Internship report 4th year Chimie et Génie Chimique

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Prepared within the Aachen Maastricht Institute of Biobased Materials AMIBM

Academic year 2023-2024

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Acknowledgements:

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Finally, I want to thank all the people who advised me for the writing of this report and who checked it, especially Ms. Oriane Dutertre, student in the engineering school ENSISA in Mulhouse.

Summary:

Glossary:

Multicomponent reaction: A reaction which implies at least three compounds in order to form a complex product out of this reaction.

Cascade synthesis: A cascade synthesis is a reaction that implies at least two reaction steps that occur consecutively, meaning that each step depends on the previous one.

Schlenk Line: A Schlenk Line is an apparatus used to perform chemical reactions under inert atmosphere. It is composed of two manifolds, one connected to a vacuum pump, the other one to a source of inert gas (Argon, Nitrogen). Then the principle consists in degassing the closed container, switching line for an influx of inert gas, and to repeat the process to remove as much air as possible and work in inert atmosphere.

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Introduction:

The Aachen-Maastricht Institute for Biobased Materials (AMIBM) has been created in 2016 with the collaboration of three parties: the Maastricht University (UM), the Aachen University (RWTH), and the Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung (Fraunhofer). It is a cross-border organization, located on the Brightlands Campus, a huge Chemistry Industry Complex near to Maastricht, Limbourg, Netherlands, a region which takes place between Germany and Belgium. The AMIBM focuses on creating new biobased materials via the development of biobased molecules, processes and materials. This internship was done inside the Organic Chemistry department of the AMIBM, which main topics are Cascade Syntheses, Sustainable catalysis, multicomponent reaction, and heterocycles and advanced functional material.

Cascade Synthesis is a specific type of synthesis in which at least two reactions occur consequently, the next step depending on the success of the previous step. In that case, the isolation of the intermediates is impossible because they are consumed as soon as they are formed. The sustainable Catalysis field focuses on new catalytic reactions which fit better with the green chemistry principles, mostly with less toxic catalysts, and less expensive. Multicomponent reactions allow to synthetize complex products from several components in the same reactions, such as assembling blocks to create a more sophisticated molecule. This way of synthetising is time saving and also better for the atom economy, still regarding to the green chemistry principles.

The main goal of this internship is to get used to the daily life of a research organic chemistry laboratory, from the fundamental research to the publication, with all the experiments and interpretations that it implies. The studied project during this internship was the Nickel Catalysed Isocyanide Insertion.

I Introduction of the reaction, first tries, of synthesis and isolation

A Theoretical aspect

The goal of this project is to perform an insertion of an isocyanide in a three-components reaction, via a Nickel photocatalyzed way.

Photocatalysis is a technique which uses a photocatalyst, a compound able to undergo Single-Electron Transfers (SET) at mild conditions, using UV-Visible light. That way, harsher conditions and hazardous reagents are avoided. During the reaction, the photocatalyst will be excited by light. At the excited state, the photocatalyst is a better oxidant than the other ground state species but at the same time a better reductor than the ground state species. Using a single electron transfer, the photocatalyst will react with the Nickel (II) complex, which will be able to undergo oxidative additions and reductive eliminations.

This reaction is made with a nucleophile, a Nickel source, and finally, an Isocyanide (*see Picture n°1*). The Isocyanides are very interesting in multi-component, cascade synthesis because of their particular reactivity. Isocyanides are versatile building blocks capable of reacting with nucleophiles, electrophiles, and radicals. In organometallic chemistry, they commonly function as ligands for transition metals. Additionally, isocyanides also exhibit a Carbene nature, which can be really interesting in some synthetic pathways. Their interest lies in their isoelectronic properties and well-defined reactivity patterns. One highly valuable application for the isocyanides is their use in cross-coupling reaction with transition metal instead of carbon monoxide, because of the better isoelectronic feature of isocyanides and also for safety issues. The performed reaction, is expected to perform an imidoyle insertion of the isocyanide with the following mechanism:

FIGURE 1: AN ISOCYNAIDE

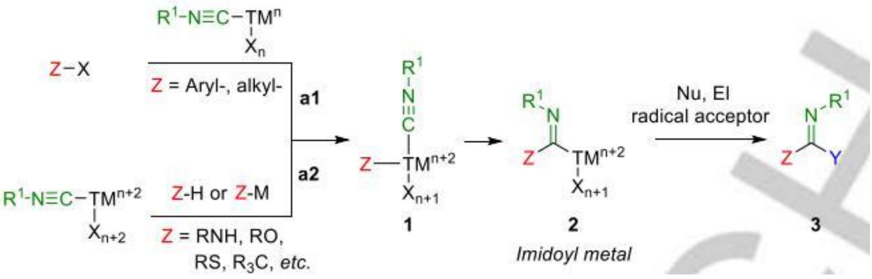

FIGURE 2: MECHANISM OF AN ISOCYANIDE INSERTION

It is a 1,1-migratory insertion in a σ bond. It is important to notice that this mechanism happens but the reaction conditions may change the way it happens. The side products the reaction gives proves this. This project focuses on the incomes from certain reaction conditions, not the mechanism.

This reaction is inspired by the König group and the Adaptative Dynamic Homogenous Catalysis principles[3] . It allows cross-coupling chemical reactions with a specified catalyst by screening the reaction conditions and optimising them case by case. The cross-coupling

reactions had gained a recent interest because of their ability to create complex molecules with heteroatom bonds (C-O, C-N, C-S, …) easily and this in only one step. Cross-coupling reactions have been using several transition metals, but the one which is seen as more efficient is Palladium (Pd). The problem is that this metal is scarce and very expensive. Several studies have tried or are still trying to find new catalysts other than Palladium, and Nickel has been picked up as a serious candidate because of its abundance on earth and its cost-saving price. One breakthrough that was made for cross-coupling reactions was the use of photocatalysis to improve the yields of such reactions.

The reaction on which the project is based is the following one:

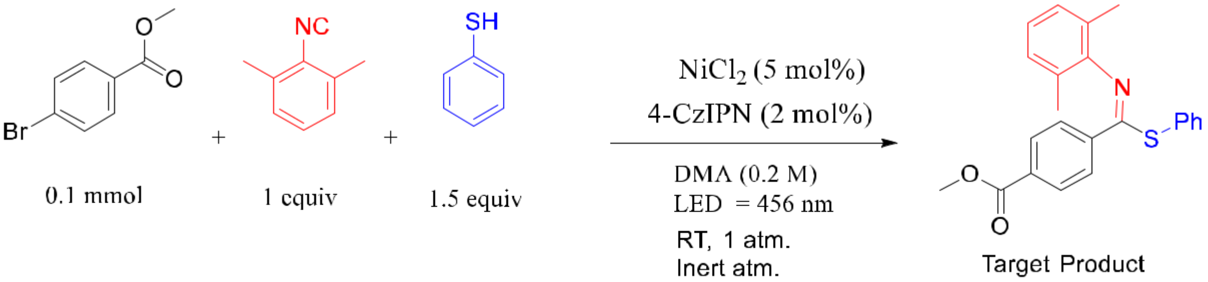

FIGURE 3: STARTING REACTION OF THE PROJECT

Where the 4-CzIPN is the 1,2,3,5-Tetrakis(carbazole-9-yl)-4,6-dicyanobenzene, a photocatalyst, and the N,N-Dimethylacetamide is the solvent of the reaction. The role of the catalyst is played by the Nickel (II) Chloride.

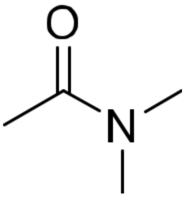

FIGURE 4: N,N-DIMETHYLACETAMIDE

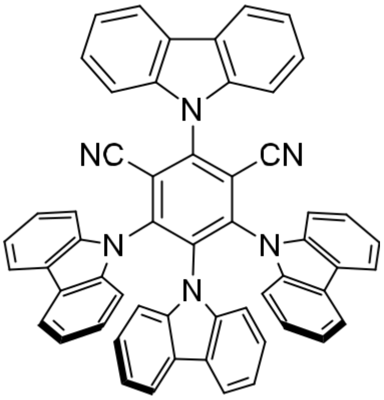

FIGURE 5: 4-CZIPN

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[3]: Ghosh, I., Shlapakov, N., Karl, T. A., Düker, J., Nikitin, M., Burykina, J. V., Ananikov, V. P., & König, B. (2023). General cross-coupling reactions with adaptive dynamic homogeneous catalysis. *Nature*. https://doi.org/10.1038/s41586-023-06087-4

The Aryl Bromide plays the role of the electrophile, the thiophenol is the nucleophile but as it is a stronger sigma donor than the isocyanide, it is important to notice that the thiophenol will coordinate to the Nickel. The 2,6-dimethylphenylisocyanide will react here both as a ligand and will be inserted to give the target product.

B First experiment

1) Setting the reaction

The main goal was at first to try to reproduce the reaction in the lab, to get used to it and to the working environment.

Regarding to the previous reaction, the conditions, weights and volumes of the different components of the reaction were:

Compounds	**Number of equivalents/% molar**	**Mass/volume**
1,4 bromobenzoate	1.0 equiv.	21.5 mg
2,6-dimethylphenylisocyanide	1.0 equiv.	26.2 mg
Thiophenol	1.5 equiv.	15 µL
Nickel Chloride	5% M	1.0 mg
4-CzIPN	2% M	1.6 mg
N,N-Dimethylacetamide	0.2 M	2 mL

TABLE 1: REACTION CONDITIONS OF THE FIRST ATTEMPT

The reaction scale is 0.1 mmoles here.

For this reaction, a microwave vial is used (*see Picture n°6*). All the solids are first put in it, then the vial is purged from air. Indeed, Dioxygen can quench the excited state of the photocatalyst, so as a preventive measure in order to avoid the oxidative conditions, the whole process will be done under inert atmosphere, using (N_2), via a Schlenk Line (*see Picture n°7*). The air is first removed using a vacuum pump, then the Nitrogen is put in the vial. This operation is done three times in a row to remove as much air as possible from the vial.

FIGURE 6: MICROWAVE VIAL

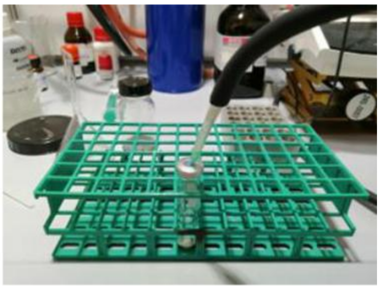


FIGURE 7: SCHLENK LINE

Once this is done, the same manipulation is realised on smaller empty vials. They will be used to transfer the thiophenol and the solvent, which are both liquids.

To optimise the transfer of the thiophenol, it will be done in two times. A first millilitre of solvent is directly added to the vial microwave vial with the other components. In a second step, 0.5 mL is added to the vial containing the thiophenol to rinse a fist time the vial. The solution of Thiophenol and N,N-Dimethylacetamide is taken out with a syringe and added to the microwave vial. The vial which contained the Thiophenol is rinsed a second time the same way with the 0.5 mL of N,N-Dimethylacetamide that are missing. All those operations are realised under nitrogen coming from the Schlenk Line with a syringe to puncture the vials (*see Pictures n°8 and 9)*.

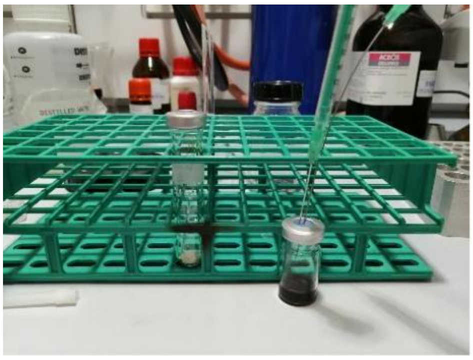


FIGURE 8: ADDITION OF THE THIOPHENOL

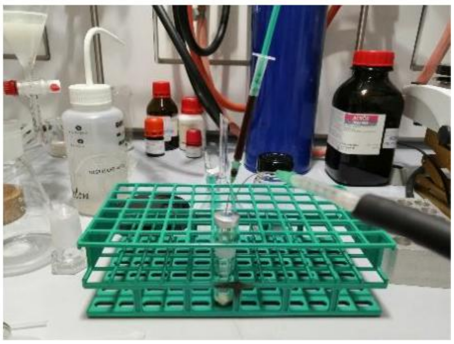


FIGURE9: TAKING OF THE THIOPHENOL

Once the transfer of the Thiophenol is done, the syringe which is providing Nitrogen is plunged into the liquid, and a needle still at the top of the vial to let the Nitrogen escape. The Nitrogen bubbles into the liquid and that way, the vial is purged from the traces of air that could poison the reaction. (*see Picture n°10*)

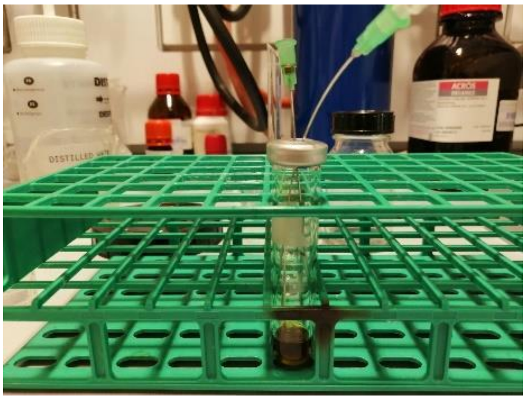


FIGURE 10: PURGING OF THE VIAL

The Microwave vial is put in the photoreactor, exposed to a 456nm LED, agitated with a stirring bar and cooled with air overnight. (*see Picture n°11*)

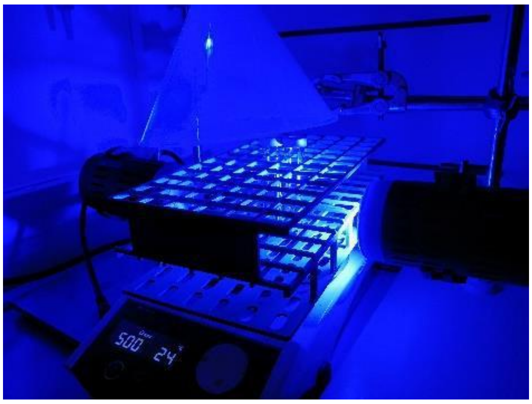
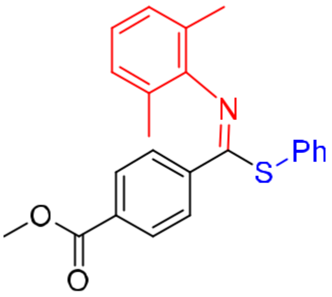


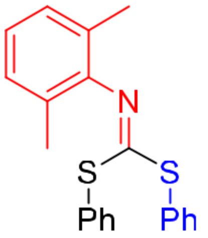
FIGURE 11: PHOTOCATALYSIS REACTOR

The crude is then analysed with the Gas Chromatography-Mass Spectroscopy. Four main products are found:



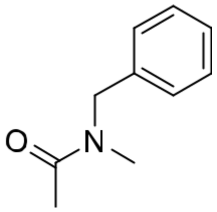
M=375 g/mol

Figure 12: Target Product



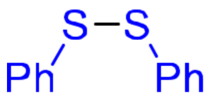
Mass=349 g/mol

Figure 13: Double insertion of the Thiophenol



Mass=220 g/mol

Figure 14: Coupling of the Thiophenol and of the Dimethylacetamide



Mass=218 g/mol

Figure 15: Homocoupling of the Thiophenol

The first one is the target product, the second one is a double insertion of the Thiophenol, the third one is a coupling of the N,N-Dimethylacetamide and the Thiophenol. Nevertheless, this third product is only an assumption from the analysis of the GC-MS fragment pattern. The fourth one is the homocoupling of the Thiophenol. The target product's presence in the crude is low.

