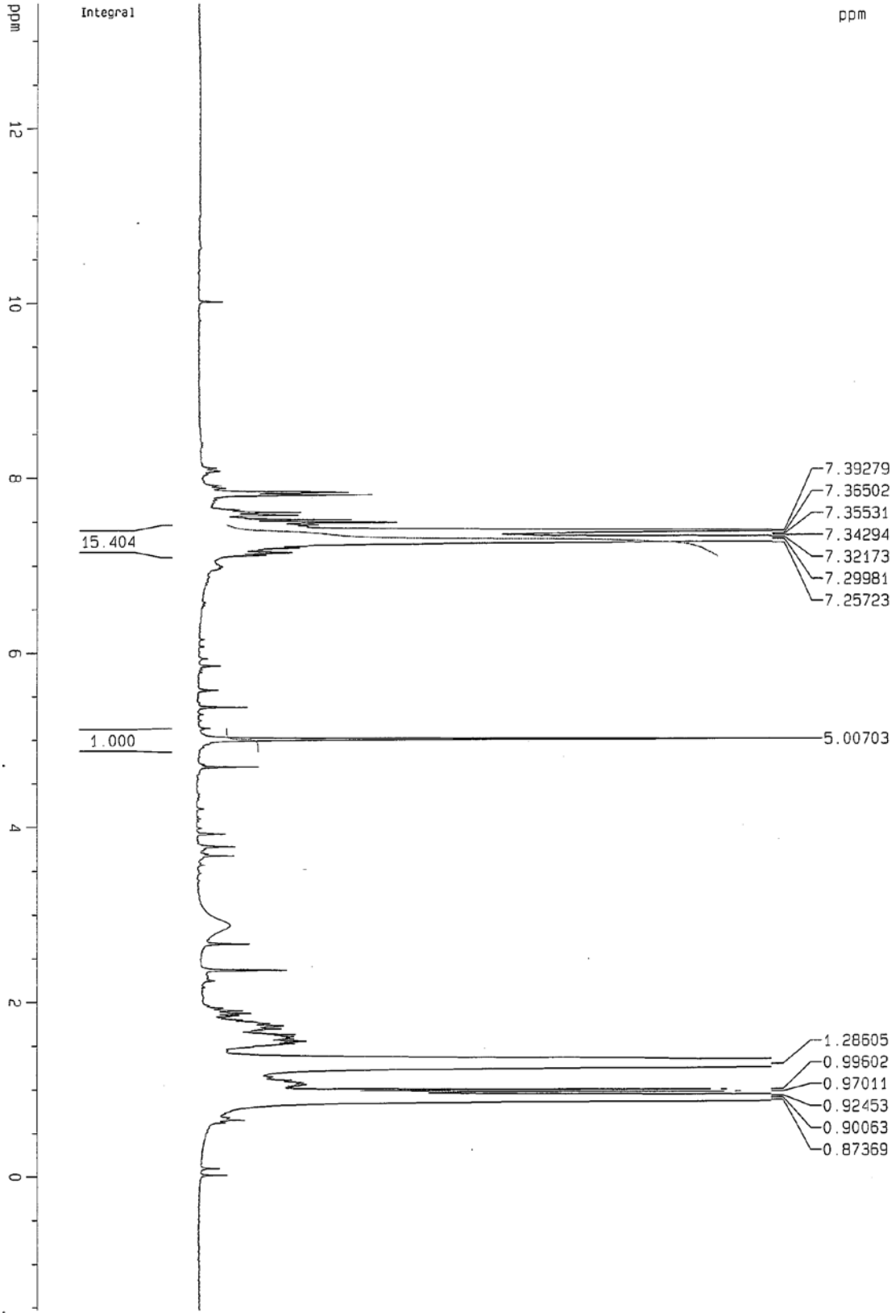
24 ^{1}H NMR


ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
6.0939
1.0000
3.8136
0.9615
7.37303
3.74204

