UNIVERSITY OF OVIEDO

FACULTY OF CHEMISTRY

HALONITRO COMPOUNDS: A MASTER KEY IN DRUG INDUSTRY

(Organic Chemistry)

End-of-Degree Project

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INDEX

ABREVIATIONS

Gem - geminal

SolFC - solvent free conditions

MsCl – methanesulfonyl chloride

THF - tetrahydrofuran

TLC - thin layer chromatography

NMR - nuclear magnetic resonance

Rf - retention factor

Hex - hexane

EtOAc - ethyl acetate

J - coupling constant

rt - room temperature

E1cb – Unimolecular elimination of the conjugate base

1. INTRODUCTION

Gem-halonitro compounds have the characteristic of being substituted at the same position by a nitro group and a halogen giving geminal position. There are two different classes: *gem*-halonitro alkanes and *gem*-halonitro alkenes, being the latest the ones of interest in this project.

In particular, this work will be focused on the study of *gem*-bromo nitroalkenes (Figure 1) and their synthesis, as they are potentially important as intermediates in drug synthesis[1] and relevant organic reactions[2].

Gem-halonitro alkenes represent a large family of compounds. They present a variety of characteristics and applications depending on the nature of the halogen and R substituent utilized.[3]

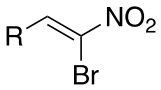

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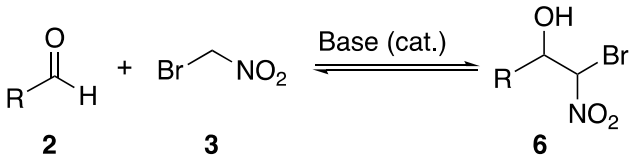
Figure 1: General structure of gem-bromo nitroalkenes.

1.1 Synthetic routes to prepare *gem*-bromo nitroalkenes

Over the years, there have been many different routes for the preparation of *gem*-bromo nitroalkenes. Given the fact that there are different *gem*-bromo nitroalkenes depending on the nature of the R substituent, some of the most relevant ones will be revised. There are two main different procedures to be followed when preparing *gem*-bromo nitroalkenes: Henry reaction followed by dehydration and bromination/ dehydrobromination.

1.1.1. Henry reaction and dehydration

Henry type reaction was discovered in 1895 by L. Henry and consists on the combination of a nitroalkane **3** and a carbonyl compound **2** in the presence of catalytic amounts of a base to form nitroalcohols **6** (Scheme 1)**.**[3]

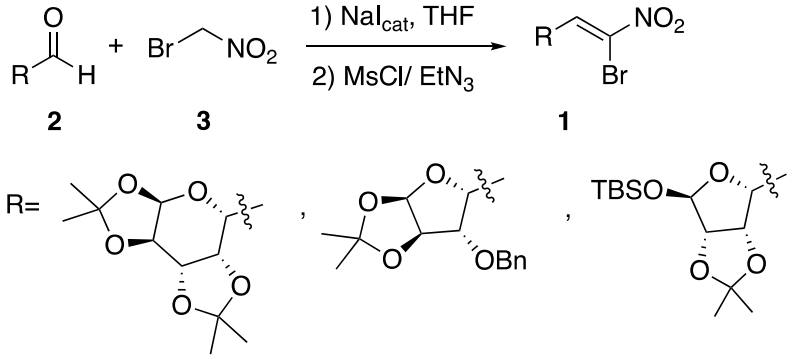


2 **3** **6**

Scheme 1: General scheme for the Henry reaction.

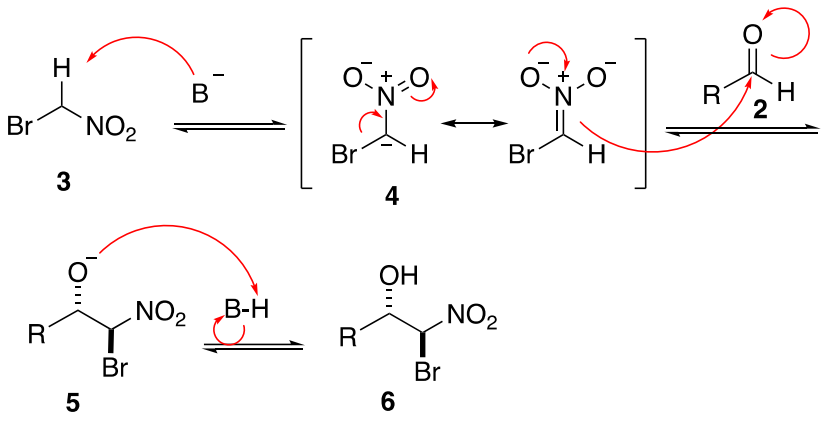
Dehydration of the resulting nitroalcohols **6** afford the corresponding nitroalkenes **1.** To facilitate the dehydration, the hydroxyl is usually transformed into a good leaving group.

