COLLEGE OF DUPAGE

PASSERINI REACTION

A REPORT SUBMITTED TO

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CLASS IN CHEMISTRY

BY

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CHAPTER ONE

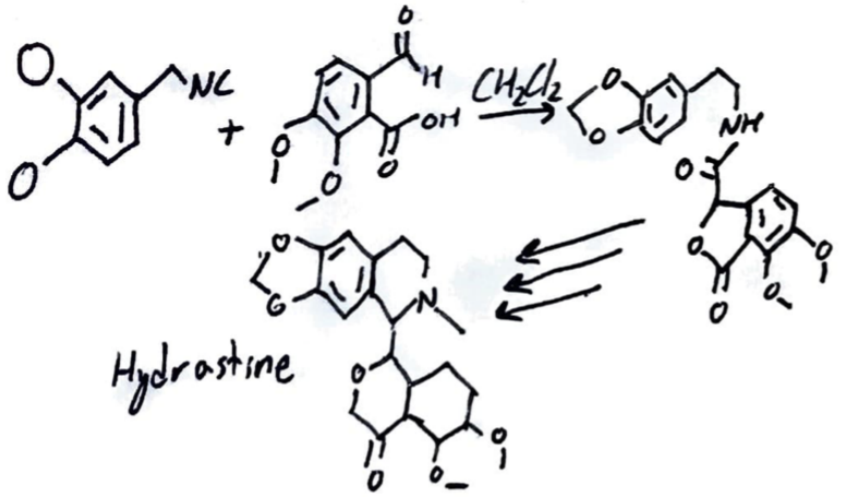
HISTORICAL

The Passerini reaction is the first isocyanide-based multicomponent reaction that today has a large role in the field of combinatorial chemistry. Involving an aldehyde or ketone, an isocyanide, and a carboxylic acid, it offers direct access to α-hydroxy carboxamides and paved the way to direct synthesis of hydroxilates and carbossamides. It was originally believed that the reaction followed an ionic mechanism but after later kinetic examinations done by Ivar Karl Ugi, it was re-established as a reaction that progresses quicker in aprotic solvents and thus is understood by modern chemists today that its mechanism does not follow an ionic pathway. The reaction finds uses in the synthesis of imaging agents, cytotoxic/ anticancer agents, photocaged compounds, and dendrimers.

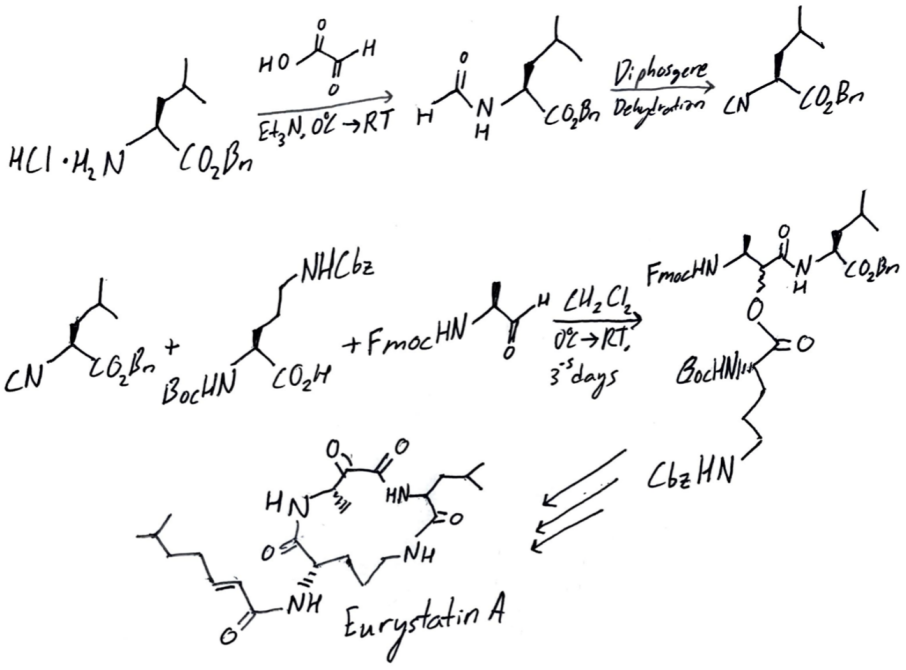
Isocyanide-based multicomponent reactions such as the Passerini reaction form the backbone of today's multicomponent reaction chemistry however its discovery dates back to 1921. Mario Torquato Passerini was born in 1891 in the town of Casellina. He published his first paper reporting on the newly discovered reaction later officially named the "Passerini Reaction". His chemistry career did not stop there and in 1930 he became professor in charge of pharmaceutical chemistry and in 1936, full professor at the University of Florence. During his time as a professor, he characterized natural chemicals found in olive trees (Olea Europea), wax-leaf privet leaves (lygustrum japonicum), and in the curry plant (helichrysum italicum). He retired, ending his career in 1961 at his home of Florence.

