UNIVERSITY OF OVIEDO

FACULTY OF CHEMISTRY

Unleashing the Power of Katritzky Salts for the Formation of C-C Bonds (Organic Chemistry)

End-of-Degree Project

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INDEX

ABBREVIATIONS

CaSR – Calcium-sensing receptor

DCM – Dichloromethane

DMF – Dimethylformamide

DMSO – Dimethylsulphoxide

EtOAc – Ethyl acetate

Et_2O – Diethyl ether

Hex – Hexane

MeOH – Methanol

NMR – Nuclear Magnetic Resonance

NPS-2143 – 2-chloro-6-[(2R)-3-([1,1-dimethyl-2-(2-naphthalenyl)ethyl]amino)-2-hydroxypropoxy]benzonitrile

PC – Photocatalyst

Rf – Retention factor

SCE – Saturated Calomel Electrode

SET – Single Electron Transfer

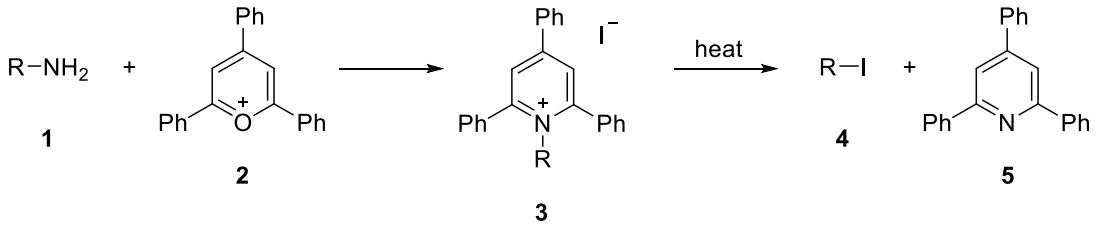
TLC – Thin Layer Chromatography

TMS – Tetramethylsilane

1. INTRODUCTION

Over the years, pyridinium salts have become extremely relevant building blocks in organic synthesis due to their impressive versatility. Pyridinium salts can be used to synthesize pyridinic derivatives, such as dihydropyridines, tetrahydropyridines, piperidines and indolizines; as well as undergo ring openings resulting in conjugated dienes, dienals, and diamines. [1] Katritzky salts are a sub-group of these compounds that can form radicals, further expanding their utility as intermediates in synthetic routes.

Katritzky salts are pyridinium salts that present three phenyl substituents on positions 2, 4, and 6 of the pyridine ring. These phenyl groups make them quite bulky and enhance their performance as leaving groups. This property made them the subject of study of Alan Katritzky in the 70's, who developed a procedure to convert primary amines into iodides using pyridinium salts as intermediates. Pyridinium iodides **3** could be synthesized from pyrylium iodides **2** and alkyl-, benzyl- or pyridyl-amines **1** Through pyrolysis, pyridinium iodides decompose into 2,4,6-triphenylpyridines **5** and the corresponding iodides **4** (Scheme 1).[2]

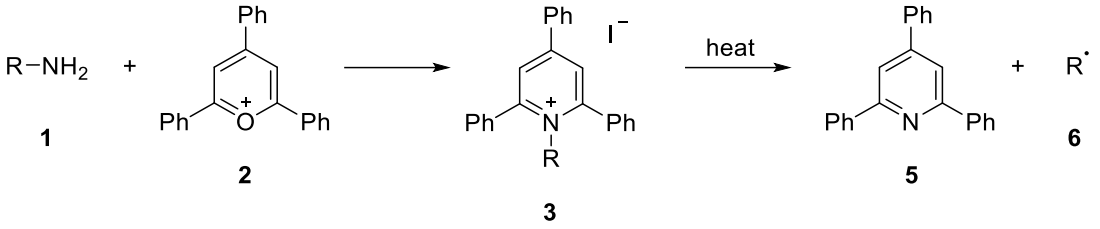


R = Alkyl, benzyl, pyridyl

Scheme 1: Formation of a Katritzky salt and subsequent pyrolysis into the corresponding alkyliodide.

Katritzky salts are stable to both air and moisture, and can be prepared through a single condensation step between a primary amine and 2,4,6-triphenylpyrylium salts; for most synthetic routes 2,4,6-triphenylpyrylium tetrafluoroborate is used, as it is commercially available.[3]

The amine functional group has been thoroughly studied over the years; amines are present in a wide range of biologically relevant products and can also be derivatized into other functionalities. Therefore, there are numerous ways of installing the amino group into a molecule. [3] These properties make amines interesting intermediates to consider in many synthetic routes. Katritzky salts expand on their utility by making them able to form alkyl radicals **6** (Scheme 2), and take part in alkylation reactions.



R = Alkyl, benzyl, pyridyl

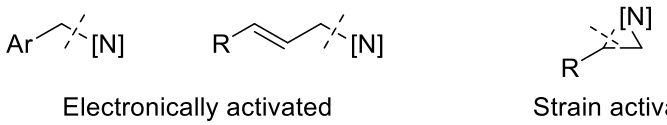
Scheme 2: Alkyl radicals can be formed through a fragmentation step.

The C(sp^3)-N bond of the pyridinium cation possesses very low energy, in junction with their low reduction potential ($E_{1/2}$ ~ −0.90 V *vs.* SCE in DMF)[4], makes them susceptible to forming alkyl radicals under mild conditions. This fragmentation process, caused by the cleavage of the C-N bond, can be initiated through metal catalysis, photocatalysis, and heating, among others.[5]

Katritzky salts have gained newfound relevance in the recent years, the simplicity of their preparation, high stability, and recently widened range of applications make Katritzky salts particularly handy reagents for generating alkyl radicals.

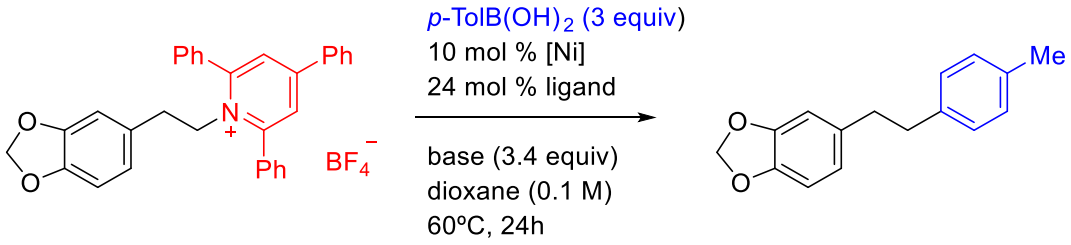
1.1 Fragmentation through metal catalysis.

The alkylating properties of amines can be accessed through metal-catalyzed C-N bond activation, this is done in reactions such as cross coupling Suzuki reactions. Usually, this method is limited to few amine derivatives (Scheme 3), as amines with unactivated alkyl groups are not able to participate in cross coupling reactions. [6]



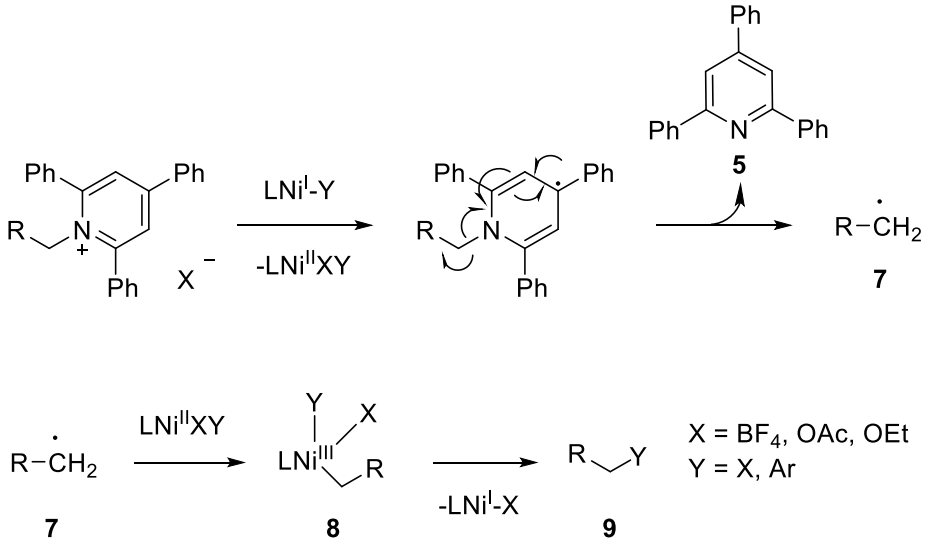
Scheme 3: Amines with activated alkyl substituents able to undergo cross coupling.

To circumvent this problem, a strategy involving Katritzky salts was developed by the Watson group.[3] Katritzky salts synthesized from the unactivated amine would be used in the Suzuki-reaction to act as alkyl electrophiles, allowing the alkylation of different aryl substrates (Scheme 4).



Scheme 4: Example of a Suzuki reaction using *p*-tolylboronic acid and nickel.

Ni(I) acts as a reductant, transferring a single electron to the pyridinium ring. This causes the homolytic cleavage of the C-N bond, forming an alkyl radical **7** that binds to the formed Ni(II)-centre in an oxidative addition resulting in **8**. A reductive elimination step recovers the Ni(I) catalyst and forms the final product **9**.