A representative example is illustrated in Scheme 2.[4] Thus, treatment of corresponding aldehyde **2** and bromo nitromethane **3** with a catalytic amount of base yielded crude alcohols **6**. Reaction of the Henry adducts **6** with MsCl gave the intermediate methanosulfonyl derivatives which undergo an E1cb elimination to finally afforded the desired *gem*-bromo nitroalkenes **1** in excellent yields (87%-92%) and with *Z*/*E* 98/2 selectivity.



Scheme 2: General synthesis for gem-bromo nitroalkenes through NaI-catalyzed Henry reaction and dehydration.

Regarding the mechanism of this process, it can be appreciated in Scheme 3 that first the nitroalkane **3** is deprotonated by the base and then, the nitronate **4** attacks the carbonylic carbon of the aldehyde **2**. Afterwards, the oxygen gets protonated by the conjugated acid of the base, recovering the catalytic base and giving the corresponding nitro alcohol **6**.



Scheme 3: General mechanism for the Henry reaction.

This reaction is stereoselective to give the *anti*-adduct as major product. That is explained in Figure 2.

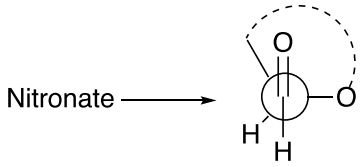
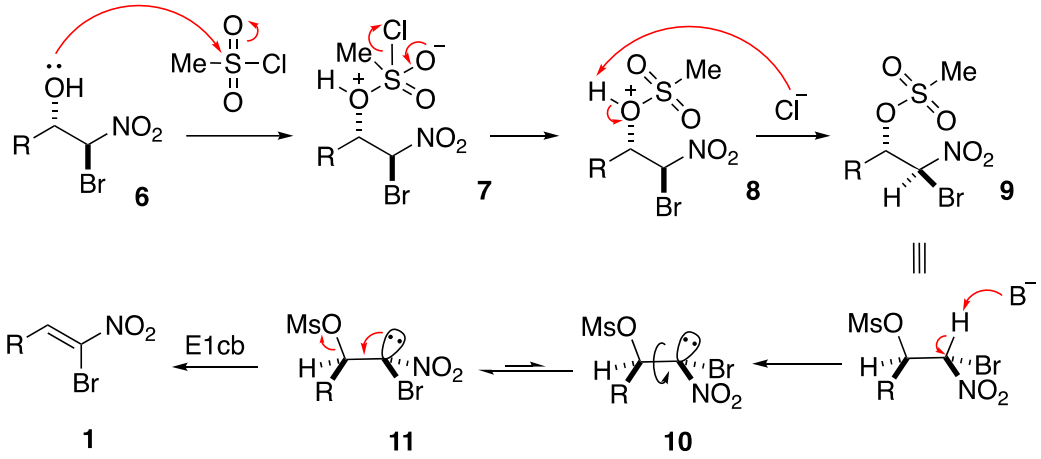


Figure 2: Felkin-Ahn model for sugar aldehydes.

Following Felkin-Ahn model, Figure 2 clearly shows how the nitronate **4** attacks the aldehyde perpendicular to the carbonyl group and through the opposite position with respect to the other oxygen. This attack is the preferred one due to the reduction of the coulombic repulsion between the nucleophile (nitronate) and the electronegative atom. The depicted interaction clearly shows the stereospecific formation of *anti*-product.

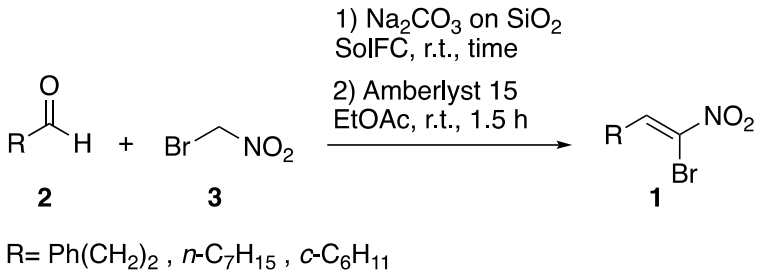
As previously mentioned, the Henry adducts **6** undergo dehydration in basic conditions[5] to give the corresponding bromo nitroalkenes **1** as shown in Scheme 4. This dehydration is the driving force for the equilibrium to be displaced to the formation of the nitro alkene.