The Passerini reaction, although discovered in 1921, was underappreciated and underutilized for its time until the 1950s. The first notable publication was written by chemists Robert H. Baker and David Stanonis who through their publication dissected the accepted ideas Passerini proposed regarding the mechanism through prior research and experiments regarding the multicomponent reaction's stereochemistry as well as similar reactions, introduced a new ionic mechanism that would later be disputed once more by Ivar Karl Ugi who would prove the mechanism followed a non-ionic pathway.

Around the year 1931, chemist Sir Robert Robinson was looking to find a synthesis for hydrastine, a chemical found in Goldenseal extract and is known for its healing properties. He attempted many different paths towards a synthesis but commonly failed due to a lactonic amide intermediate that was not forming properly. It was not until 1981 where this problem was solved. As the Passerini reaction began to gain popularity, chemist J. R. Flack was able to employ the reaction allowing for a simple and effective 4 step synthesis from starting materials that were basic and easily accessible. The key passerini step in his synthesis is displayed below: [2]



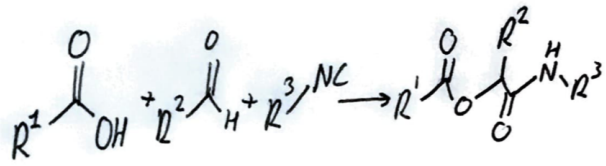
Today, many isocyanide-based multicomponent reactions such as the classical Passerini and Ugi reactions are heavily relied upon by the pharmaceutical industry due to their high efficiency combining several operational steps without isolating intermediates or changes of the reaction conditions. Isocyanide-based multicomponent reactions are particularly used because of their versatility compared to the remaining multicomponent reactions. The use of isocyanides in the development of multicomponent reactions lies in the bond-forming process where characteristic chemo-, regio-, and stereoselectivity are often seen. Isocyanides reactivity can be given credit to its functional group reactivity towards nucleophiles and electrophiles of the same atom that is rarely found in any other functional groups. Its presence is often a key step in the synthesis of many products due to the α-acyloxycarboxamide group being a common sight in many interesting pharmacological chemicals. An example of this can be found in the synthesis of Eurystatin A shown below: [2]



