Developing an Ortho-metalation Organic Synthesis Laboratory Activity with Applications to Agriculture

CHEM 4480

Directed Studies

By
Connor Johnson

Supervisor:
Dr. Jessica Allingham

Co-Supervisor:
Dr. Bruno Cinel

ABSTRACT

The *ortho* directed metalation of tertiary amides proves useful in the production of various herbicides to protect a variety of plants. The purpose of this project was to react several different secondary amines with o-toluoyl chloride followed by an *ortho*-metalation reaction to create different herbicides. The impact of changing secondary amines on yield and reaction success was investigated. Purification techniques such as Kugelrohr distillation and column chromatography were employed. Product characterization was carried out using infrared spectroscopy and nuclear magnetic resonance. Four tertiary benzamides were synthesized in this project, with yields varying from 29.47-95.87%. The synthesis of the benzamides is supported by NMR and IR spectra. This work is being used to create an upper-level organic chemistry laboratory activity for fourth-year students.

INTRODUCTION

Dr. Norman Reed synthesized an *ortho*-metalated analogue in Dr. Victor Snieckus' laboratory[1a] and was published in a large research project[1b]. The agricultural conglomerate Monsanto tested these products for antifungal activity, discovering that it was effective at killing a soil fungus known as *Gaeumannomyces graminis*, protecting crops from further attack[2]. With this discovery, Monsanto researched further into these products to find the most effective fungicide that wasn't already patented. They came up with the discovery of 4,5-dimethyl-*N*-(2-propenyl)-2-trimethylsilyl-3-thiophenecarboxamide, which they termed "Silthiofam". Silthiofam was then marketed and sold under the name "Latitude" in 1999[2].

Dr. Reed wanted to further research antifungal compounds and came up with a structure that attaches a secondary amine to the chlorine of an *o*-toluoyl chloride and a trimethylsilyl (TMS) group attached to the benzylic carbon. He recognizes that the steric hindrance caused by the large TMS group, and the tertiary amide were very similar to the one in Silthiofam. This will cause slowing of the free bond rotation for the carbonyl carbon bond to the benzene, inhibiting the targeted fungi[1]. The main difference with the use of *o*-toluoyl chloride in this instance is that the addition of a methyl group in the *ortho* position to be metalated can cause drastic changes in the activity of chemicals, potentially making it stronger or more effective as a fungicide. Additionally, adding the methyl group can increase the steric hindrance of the molecule, slowing the free bond rotation even further

Directed *ortho*-metalation reactions describe a way to coordinate a metal group at the benzylic position. These directed metalation reactions are regioselective due to the amide directing group, promoting the lithiation of the benzyl carbon[3]. It promotes directed lateral lithiation due to the methyl group having more acidic hydrogens than the other hydrogens in the molecule since the amide is an electron-withdrawing group and coordinates with the lithium. Deprotonation is thus promoted at the benzyl carbon, allowing for lithiation and formation of a nucleophilic carbanion to occur. The carbanion then allows for the easy addition of a silyl group to the benzylic position, creating the final silyl product. The discovery of directed lateral lithiation makes it a great way to synthesize at an otherwise difficult synthesis region.

The continuation of this research came as a fourth-year lab activity, where students synthesized various benzamide intermediates to be silylated with TMS. Dr. Reed did not proceed with this research further than conducting a lab activity every year, so some time was taken to formally synthesize and characterize the possible silylated products for future agricultural studies. Throughout the study, four benzamide intermediates were created and characterized by mixing *o*-toluoyl chloride with different secondary amines: diisopropylamine, diethylamine, di-*sec*-butylamine, and ethylbutylamine. Furthermore, a new proposed laboratory manual will be created for the lab activity as there are some steps which could be clarified and improved upon.

Additionally, this work looks to publish the procedure and characterization data so the experiment can be used at other institutions. Directed *ortho*-metalation reactions and directed

lateral metalation are not learned in undergraduate organic chemistry studies but play an important role in synthetic organic chemistry. Publishing this work would potentially provide many more students the opportunity to experience and practice this important synthesis technique. This work is done as an upper-level lab activity at Thompson Rivers University, but it could be great at other institutions that have a lack of upper-level organic chemistry labs. The findings will be published in a chemistry education journal, allowing open access to other institutions to use this work as the basis for expanding organic chemistry knowledge.

Methods

The reactions are carried out in two parts shown in Figures 1 and 2 below.

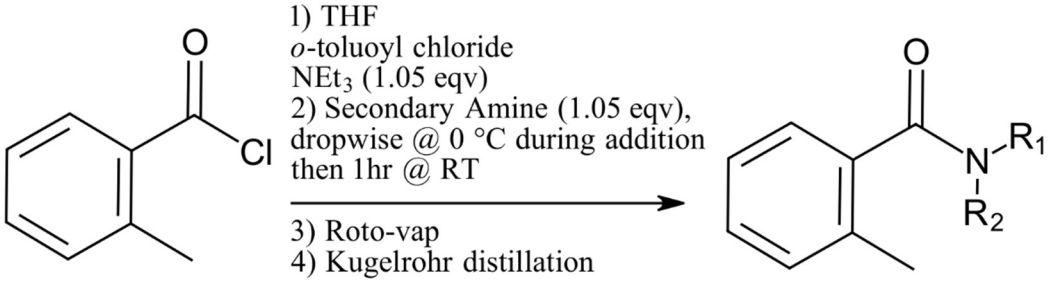

Figure 1. Part 1: Synthesis of a tertiary amide intermediate for part 2.

The reaction in part 1 is an SN_2 reaction where the secondary amine attacks the *o*-toluoyl chloride. It also utilizes triethylamine to help drive the reaction forward according to Le Chatelier's principle by removing the chloride as a precipitate, favouring the formation of more product.

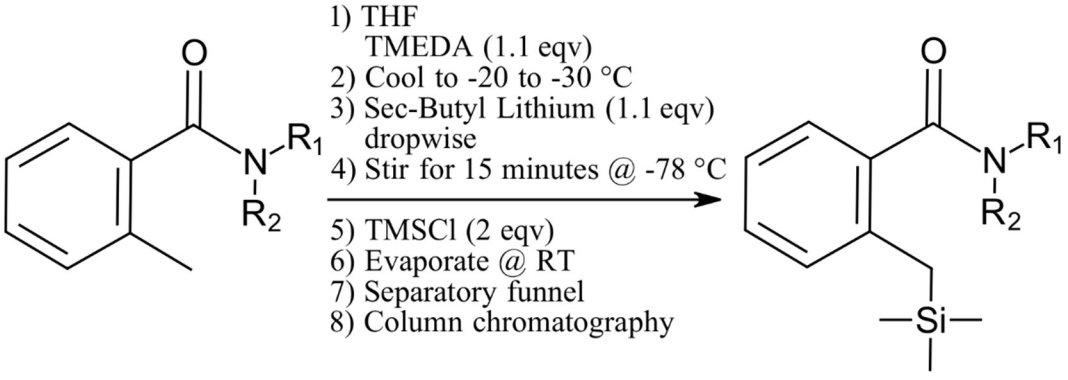

Figure 2. Part 2: Benzylic lithiation and electrophile reaction.

The amide intermediate in part 2 acts as a directing group for the lateral lithiation of the benzylic carbon. The *sec*-butyl lithium is a strong base that deprotonates the benzylic carbon, creating a carbanion. It will then act as a nucleophile, promoting an SN_2 reaction where the benzylic carbanion attacks the trimethylsilyl chloride, creating the final silylated product.