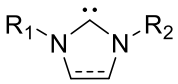
Scheme 5: General mechanism for the Nickel-catalysed cross coupling reaction of Katritzky salts.

This procedure demonstrated remarkable versatility, as both primary and secondary (cyclic and acyclic) alkyl groups could be coupled to aryl chlorides, fluorides, methyl ketones, esters, amides, ethers, alkynes, silyl-protected alkynes, acetals, and nitriles.[3]

1.2 Fragmentation through organocatalysis.

In recent years, organocatalysis has emerged as a convenient alternative to transition metal catalysis. This is because organocatalysts tend to be less toxic, polluting, and costly than the traditional metallic catalysts, making them preferable in many circumstances.[7]

N-heterocyclic carbenes **10** (Scheme 6) are able to form enolates (referred as Breslow intermediates **11**) when mixed with aldehydes in basic conditions [8] (Scheme 7). These species can reduce redox-active amines, such as Katritzky salts **12**, through single electron transfer (SET), prompting the formation of alkyl radicals **13**. (Scheme 8).[9, 10]



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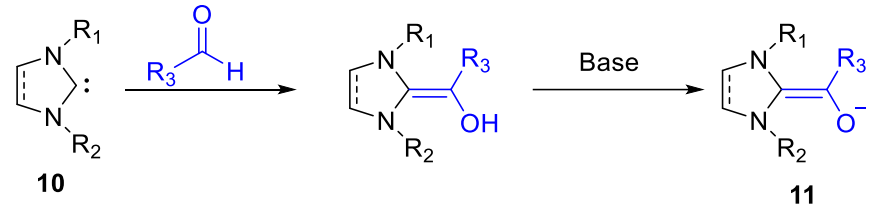
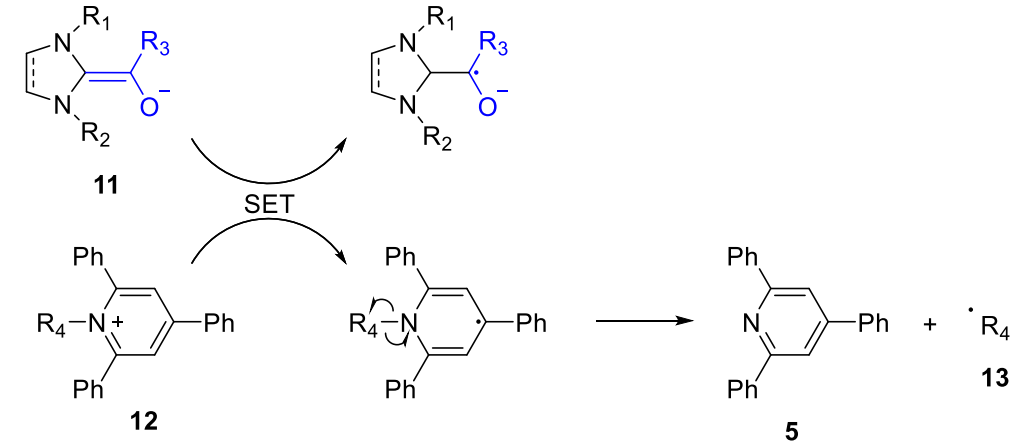
Scheme 6: General structure of *N*-heterocyclic carbenes



R_1, R_2 = Alkyl, aryl

Scheme 7: Formation of the Breslow intermediate.



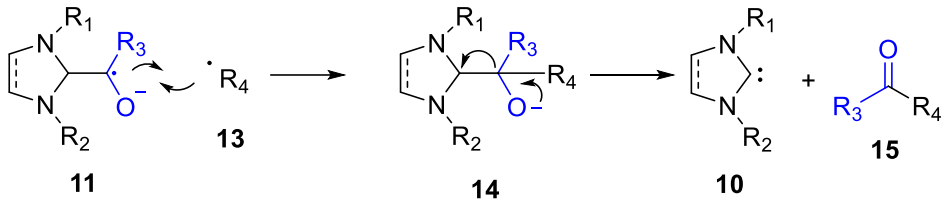
R_1, $R_{2,}$ = Alkyl, aryl

R_3 = Aryl, heteroaryl

R_4 = Alkyl, benzyl, pyridyl

Scheme 8: Single electron transfer between the Breslow intermediate and the Katritzky salt.

The resulting radicals **13** can undergo a radical heterocoupling, generating an alkoxide **14** that decomposes into a carbonyl compound **15** and the starting *N*-heterocyclic carbene **10** (Scheme 9).



R_1, $R_{2,}$ = Alkyl, aryl

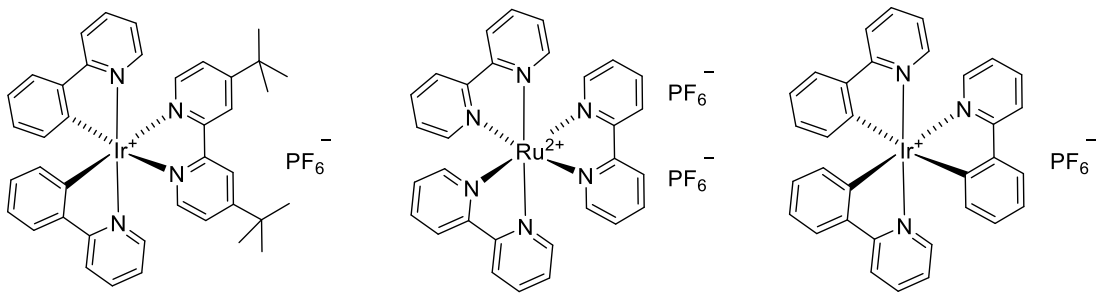
R_3 = Aryl, heteroaryl

R_4 = Alkyl, benzyl, pyridyl

Scheme 9: Mechanism of the alkylation of an aldehyde through a Katritzky salt catalyzed by *N*-heterocyclic carbene.

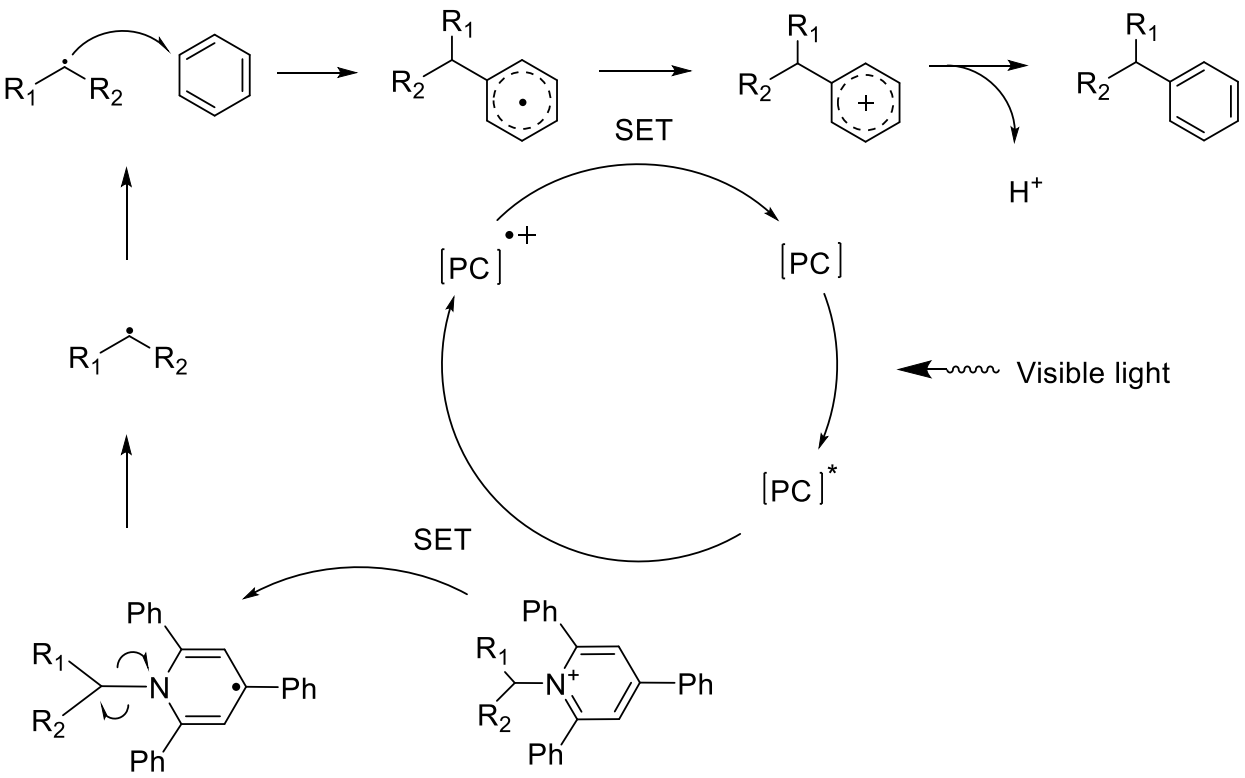
1.3 Fragmentation through photocatalysis.