2)Isolation of the target product

Upon completion of the reaction in the photoreactor, the initial step before product isolation involves extracting the crude mixture from N,N-Dimethylacetamide (DMA). The extraction is performed using water and diethyl ether (*see Figure n°16*). This process facilitates the transfer of all products into diethyl ether, which has a lower boiling point (34.6°C) compared to N,N-Dimethylacetamide (165.1°C) and exhibits a greater affinity for water. Subsequently, the crude extract in diethyl ether is dried over magnesium sulfate and filtered through cotton. The solvent is then removed by evaporation under reduced pressure, and the remaining product is subjected to vacuum to eliminate any residual solvent traces. Since the product is non-volatile, there is no risk of its evaporation during this process.

FIGURE 16: EXTRACTION FROM THE DIMETHYLACETAMIDE

The next step is the isolation of the different products. The crude is first studied on a Thin Layer Chromatography in order to find the best eluant for the crude, an eluant which separates the different products. The best eluant found is five equivalents of Heptane and one of Ethyl Acetate.

1a/1b: First experiments spots

NC: Isocyanide spot

PC: Photocatalyst spot

Ar: Aryl Bromide spot

M: Mixture

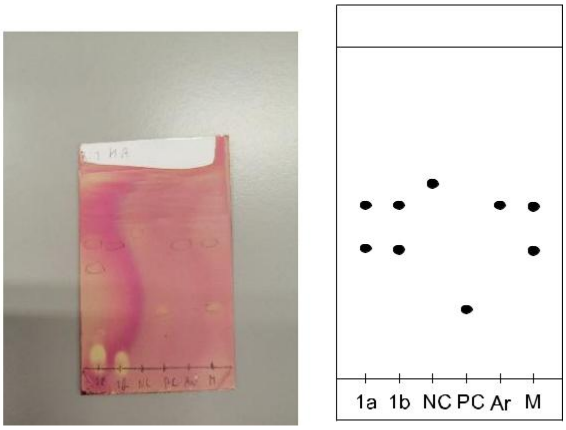


FIGURE 17: THIN LAYER CHROMATOGRAPHY OF THE FIRST EXPERIMENT

Then, the products are separated on an Automated Chromatography Column made with Silica gel. The separation will be done with a gradient of polarity of the solvent. It will be increased along the separation to improve the separation of the different products and starting materials that are composing the crude. It starts from 2% of Ethyl Acetate to 16.7% of Ethyl Acetate.

The sample is analysed with NMR. The product is clearly appearing in the samples with the presence of both the methyl protons (3H, 3,89ppm) from the ester and from the two methyl groups from the isocyanide (6H, 2,25 ppm). Impurities are still remaining, such as N,N-Dimethylacetamide, water, and other ones undetermined (*see Figure n°18*).

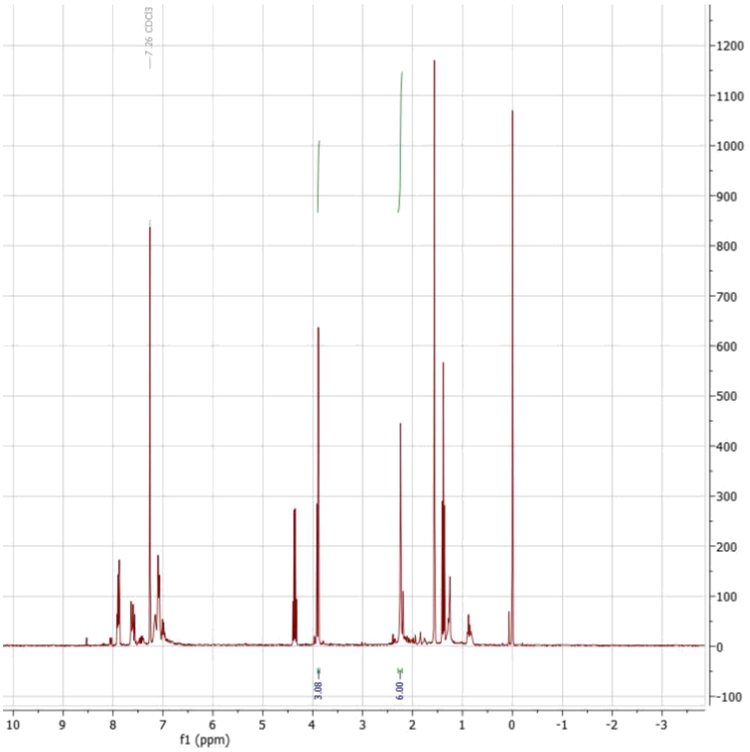


FIGURE 18: NMR SPECTRUM OF THE FIRST ATTEMPT OF ISOLATION

C Next experiment

1) Other trial: Change of the isolation method

Another trial was made with the same protocol. The only difference is that during the isolation, the weight of the column (4g) was too low to separate enough our products, the product, all the side products and impurities were extracted almost together. The following spectrum of GC-MS and NMR were obtained. (*see Figures n°19 and 20*). The product's presence here is very low and the extracted product is not the target product but here the double insertion of the thiol (M=249,0959 g/mol).

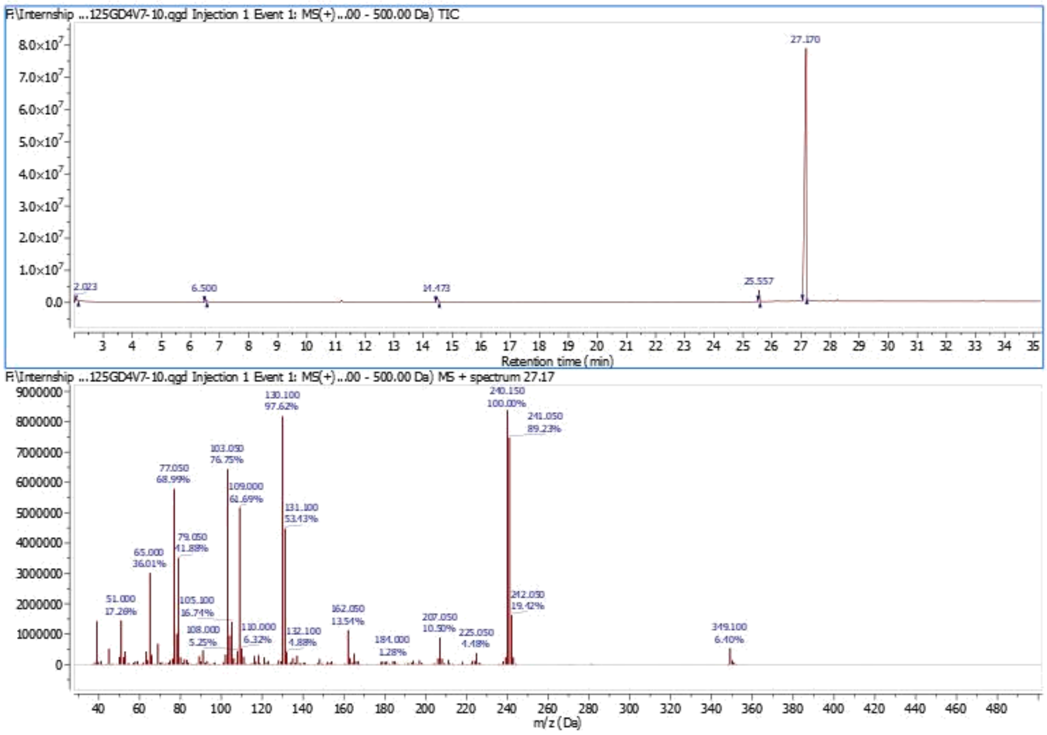


FIGURE 19: GC-MS SPECTRUM OF THE SECOND ATTEMPT

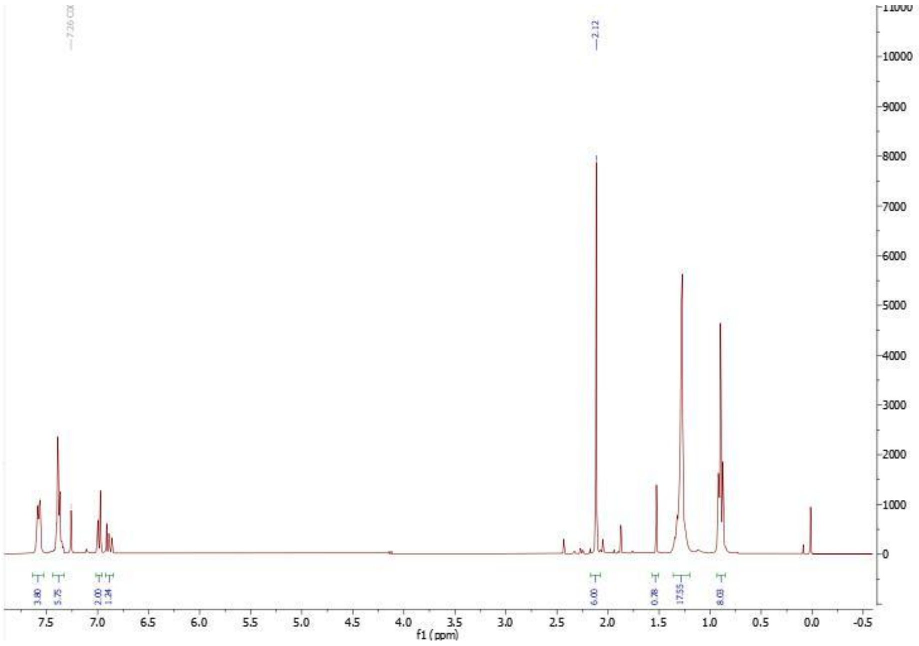


FIGURE 20: NMR SPECTRUM OF THE SECOND ATTEMPT

2) New electrophile

To improve the yield of this reaction, another electrophile was used: iodobenzene. The mechanism and the protocol remain the same. If we can clearly see the product in the crude (*see Figure n°21*) (Mass=317 g/mol), it is not the case after the isolation attempt, made with the auto-column (*see Figure n°22*). To solve the isolation problem, it was decided to do a manual Chromatography Column to be more precise and to use a bigger column and a bigger amount of eluent. The eluent was a gradient of Ethyl Acetate to increase the polarity, starting from ten equivalents of Heptane and one of Ethyl Acetate (10:1) to (5:1). But the target product was not isolated at all, not found in the different products collected. The product overly retained by the column it was stuck in the column, or the reaction may also have yield too little. Thus, optimisation trials were conducted and are detailed in the second part of this report. Due to cost and shipping constraints, the synthesis of the starting materials, 2,6-dimethylphenyl Isocyanide, has been undergone.

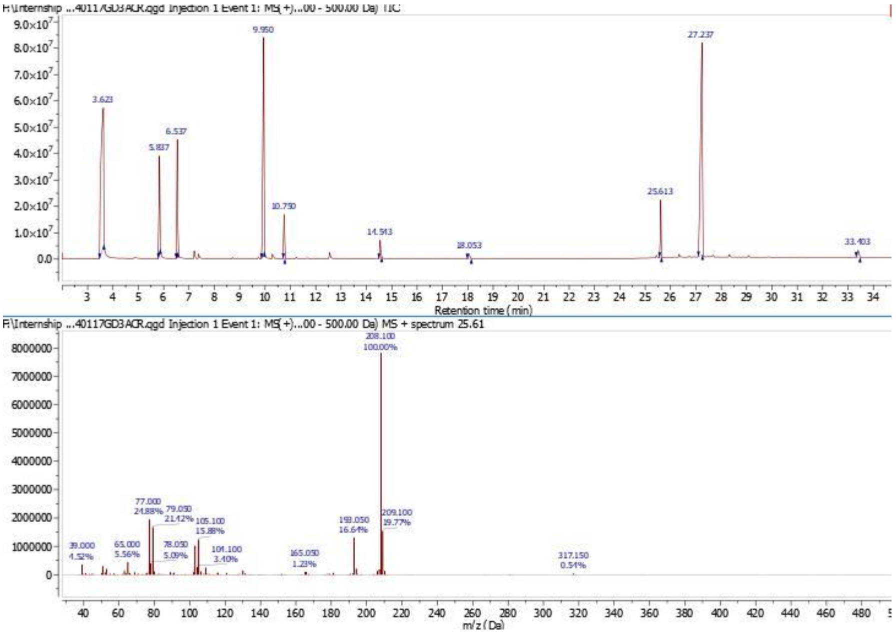


FIGURE 21: GC-MS SPECTRUM OF THE CRUDE OF THE THIRD EXPERIMENT

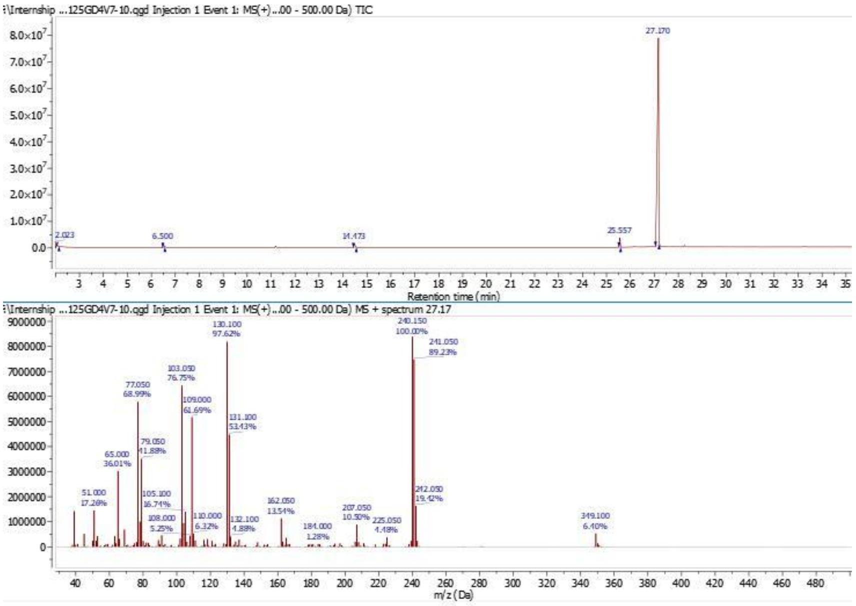


FIGURE 22: GC-MS SPECTRUM AFTER ISOLATION OF THE THIRD EXPERIMENT

D Synthesis of the 2.6-dimethylphenyl Isocyanide

The first step consists in the formylation of the 2,6-dimethylaniline using formic acid and acetic anhydride. Here is the scheme of this first step:

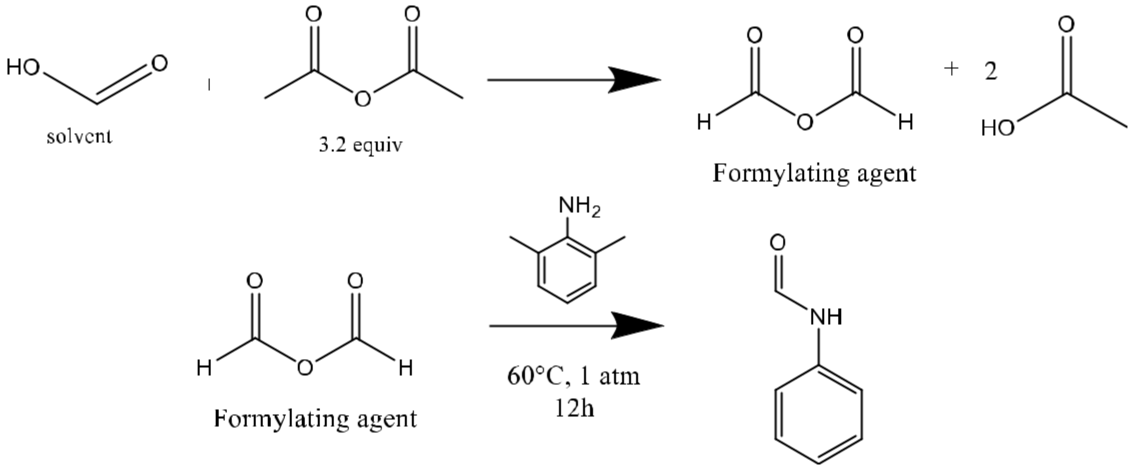


FIGURE 23: FIRST STEP OF THE SYNTHESIS OF THE 2,6 - DIMETYLPHENYLISOCYANIDE

During this step, the formic acid will attack one of the electrophilic sites of the acetic anhydrides two times to give formic anhydride. After 12 hours at 60°C, the 2,6-dimethylaniline is then added. The amine attacks one of the electrophilic centres of the formic anhydride to give formic acid and the target N-formyl group. The Thin Layer Chromatography show two different products, so they have to be separated with a manual column.