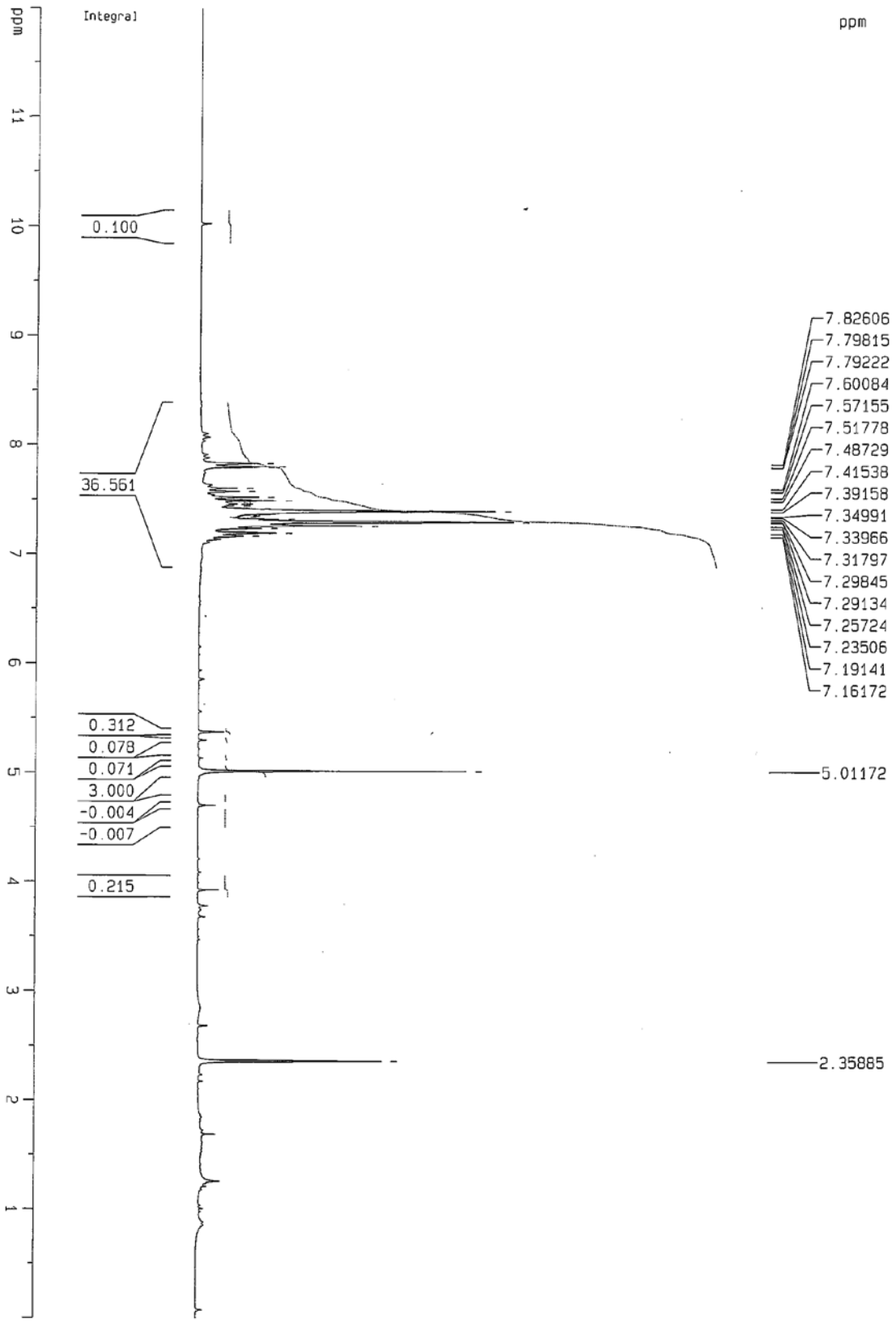
24 IR Spectroscopy



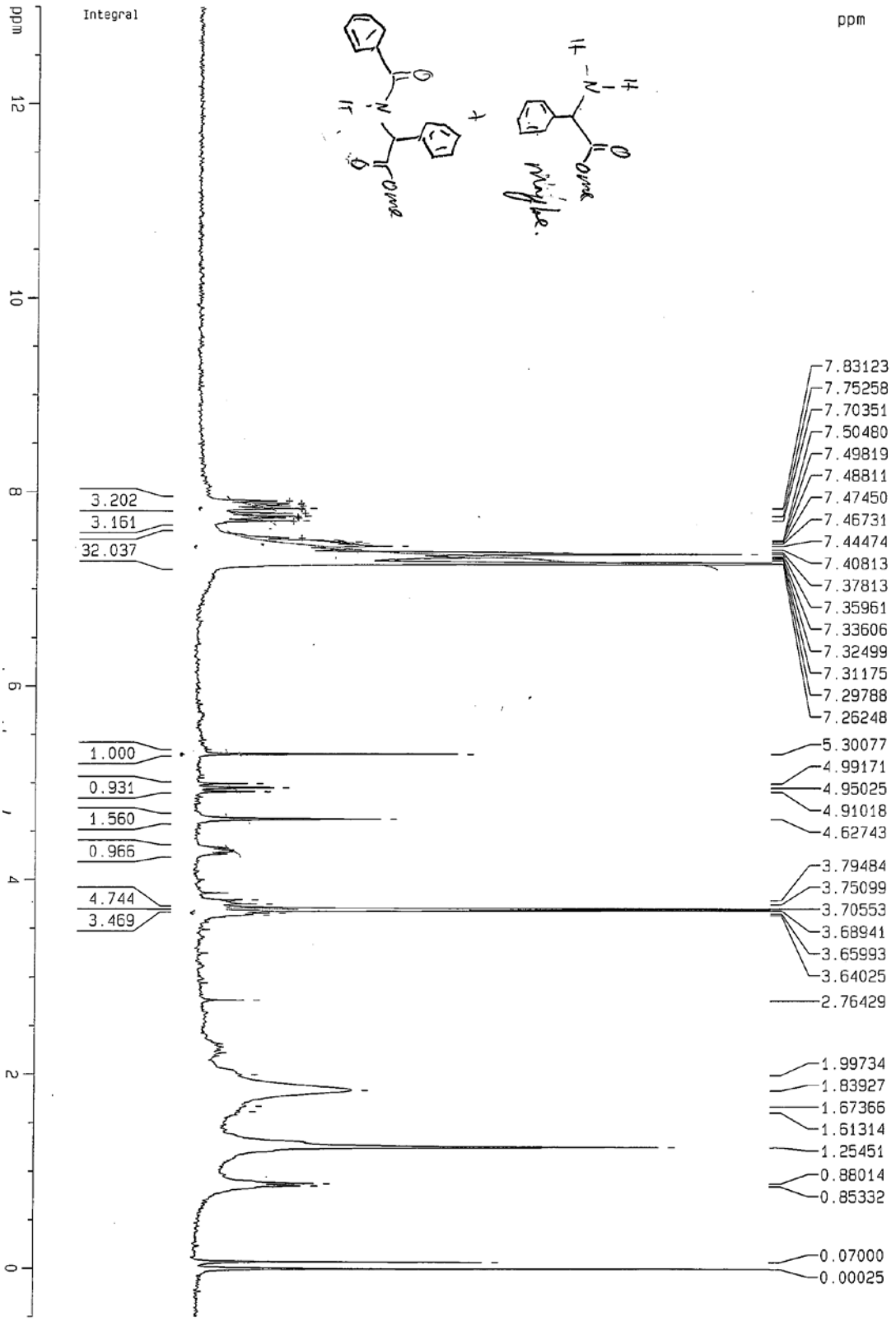
26 ^{1}H NMR Solid Portion



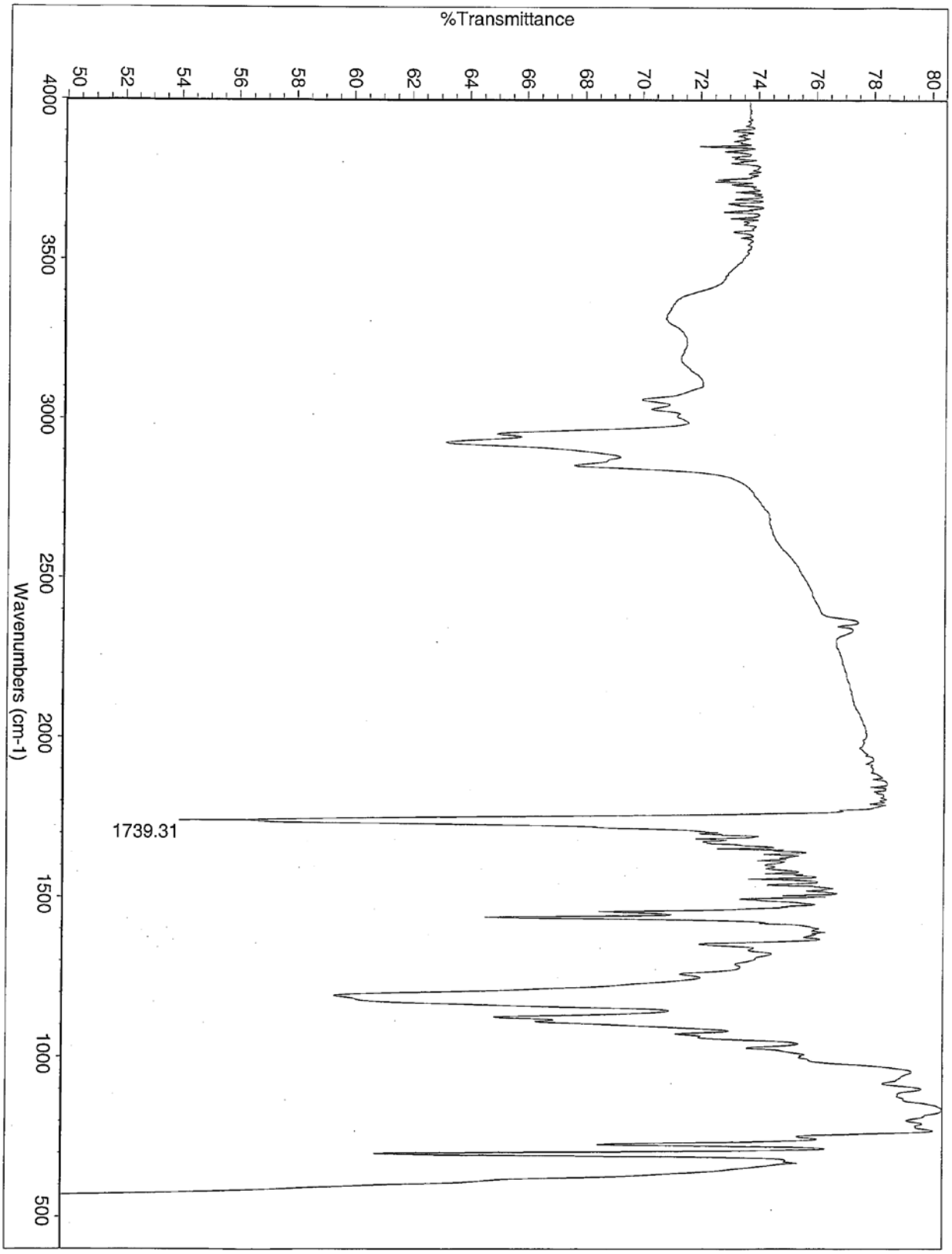
26 ^{1}H NMR Liquid Portion



26 ^{1}H NMR After Column Chromatography (Fractions 10-12)



26 IR Spectroscopy After Column Chromotography (Fractions 10-12)



[1] Albericio, F.; Chinchilla, R.; Dodsworth, D.J.; Najera, C. *J. Org. Prep. and Proc. Intl*. **2001**, *33:3*, 203-303.