Another option to kickstart the formation of the alkyl radical is photocatalysis (Scheme 10).[11] A deaminative strategy using iridium photocatalysts to reduce the pyridinium ring, was developed by the Glorious group.[12] The resulting radical could then be trapped by an aromatic molecule, that would in turn reduce the photocatalyst ([PC]) back to its initial form closing the catalytic cycle (Scheme 11).



$[Ir(dtbbpy)(ppy)_2]PF_6$ $[Ru(bpy)_3](PF_6)_2$ $[fac\text{-}Ir(ppy)_3]PF_6$

Scheme 10: Photocatalysts commonly employed for reactions involving the reduction of Katritzky salts.



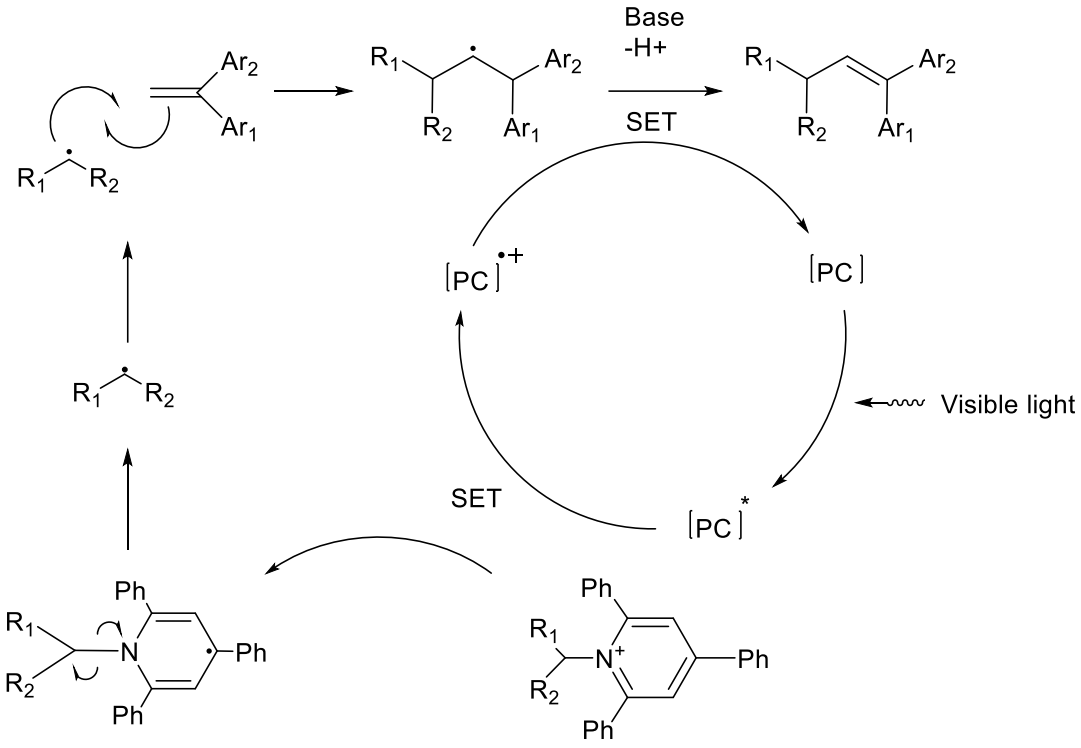
Scheme 11: Photocatalytic cycle of the fragmentation of a Katritzky salt and the entrapment of the alkyl radical by an aromatic ring.

This approach was proven to work with *N*-heteroarenes as pyrrols, quinolines and indols, and less common systems such as phenanthridines and phenanthrolines, being able to install different substituents efficiently. Among these, a group of particular relevance were those derived from amino acids.

Amino acids are a natural and abundant feedstock for the chemical industry, and thus a method able to exploit their availability is highly valuable. The Katritzky salts derived from amino acid methyl esters could generate the corresponding alkyl radical through the photocatalytic process described above, and be installed in a variety of *N*-heteroarenes.[12]

Another photocatalytic cycle was developed by Xiao and co-workers, in the form of an alkyl-Heck-type reaction.[13] This pathway is quite similar to the one described in Glorious' work, but the radical is trapped by an alkene instead of an arene (Scheme 12).

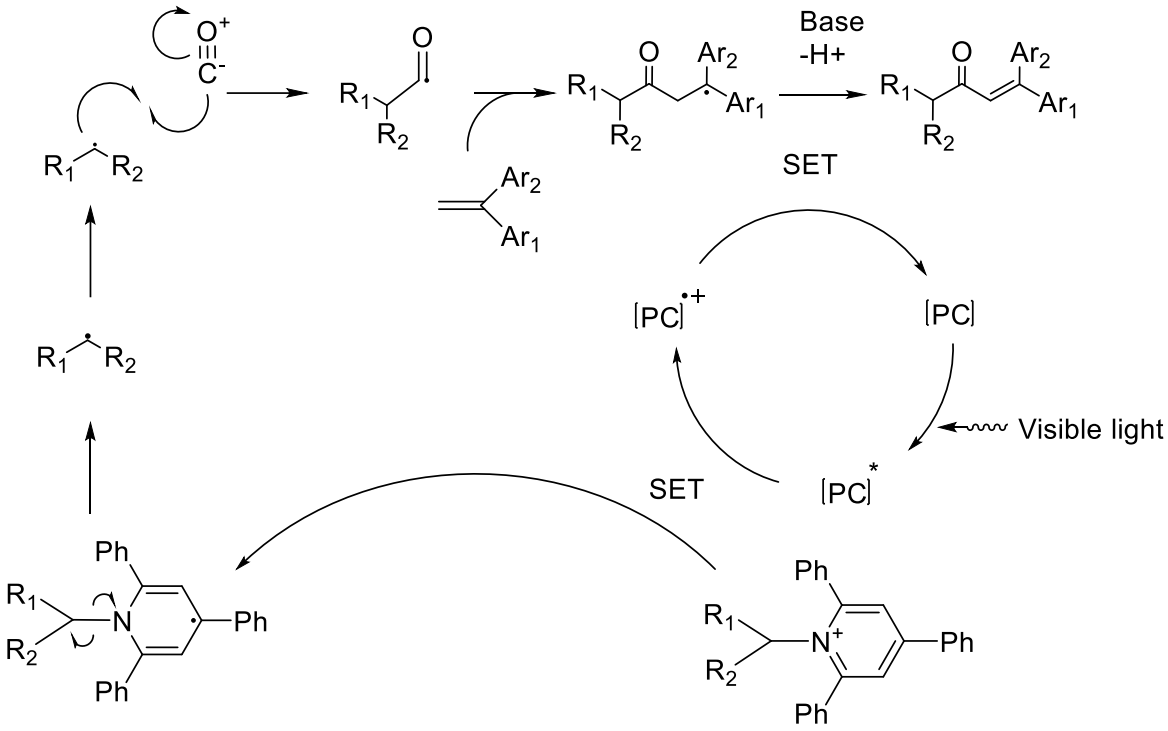
This procedure worked with coupling partners other than the usually employed α-aryl alkenes. Using α-aryl silyl enol ethers afforded ketones as products, whereas using amide-derived enamines resulted in enamines as products.



Scheme 12: Alkyl-Heck-type photocatalyzed reaction.

A variation of the alkyl-Heck-reaction, the carbonylative Heck reaction, was shown to be compatible with this procedure as well. The carbonylative Heck reaction is a useful tool for the synthesis of α,β-unsaturated ketones, however few alkyl substituents could be installed as this method was mostly limited to aryl and vinyl electrophilic reagents.[14] Using Katritzky salts as electrophiles opens up this reaction to multiple alkyl substituents that were unable to undergo a carbonylative reaction through traditional means.[13]

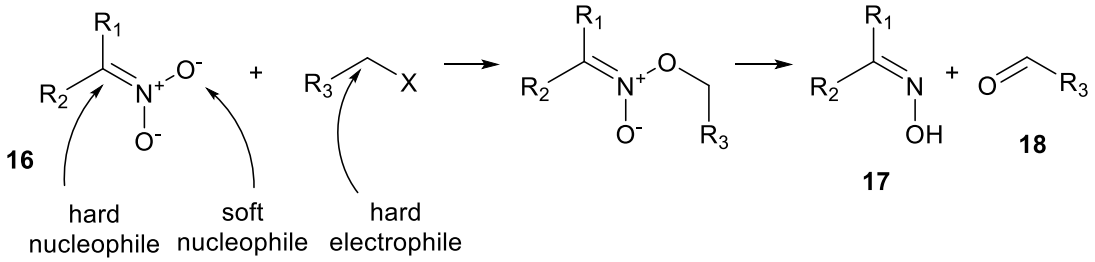
When the alkyl-Heck reaction is performed in the presence of carbon monoxide, the alkyl radical generated from the Katritzky salt will attack the carbon centre of the monoxide instead of coupling to the alkene. The resulting carbonyl compound will couple to the alkene and proceed with the Heck reaction in the same way an alkyl radical would do, recovering the photocatalyst as well as the double bond of the alkene (Scheme 13).[13]



Scheme 13: Alkyl-Heck-carbonylative photocatalyzed reaction.