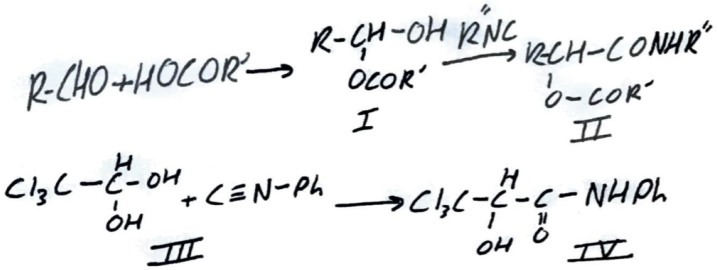
CHAPTER TWO

METHODOLOGY AND RESULTS

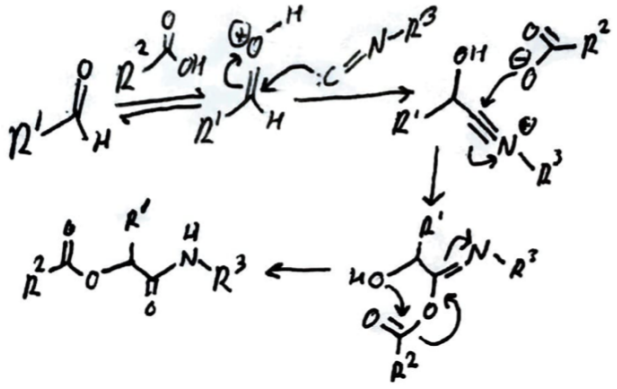
The passerini reaction is an isocyanide-based multicomponent reaction that involves an aldehyde or ketone, an isocyanide, and a carboxylic acid all in a single pot style reaction [2] (follows the general scheme shown below):



In 1951, scientists Robert Baker and David Stanonsis analyzed the mechanism proposed by passerini stating the weakness in his proposed mechanism to be the formation of intermediates II and IV from I and III from an isocyanide reaction [9] (shown below):

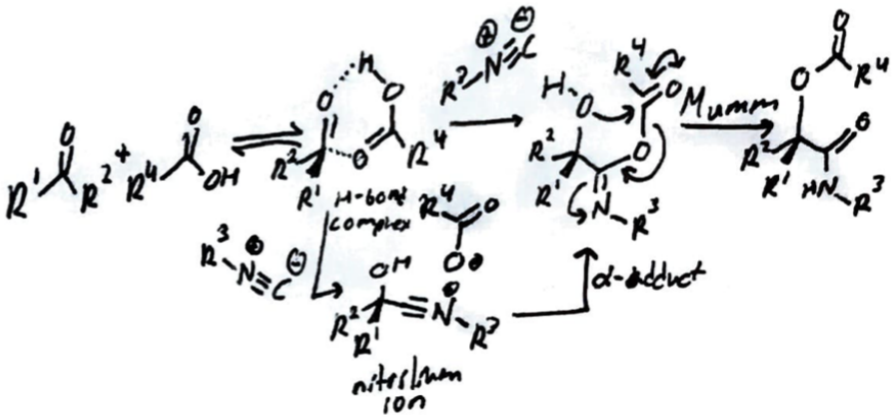


Applying modern synthesis at the time in combination with experiments they conducted to test their theory, Baker and Stanonsis proposed an alternate ionic mechanism [2] (shown below):



Their altered mechanism proposed a nucleophilic attack on the aldehyde instead of a reaction between the carboxylic acid and the aldehyde before a nucleophilic attack from the isocyanide. This first step allowed for a smoother attack from the carboxylic acid to occur due to the electron density caused by the prior step thus ending the mechanism with a rearrangement for the product to emerge.

Ivar Karl Ugi in 1961 noticed the reaction would progress quicker in aprotic solutions causing him to hypothesize and later develop a mechanism that would follow a non-ionic pathway [3] (shown below):



Răzvan (2017) states the reaction follows two main pathways, one in aprotic solutions and another in protic solutions. The aprotic pathway begins with a hydrogen-bonded complex

forming between the aldehyde and the carboxylic acid. The isocyanide then inserts itself in a concerted fashion leading to an acyl-imidate intermediate that undergoes an acyl transfer (Mumm rearrangement) to provide the final product. This specific pathway prefers solvents such as dichloromethane, toluene, and THF at high molarities. Under protic solvents, the ionic pathway is preferred and intermediates such as the nitrilium ion, which generally is not considered relevant for the Passerini reaction, form.