The rotary evaporator (rotovap) was used to remove any excess solvent throughout the experiment to ensure purity of intermediates and final product. This is crucial when determining the purity and mass of the products, as well as when obtaining either infrared (IR) or nuclear magnetic resonance (NMR) spectra. While it is possible to obtain spectra of the product with solvent and discern the solvent peaks, it does not take long to remove solvent by rotovap and aids in the sensitive detection of the product by removing it.

When distilling the crude product in part 1 of the procedure, a small-scale distillation must occur to extract the desired product from the remaining materials present in the round-bottomed flask (RBF). The chosen apparatus used for the distillation is a Kugelrohr as it can distill small volumes at high temperatures. The RBF is placed inside of the heating chamber, with the Kugelrohr flask is attached to the RBF on the outside of the heating chamber in an ice bath to remove the distillate. The glassware is rotated by an external motor which is attached to the glassware by rubber tubing with a very strong vacuum running through it. The vacuum for distillation is under ~ 75-100 mTorr (~ 0.000010 – 0.00010 atm) of pressure per distillation, greatly reducing the boiling point of the contents in the RBF for distillation. The temperature inside the heating chamber was taken, however the thermometer used is not precise and had

latency issues for accurate temperature readings, so a different method to determine the temperature inside the RBF will be used moving forward. All distilled products are removed from the Kugelrohr flask with acetone and rotovapped to remove the acetone, maximizing potential yield.

Figure 3. Kugelrohr apparatus. The RBF with the product is placed in the heating chamber (left) and cooled in the Kugelrohr flask in an ice bath. The motor (right) spins the RBF and Kugelrohr flask to maximize the surface area for distilling.

In part 2, the final product is purified through the use of column chromatography. The column was filled with sand and silica with a cotton plug to prevent the solids from falling out. This was used to separate the product based on the polarity of the compound added to it. A solvent was created using a 50:50 mixture of ethyl acetate and hexanes to carry the compound through the silica. The solvent mixture was allowed to escape from the bottom of the column

and individual samples were removed in test tubes, and thin-layer chromatography was run to identify which samples contained the desired product. The test tubes determined to contain the desired product were mixed in an RBF and rotovapped for a final time for characterization.

For characterization, ^{1}H NMR was taken of the products in both part 1 and 2 and compared to each other to confirm the presence of a trimethylsilyl group in the final product. The NMR is also beneficial to make sure that the reaction occurred at the desired location based on the hydrogen splitting exhibited. On top of taking NMR of the products, IR spectra were obtained as well. This was to further verify that the correct product was synthesized based on the peaks seen on the spectra that correspond to certain functional groups. Melting points were determined using a Mel-Temp apparatus if the product was solid at room temperature – liquid products were deemed liquid at room temperature, with a melting point < 25 °C. Lastly, masses were taken to find the percent yields of all products.

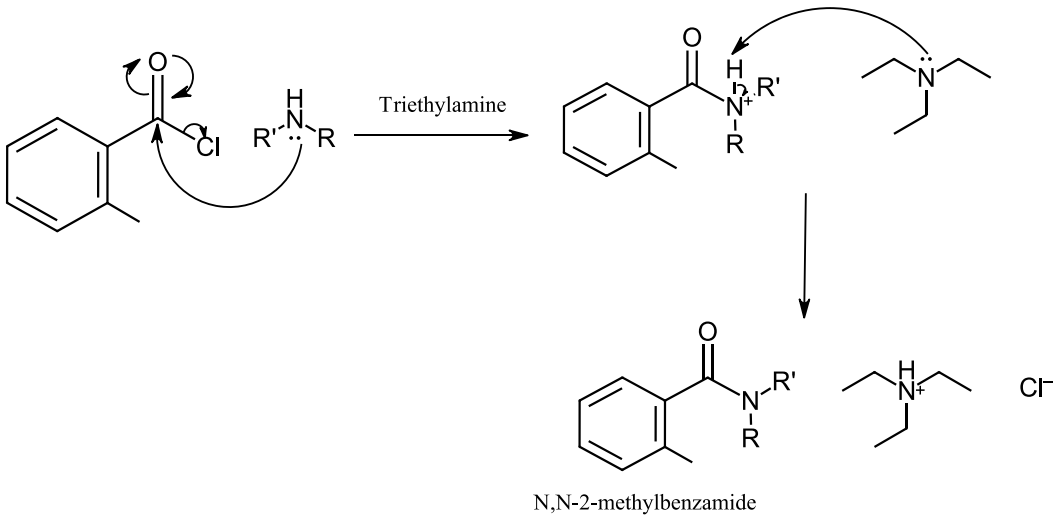

Figure 4. Synthesis mechanism of tertiary benzamide intermediates in part 1.

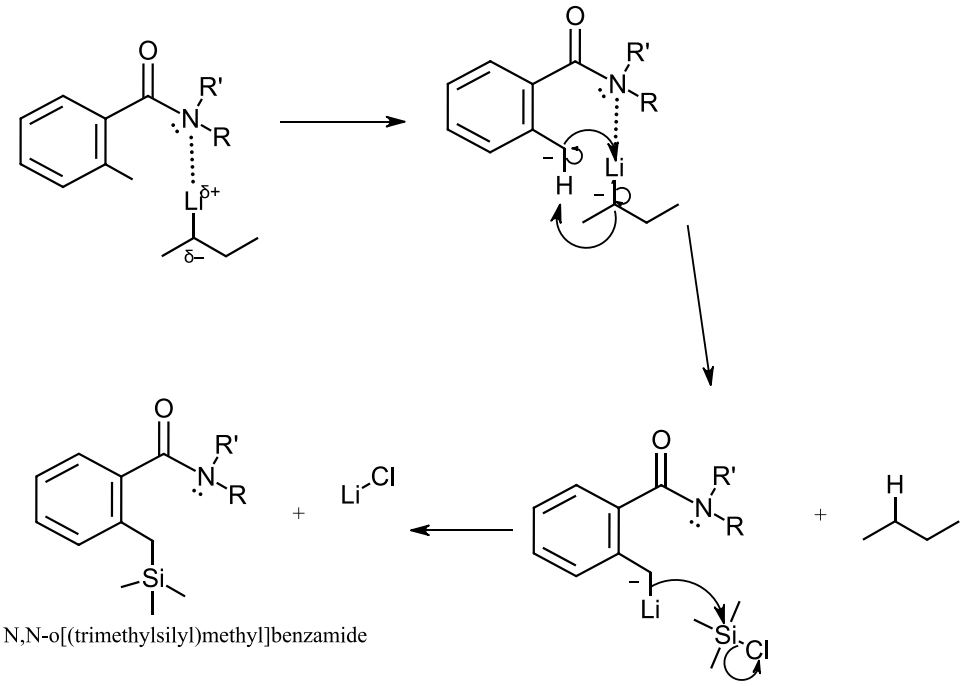

Figure 5. Synthesis mechanism of the lateral metalated product in part 2.

Results

Table 1. Summary of synthesized tertiary benzamides.

Product name	Mass (g)	Percent Yield	Melting Point (°C)
N,N-diethyl-2-methylbenzamide	3.1282	77.88%	< 25
N,N-diisopropyl-2-methylbenzamide	1.3635	29.47%	80-84
N,N-disec-butyl-2-methylbenzamide	3.8412	73.94%	< 25
N-butyl-N-ethyl-2-methylbenzamide	4.4154	95.87%	< 25

N,N-diethyl-2-methylbenzamide

Approximately 1.61 g of diethylamine was added to 2.75 mL of *o*-toluoyl chloride and 3.08 mL of triethylamine to create N,N-diethyl-2-methylbenzamide, creating a clear colourless oil with a grape odour with a 77.88% yield.