The second step is the cleavage of the formyl group to give the desired Isocyanide thanks to Phosphorous Oxychloride at reduced temperature because of the exothermic feature of this reaction. Here is the scheme of this second step:

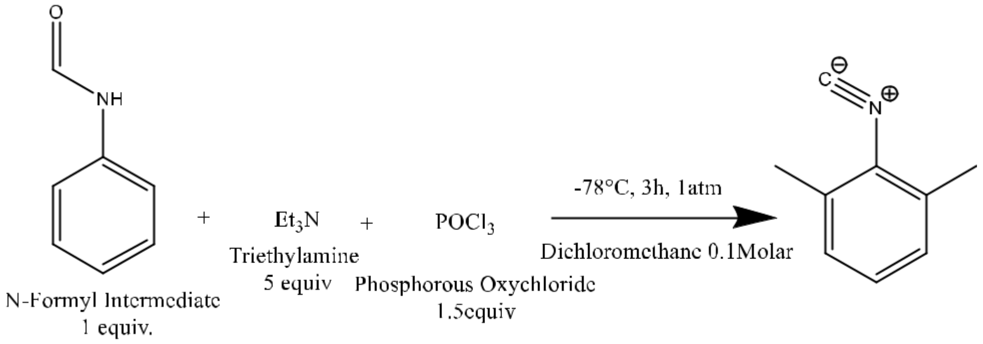


FIGURE 24: SECOND STEP OF THE SYNTHESIS OF THE 2,6-DIMETHYLISOCYANIDE

The -78°C temperature is reached using a mix of liquid Nitrogen and Ethyl Acetate (*Picture n°23*). The crude is then progressively brought back to the Room Temperature. The solvent is then evaporated in order to concentrate the reaction mixture to purify it then with a column with Dichloromethane. The following spectrum is obtained (*see Picture n°24*), showing a quite pure product, enough for synthesis. Although the amount of Isocyanide is satisfying (1.7 g), the yield is low (16% yield). This can be explained by the first separation that was made which would not have happened and led to a loss of product.

FIGURE 25: REACTION STEP UNDER LIQUID NITROGEN

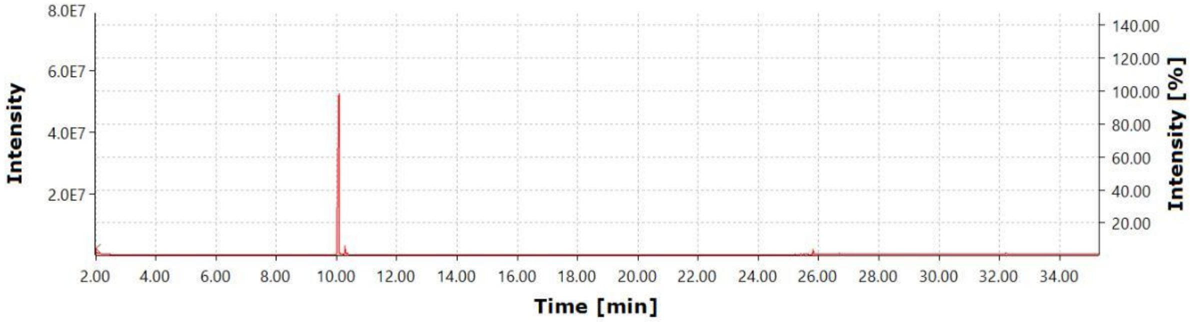


FIGURE 26: GC-MS SPECTRUM OF THE DESIRED ISOCYANIDE

II Optimisation

During this part of the Internship, the goal was to improve the yield of the synthesis by screening different conditions and different additives to see what are the effects of those ones and by the way trying to have a better idea of the mechanism that is taking place with this reaction. The point of this part is to find new conditions that provides a better yield, then optimising the reaction starting from the previous conditions, to build step by step a viable reaction. For this part, the analysis and yield calculations are based on the GC-MS spectrums only, comparing the peak area of the target product to the one of the Aryl Bromide that is still in the crude. The work up of those samples after the reaction is only taking 0.1 mL from the crude with a syringe, filtering it, putting it in a 1.5 mL vial, and diluting it with Acetonitrile. Even if this is not the most accurate analysis technique, it will avoid the extraction of the crude from N,N-Dimethylacetamide, which is time-saving. That way, more reactions could be performed. The interesting thing this fast analysing gives is the trend to follow to improve the reaction conditions.

A) Screening of reaction conditions

This first step consists in observing the impact of the screening of some reagents that could change the interactions between them and improve the yield.

The reagents that will be screened here are the Thiophenol, the Isocyanide, and the Nickel source, here, Nickel (II) Chloride. The other reaction conditions remain unchanged, only the number of equivalents of the chosen reagents will vary.

1) Screening of the isocyanide

First, the number of equivalents of Isocyanide were screened, to see the impact on the reaction’s yield.

Equivalents of Isocyanide	Mass weighted (Mg)	Yield (%)
2	26.2	8.67
1	13.1	13.55
0.5	0.56	12.83

TABLE 1 : SCREENING OF THE ISOCYANIDE

The best conditions here are the ones using 1 equivalent of isocyanide, a condition that will be kept for the next steps of the optimisation.

Then, the number of equivalents of the Thiophenol were screened.

2) Screening of the Thiophenol

Equivalents of Thiophenol	Volume measured (µL)	Yield (%)
3	30	8.55
2.5	25	12.08
2	20	10.16
1.5	15	12.81
1	10	9.60
0.5	5	2.58

TABLE 2 : SCREENING OF THE THIOPHENOL

The starting condition (1.5 equivalent) was the best one, the other ones are not able to provide the same yield. This condition will be kept for further study of this experiment.

3) Screening of the Nickel Chloride

Then, the number of equivalents of the Nickel (II) Chloride was screened.

Equivalents of Nickel Chloride (%mol)	Mass weighted (Mg)	Yield (%)
5	1	13.26
10	2	12.84
20	4	12.83

TABLE 3 : SCREENING OF THE NICKEL (II) CHLORIDE

Here again, the starting condition was the best one, meaning that 5% molar amount of Nickel Chloride is the best condition here.

This allows a first statement of the optimisation of the reaction, with this scheme:

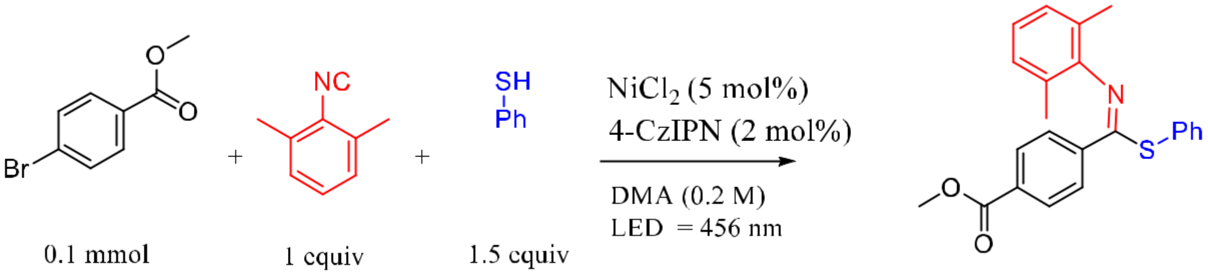


FIGURE 27: FIRST MODIFICATION OF THE REACTION SCHEME

According to the König Group[3], the best condition reaction implies a 0.5 molar reaction, so the following conditions will be kept for further optimisation:

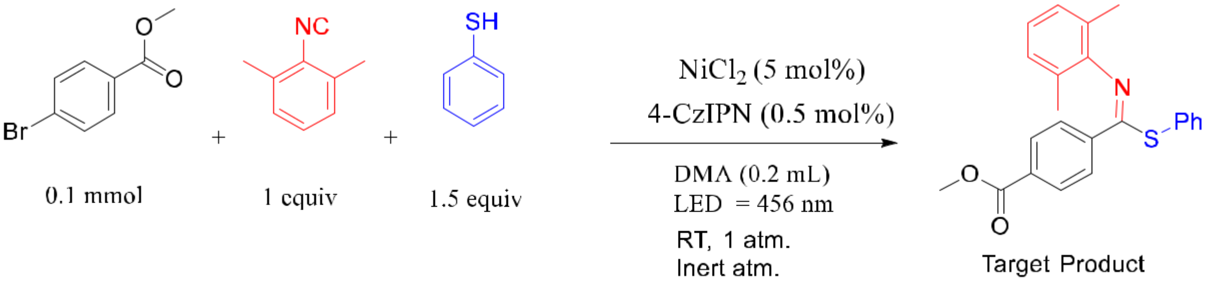


FIGURE 28: SECOND MODIFICATION OF THE REACTION SCHEME

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[3]: Ghosh, I., Shlapakov, N., Karl, T. A., Düker, J., Nikitin, M., Burykina, J. V., Ananikov, V. P., & König, B. (2023). General cross-coupling reactions with adaptive dynamic homogeneous catalysis. *Nature*. https://doi.org/10.1038/s41586-023-06087-4

B Further Optimisation

1) Impact of the Isocyanide

Now that the starting reaction conditions are optimised, the next step of the optimisation could begin by screening the Nickel Source and screening some additives.

The first experiment was designed to observe the impact of the Isocyanide on the reaction.

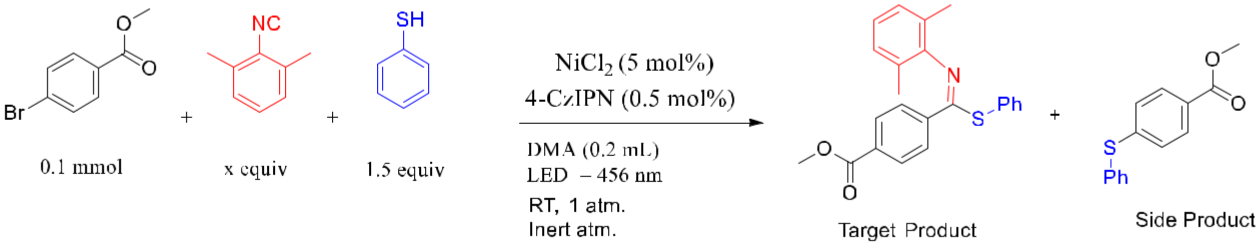

FIGURE 29: SCHEME REACTION FOR THE IMPACT OF THE ISOCYANIDE

Equivalents of Isocyanide (Equiv.)	Mass weighted (Mg)	Target Product Yield (%)	Side Product Yield (%)
0	0	0	66.06
1	13.1	19.06	1.22

TABLE 4 : IMPACT OF THE PRESENCE OF THE ISOCYANIDE

That way, the formation of the side product resulting from the combination of the Aryl Bromide and the thiol is favoured in the absence of the isocyanide, whereas in the presence of the Isocyanide, the side-product yield plummets and the target-product yield slightly increases. This means that the step of the 1,1 migratory insertion of aryl moiety in the Isocyanide is not possible because of the absence of the compound. This directly gives the coupling product. The other side product, the homocoupling of the thiophenol, is still observed.

With the aim of this project being to generalise this reaction to other nucleophiles like amines, the same experiment was done using aniline, in the same conditions, with and without Isocyanide. The following table is obtained:

Equivalents of Isocyanide (Equiv.)	Mass weighted (Mg)	Target Product Yield (%)	Side Product Yield (%)
0	0	0	24.11
1	13.1	0.69	0

TABLE 5 : IMPACT OF THE PRESENCE OF THE ISOCYANIDE WITH ANOTHER NUCLEOPHILE

According to (reference paper), an additional amine has to be added to the reaction. Here, the triethylamine.

Here the same effect is seen, but with a lower yield. The other impact of the use of another nucleophile is the absence of the homocoupling of the nucleophile, explained by the fact that radicals on Nitrogen atoms require a higher dissociation bond energy than for the Sulphur atoms from the thiol.

2)Screening of some Ligands

This part will pay attention on the screening of some ligands. The chosen ligands will be based on the ones available in the lab, more ligands can be tested but it would have taken too much time here. This study will be based on the following reaction conditions:

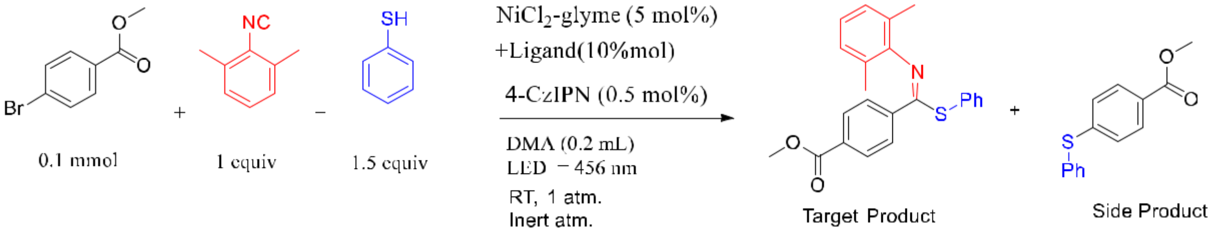

FIGURE 30: REACTION SCHEME FOR LIGAND SCREENING

Ligand	Target Product Yield (%)	Side Product Yield (%)
L1	18.65	0.66
L2	15.05	0.34
L3	49.63	1.01
L4	40.71	0.71
L5	-	1.49
L6	-	1.85
L7	1.25	-

TABLE 6 : SCREENING OF DIFFERENT LIGANDS

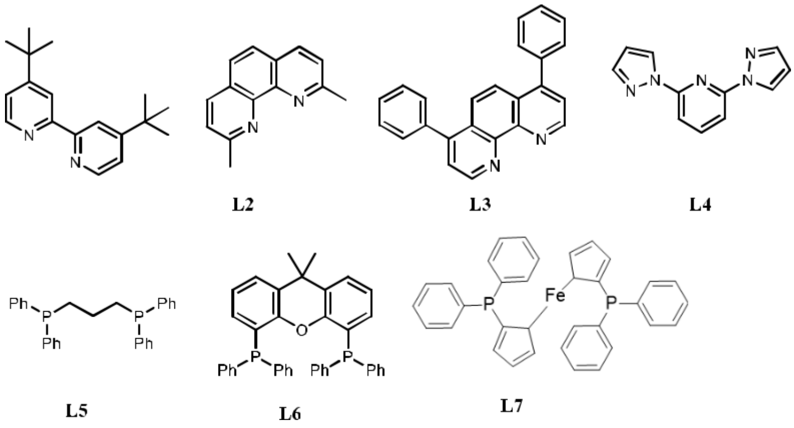

FIGURE 31: TESTED LIGANDS FOR THE SCREENING

The best ligand which gives the best yield according to the GC-MS analysis, is the Neocuproine (L2). The other one which works is the (L4). This may be explained by the absence of a rotative axis and a ortho-methyl group which helps the coordination to the Nickel for L3, and a higher denticity for L4. Regarding phosphorous-based ligands, the low yields may be explained by their strong binding to the complex, making it less reactive.