CHAPTER THREE

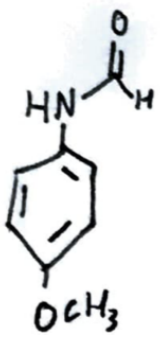
FUTURE STUDIES

The first priority for future studies would be to apply a single reactant replacement approach as a way both to improve known multicomponent reactions and design new multiple-component routes to bioactive structures. The goal would be to replace a component in a known multicomponent reaction with another chemical of similar reactivity and behavior still allowing the reaction to progress but with goals to direct the multicomponent reaction towards a different outcome such as a new structural framework or ring system. This strategy can use a chemist's mechanistic insight into a known MCR and serve as a platform from which to design or create imaginative single reactant replacement substitutions.

The next priority would be to explore increasing the dimensionality (number of starting components in a reaction from n to (n+1)). Applying retrosynthetic analysis towards intermediates in passerini reactions done within priotic environments offers a position that can be used towards identifying independent routes for those intermediates to be formed allowing for a more diverse set of reactants to be used thus broadening the potential scope of the chemical library synthesis.

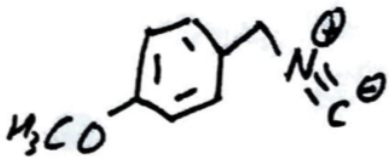
CHAPTER FOUR

EXPERIMENTAL



N-(4-methoxybenzyl)formamide CAS 5470-34-8

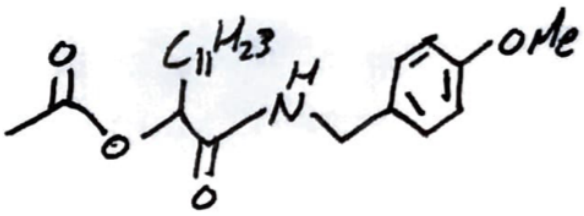
This compound has been previously reported by Paprocki *et al.*[8]The method for which its preparation is based on has been previously reported by Paprocki *et al.*[8]Heat 3.8 mL (30 mmol) 4-methoxybenzylamine and 12.5 mL ethyl formate under reflux overnight. Add 5 mL hexane after the reaction cooled to room temperature. The precipitate was filtered by means of buchner vacuum filtration and washed with hexane. The yield was 78 % (3.86 g).



1-(Isocyanomethyl)-4-methoxybenzene CAS 1197-58-6

This compound has been previously reported by Paprocki *et al.*[8]The method for which its preperation is based on has been previously reported by Paprocki *et al.*[8] Add 2.64g (16 mmol N-(4-methoxybenzyl)formamide and 6.7 mL (48mmol) triethylamine in 20 mL dry

dichloromethane at -78°C. Add 1.85 mL (20 mmol) phosphoryl oxychloride dropwise. Stir for one hour and quench the reaction with 20 mL of saturated NaHCO3 then extract with 2 additions of 20 mL dichloromethane. The organic layer is dried with MgSO4. The initial product was then purified by column chromatography on silica gel using hexane/AcOEt. The yield is 80 % (1.88 g).