Kugelrohr conditions: Pressure = 100 mTorr

Temperature = 82.2 °C

Table 2. IR analysis of N,N-diethyl-2-methylbenzamide.

Experimental Frequency (cm^{-1})	Appearance	Bond
2972.64	Weak, sharp	C-H
1627.98 – 1714.85	Strong, sharp	C=O
1424.40	Medium, sharp	C=C, aromatic
1291.83	Medium, sharp	C-N

Table 3. NMR analysis of N,N-diethyl-2-methylbenzamide.

Peak Label	Chemical Shift (ppm)	Integration/Ratio	Splitting	Identity of Signal
A	0.95-0.98	3H	Triplet	$-CH_2-CH_3$
B	1.19-1.22	3H	Triplet	$-CH_2-CH_3$
C	2.21-2.25	3H	Singlet	$-Ar-CH_3$
D	3.04-3.07	2H	Quartet	$-CH_2-CH_3$
E	3.35-3.40	2H	Quartet	$-CH_2-CH_3$
F	7.09-7.21	4H	Multiplet	-Ar-H

N,N-diisopropyl-2-methylbenzamide

Approximately 1.92 g of diisopropylamine was added to 2.75 mL of *o*-toluoyl chloride and 3.08 mL of triethylamine to create N,N-diisopropyl-2-methylbenzamide, creating a colourless crystallized solid with a grape odour with a 29.47% yield.

Kugelrohr conditions: Not recorded

Melting point = 80-84 °C

Table 4. IR analysis of N,N-diisopropyl-2-methylbenzamide.

Experimental Frequency (cm^{-1})	Appearance	Bond
2968.80	Weak, sharp	C-H
1616.24 - 1712.56	Strong, sharp	C=O
1442.19	Medium, sharp	C=C, aromatic
1341.72	Strong, sharp	C-N

Table 5. NMR analysis of N,N-diisopropyl-2-methylbenzamide.

Peak Label	Chemical Shift (ppm)	Integration/Ratio	Splitting	Identity of Signal
A	0.96-1.02	6H	Doublet of Doublets	-CH-CH_3
B	1.45-1.46	6H	Doublet of Doublets	-CH-CH_3
C	2.17-2.22	3H	Singlet	-Ar-CH_3
D	3.41-3.43	1H	Septet	CH_3-CH-CH_3
E	3.54-3.56	1H	Septet	CH_3-CH-CH_3
F	6.97-7.13	4H	Multiplet	-Ar-H

N,N-disec-butyl-2-methylbenzamide

Approximately 2.85 g of di-sec-butylamine was added to 2.75 mL of *o*-toluoyl chloride and 3.08 mL of triethylamine to create N,N-disec-butyl-2-methylbenzamide, creating a clear colourless oil with a dusty/earthy fruit odour with a 73.94% yield.

Kugelrohr conditions: Pressure = 84 mTorr

Temperature = 146 °C

Table 6. IR analysis of N,N-disec-butyl-2-methylbenzamide.

Experimental Frequency (cm^{-1})	Appearance	Bond
2968.77	Weak, sharp	C-H
1627.62	Strong, sharp	C=O
1431.78	Medium, sharp	C=C, aromatic
1330.07	Medium, sharp	C-N

Table 7. NMR analysis of N,N-disec-butyl-2-methylbenzamide.

Peak Label	Chemical Shift (ppm)	Integration/ Ratio	Splitting	Identity of Signal
A	0.77-0.79	3H	Triplet	$-CH_2-CH_3$
B	0.97	3H	Triplet	$-CH_2-CH_3$
C	1.10	3H	Doublet	$-CH-CH_3$
D	1.37-1.39	2H	Multiplet	$-CH-CH_2-CH_3$
E	1.55	3H	Doublet	$-CH-CH_3$
F	1.85-1.90	2H	Multiplet	$-CH-CH_2-CH_3$
G	2.33	3H	Singlet	$-Ar-CH_3$
H	3.10	1H	Multiplet	$CH_3-CH-CH_2$
I	3.37-3.40	1H	Multiplet	$CH_3-CH-CH_2$
J	7.10-7.18	4H	Multiplet	Benzene

N-butyl-N-ethyl-2-methylbenzamide

Approximately 2.23 g of ethylbutylamine was added to 2.75 mL of *o*-toluoyl chloride and 3.08 mL of triethylamine to create N-butyl-N-ethyl-2-methylbenzamide, creating a clear colourless oil with a dusty/earthy odour with a 95.87% yield.

Kugelrohr conditions: Pressure = 75 mTorr

Temperature = 134 °C

Table 8. IR analysis of N-butyl-N-ethyl-2-methylbenzamide.

Experimental Frequency (cm^{-1})	Appearance	Bond
2872.57 - 2959.60	Weak, sharp	C-H
1630.63 - 1715.21	Strong, sharp	C=O
1422.56	Medium, sharp	C=C, aromatic
1292.65	Medium, sharp	C-N

Table 9. NMR analysis of N-butyl-N-ethyl-2-methylbenzamide.

Peak Label	Chemical Shift (ppm)	Integration/ Ratio	Splitting	Identity of Signal
A	0.76	2H	Multiplet	$-CH_2-CH_2-CH_3$
B	0.96-1.02	3H	Multiplet	$-CH_2-CH_3$
C	1.24-1.27	2H	Doublet of Triplets	$-CH_2-CH_2-CH_2$
D	1.38-1.42	3H	Triplet	$-CH_2-CH_3$
E	2.27	3H	Singlet	$-Ar-CH_3$
F	3.04	2H	Triplet	$-CH_2-CH_2-$
G	3.11	2H	Triplet	$-CH_2-CH_3$
H	7.14-7.22	4H	Multiplet	-Ar-H

Discussion

Four tertiary benzamides were synthesized throughout the study with yields ranging from 29.47% to 95.87%. Unfortunately, no lateral-metalated analogues were synthesized due to an experimental error, where the concentration of the *sec*-butyl lithium was misread on the reagent bottle. This led to not enough being used, so no lithiation occurred to allow for the addition of trimethylsilyl chloride. This was discovered when comparing the NMR spectra of the assumed lateral-metalated analogues to the tertiary benzamide spectra as they look identical (see Figures 12 and 13, the two different peaks that can be seen between the two spectra for N-butyl-N-ethyl-2-methylbenzamide corresponds to some ethyl acetate being present in the final product). The actual amount of *sec*-butyl lithium used was approximately one-fifth of the required amount needed to successfully deprotonate the benzylic carbon, preventing the reaction from fully taking place.

In the future, more time will be spent on part 2 of the reaction to try to have a successful directed *ortho*-lithiation of our benzamide intermediates. To ensure this does not happen again, the amount of *sec*-butyl lithium used will increase to 2 equivalents from the 1.1 suggested in Figure 2. Some other works with lateral lithiation have been shown to use 2 to 5 equivalents of either *sec*-butyl lithium or *tert*-butyl lithium with high yields[4], so an increase will not only give a better yield but also drive the reaction further to completion[5]. Additionally, the benzamide intermediates will have to be remade to optimize the percent yield and validate the

procedure for publishing in the future. From here, the lab procedure will be updated to clarify steps for future students and include the optimized conditions as the current one requires some clarification on steps that led to errors throughout the project, requiring some compounds to be remade. Lastly, the lateral-lithiated products will be tested for bioactivity as similar other structures have shown anti-fungal activity in wheat[2].