[2] Food and Drug Administration. *Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use*; DHHS Vol. 65, Pub. Number 182/21CFRPart201. U.S. Department of Health and Human Services, Government Printing Office: Washington, D.C., 2000; 56511-56518
[3] Center for Substance Abuse Research: Maryland University. Benzodiazepines. http://www.cesar.umd.edu/cesar /drugs/benzos.asp (accessed 3/3/08).
[4] Gawne, G.; Kenner, G.W.; Sheppard R.C. *J. Amer. Chem. Soc*.**1969**, 91, 5669-5671.
[5] Gololobov, Y.G.; Kasukhin, L.F.; *Tetrahedron Letters*. **1992**, *48:8*, 1353-1406.
[6] Caddick, S. *Tetrahedron Letters*. **1995**, *51:38*, 10403-10432.
[7] Garcia, J.; Felix, U.; Vilarrasa, J. *Tetrahedron Letters*. **1984**, *25*, 4841-4844.
[8] Baghurst, D.R.; Mingos, D.M.P.; *J. Chem. Soc. Chem. Comm.* **1992**, 674.
[9] Sechi, M.; Angotzi, G.; Dallochio, R.; Dessi, A.; Carta, F.; Sannia, L.; Mariani, A.; Fiori, S.; Sanchez, T.; Movsessian, L.; Plasencia, C.; Neamati, N. *Antiviral Chem. & Chemotherapy*. **2004**, *15*, 67-81.