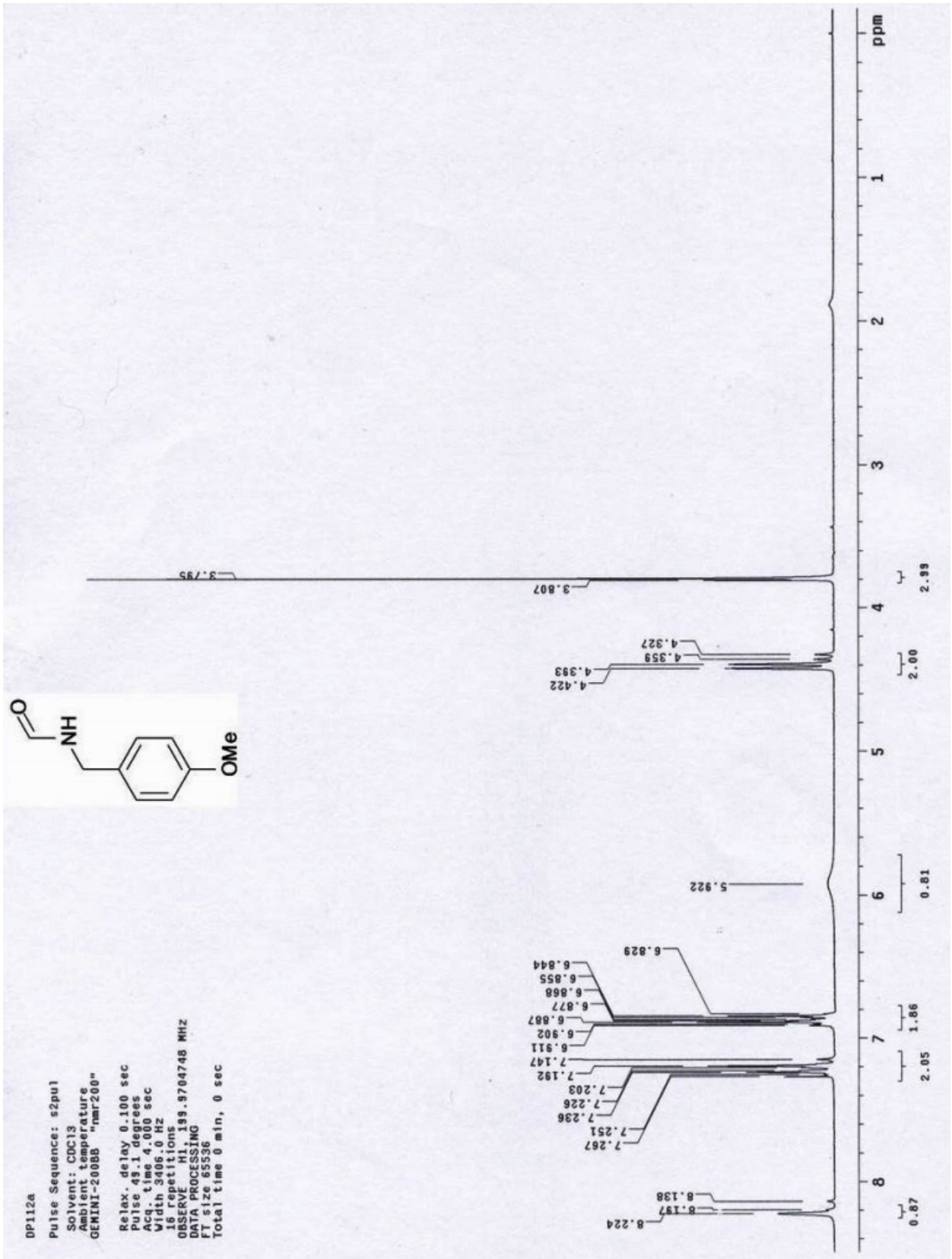


1-(4-Methoxybenzylamino)-1-oxotridecan-2-yl acetate CID 134818040

This compound has been previously reported by Paprocki *et al.*[8]The method for which its preparation is based on has been previously reported by Paprocki *et al.*[8]Add 0.2 mmol benzoic acid, 0.2 mmol dodecyl aldehyde, and 0.2 mmol p-methoxybenzyl isocyanide in 2 mL PBS with the addition of 0.04 mmol DODAB at 25 °C and stir for 1 day.