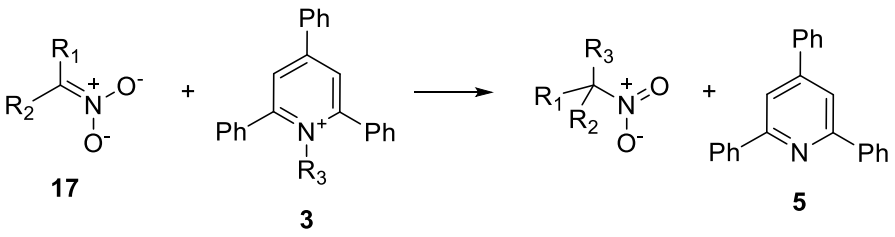
1.4 Alkylation of nitronate anions.

Achieving a *C*-alkylation of nitronate anions **16** is usually a challenging endeavour, as most procedures, such as nucleophilic substitutions, end up resulting in a *O*-alkylation of the nitronate (Scheme 14). The resulting intermediate is highly unstable and decomposes into an oxime **17** and an aldehyde **18**, without creating a C-C bond.[15]



Scheme 14: As a soft-hard interaction is favoured, substitution reactions will result in *O*-alkylations, affording undesirable products.

Radical additions on the other hand, target the carbon centre over the oxygen one, providing a route for *C*-alkylation (Scheme 15). As seen throughout this work, Katritzky salts are able to generate radicals and can be made from a wide variety of amines, facilitating the installation of many alkyl substituents in nitro compounds.[16,17]



Scheme 15: *N*-alkylation of a nitronate by an alkyl radical generated by a Katritzky salt.

This reaction will be employed in the experimental part of the project, as it provides a valuable pathway for the synthesis of 2-methyl-1-(naphthalen-2-yl)-2-nitropropane. One possible precursor for the calcilytic drug NPS-2143. [18]

2. OBJECTIVES

The main objective of this project is to showcase the utility of Katritzky salts as synthetic intermediates. The ability of these compounds to form radicals allows for reactions inaccessible to other alkylating reagents, such as the *N*-alkylation of nitronates, making them an asset to consider during the design of a synthetic route.

To achieve this general objective, the following specific objectives were set:

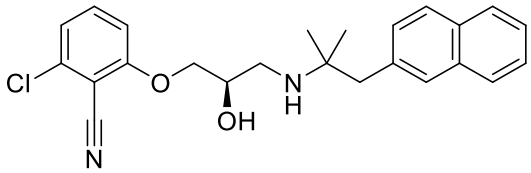
1. To synthesize 2-methyl-1-phenyl-2-propanamine, using Katritzky salts as intermediates. This amine is analogous to the one used in the synthesis of NPS-2143, a calcilytic drug whose applications for the treatments of different bone diseases are being investigated. By synthesising a compound of interest in the pharmaceutical industry we expect to demonstrate the relevance of Katritzky salts in organic synthesis.

2. To provide an insightful review of the different pathways for the fragmentation of Katritzky salts and the formation of radicals: transition metal catalysis, organocatalysis, and photocatalysis. As well as describing the catalytical cycles involved in these processes.

3. RESULTS AND DISCUSSION

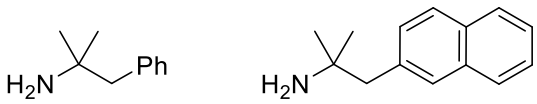
In this section, the results obtained from the synthesis of 2-methyl-1-phenyl-2-propanamine **19** will be discussed. A mechanistical proposal is also included along with the most relevant spectroscopic data.

Firstly, we will briefly discuss the choice of 2-methyl-1-phenyl-2-propanamine **19** as the molecule to be synthesized in this project. NPS-2143 is a calcilytic drug, a molecule able to block the Calcium-sensing receptor (CaSR) of the human body, prompting bone growth. As such, it is a compound of interest for the pharmaceutical industry, investigated as a treatment for diseases such as osteoporosis and to alleviate inflammation produced by asthma. [19]



Scheme 16: Calcilytic drug NPS-2143.

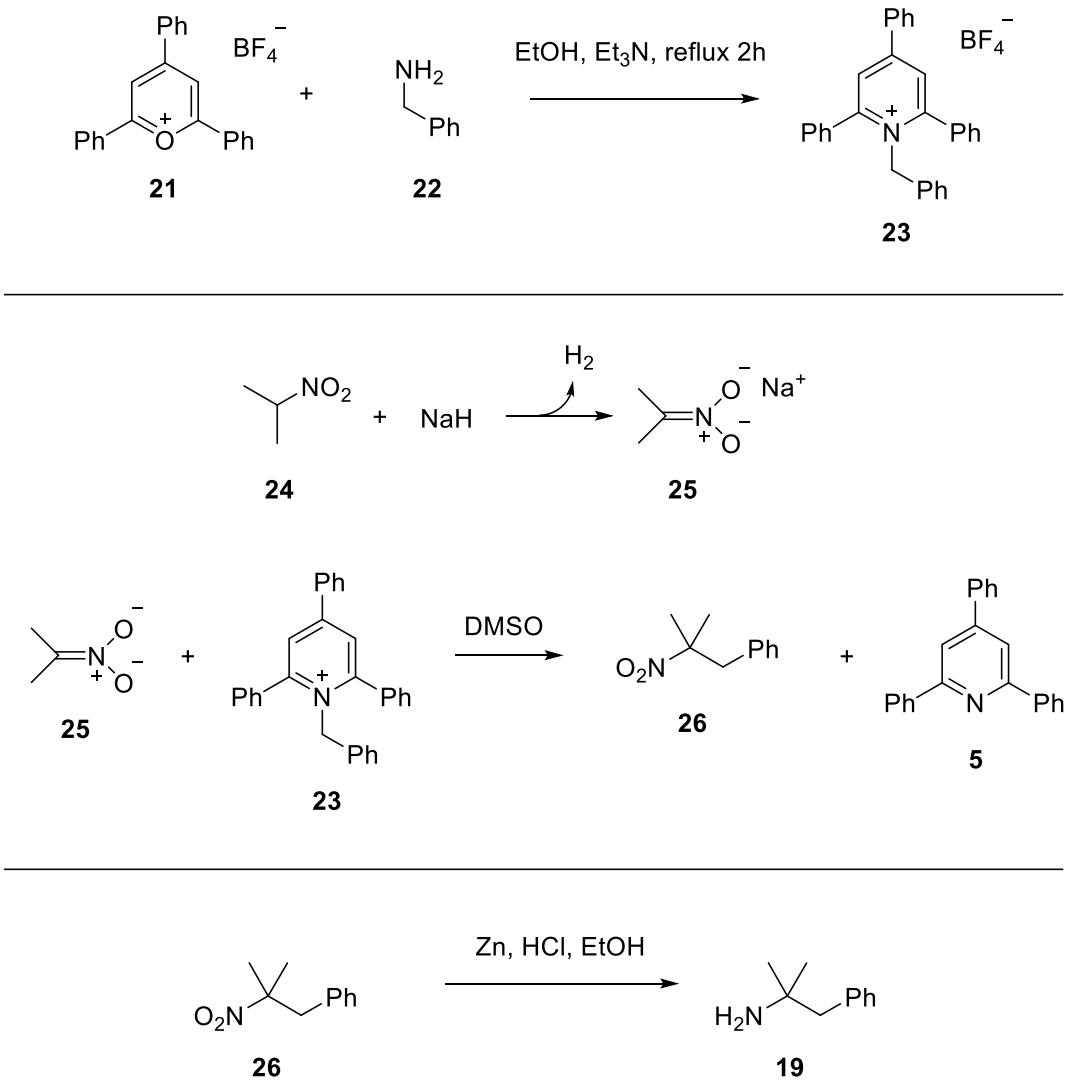
Due to its relevance in the medical field, it has been considered a good example to showcase the utility of Katritzky salts in organic synthesis. Thus, 2-methyl-1-phenyl-2-propanamine **19**, a compound analogous to the precursor of NPS-2143, 2-methyl-1-(naphthalen-2-yl)-propan-2-amine **20**, was prepared by synthesizing a Katritzky salt and using it to alkylate a nitronate.



19 **20**

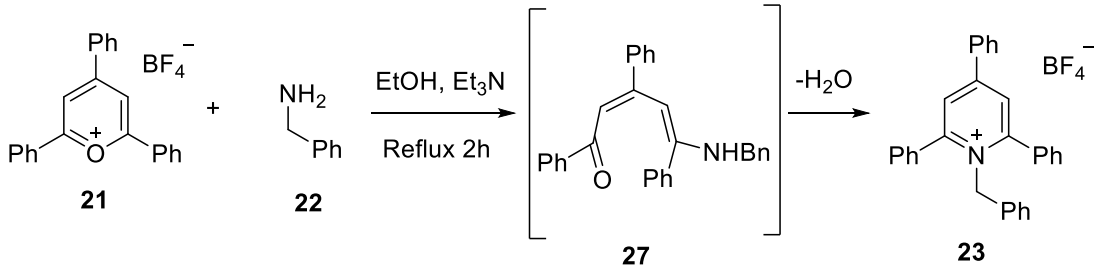
Scheme 17: 2-Methyl-1-phenyl-2-propanamine **13** and 2-methyl-1-(naphthalen-2-yl)-propan-2-amine **14**.