For the next experiments, the Neocuproine will be chosen as a ligand in the reaction conditions.

3) Other additives

Starting from the previous conditions, some additives were tried to improve this reaction conditions. The aim is to improve the yield of this reaction, and to screen some conditions and to have a better understanding of the mechanism and the impact of those additives on it.

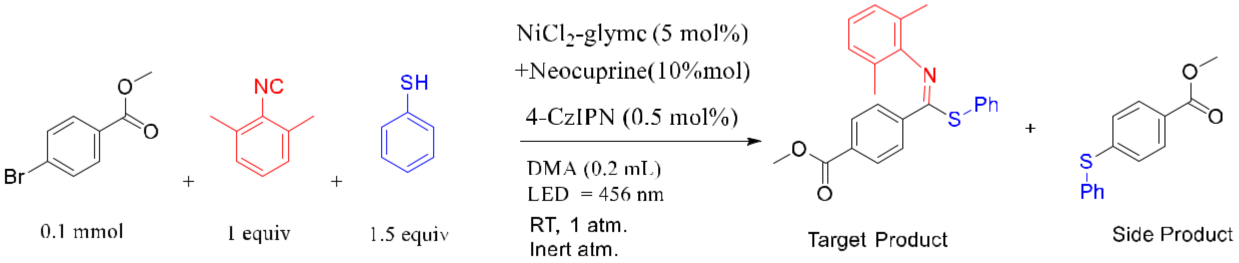

FIGURE 32: REACTION SCHEME FOR THE SCREENING OF SOME ADDITIVES

The results are presented in the following table:

Ligand	Target Product Yield (%)	Side Product Yield (%)
Tert-Butylamine	36.76	54.6
Cyclohexylamine	32.43	?
Triphenylamine	3.88	48.35
Copper Bromide II	-	13.05
Tetrabutylammonium Bromide	35,18	19,02

TABLE 7 : SCREENING OF SOME ADDITIVES

The first additives that were used are amines. The purpose here is to observe the impact of an electron sucker in the reaction, amines allowing a better circulation of radicals in the vial. The results extracted from these experiments are that there is a clear selectivity: the addition of an amine leads to the formation of the side product, which decreases the yield of the target product. They may also act as a base for simple aromatic substitution.

The reaction uses the isocyanide as a ligand with the Nickel source but can also act as a radical source for example. The issue of this reactivity is that if the Nickel source is too much coordinated with the isocyanide, the reaction will not be able to be efficient enough and the yield will decrease. To avoid this problem, an additive was tried: Copper Bromide (II). The aim here is to delay the action of the isocyanide, making it complexate on the Copper rather than on the Nickel Source and reduce this negative impact the isocyanide could have on the reaction. But here, it has not a positive effect at all on the reaction, as the target product was absolutely not formed.

The last tried additive was the tetrabutylammonium bromide, in order to see the impact of another radical source on the reaction. Apparently, it has the same effect as the addition of amines, as the yield of the target product is quite lower and above all, the side product's yield has increased.

Now that the yield is better, the first tries of isolations can start, to have a better idea of the real isolated yield, because the GC-MS analysis without internal standard is not precise enough.

C Isolation Optimisation

To perform this isolation, the reaction will be performed on a bigger scale to avoid the risks of losing some product and decreasing the final yield. The calculation of the yield is also made by adding an internal standard.

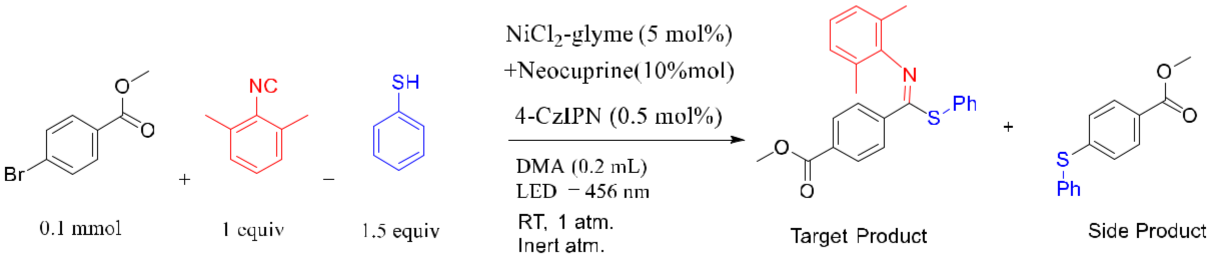

FIGURE 33: REACTION CONDITIONS FOR THE ISOLATION ATTEMPTS

The first attempt of isolation was realised with three 0,1 mmol-scale reactions, so this will be a 0,3 mmol scale. As depicted in the first part, the three reactions are gathered, and extracted with Diethyl Ether and Water. The organic phase is then purified with an automatic column. The eluant is made by a gradient of an increasing polarity starting from 2% of Ethyl Acetate and 98% of Heptane, to 15% of Ethyl Acetate, the optimum studied on Thin Layer Chromatography. The outcome of this whole process is depicted with the spectra (*see Figure n°33*). It is clear here that the product is not pure at all, and the yield is not satisfying at all, with a 5,7% yield. Another attempt must be carried out.

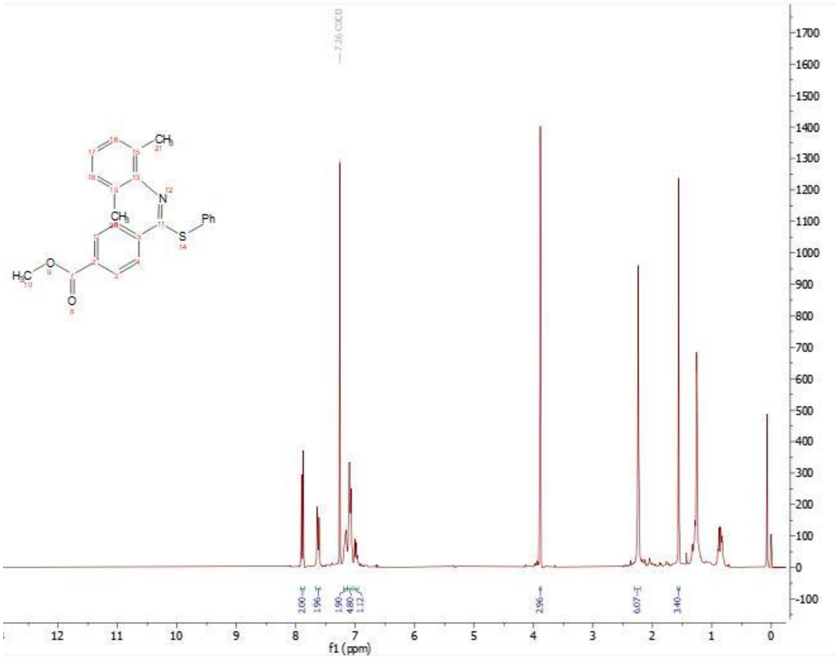

FIGURE 34: NMR SPECTRUM OF THE FIRST ISOLATION ATTEMPT

The second attempt will be performed with a higher scale and with a fewer number of reactions. This time, two reactions of 0,2 mmol scale each will be carried out to avoid the risks of losing some product by reducing the number of vials. To improve the purity of the target product's sample, the work up of the samples has been changed. To purify it, and to only let the product for the NMR sample, removing Ethyl Acetate, Heptane and grease of Heptane, the product will be mixed with Dichloromethane, then the solvent will be evaporated. This will be done again with pentane and one last time with Dichloromethane. This leads to a better purity and a better yield, 20,7% on this second experiment. But it is far from the nearly 50% expected, and in order to screen some conditions of isolation of product, a third try will be carried out.

This third try will be performed with only one reaction of a 0,4 mmol scale in the same conditions as before. The process remains the same, as well as for the workup of the second attempt. The product is now clearly obtained, pure (*see Figure n°34*), and with a quite decent yield: 30,3 %. This yield is now satisfying compared to the yield of the starting reaction (8 %) and can be the base of further experiments, with other nucleophiles, which can lead to other molecules with interesting properties.

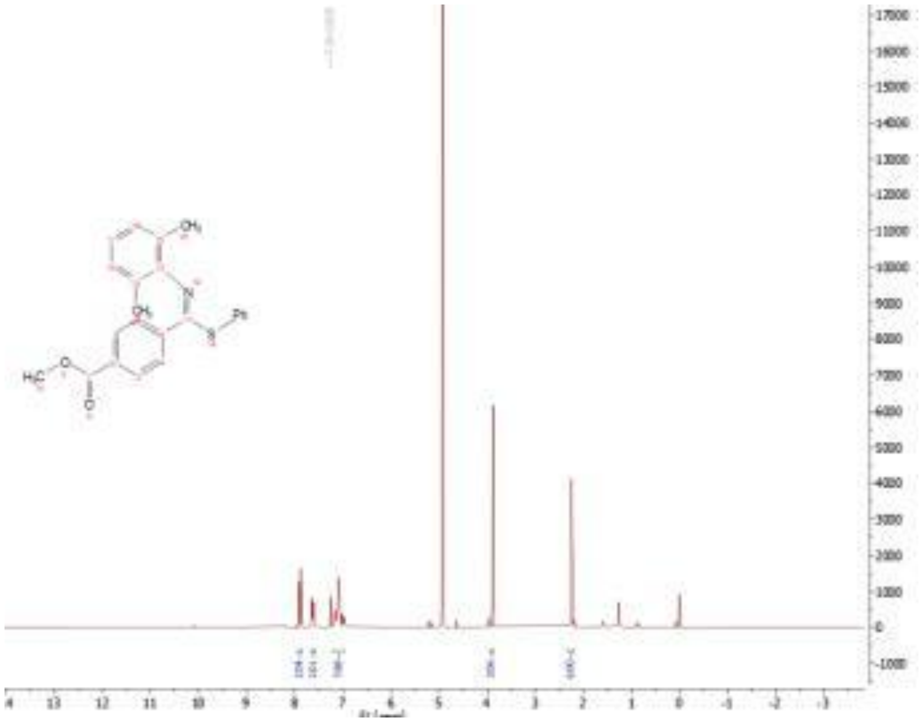

FIGURE 35: NMR SPECTRUM OF THE THIRD ISOLATION ATTEMPT

III Personal Aspect

A Completed Tasks

During this Internship, I had the opportunity to optimise the synthesis of a complex molecule, thanks to photocatalysis, Nickel-Catalysed coupling and an Isocyanide insertion. This allowed me to have a better idea of the daily life of a researcher, both in the office and in the lab. Moreover, the particularity of the Institute, located on a huge industrial chemistry campus, raises awareness about all the safety rules and plans that it implies, and this was very instructive.

All along this internship, I learned some very important practical techniques such as using a Schlenk line and a Schlenk vial, implementing Chromatography Columns, manipulating liquid nitrogen and manipulating under a glove box. I also had the chance to implement and lots of other skills regarding analysis, GC-MS, NMR, HPLC, to identify the different molecules that are formed during the reaction, and the NMR is also used to calculate the yield, by using an internal standard.

B Hardships Encountered

During this internship, there were some difficulties that I had to face, even though I had the best possible working conditions. The first one was the language, and the lab-related vocabulary, which I had to learn in the first weeks.

The other difficulty that I encountered is the complexity of the subject, with different fields of chemistry implied. This difficulty was also felt because of the project, which was quite innovative and introduced me the fundamental research. As the field of possibilities to try another reactant and other conditions was tremendous, I had sometimes to be backed by my supervisors and to ask them some pieces of advice to improve this synthesis, as no paper was really dealing with the main issues of the project.

Finally, I tried to change the electrophile in order to find more interesting molecules with properties. Even though the number of experiments to screen those reactants is not relevant enough (only few ones), the results of those experiments were absolutely not exploitable, as the target product was formed with approximately 1% yield, calculated with the GC-MS, which means that it is not very precise and 1% is the maximum yield, not the isolated one. This is explained by the fact that it is easier to use the thiol as it is more eager to create radicals than amines. This phenomenon may also explain why the double insertion of the thiol is produced in such a good yield in the different reactions.

Conclusion

To conclude, this internship was the opportunity for me to discover the daily life in an academic laboratory, and the different tasks of a researcher. This way I was introduced to the research and the fundamental research. I had to work on a project consisting in the improvement of a reaction's yield and conditions. For this, I had to screen some reactants, scales, conditions, to find the best one. I would say that for a 3-months internship, and my first experience in an academic laboratory, it was quite a success as I managed to bring the reaction's yield from 8% to 30,3% with a good purity according to the NMR spectrum. It is clearly not enough to be considered as completely optimised, but it allowed us to have a better understanding of the reactivity of the Nickel Photocatalyzed Isocyanide Insertion, which is quite unexplored for the moment.

This allowed me to learn the work of a fundamental researcher, which is very interesting for me as I plan to do a Ph-D after being graduated by the INSA. This experience in Organic Chemistry also reinforced my wish of working in this field later.