APPENDIX A

SPECTRA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Relax. delay 0.100 sec
Pulse 49.1 degrees
Acq. time 4.000 sec
Width 3406.0 Hz
16 repetitions
OBSERVE H1, 199.9704748 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
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OMe
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8.197
8.138
7.267
7.251
7.236
7.226
7.203
7.192
7.147
6.911
6.902
6.887
6.877
6.868
6.855
6.844
6.829
5.922
4.422
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ppm
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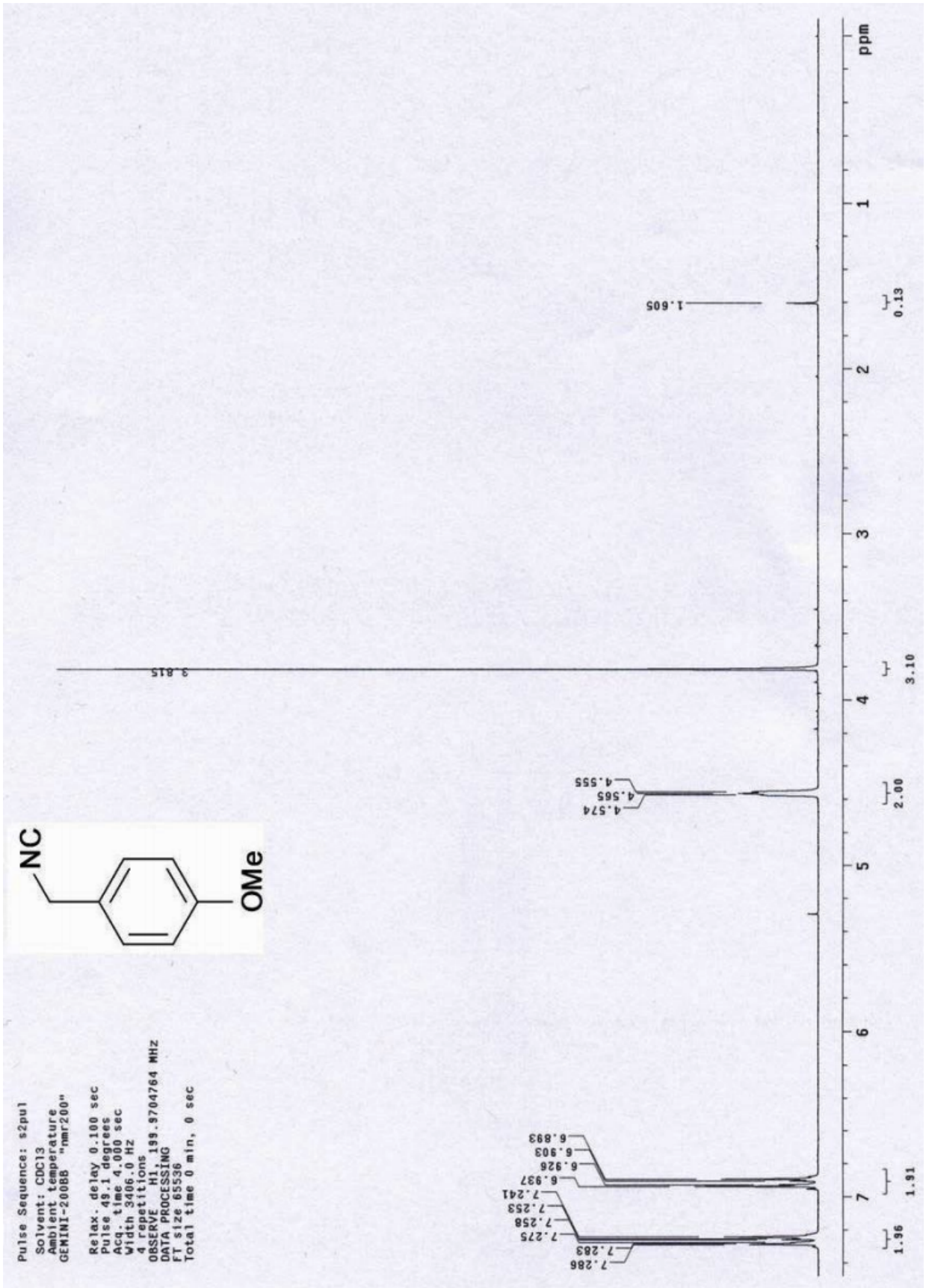
1.86
0.81
2.00
2.99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Solvent: CDCl3
Ambient temperature
GEMINI-200BB "mar200"
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Pulse 49.1 degrees
Acq. time 4.000 sec
Width 3406.0 Hz
4 repetitions
OBSERVE H1, 199.9704764 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
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OMe
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4.565
4.555
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ppm
1.96
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2.00
3.10
0.13

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