Scheme 4: Mechanism for the dehydration of Henry adduct.

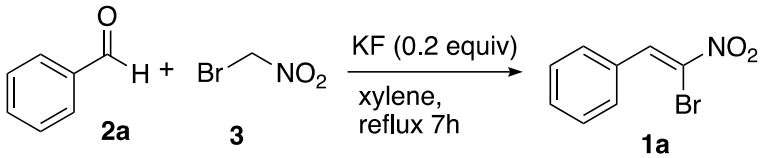
The dehydration usually occurs through the conversion of the hydroxyl group into a better leaving group, such as the OMs as previously depicted in Scheme 4. From mesylate **9**, an E1cb elimination afford the desired bromo nitroalkene **1**.

In the search for more environmentally friendly conditions, the synthesis of *gem*-bromo nitroalkenes **1** was also achieved under solvent-free conditions (carbonate on silica). The dehydration was performed directly over the crude Henry adducts **6** with strongly acidic Amberlyst 15, to afford the corresponding *gem*-bromo nitroalkenes **1** in moderate to good yields (31%-85%) and with total *Z*-selectivity (Scheme 5).



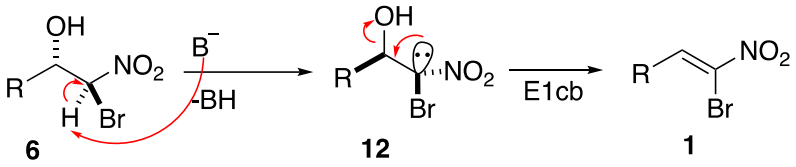
Scheme 5: Synthesis of bromo nitroalkenes under solvent-free conditions.

Pechalrieu *et al.*[6] recently described an example of the direct one-step synthesis of *gem*-bromo nitroalkenes from bromo nitromethane **3** and aldehyde **2** (Scheme 6).



Scheme 6: Direct one-pot synthesis of gem-bromo nitroalkenes.

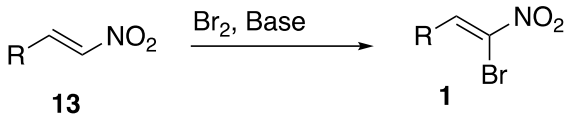
Thus, the reaction of benzaldehyde **2a** with bromo nitromethane **3** in the presence of catalytic amounts of KF in refluxing xylene afforded the corresponding *gem*-bromo nitroalkene **1a** in a 32% yield and total *Z* selectivity (Scheme 6). The low yield can be explained by the fact that elimination of hydroxyl is thermodynamically unfavored (Scheme 7).



Scheme 7: Dehydration of an alcohol mechanism.

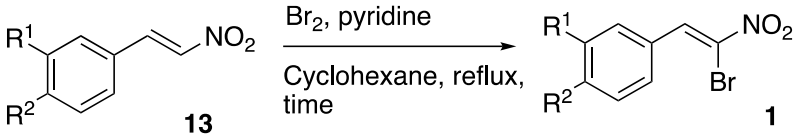
1.1.2. Bromination and dehydrobromination of nitroalkenes

Other main strategy for the synthesis of *gem*-bromo nitroalkenes **1** is the bromination and subsequent dehydrobromination, whose general scheme is as follows:



Scheme 8: General scheme for the formation of bromo nitroalkene through bromination and dehydrobromination.

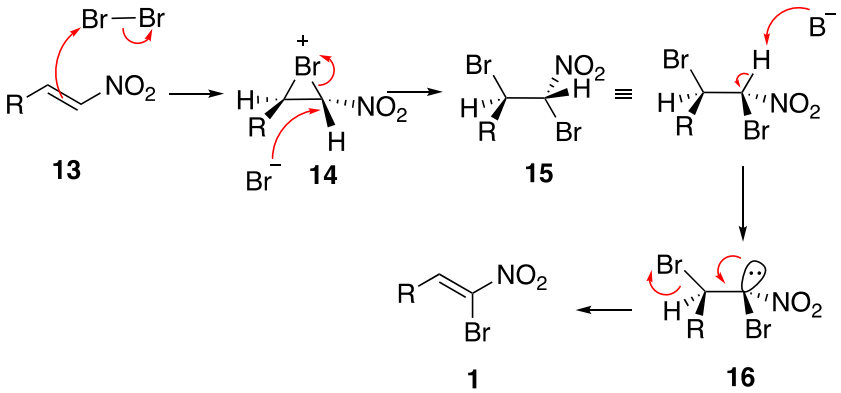
A representative example is depicted in Scheme 9. Nitroalkene **13** was treated with bromine and pyridine in refluxing cyclohexane to afford bromo nitroalkenes **1** in moderate to good yields (17%-86%) and with total *Z* stereoselectivity.