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[1]: Prier, C. K., Rankic, D. A., & MacMillan, D. W. C. (2013). Visible Light Photoredox Catalysis with Transition Metal Complexes : Applications in Organic Synthesis. *Chemical Reviews*, *113*(7), 5322-5363. https://doi.org/10.1021/cr300503r

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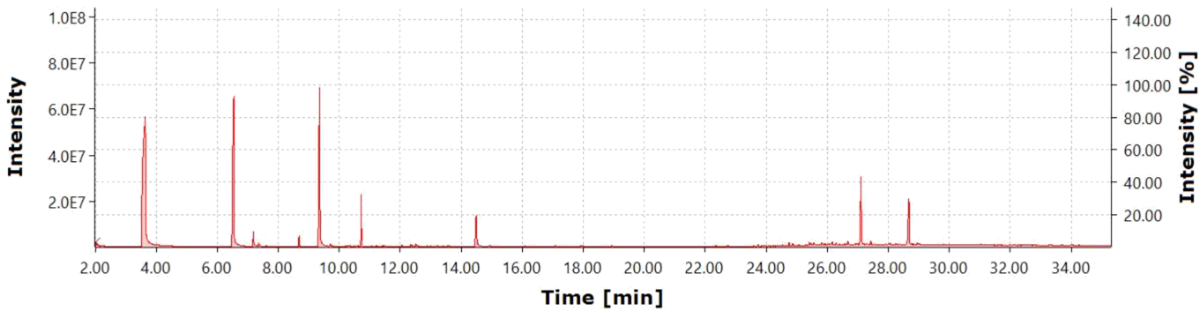
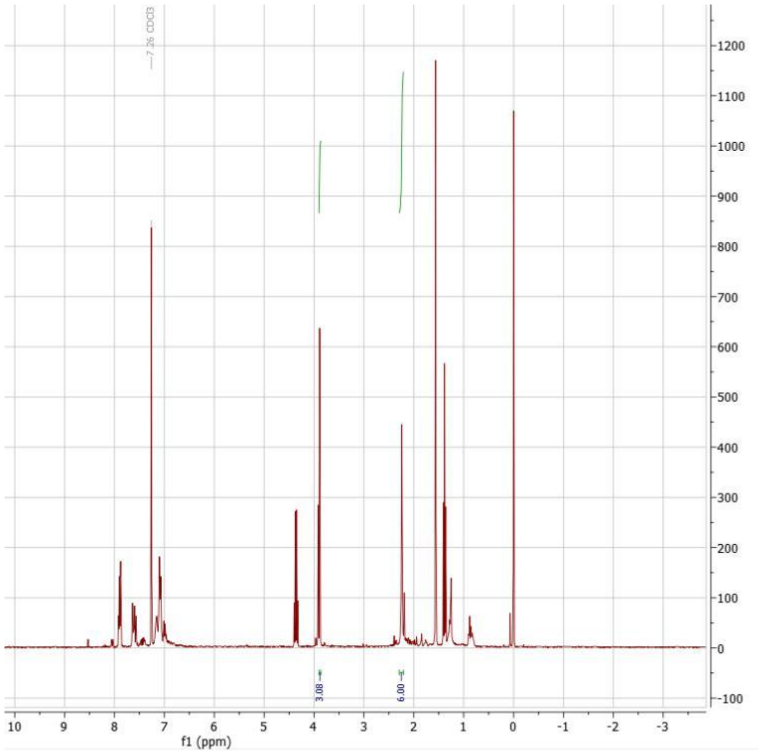
[6]: Zhu, C., Yue, H., Chu, L., & Rueping, M. (2020). Recent advances in photoredox and nickel dual-catalyzed cascade reactions : pushing the boundaries of complexity. *Chemical Science*, *11*(16), 4051-4064. https://doi.org/10.1039/d0sc00712a

Appendices:

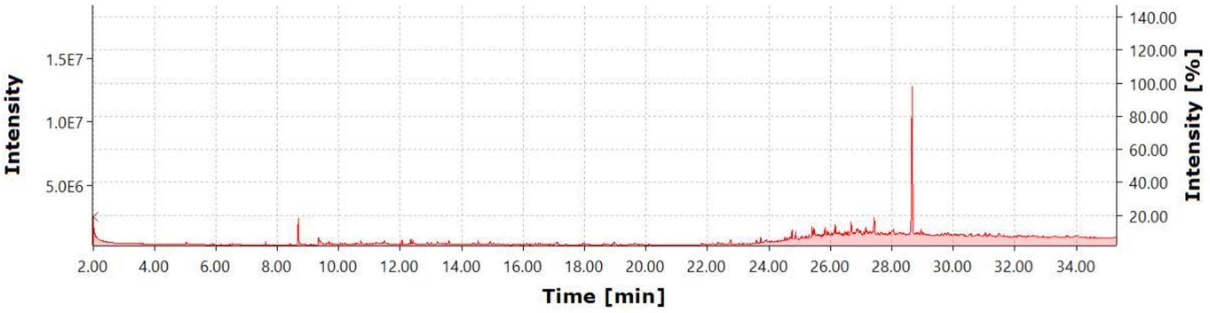
List of appendices:



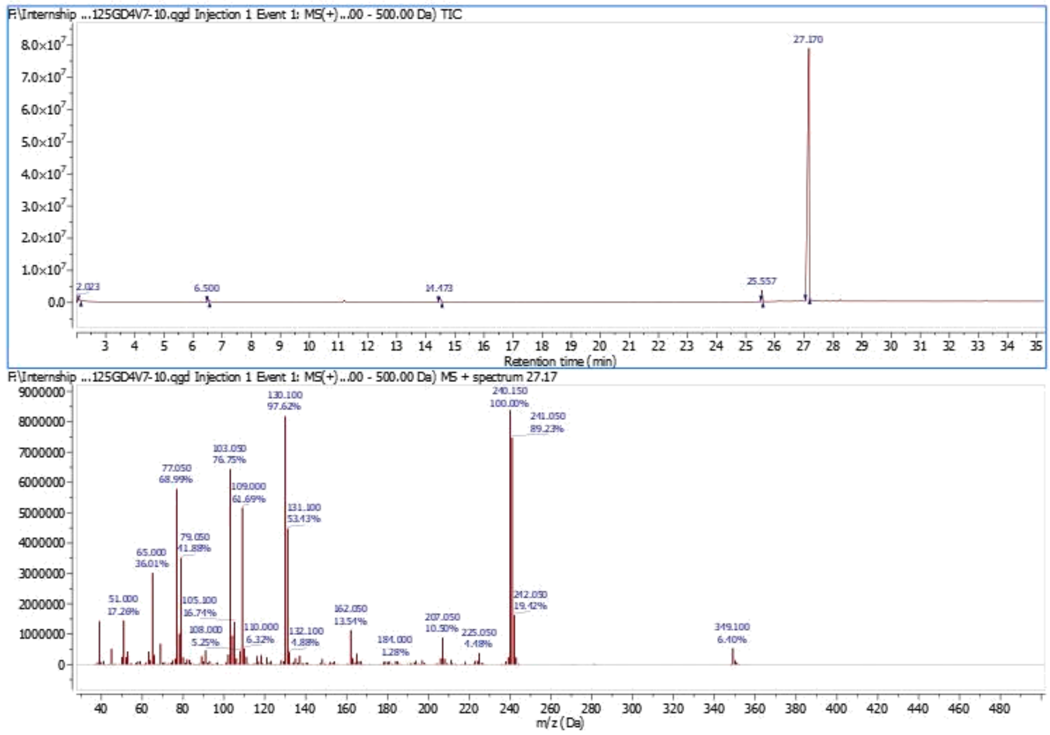
APPENDIX 1: GC-MS SPECTRUM OF THE CRUDE OF THE FIRST ATTEMPT



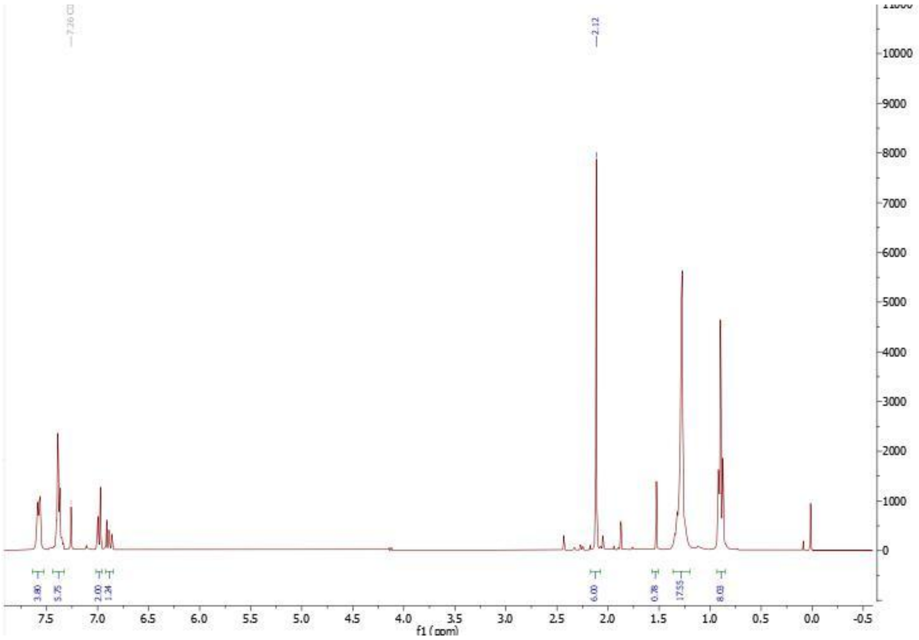
APPENDIX 2: NMR SPECTRUM OF THE FIRST ATTEMPT OF ISOLATION



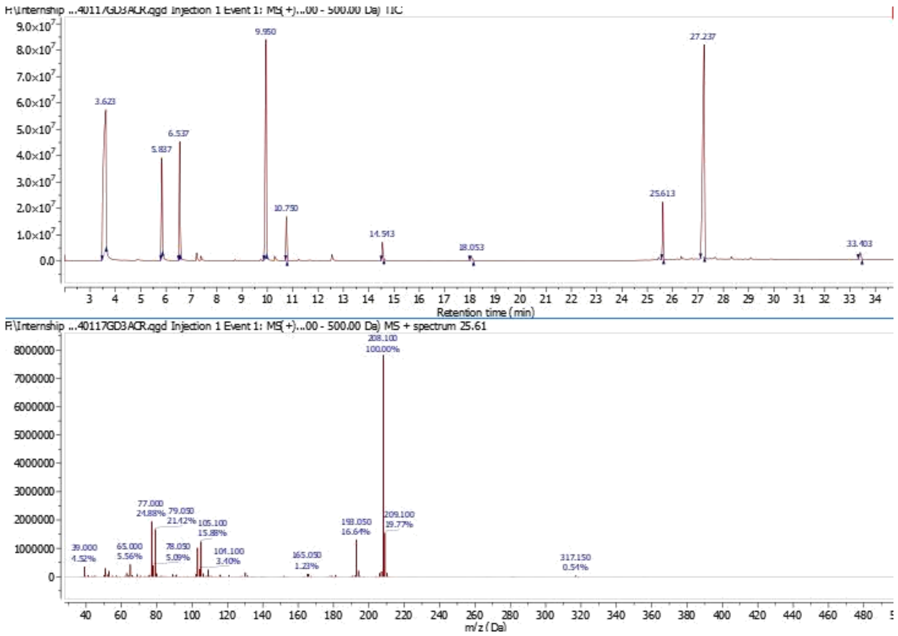
APPENDIX 3: GC-MS OF THE FIRST ATTEMPT OF ISOLATION



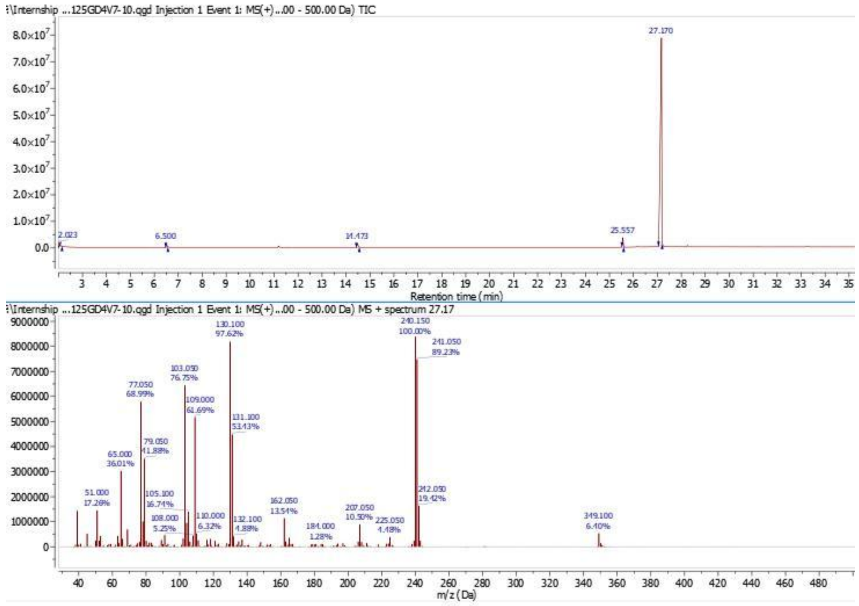
Appendix 4: GC-MS Spectrum of the second attempt



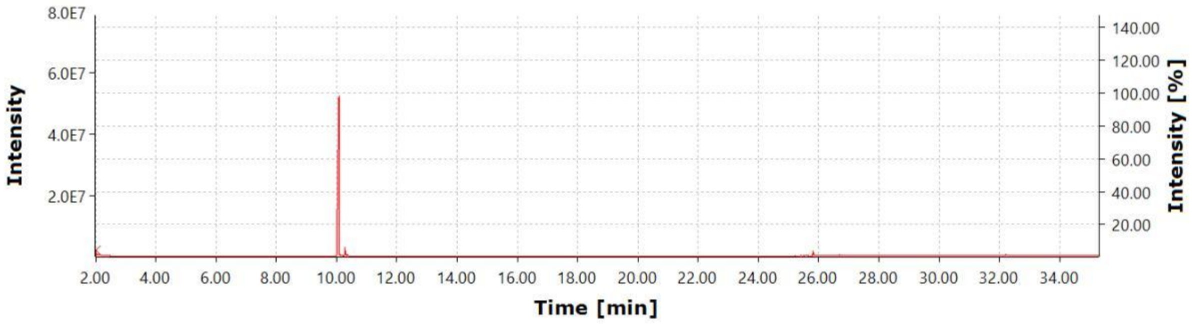
Appendix 5: NMR Spectrum of the second attempt