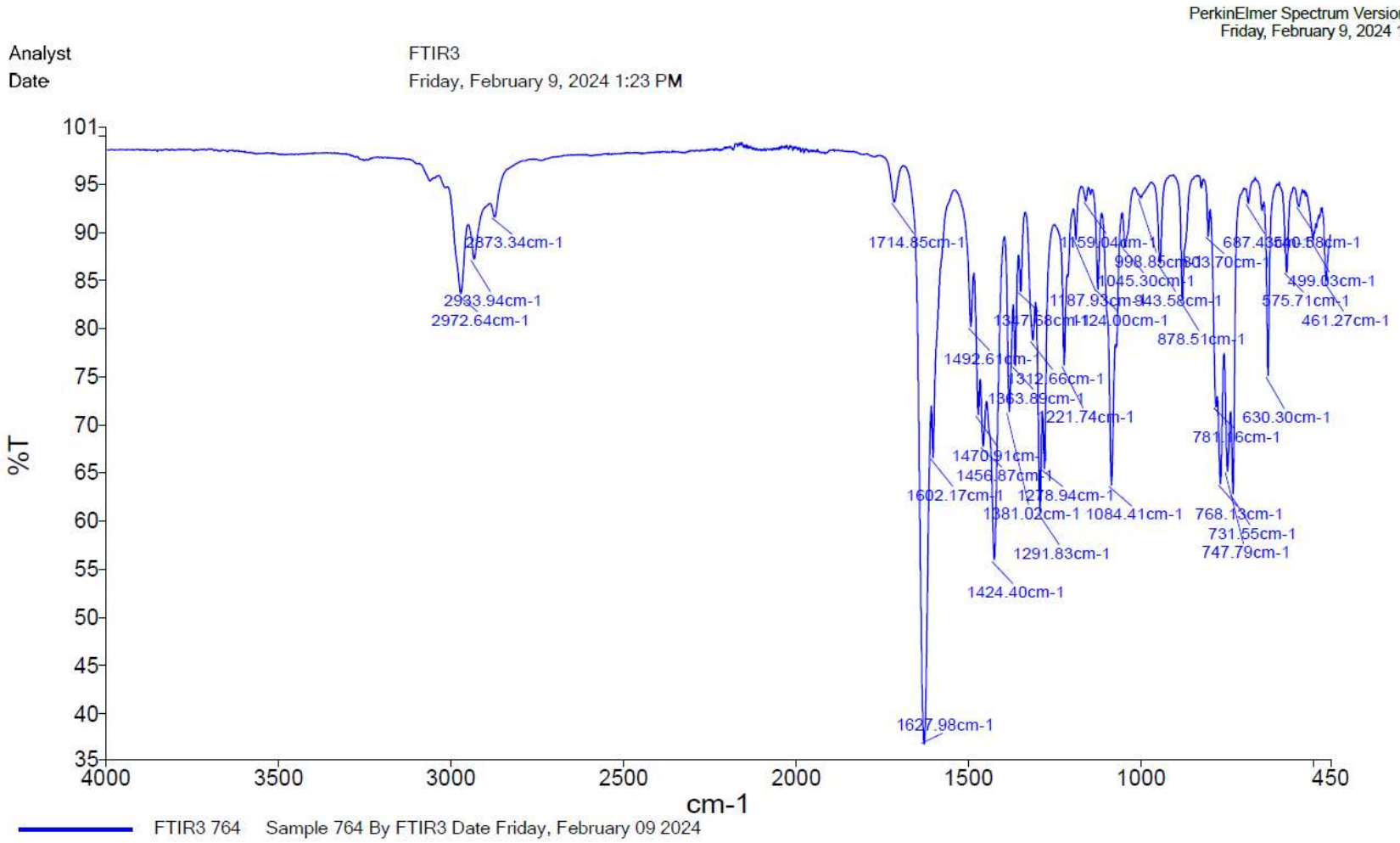

Figure 6. Infrared spectra of N,N-diethyl-2-methylbenzamide. IR obtained by PerkinElmer Spectrum Two FT-IR Spectrometer.

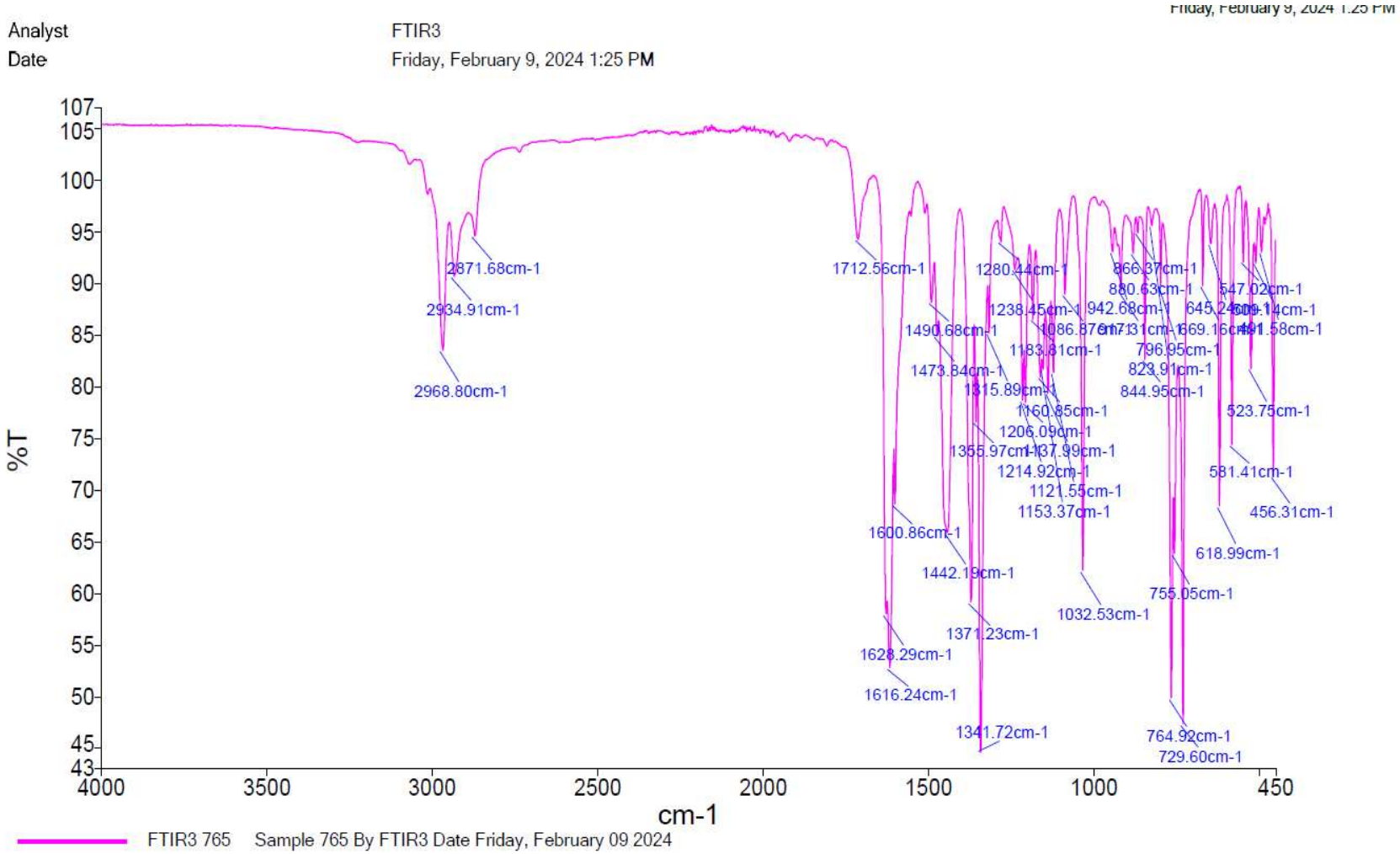

Figure 7. Infrared spectra of N,N-diisopropyl-2-methylbenzamide. IR obtained by PerkinElmer Spectrum Two FT-IR Spectrometer.