For the synthesis of 2-methyl-1-phenyl-2-propanamine **19,** the synthetic sequence depicted in Scheme 18 was envisioned.



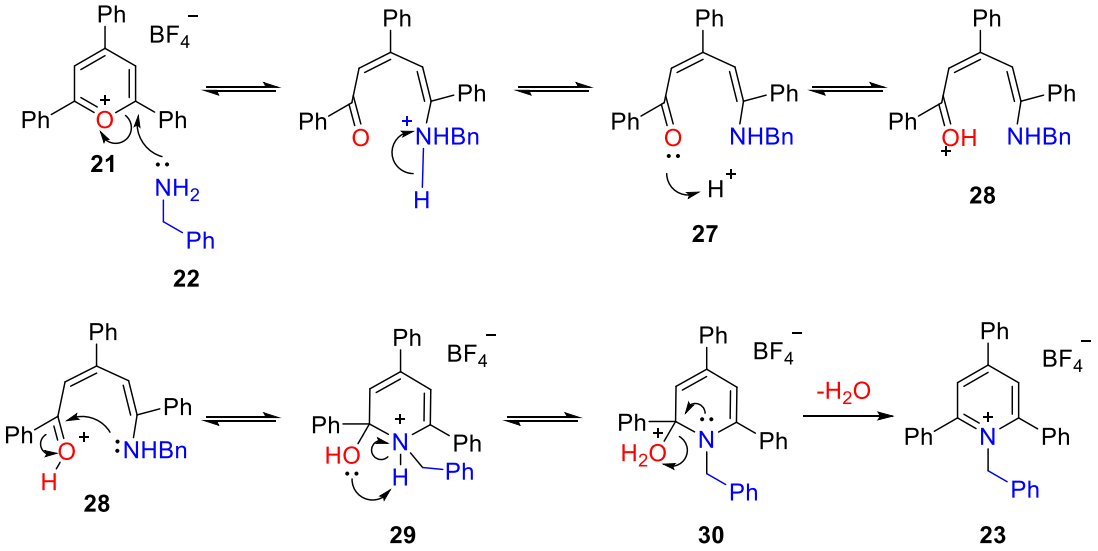
Scheme 18: Synthetic route towards 2-methyl-1-phenyl-2-propanamine **19**.

During the first step, the Katritzky salt **23** was prepared from a condensation reaction between the commercially available starting reagents 2,4,6-triphenylpyrylium tetrafluoroborate **21** and benzylamine **22.** Triethylamine was used as base, to prevent the protonation of benzylamine. (Scheme 19).



Scheme 19: The attack of the amine **22** opens the pyrylium ring.

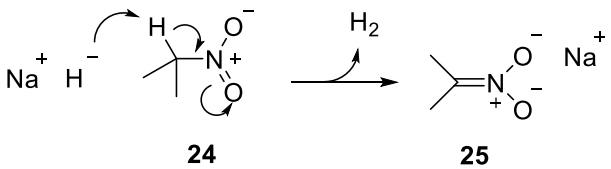
A mechanistic proposal for the formation of the Katritzky salt **23** is presented in Scheme 20. The pyrylium ring of the salt **21** is opened by a nucleophilic attack performed by the amine functional group of benzylamine **22,** giving rise to an intermediate enamine **27.** A subsequent nucleophilic attack to the generated carbonyl centre closes a cycle giving intermediate **29**, which recovers the aromaticity by transferring a proton from the nitrogen atom to the newly formed hydroxy group and then losing a water molecule. (Scheme 20).



Scheme 20: Mechanism for the formation of Katritzky salt **23**.

Both the starting salt **21** and the product **23** are quite insoluble in ethanol. By performing the reaction under reflux, we increase the solubility of the reagents and accelerate the reaction. Katritzky salt **21** was easily isolated from the reaction mixture by filtration and further purified by crystallization from ethanol.[17] The yield for this step was 47%, which is in the lower end of the range reported in the literature for the synthesis of 1-alkyl-2,4,6-triphenylpyridium tetrafluoroborates (51-81%).

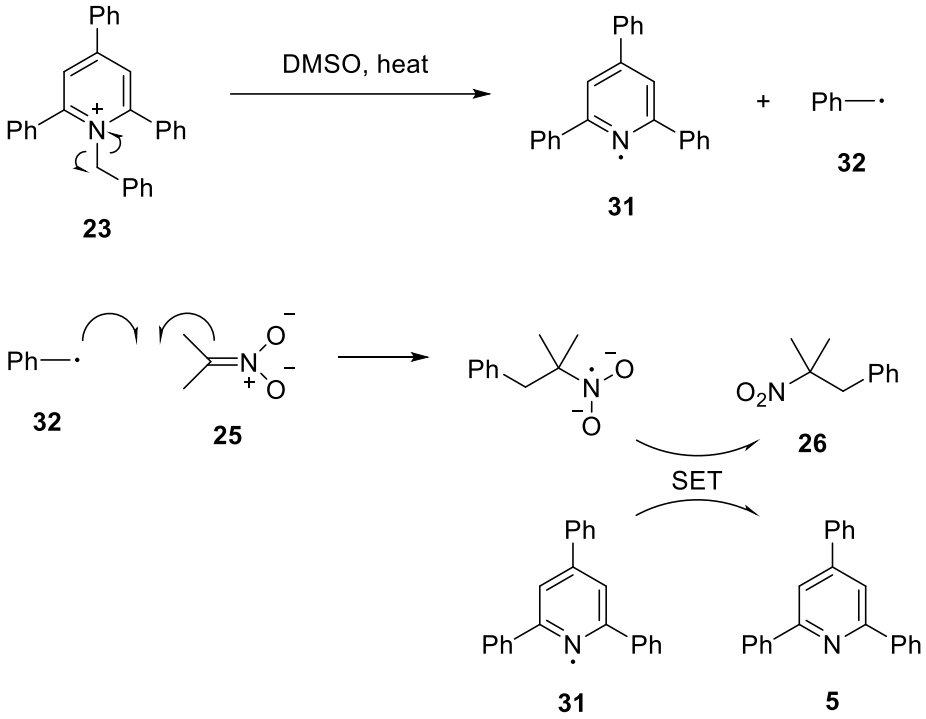
The next step is the addition of the nitronate **25** over the Katritzky salt **17**. For this purpose, the nitronate of the nitroalkene 2-nitropropane **24** was obtained by deprotonation using NaH as base in ethanol and under inert atmosphere. (Scheme 21).



Scheme 21: Mechanism for the deprotonation of 2-nitropropane **24**.

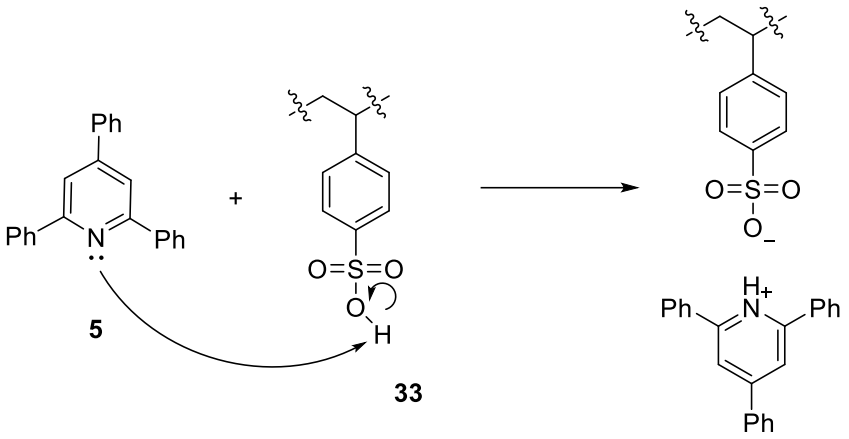
The addition step was performed in DMSO at 60ºC. It was left stirring overnight, this induced the fragmentation of the Katritzky salt, generating alkyl radicals that attack the α-carbon of the nitronate **25**.

In the proposed mechanism (Scheme 22), the fragmentation of the Katritzky salt **23**, results in the formation of radicals **31** and **32**. The benzyl radical **32** is able to attack the nitronate **25**; as radicals are soft electrophiles, thus the reaction with a hard nucleophile is favoured resulting in a *C*-alkylation. The resulting radical engages in single-electron transfer with the leftover radical previously generated **31** to give the final nitro compound **26** and 2,4,6-triphenylpyridine **5** as a byproduct.



Scheme 22: *C*-Alkylation of nitronate **25** by a radical generated through the fragmentation of Katritzky salt **23**.