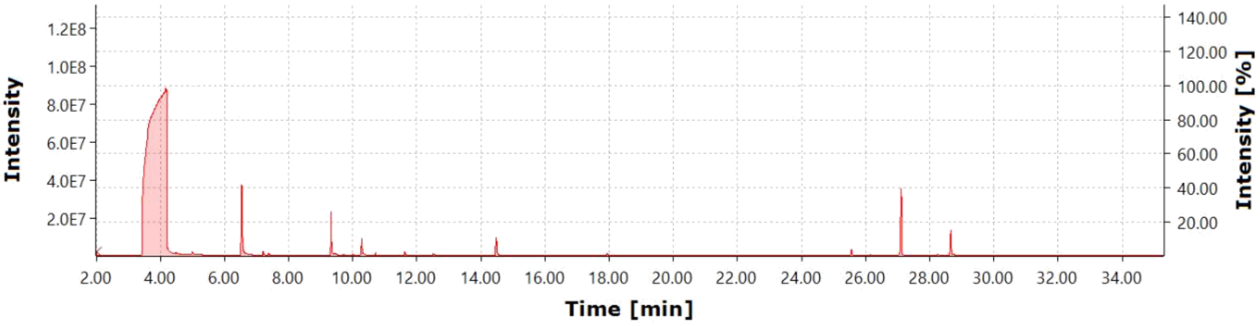
APPENDIX 6: GC-MS SPECTRUM OF THE THIRD ATTEMPT



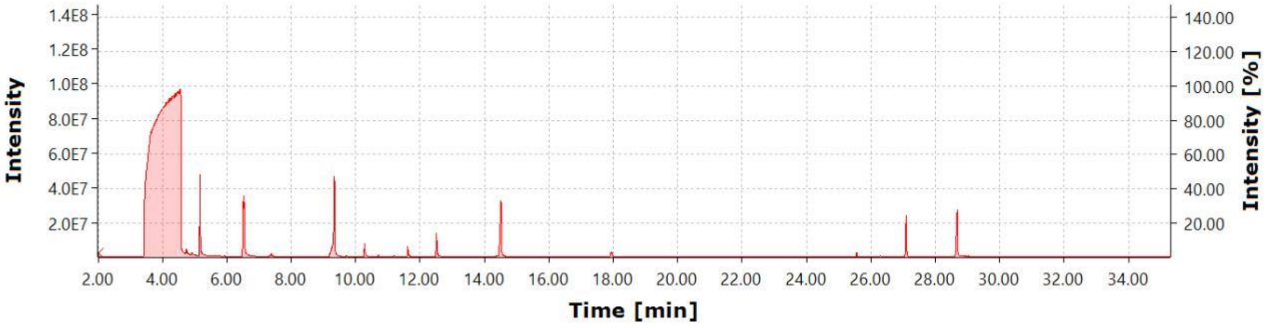
APPENDIX 7: GC-MS SPECTRUM OF THE THIRD ATTEMPT AFTER ISOLATION



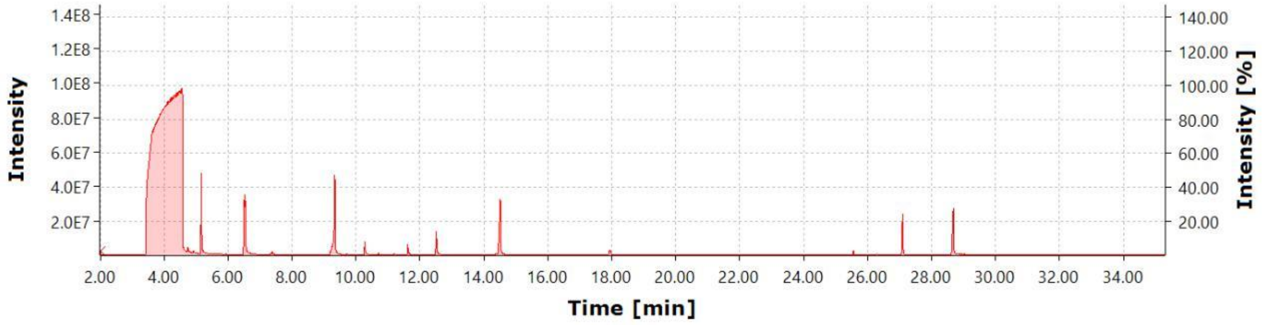
APPENDIX 8: GC-MS SPECTRUM OF THE DESIRED ISOCYANIDE



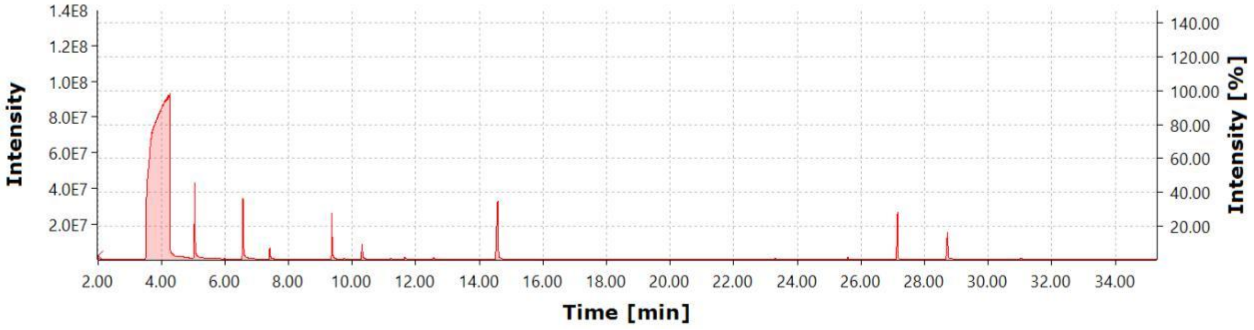
Appendix 9: GC-MS Spectrum of the Screening reaction with 2 equivalents of isocyanide crude



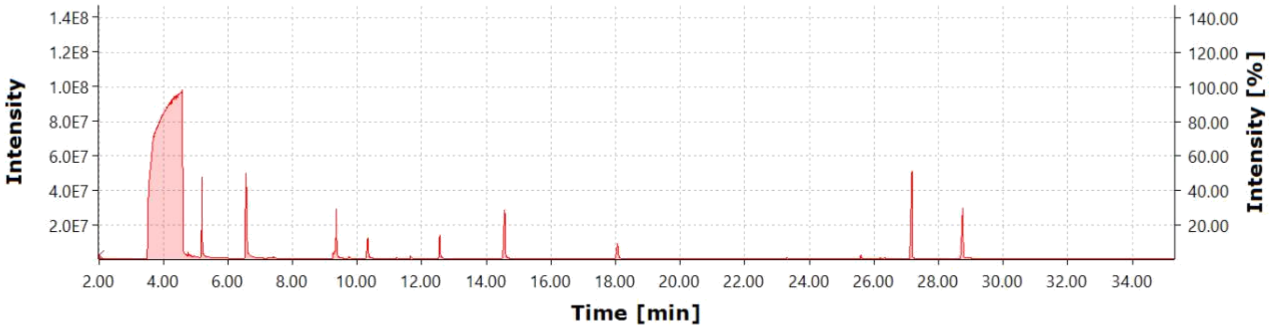
Appendix 10: GC-MS Spectrum of the Screening reaction with 1 equivalent of isocyanide



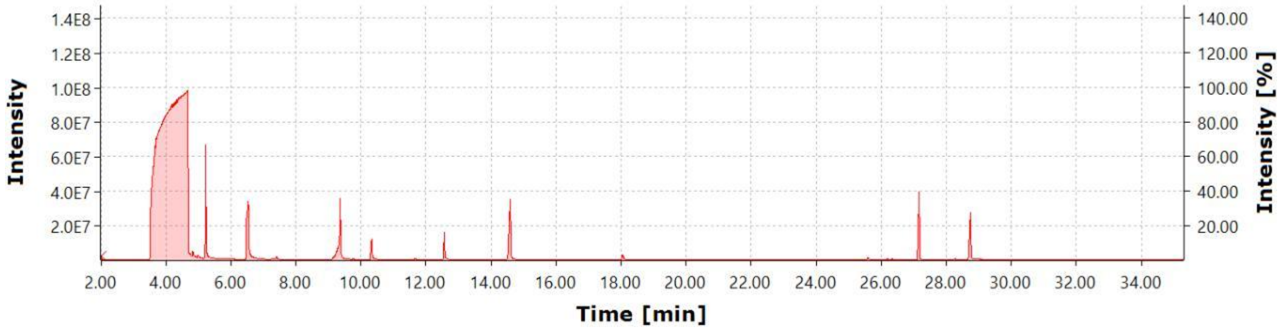
Appendix 11: GC-MS Spectrum of the Screening reaction with 0.5 equivalent of isocyanide



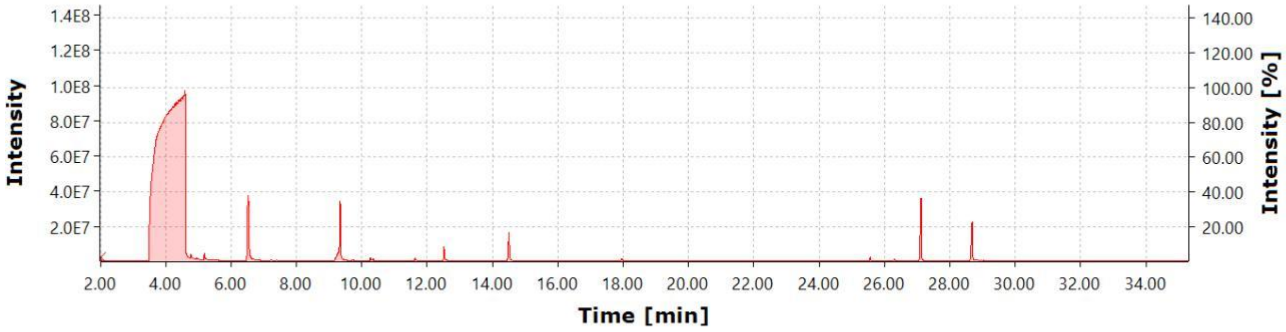
Appendix 12: GC-MS Spectrum of the Screening reaction with 3 equivalents of thiophenol



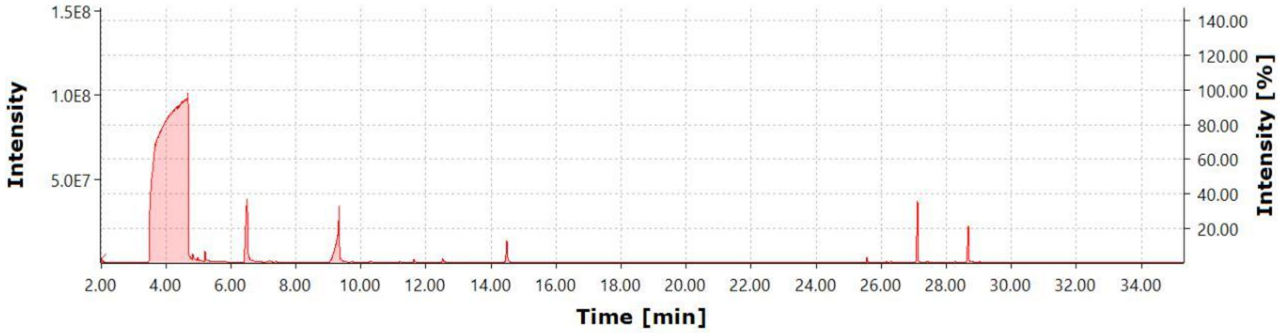
Appendix 13: GC-MS Spectrum of the Screening reaction with 2.5 equivalents of Thiophenol



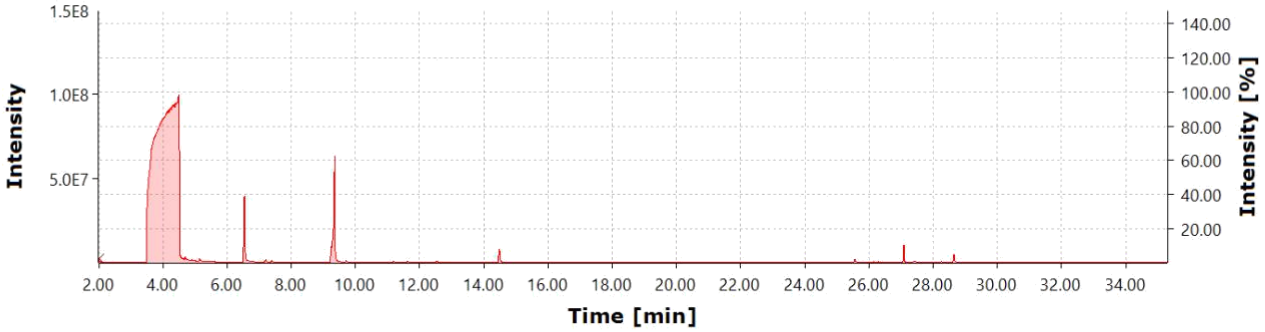
Appendix 14: GC-MS Spectrum of the Screening reaction with 2 equivalents Thiophenol



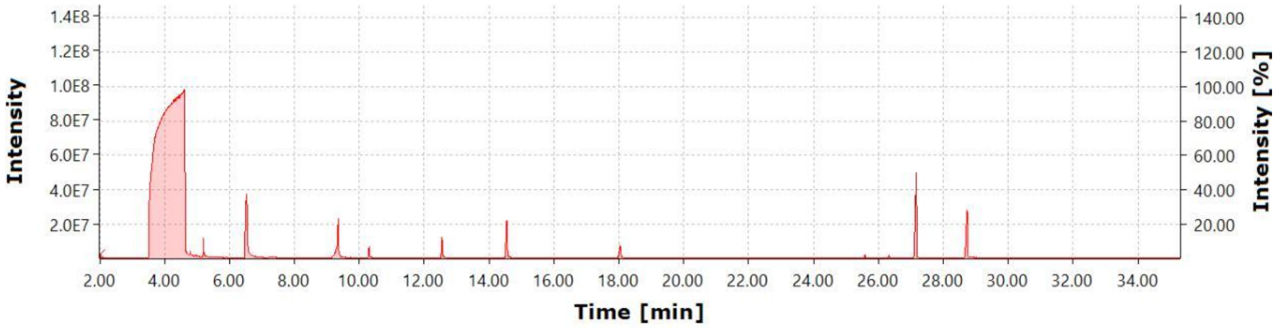
Appendix 15: GC-MS Spectrum of the Screening reaction with 1.5 equivalents of Thiophenol



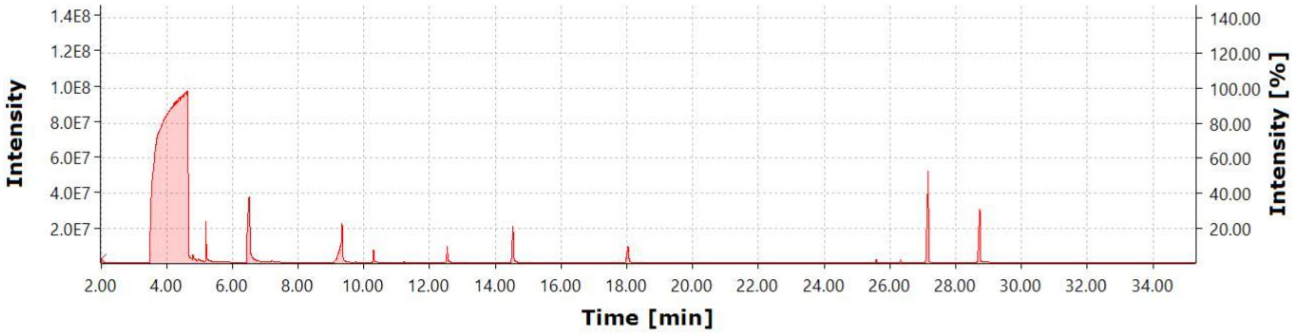
Appendix 16: GC-MS Spectrum of the Screening reaction with 1 equivalent of thiophenol



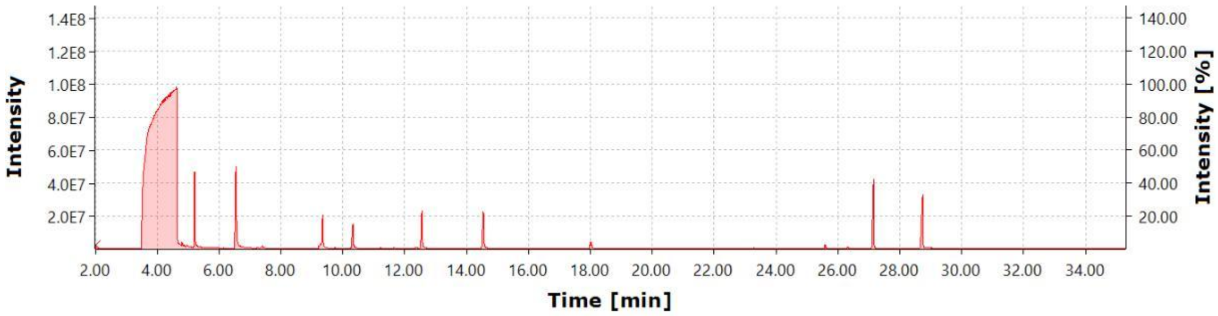
Appendix 17: GC-MS Spectrum of the Screening reaction with 0.5 equivalent of Thiophenol