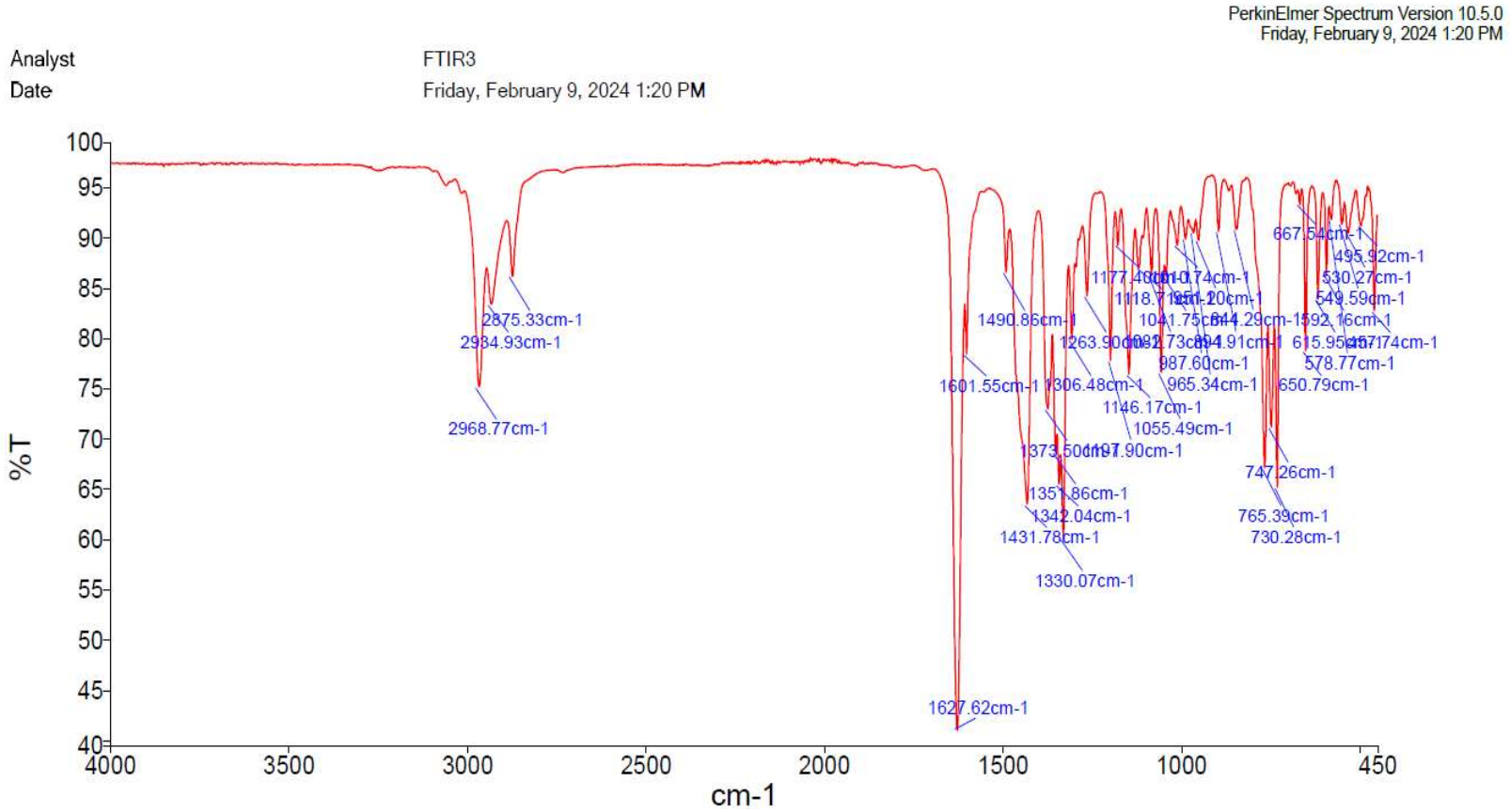

Figure 8. Infrared spectra of N,N-disec-butyl-2-methylbenzamide. IR obtained by PerkinElmer Spectrum Two FT-IR Spectrometer.

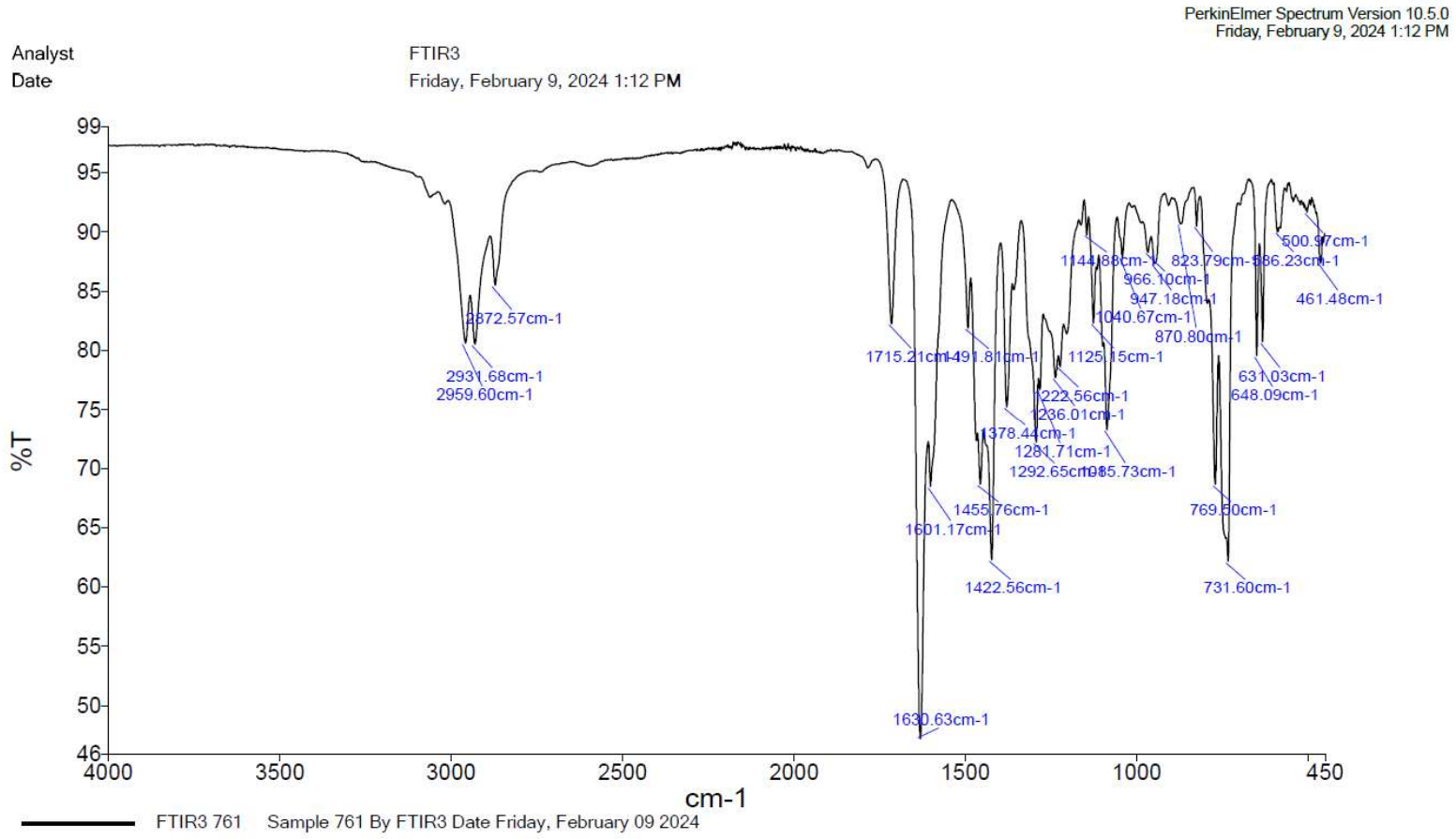

Figure 9. Infrared spectra of N-butyl-N-ethyl-2-methylbenzamide. IR obtained by PerkinElmer Spectrum Two FT-IR Spectrometer.