13a: $R^1 = R^2 = H$
13b: $R^1 = H$, $R^2 = OMe$
13c: $R^1 = R^2 = OBn$

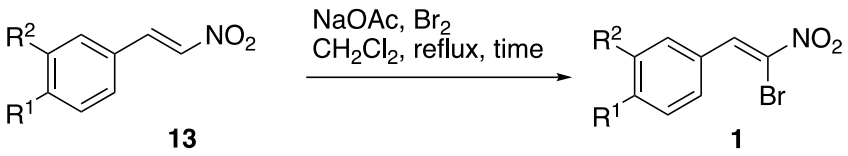
Scheme 9: Synthesis of gem-bromo nitroalkenes via one-pot bromination/dehydrobromination.

The bromination/dehydrobromination mechanism is depicted in Scheme 10. The mechanism starts with the reaction of nucleophilic alkene to the polarizable bromine to afford intermediate cyclic bromonium **14**. Then, attack of the released bromide over the electron deficient carbon forms dibrominated intermediate **15**. From vicinal dibromide **15**, an E1cb elimination finally affords the desired *gem*-bromo nitroalkene **1**.



Scheme 10: General mechanism for the bromination and dehydrobromination reaction.

Similarly, Han *et al*.[7] and Yavari *et al*.[8] synthesized several 2-aryl *gem*-bromo nitroalkenes **1** from 2-aryl nitroalkenes **13**. In this case, sodium acetate was used as the base instead of pyridine, affording desired *gem*-bromo nitroalkenes in moderate yields (64-67%) and with total *Z*-stereoselectivity, as depicted in Scheme 11.



13d: R^1= H, R^2 = CN
13e: R^1= CN, R^2 = H
13f: R^1= H, R^2 = F

Scheme 11: Synthesis of gem-bromo nitroalkene through bromination/dehydrobromination.

Considering the previous examples, we can conclude that bromination/dehydrobromination is a reliable procedure for the synthesis of *gem*-bromo nitroalkene. Not only the experimental setup is easy but also the starting materials are commercially available and cheap, and the yields are consistently good.

As previously stated, *gem*-halo nitroalkenes are useful synthetic intermediates and can be employed for the synthesis of different organic compounds. One example is the synthesis of functionalized alkenes by means of a transition metal-catalyzed cross-coupling reaction.

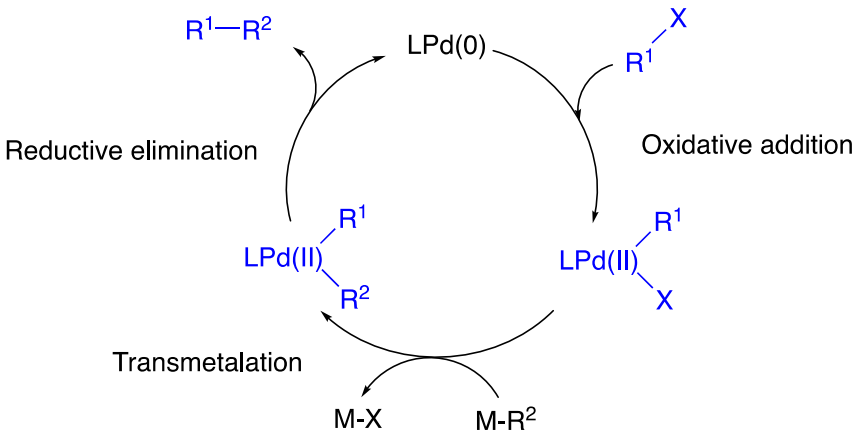
1.3 Palladium-catalyzed cross-coupling reactions

Cross-coupling reactions involve the combination of an organometallic reagent and an organic electrophile, facilitated by a metal catalyst, to form new covalent bonds such as C-C, C-N, or C-O.[9] In these reactions, both the organometallic reagent and the organic electrophile contain activating groups that react with each other, resulting in the formation of a new covalent bond while losing their individual activating properties.[10]

There are a variety of reactions depending on the reagents and metal catalysts used. The first reported cross-coupling reaction was Cadiot-Chodkiewicz one.[11] However,

nowadays, there are many different important ones, such as Heck[12], Sonogashira[13], Negishi[14], Stille[15] and Suzuki[16].