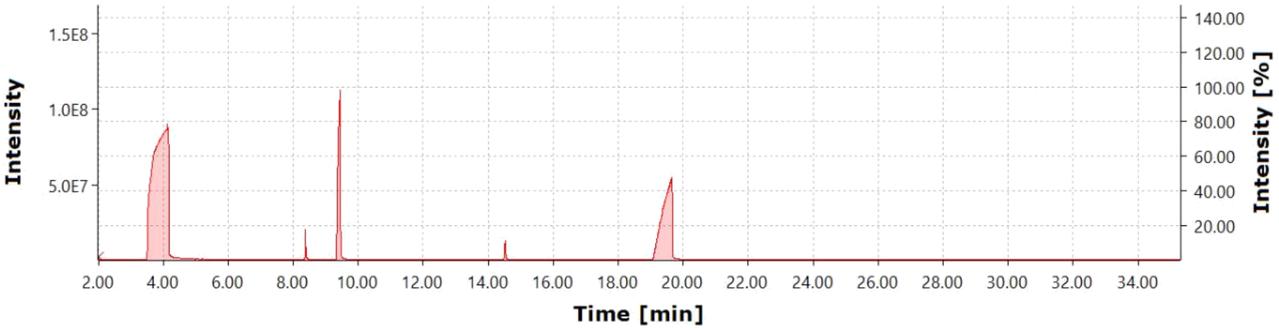
Appendix 18: GC-MS Spectrum of the Screening reaction with 5% mol of Nickel (II) Cholride



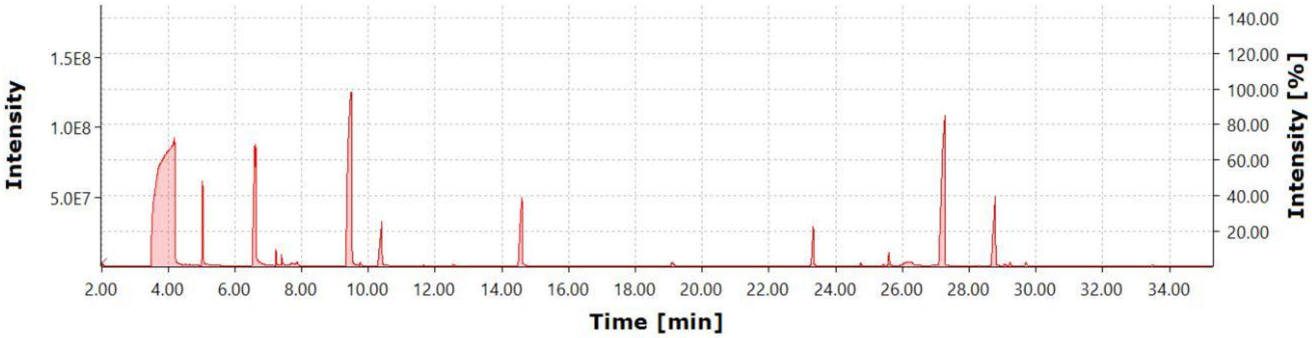
Appendix 19: GC-MS Spectrum of the Screening reaction with 10% mol of Nickel (II) Chloride



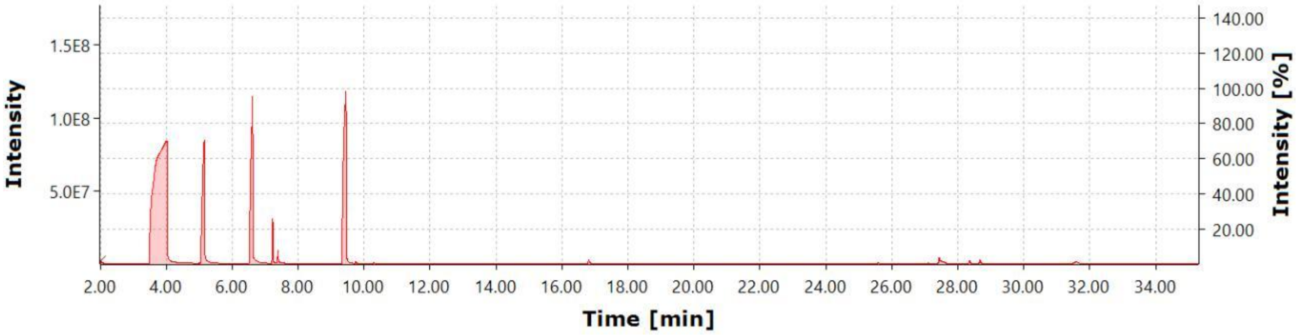
Appendix 20: GC-MS Spectrum of the Screening reaction with 20% mol of Nickel (II) Chloride



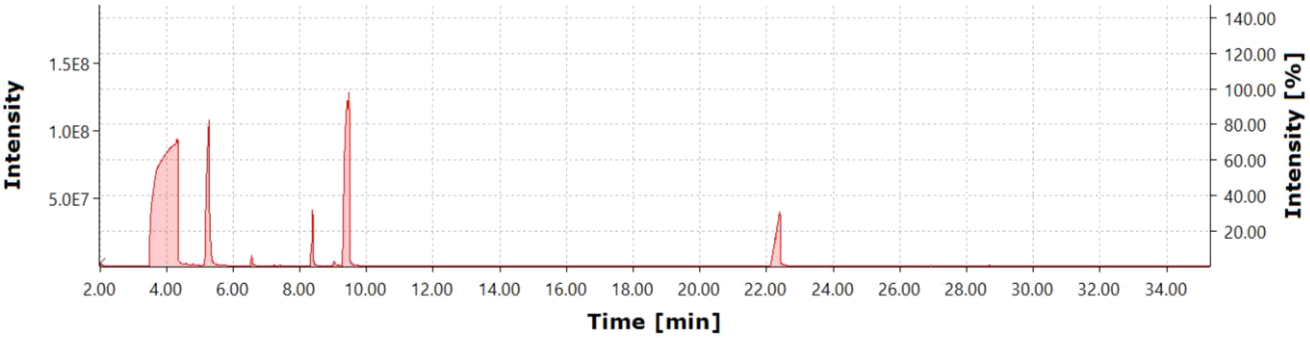
Appendix 21: GC-MS Spectrum of the Screening reaction with 0 equivalent of isocyanide



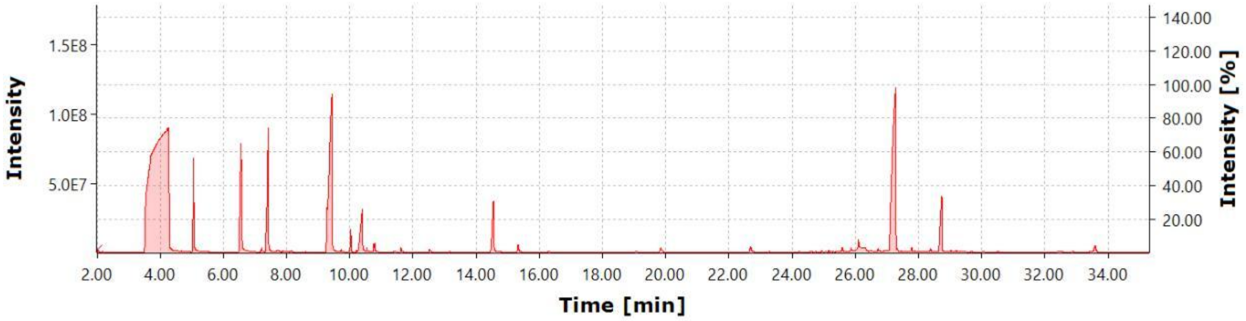
Appendix 22: GC-MS Spectrum of the Screening reaction with 1 equivalent of isocyanide



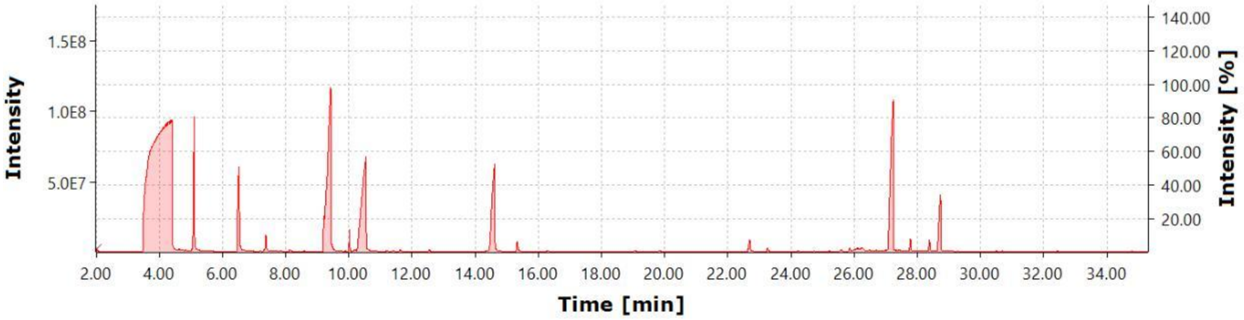
Appendix 23: GC-MS Spectrum of the Screening reaction with 0 equivalent of isocyanide and aniline



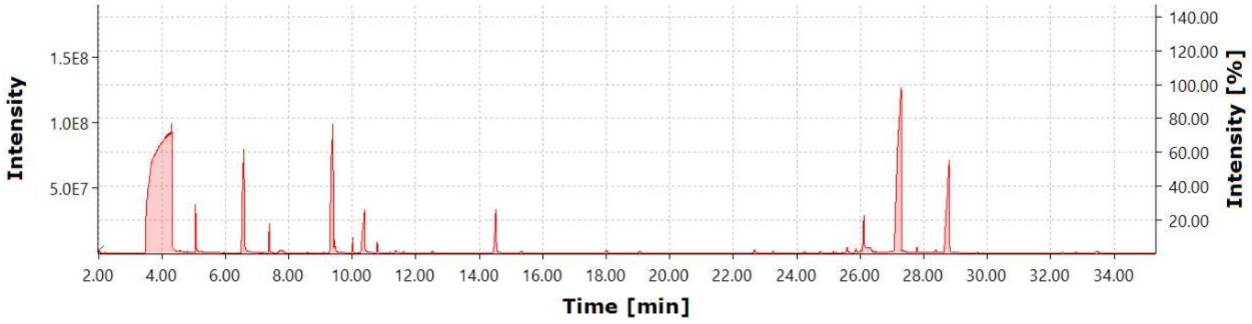
APPENDIX 24: GC-MS SPECTRUM OF THE SCREENING REACTION WITH 1 EQUIVALENT OF ISOCYANIDE AND ANILINE



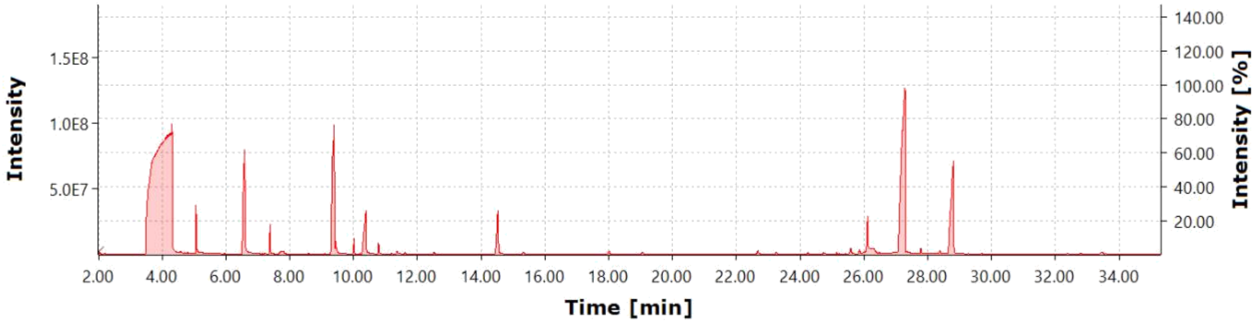
APPENDIX 25: GC-MS SPECTRUM OF REACTION USING (L1)



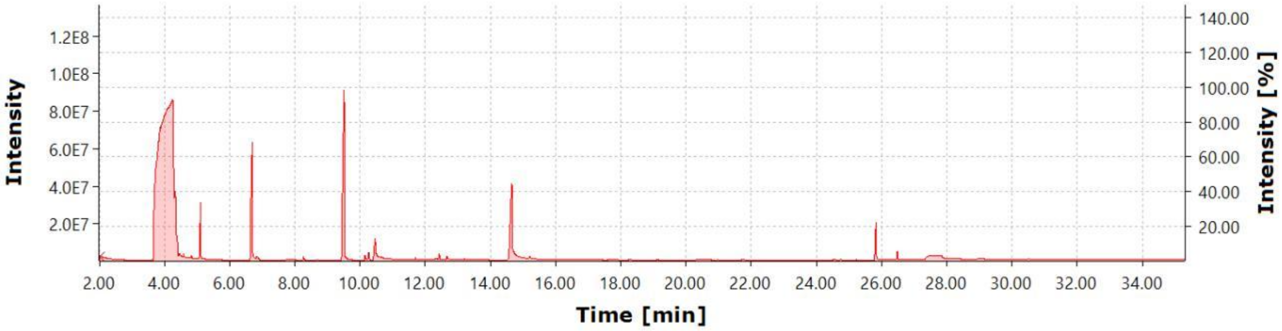
APPENDIX 26: GC-MS SPECTRUM OF REACTION USING (L2)



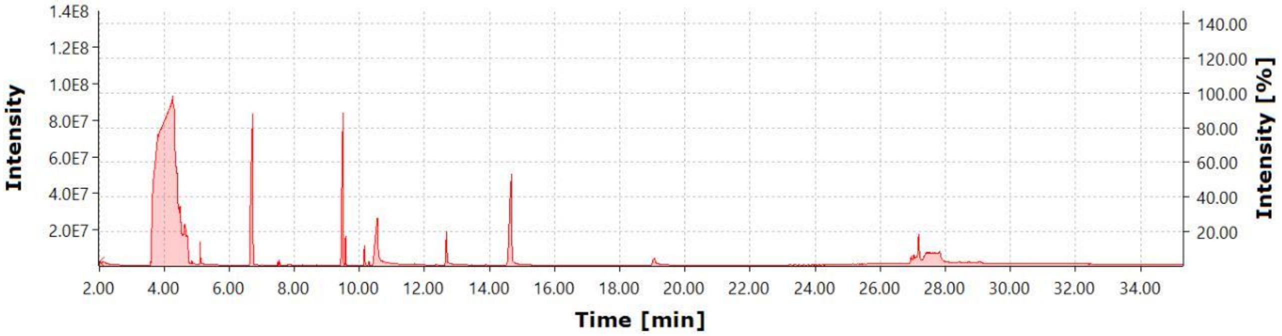
APPENDIX 27: GC-MS SPECTRUM OF REACTION USING (L3)



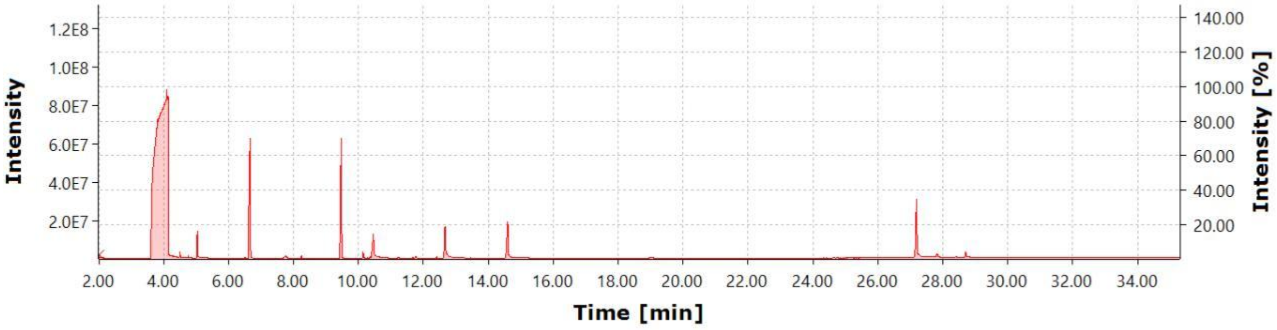
Appendix 28: GC-MS Spectrum of reaction using (L4)