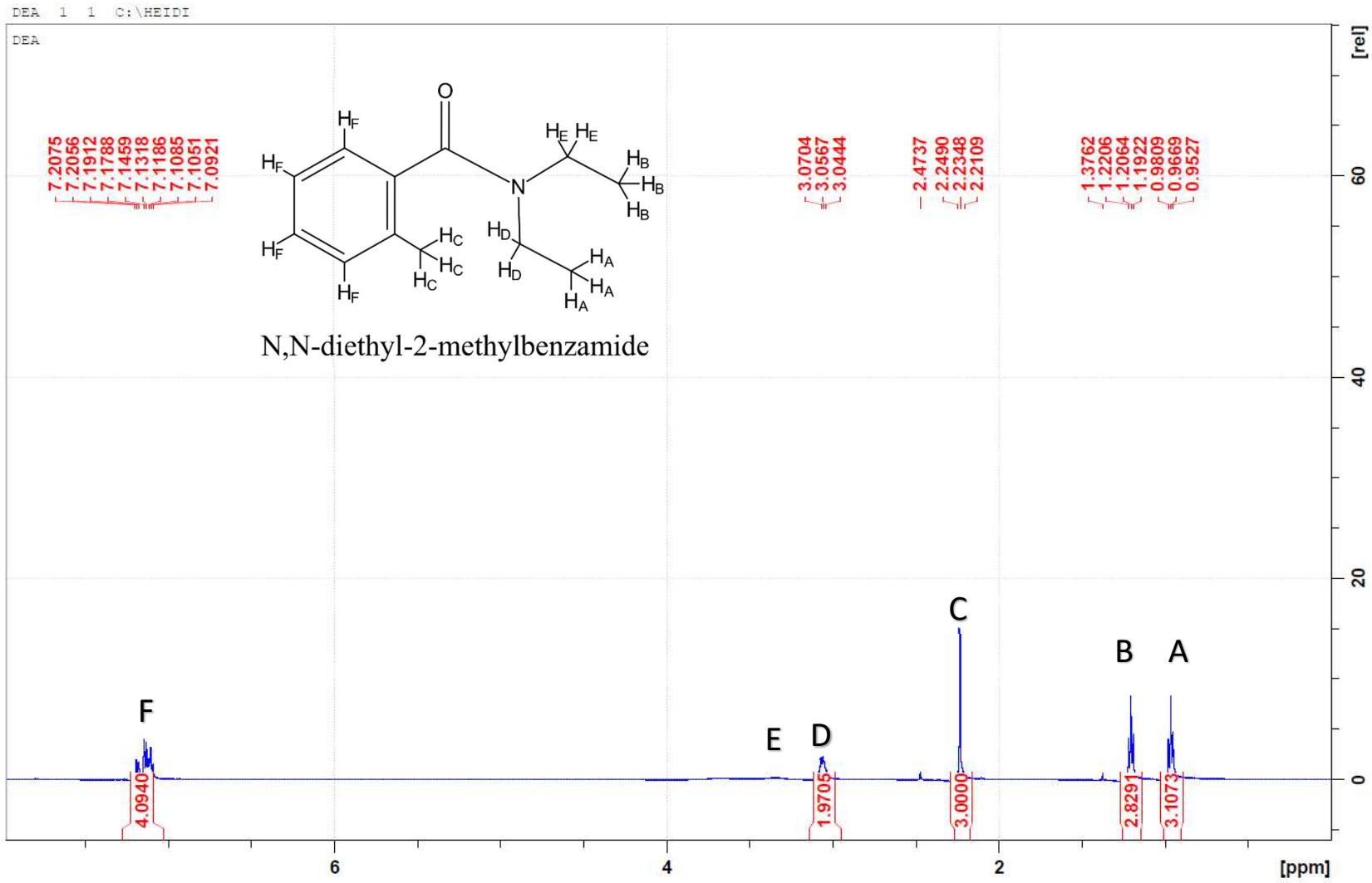

Figure 10. ^{1}H NMR spectra of N,N-diethyl-2-methylbenzamide. NMR obtained by Bruker 500MHz with $CDCL_3$ as solvent.