Although several transition metals can be used as catalysts in cross-coupling reactions, undoubtedly the most used is Pd. All the Pd-catalyzed cross-coupling reactions follows the same general mechanism, the catalytic cycle depicted in Scheme 12.
The mechanism of this reaction consists of the following steps. In the first one, a Pd(0) complex reacts with an alkyl halide through oxidative addition. Palladium inserts into the alkyl halide getting oxidized to Pd(II). Secondly, a transmetalation occurs by the reaction of the previously generated compound with an alkylmetal in the presence of a base. This generates an organopalladium substituted compound. Finally, the C-C bond of interest is generated through a reductive elimination, which regenerates the Pd catalyst and yields the desired cross-coupling product.[17]



Scheme 12: Catalytic cycle for the Pd-catalyzed cross-coupling reactions.

The rate determining step is usually the oxidative addition because it depends on the strength of the C-X bond (being X a halide atom). Improvements are tried to be made on these reactions by finding more efficient supporting ligands or alternatively by using new halides which speed up the rate-determining step. [18]

Suzuki reaction or Suzuki-Miyaura reaction is one of the most used Pd-catalyzed cross-coupling reactions. It involves the use of a base, a palladium complex as catalyst and imply the formation of a new C-C bond between an organoboron species and a halide species.[16] One of the most important parts of cross-coupling reactions is controlling the chemo-,stereo- and regioselectivities to avoid undesired substitutions and secondary products.[18] Moreover, the reaction presents some advantages such as the employment

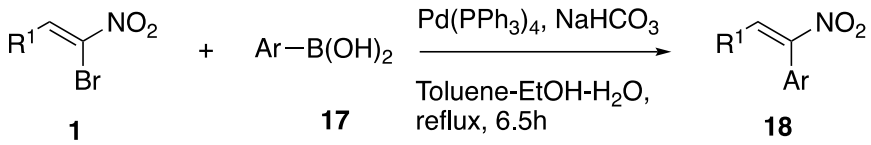
of organoboron compounds which are stable and non-toxic and the mild conditions are required.[19]

From *gem*-bromo nitroalkenes **1**, a Suzuki reaction would afford α,β-disubstituted nitroalkenes which are synthetically and biologically useful compounds.[20]

1.4 Suzuki-Miyaura reaction on *gem*-bromo nitroalkenes

For the application of the Suzuki-Miyaura reaction, an α,β-disubstituted nitroalkene **18** will be synthesized. As explained before, the Suzuki-Miyaura reaction involves the use of a boronic acid, a haloalkene and a palladium complex catalyst.

The C-B bond of the boronic acid is weakly polarized and so, it is weakly nucleophilic. Thus, it should undergo fast transmetalation instead of conjugate addition. However, it is important to choose the best reaction conditions, that means, best palladium catalyst, base and solvent.[16] The employed synthetic pathway is depicted in Scheme 13.



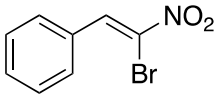
Scheme 13: General scheme for the cross-coupling Suzuki reaction.

Thus, reaction of equimolar amounts of bromo nitroalkenes **1** and aryl boronic **17** in the presence of $Pd(PPh_3)_4$ and $NaHCO_3$ in Toluene-EtOH-H2O mixture as solvent afforded desired nitroalkenes **18** in good yields (76%-86%). The reaction is general for several bromo nitroalkenes **1** and aryl boronic acids **17** with substituents.[20]

2. OBJECTIVES

The main objective of this work is to design a short and efficient synthetic route for the preparation of *gem*-bromo nitroalkenes and their application in cross-coupling reactions. Framed in this generic objective, the following specific objectives were considered:

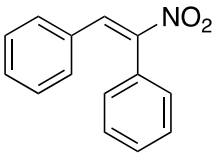
1) The synthesis of *gem*-bromo nitroalkene **1a** following a one-pot bromination/dehydrobromination (Figure 3).



1a

Figure 3: Z-(2-bromo-2nitrovinyl)benzene.