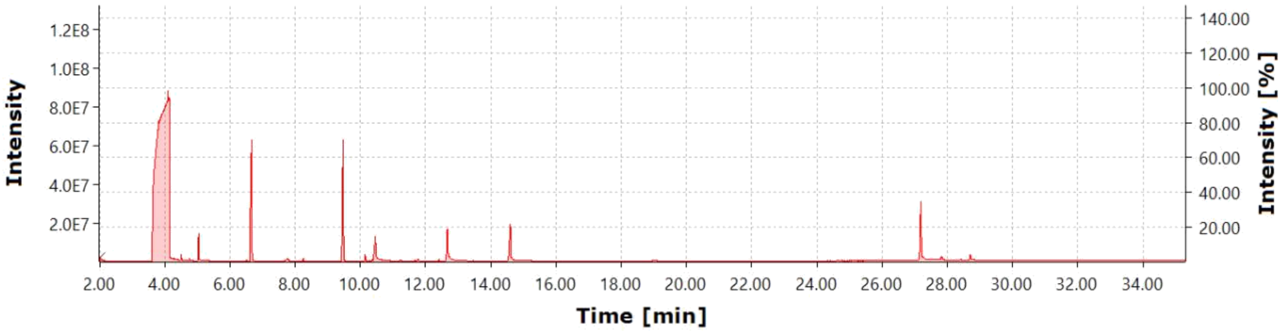
Appendix 29: GC-MS Spectrum of reaction using (L5)



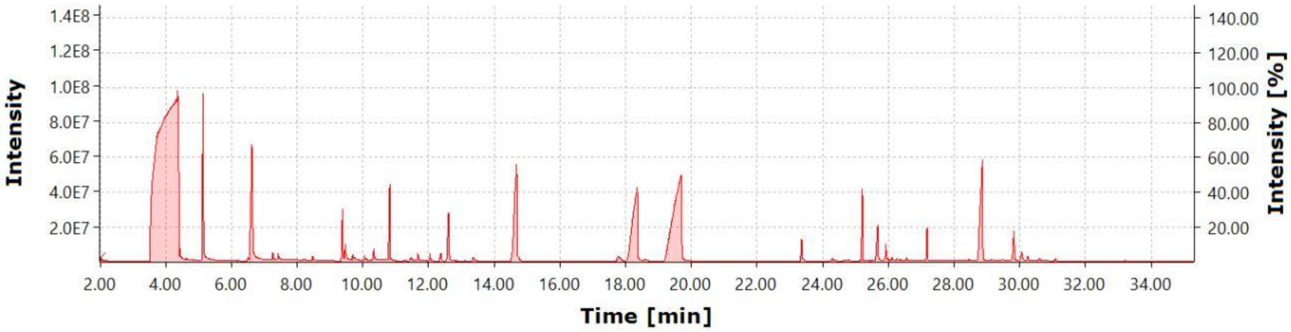
Appendix 30: GC-MS Spectrum of reaction using (L5)



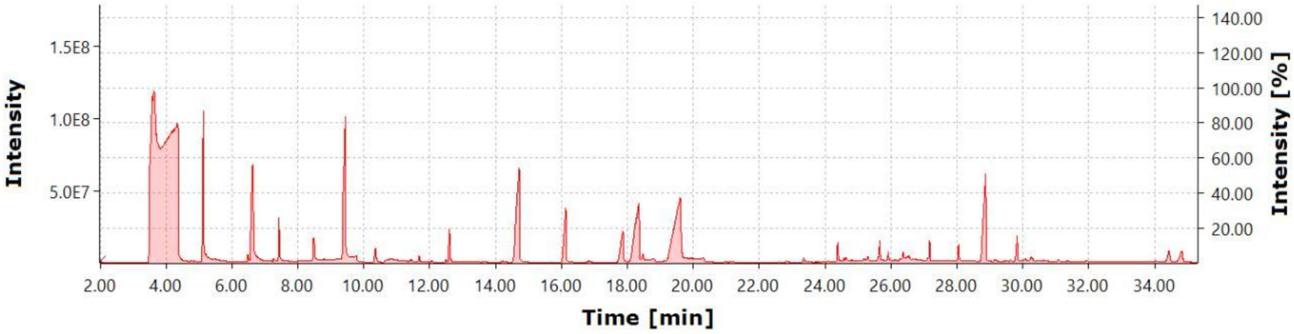
Appendix 31: GC-MS Spectrum of reaction using (L6)



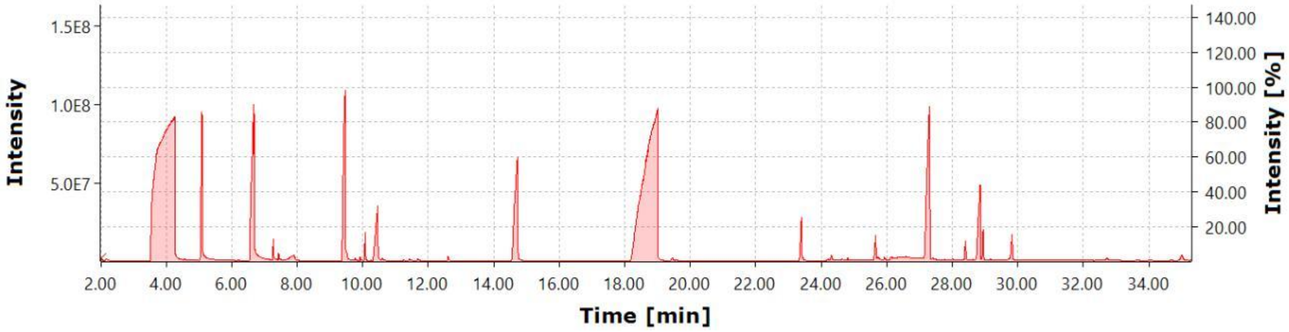
Appendix 32: GC-MS Spectrum of reaction using (L7)



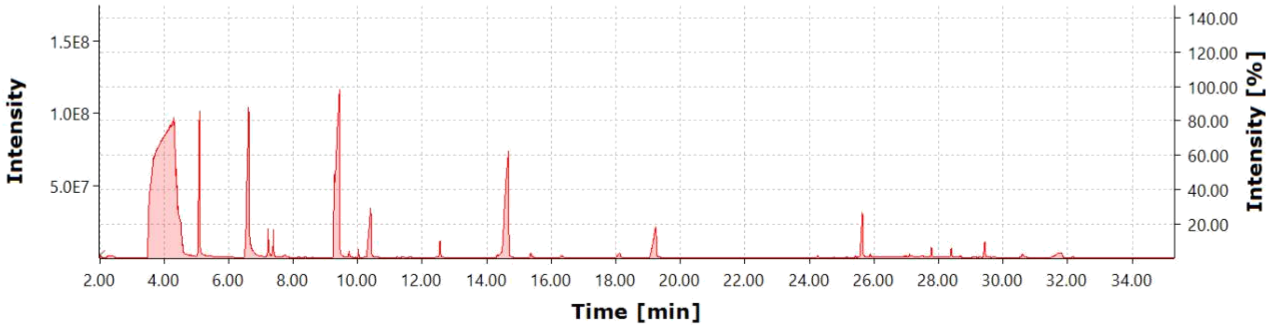
Appendix 33: GC-MS Spectrum of reaction using tert-butyl amine



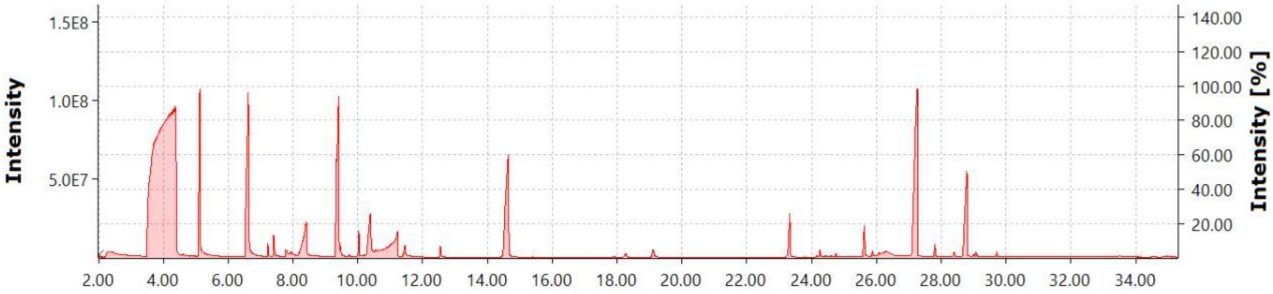
Appendix 34: GC-MS Spectrum of reaction using cyclohexyl amine



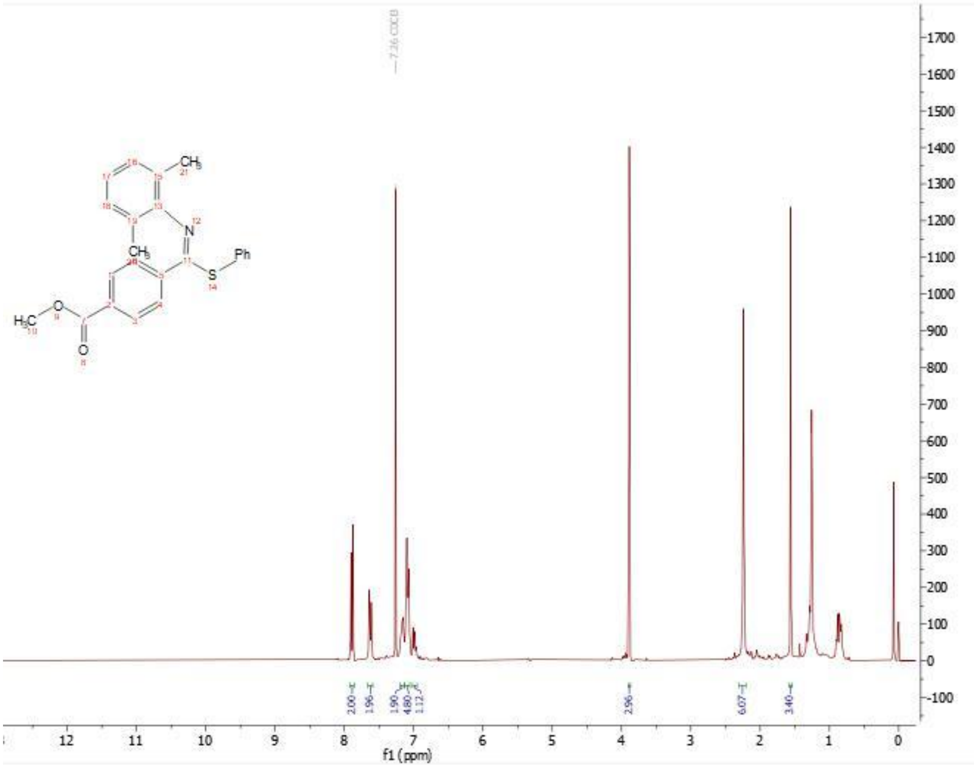
Appendix 35: GC-MS Spectrum of reaction using triphenylamine



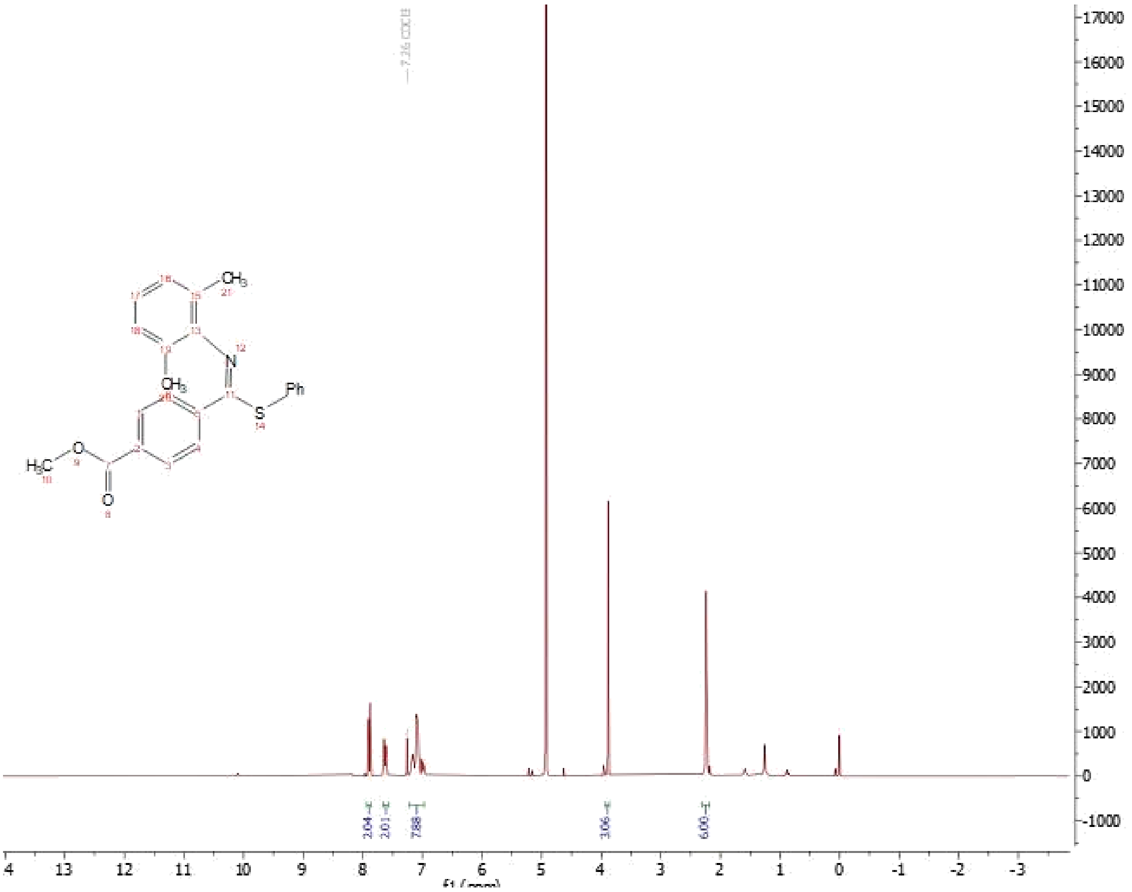
Appendix 36: GC-MS Spectrum of reaction using Copper Bromide (II)



Appendix 37: GC-MS Spectrum of reaction using Tetrabutylammonium bromide



Appendix 38: NMR Spectrum of the first isolation attempt



APPENDIX 39: NMR SPECTRUM OF THE THIRD ISOLATION ATTEMPT

APPENDIX 40: NMR MEASURING DEVICE

APPENDIX 41: GC-MS MEASURING DEVICE

APPENDIX 42: LC-MS MEASURING DEVICE

APPENDIX 43: AUTOMATED CHROMATOGRAPHY COLUMN