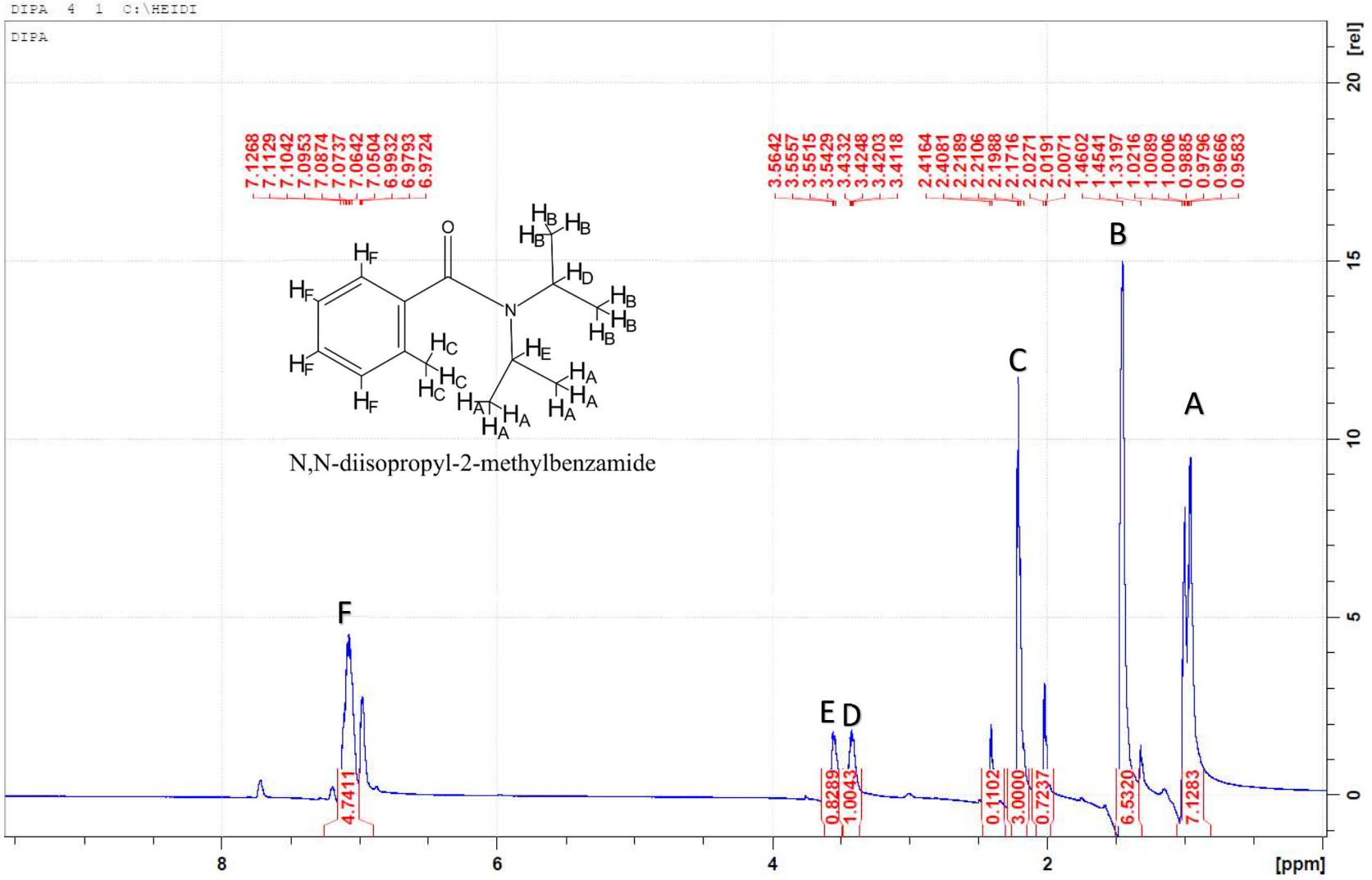

Figure 11. ^{1}H NMR spectra of N,N-diisopropyl-2-methylbenzamide. NMR obtained by Bruker 500MHz with $CDCL_3$ as solvent.

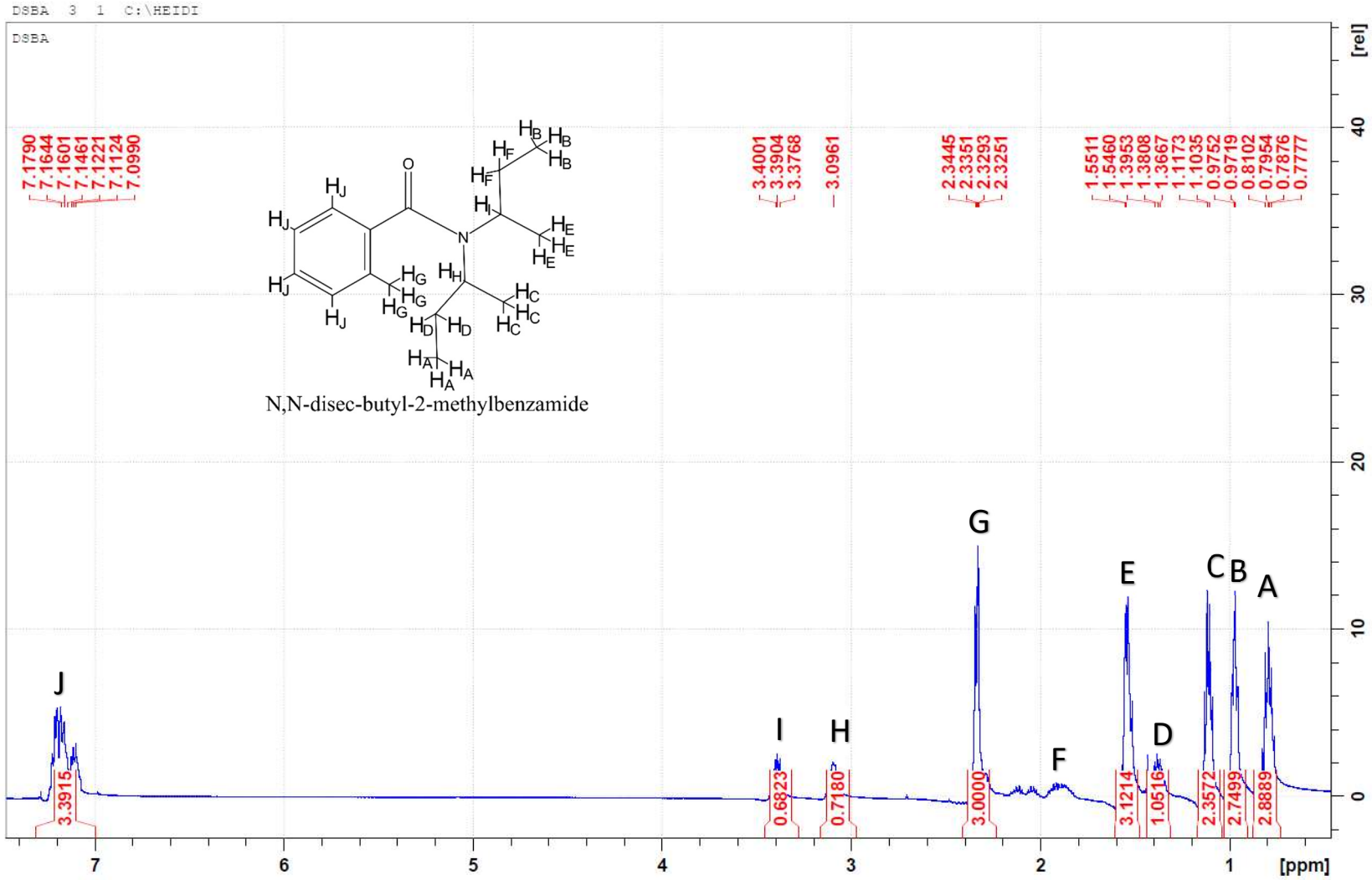

Figure 12. ^{1}H NMR spectra of N,N-disec-butyl-2-methylbenzamide. NMR obtained by Bruker 500MHz with $CDCL_3$ as solvent.