Even though the same moles of 2,4,6-triphenylpyridine **5** and of 2-methyl-2-nitro-1-phenyl-propane **26** are generated in this reaction, the former has a far greater molar weight (307.4 g/mol and 179.2 g/mol respectively). This means that there is much more 2,4,6-triphenylpyridine **5** than 2-methyl-2-nitro-1-phenyl-propane **26**, so removal of most byproduct **5** before column chromatography would be advisable. For this purpose, a strongly acidic Amberlyst 15 resin was used. This would result in the protonation of 2,4,6-triphenylpyridine **5**, which would be then retained by the resin. (Scheme 23).



Scheme 23: Acid-base reaction between 2,4,6-triphenylpyridine **5** and Amberlyst 15 resin **33**.

After removal of 2,4,6-triphenylpyridine **5**, the residue was purified by column chromatography to afford 2-methyl-2-nitro-1-phenyl-propane **26** in moderate yield (39%). The formation of the desired nitro compound **26** was confirmed by ^{1}H NMR (Figure 1).

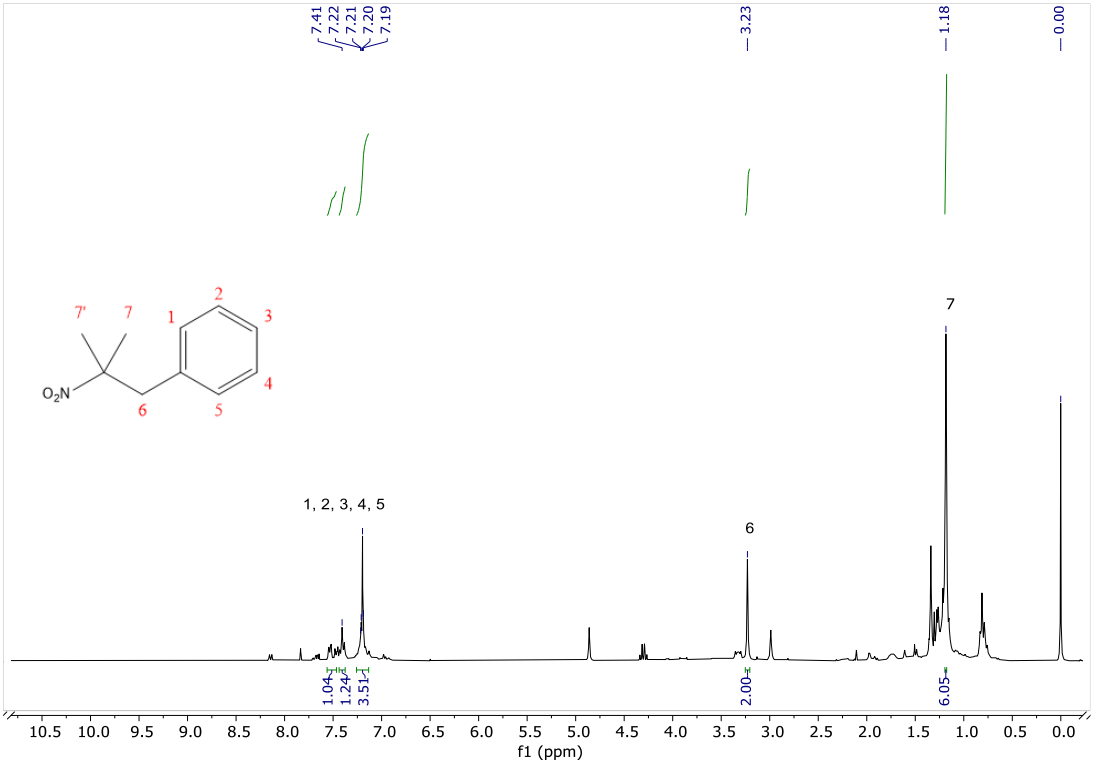
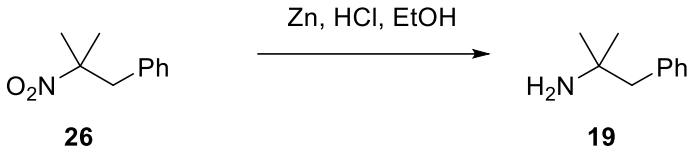


Figure 1: ^{1}H NMR spectrum of 2-methyl-2-nitro-1-phenyl-propane **26.**

Thus, the aromatic region displays three signals integrating for the five aromatic protons. The singlet at 3.23 ppm corresponds to the two benzylic and the singlet at 1.18 ppm integrating for the six protons correspond to both methyl groups.

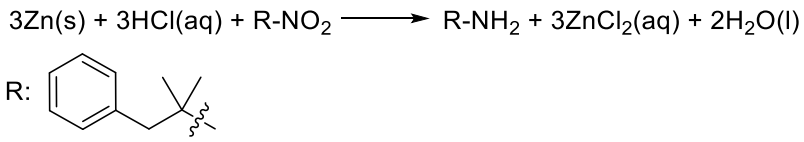
Once the synthesis of 2-methyl-2-nitro-1-phenyl-propane **26** was successfully achieved, the next step was the reduction of the nitro group to an amine functionality. For this purpose, a reduction with metallic zinc in acidic media was envisioned (Scheme 24).



26 **19**

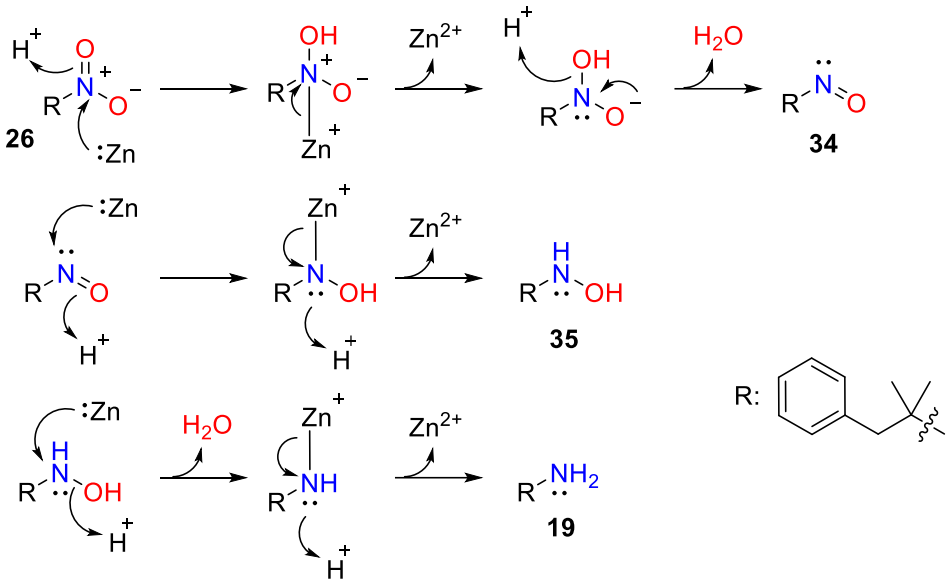
Scheme 24: Reduction of 2-methyl-2-nitro-1-phenyl-propane **26** into 2-methyl-1-phenyl-2-propanamine **19**.

Zinc is cheap, easy to handle, and have a reduction potential of -0.76V, which is appropriate to reduce nitro groups into amines. The reaction requires acidic media as a proton donor. Additionally, HCl can activate zinc powder by eliminating the outer layer of zinc oxide that forms in its surface due to exposure to air. As some zinc is then consumed, an excess is required to ensure that 2-methyl-2-nitro-1-phenyl-propane **26** is totally reduced.



Scheme 25: Balanced chemical equation for the reduction of nitro compound **26** into amine **19**.

In the proposed mechanism (Scheme 26), the nitro compound **26** receives two electrons from a zinc atom as one of the oxygen atoms is protonated twice, this leads to the loss of a water, affording intermediate nitroso compound **34**. Another zinc atom donates two additional electrons to the nitroso compound **34**, both the nitrogen and oxygen atoms of the group are also protonated once each, resulting in the hydroxylamine **35**. Finally, another zinc atom donates another pair of electrons, and one additional water molecule is lost as the hydroxy group of the amine is protonated, reducing the compound to the amine **19** after capturing one last proton.



Scheme 26: Mechanistic proposal for the zinc-promoted reduction of nitro compound **26** into amine **19** in acidic media.

The obtained residue was purified by a chromatographic column eluting with methanol in dichloromethane, due to the high polarity of the primary amine. Desired 2-methyl-1-phenyl-2-propanamine **19** was isolated in a 90% yield and characterized by ^{1}H NMR (Figure 2).