2) The synthesis of α,β-disubstituted nitroalkene **18a** (Figure 4) via a Suzuki cross-coupling reaction of nitroalkene **1a** and phenylboronic acid using Pd as transition metal catalyst.



18a

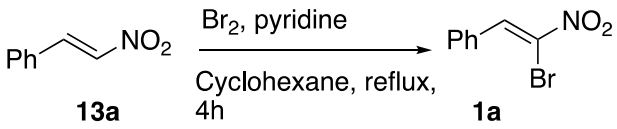
Figure 4: E-(1-nitroethene-1,2-diyl)dibenzene.

3. EXPERIMENTAL PROCEDURE

General information

Clean and dried glassware was used to perform all the reactions. An oil bath was used when heating was required. The addition of bromine was performed using an ice bath at 0ºC. There was no need for further purification of the starting materials obtained from the commercial suppliers. The reagents used for the reactions are β-nitrostyrene (98%), bromine, pyridine (99.7%), cyclohexane, phenylboronic acid (99%), $Pd(PPh_3)_4$, $NaHCO_3$, toluene, water and ethanol. For the cross-coupling reaction, it was performed under N_2 atmosphere. All TLC were performed using 0.2 mm precoated silica gel 60 F_{254} aluminum sheets with visualization of the compounds by UV light. For the column chromatography silica gel was used and they were eluted in different eluent combination of EtOAc/Hex. All ^{1}H-NMR and $^{13}C\{^1H\}$-NMR spectra were recorded on 300 MHz Bruker AV, using as reference $CDCl_3$ (7.26 ppm for ^{1}H-NMR, 77.0 ppm for ^{13}C-NMR). Coupling constants (*J* value) were expressed as hertz (HZ) and chemical shift was expressed in ppm. The multiplicity was expressed as follows: s= singlet, d= doublet, t= triplet, m= multiplet. Two software were used, ChemDraw for all the schemes and MestreNova for the analysis of the NMR spectra.

3.1 Synthesis of *gem*-bromo nitroalkene 1a



Scheme 14: General scheme for the synthesis of Z-(2-bromo-2nitrovinyl)benzene.

To a solution of nitrostyrene **13a** (2.6 g, 17.1 mmol), cyclohexane (35 mL) and pyridine (1.5 mL, 18.5 mmol) at 0ºC, bromine (0.9 mL, 17.1 mmol) was added dropwise over 5 min. Then, the reaction mixture was heated to reflux for 5h. The resulting yellow solution was decanted to a separation funnel and the solid residue was washed with EtOAc (20 mL). The combined organic layers were wash successively with $Na_2S_2O_3$ (10 mL), H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4) and filtered. The crude was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Hex to EtOAc/Hex 1:40) to afford desired *gem*-bromo nitroalkene **1a** as a bright yellow solid (1.01 g; 26% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H, H-2), 7.97-7.92 (m, 2H), 7.58-7.54 (m, 3H) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 132.0, 131.0, 130.2, 129.0, 128.1 ppm