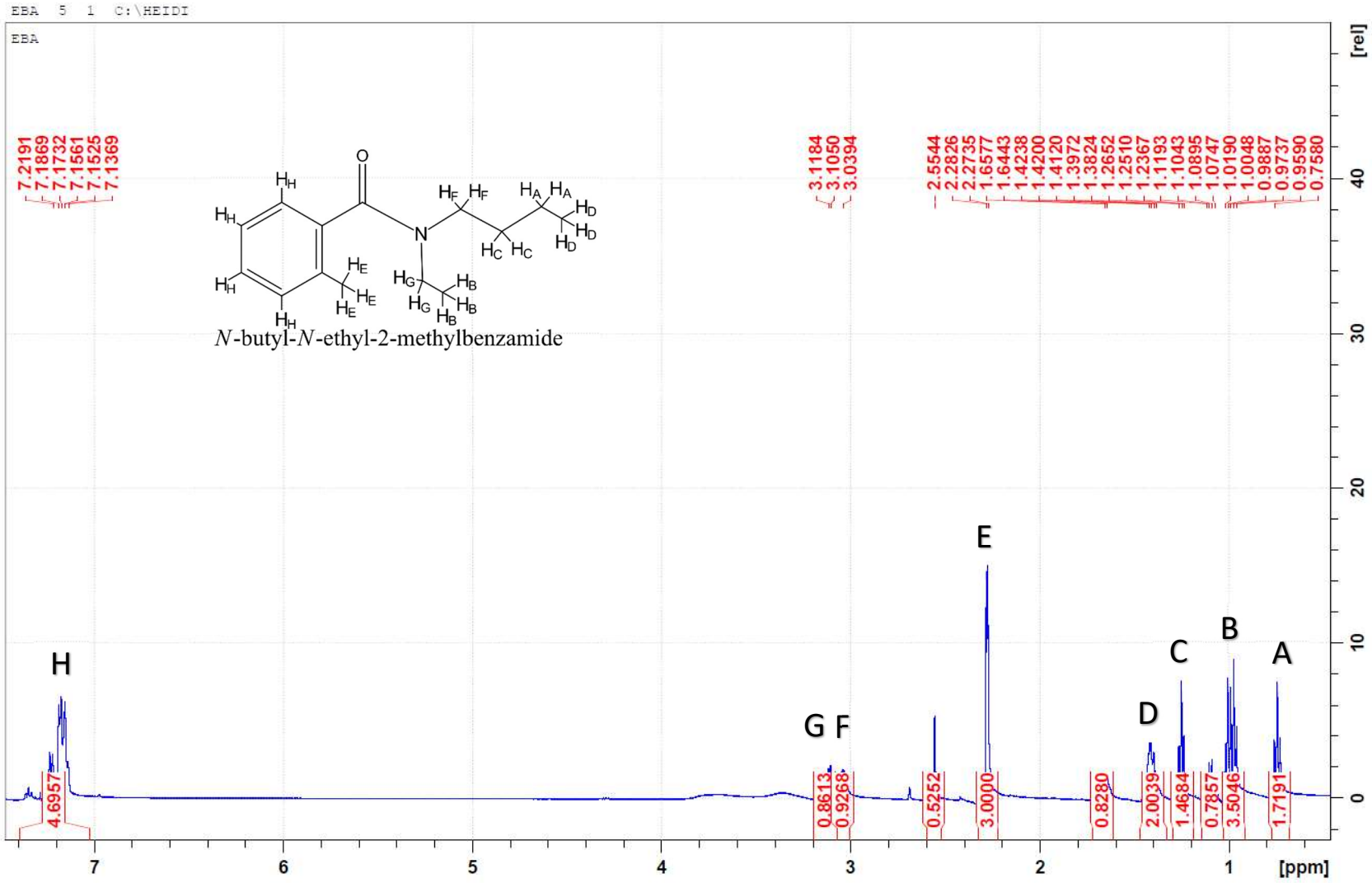

Figure 13. ^{1}H NMR spectra of N-butyl-N-ethyl-2-methylbenzamide. NMR obtained by Bruker 500MHz with $CDCL_3$ as solvent.

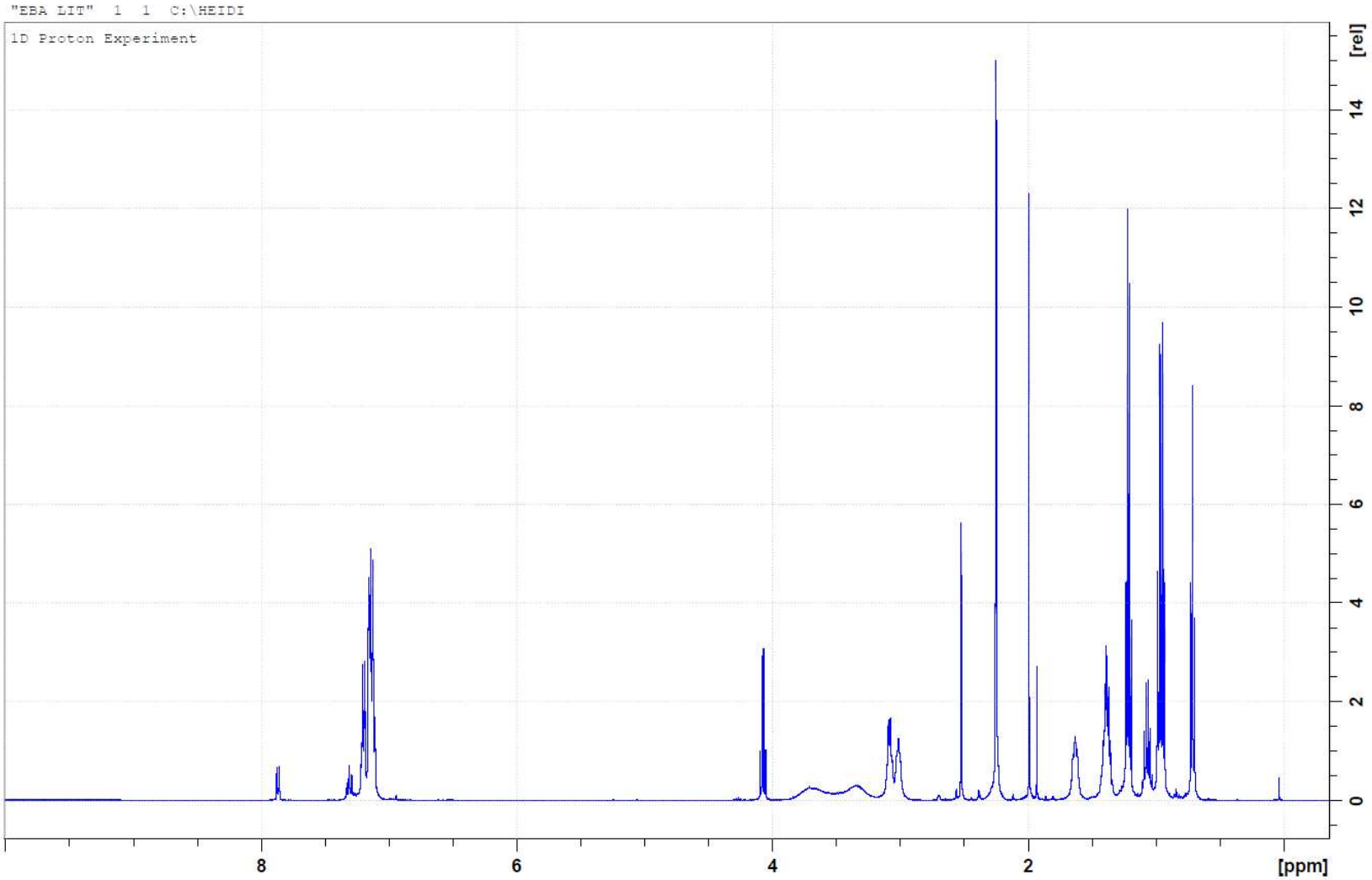

Figure 14. ^{1}H NMR spectra of the presumed silylated N-butyl-N-ethyl-2-methylbenzamide. NMR obtained by Bruker 500MHz with $CDCL_3$ as solvent.

References

(1) (a) Reed, J. N. Ph. D. Thesis, University of Waterloo, 1985. *(b) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem*. **1989**, 54, 4372.

(2) Phillips, G.; Fevig, T. L., Lau, P. H., Klemm, G. H., Mao, M. K., Ma C., Gloeckner, J. A., Clark, A. S. *Org. Process Res. Dev.* **2002**, 6, 357.

(3) Clayden, K. *Organolithiums: Selectivity for Synthesis*; Pergamon, 2002.

(4) Wong, J. Y. F.; Barker, G. Recent Advances in Benzylic and Heterobenzylic Lithiation. *Tetrahedron* **2020**, *76* (50), 131704. https://doi.org/10.1016/j.tet.2020.131704.

(5) Fässler, J.; McCubbin, J. A.; Roglans, A.; Kimachi, T.; Hollett, J. W.; Kunz, R. W.; Tinkl, M.; Zhang, Y.; Wang, R.; Campbell, M.; Snieckus, V. Highly Enantioselective (−)-Sparteine-Mediated Lateral Metalation-Functionalization of Remote Silyl Protected ortho-Ethyl N,N-Dialkyl Aryl O-Carbamates. *J. Org. Chem.* **2015**, *80*, 3368–3386. https://doi.org/10.1021/jo502561m.