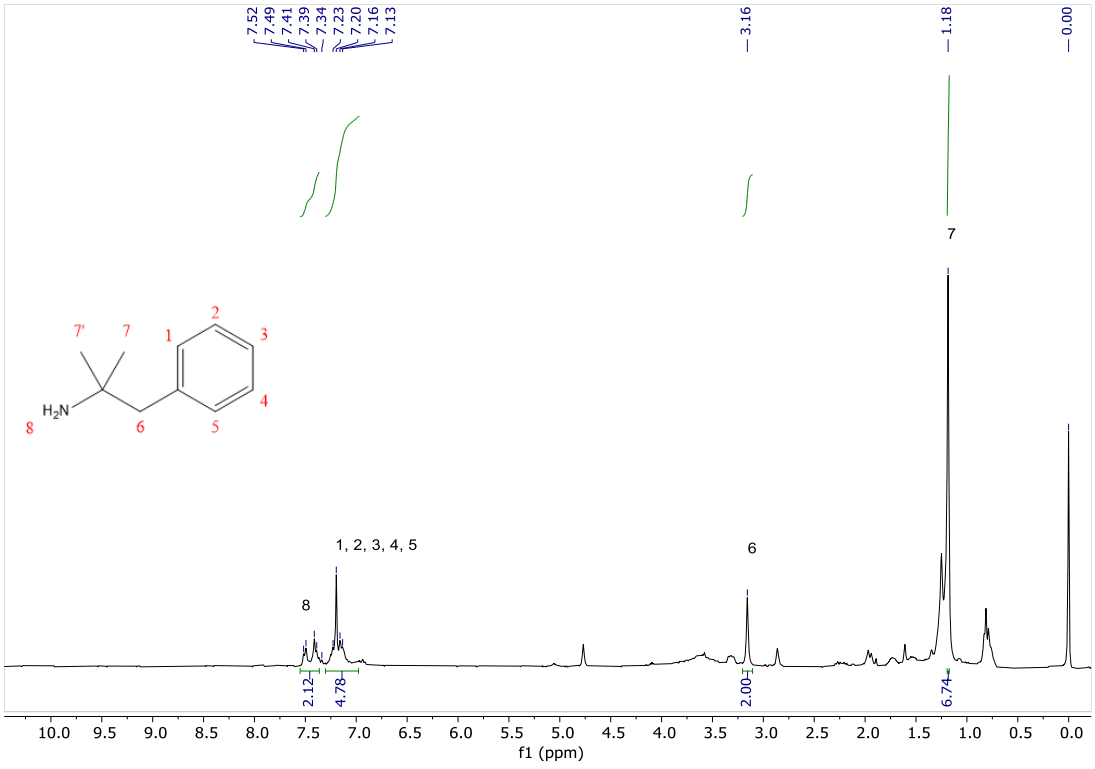


Figure 2: ^{1}H NMR spectrum of 2-methyl-1-phenyl-2-propanamine **19.**

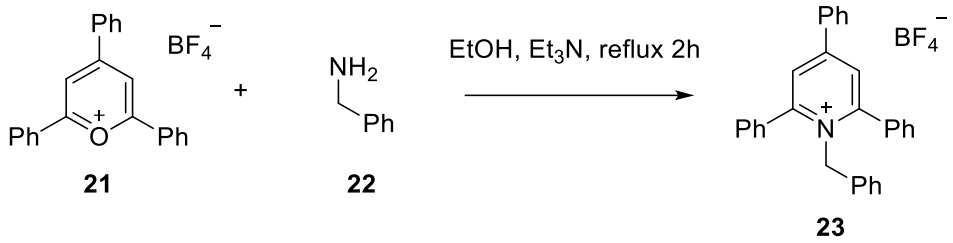
Besides the five aromatic protons in the region 7.34-7.13 ppm region, the ^{1}H NMR displays a singlet at 3.16 ppm corresponding to the benzylic protons and a singlet at 1.18 ppm for the methyl groups. The ^{1}H NMR is quite similar to that of nitro compound **26**, as the chemical environment of protons H-6, H-7 and H-7' has not changed significantly. The main difference lays on the two additional protons in the region 7.55-7.36 ppm, corresponding to the newly formed amine group.

4. EXPERIMENTAL SECTION

General experimental

All the reactions were performed in dried glassware with magnetic stirring, the anhydrous reactions were performed under N_2 atmosphere as well. Whenever heating was required a silicon oil hot bath was used. All the reagents and solvents were obtained from commercial suppliers and used without further purification. Regarding column chromatography, all columns were wet packed by mixing silica and hexane in an Erlenmeyer flask and then pouring the gel into the column and applying pressure. All ^{1}H-NMR spectra were recorded in $CDCl_3$, using TMS as reference (0.00 ppm for 1H-NMR). Data for ^{1}H-NMR were reported as follows: chemical shift (ppm) and multiplicity (s = singlet, d = doublet, m = multiplet), with coupling constants expressed in hertz (Hz). As for the software employed, all schemes were drawn on ChemDraw and all spectra was processed on MestreNova.

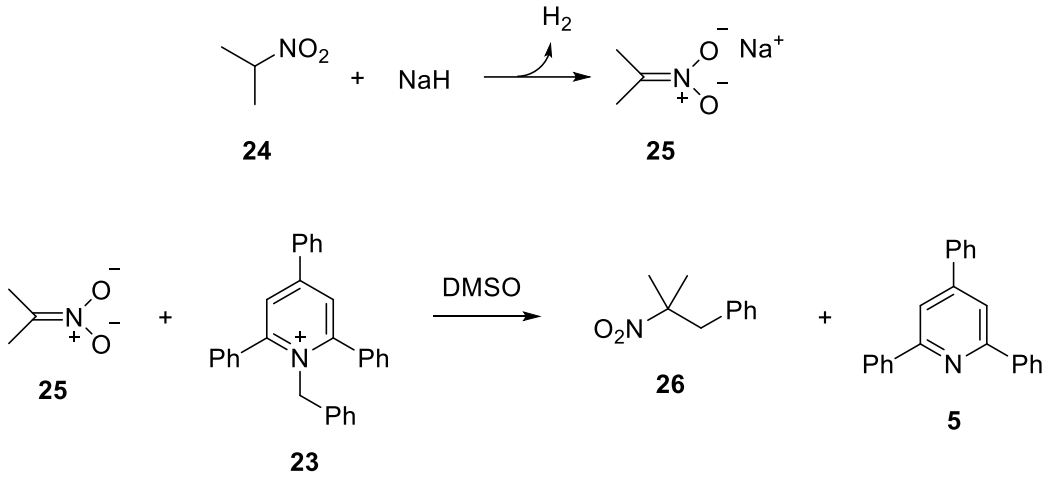
3.1 *N*-Benzyl-2,4,6-triphenylpyridyl tetrafluoroborate (23).



Scheme 27: Formation of the Katritzky salt, *N*-benzyl-2,4,6-triphenylpyridyl tetrafluoroborate **23**.

In a 50mL round-bottom flask under N_2, 2,4,6-triphenylpyrylium tetrafluoroborate (**21**) (4.78 g, 12 mmol) was suspended in 25mL of ethanol. Benzylamine (**22**) (1.31 mL, 1.29 g, 12 mmol) and triethylamine (0.16 mL, 0.12 g, 1.2 mmol) were added and the reaction mixture was stirred under reflux for two hours and then cooled to r.t. and filtered. The resulting solid was washed with ether and recrystallized from ethanol, to afford *N*-benzyl-2,4,6-triphenylpyridyl tetrafluoroborate (**23**) as a pale yellow solid (2.71 g, 47% yield). See Appendix 1.

3.2 2-Methyl-2-nitro-1-phenyl-propane (26).



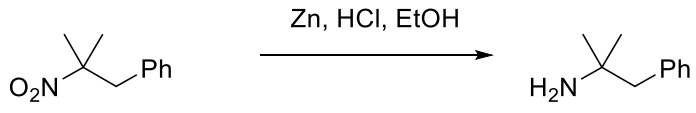
Scheme 28: Formation of the nitronate and subsequent radical addition.

An Schlenk flask was evacuated, and the remaining moisture was removed by heating it with a heat gun. Sodium hydride (65% dispersion in mineral oil, 0.6 g, 15 mmol) was added to a Schlenk under N_2 atmosphere and washed with hexane (3 x 10mL of hexane. The residue was suspended in dry ethanol (5mL) and then 2-nitropropane (**24**) (1.35 mL, 1.34 g, 15 mmol) was added dropwise. The resulting mixture was stirred for 20 minutes, evaporated under reduced pressure and dried. To a suspension of the resulting residue in DMSO (15 mL), previously obtained Katritzky salt (**23**) (1.99 g, 5 mmol) was added, and the resulting mixture was stirred at 60 ºC overnight and then cooled to r.t., quenched with water (50mL) and extracted with with Et_2O (3 x 50mL). The combined organic fractions were washed with brine (100mL), dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was redissolved in Et_2O (40mL) and 10mL of this solution were transferred to a 50 mL round bottom flask and more Et_2O (15 mL) and Amberlyst resin (8.0 g) were added. The mixture was stirred vigorously for one hour and then filtered, was washed with Et_2O and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc/Hex 1:20 to 1:9) to afford desired 2-methyl-2-nitro-1-phenyl-propane (**26**) as a brownish oil (0.09 g; 39% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 1H), 7.41 (s, 1H), 7.26 – 7.13 (m, 4H), 3.23 (s, 2H), 1.18 (s, 6H) ppm.

Rf (1:9 EtOAc/Hex) = 0.34

3.3 2-Methyl-1-phenyl-2-propanamine (20).



26 **20**

Scheme 19: Reduction of the nitro compound into the amine.