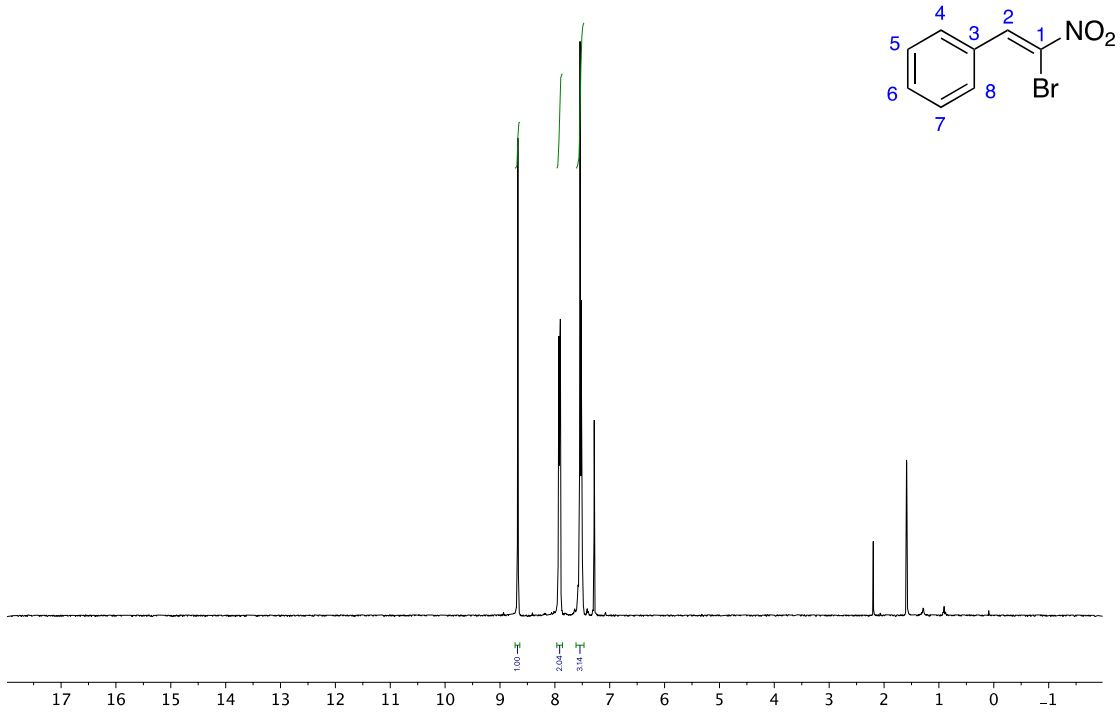


Figure 5: ^{1}H-NMR of Z-(2-bromo-2-nitrovinyl)benzene.

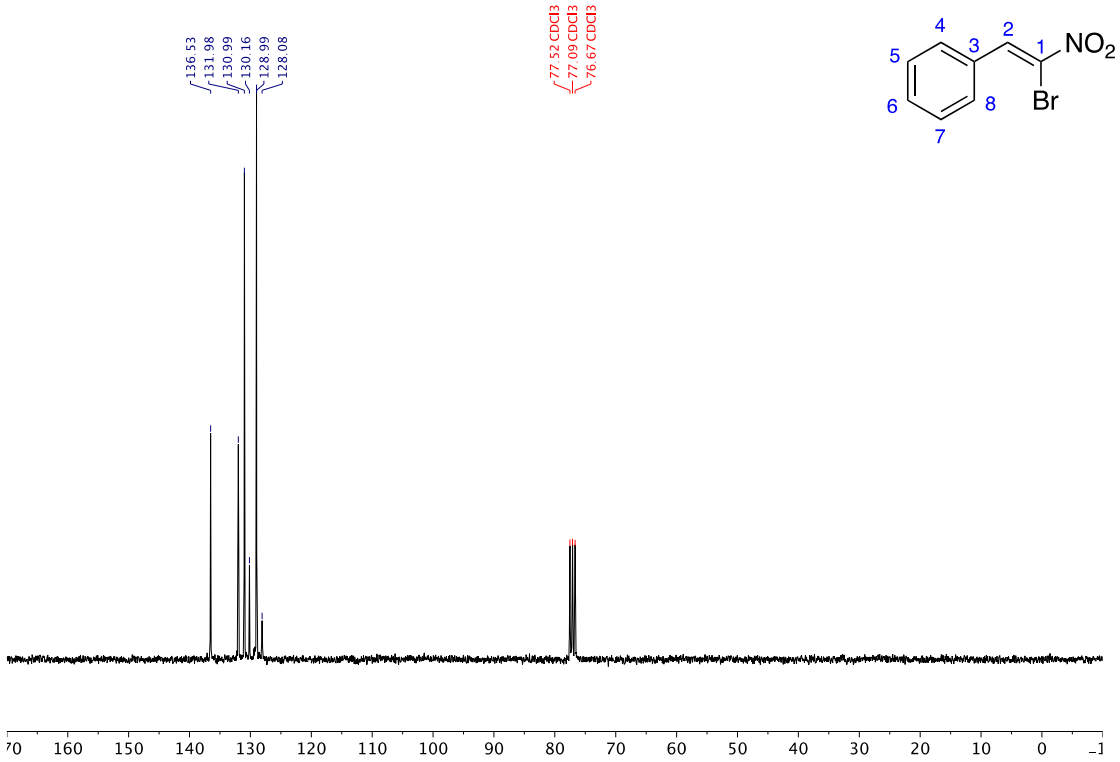


Figure 6: ^{13}C-NMR of Z-(2-bromo-2-nitrovinyl)benzene.