To a solution of 2-methyl-2-nitro-1-phenyl-propane (**26**) (0.09 g, 0.5 mmol) in ethanol (5mL), zinc powder was added (0.60 g, 9.2mmol). The resulting mixture was cooled to 0 ºC and aqueous HCl was added dropwise (4M, 2.5mL), then it was stirred at r.t. overnight. After adjusting the pH to 8 by careful addition of saturated $NaHCO_3$ solution, the mixture was filtered through a Celite pad washing with ethyl acetate. The organic layer was separated, washed with 1:1 brine/ saturated $NaHCO_3$ solution (60 mL), dried over $NaSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc/Hex 1:10 MeOH/CH_2Cl_2 1:4) to afford desired 2-methyl-1-phenyl-2-propanamine (**20**) as a pale yellow oil (0.07 g, 90% yield). See Appendix 1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.36 (m, 2H), 7.16 (d, *J* = 18.6 Hz, 5H), 3.16 (s, 2H), 1.18 (s, 7H) ppm.

5. CONCLUSIONS

In this final degree project, a summary on the history of Katritzky salts in organic chemistry has been compiled, explaining their discovery, synthesis, and the reactions they are used in nowadays. Katritzky salts have become building blocks in the field of organic synthesis, primarily as a source of alkyl radicals. As proof of concept, the Katritzky salt *N*-benzyl-2,4,6-triphenylpyridyl tetrafluoroborate **23,** was synthesized and used in the preparation of 2-methyl-1-phenyl-2-propanamine **20.** This amine is analogous to 2-methyl-1-(naphthalen-2-yl)-propan-2-amine **21**, a precursor to NPS-2143, a drug of interest in the pharmaceutical industry.

The synthetic route followed was meant to highlight the usefulness of Katritzky salts as building blocks in organic synthesis, which have proven to be very versatile reagents due to their ability to undergo radical additions. The synthesis of a Katritzky was successfully achieved in moderate yields. Then, the alkylation of a nitronate with the obtained Katritzky salt was followed by the reduction of the nitro group, to finally afford desired amine in moderate overall yield.

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APPENDIXES

Appendix 1: Pictures of the intermediate **(a)** *N*-benzyl-2,4,6-triphenylpyridyl tetrafluoroborate **17,** and the final product **(b)** 2-methyl-1-phenyl-2-propanamine **13.** The amount of 2-methyl-1-phenyl-2-propanamine **13** synthesized was very small, which made it hard to see, therefore it was dissolved in a few millilitres of DCE.

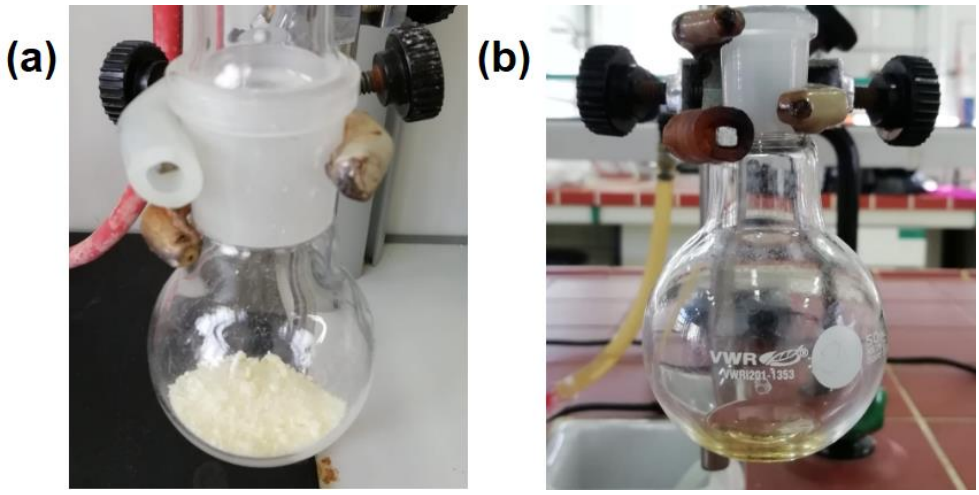

Figure 3: The intermediate *N*-benzyl-2,4,6-triphenylpyridyl tetrafluoroborate **17** and final product 2-methyl-1-phenyl-2-propanamine **13.**

Appendix 2: Aspect of the column used in the purification of 2-methyl-2-nitro-1-phenyl-propane **20,** as well as the TLC studies made to choose the appropriate eluent.

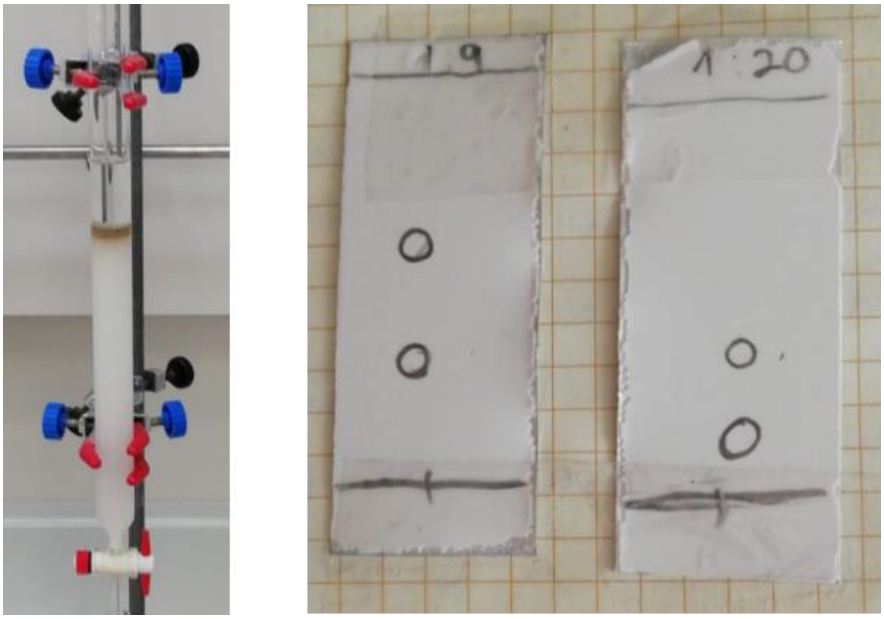

Figure 4: First column chromatography and TLC plates.

Appendix 3: Aspect of the TLC studies made to choose the appropriate eluent for the purification of 2-methyl-1-phenyl-2-propanamine **13.** The ^{1}H NMR performed to the fraction containing the compound shown in the TLC confirmed that it was not the product**.** (See Appendix 4).

Figure 5: TLC plates for the second column chromatography.

Appendix 4: ^{1}H NMR spectra of the first fraction extracted from the column chromatography used to purify 2-methyl-1-phenyl-2-propanamine **13.** The two major peaks correspond to water and chloroform, while the minor ones do not align with what was expected for the final product.

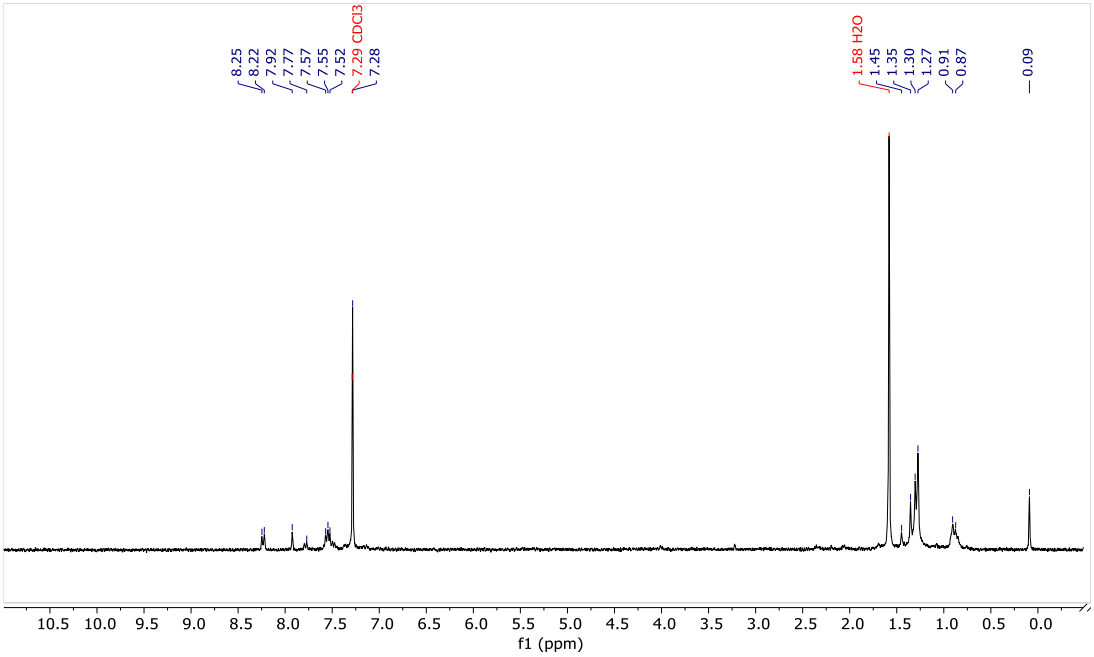

Figure 6: First fraction extracted during the second column chromatography.