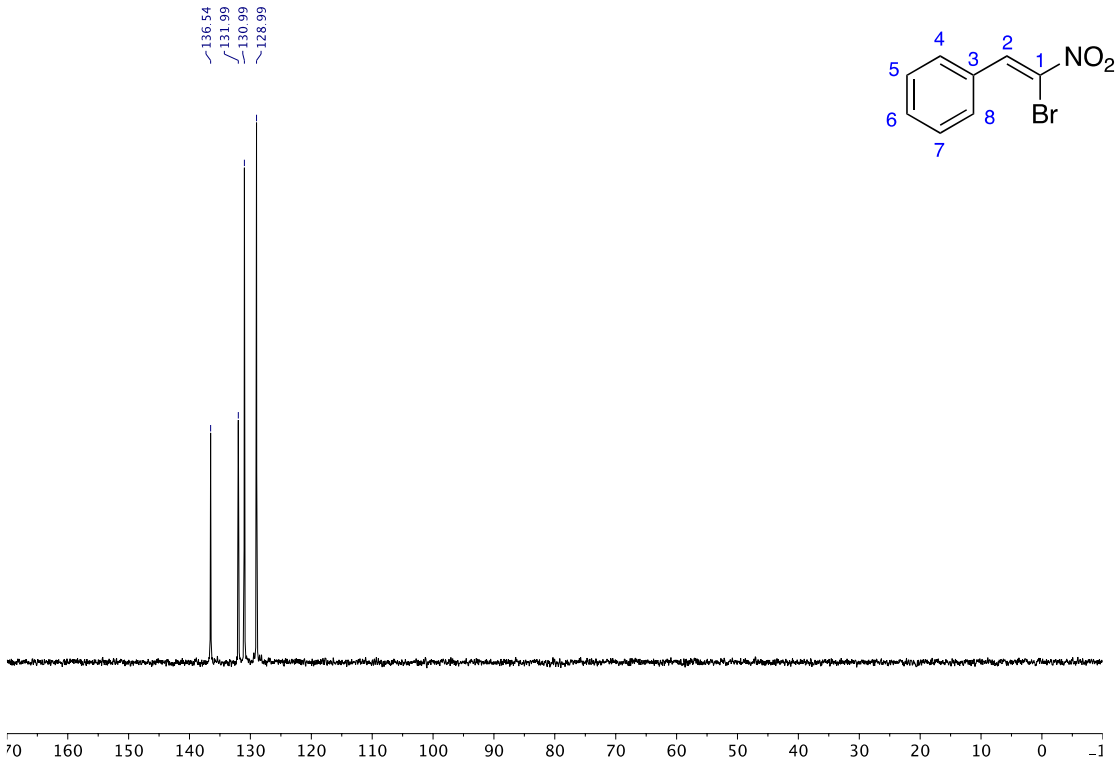
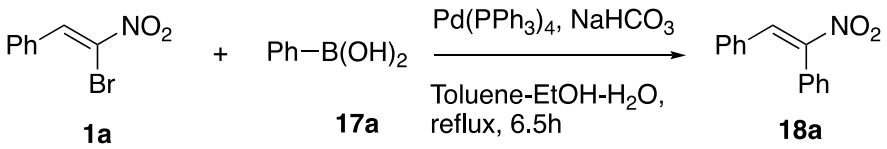


Figure 7: ^{13}C-DEPT of Z-(2-bromo-2-nitrovinyl)benzene.

3.2 Suzuki cross-coupling reaction



Scheme 15: General scheme for the synthesis of E-(1-nitroethene-1,2-diyl)dibenzene.

To a stirred solution of phenyl boronic acid **17a** (0.19 g, 1.5 mmol), $NaHCO_3$ (0.26 g, 3.0 mmol), toluene (2.2 mL), EtOH (0.12 mL) and H_2O (0.12 mL) bromo nitroalkene **1a** (0.23 g, 1.0 mmol) was added. The resulting mixture was stirred under nitrogen for 45 min. Then, $Pd(PPh_3)_4$ (0.03 g, 2.5 mmol%) was added and the resulting mixture was stirred at reflux for 6.5h, cooled down to rt and filtered through a celite pad washing with diethyl ether (6mL). After extraction with diethyl ether (2x5 mL), the organic phases were washed with brine (2x5 mL), dried under anhydrous Na_2SO_4 and filtered off. The organic solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Hex to EtOAc/Hex 1:20) to afford desired cross-coupling product **18a** as a dark yellow solid residue (0.10g; 32% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.46 (m, 3H), 7.40-7.29 (m, 3H), 7.23 (t, 2H), 7.10 (d, 2H) ppm

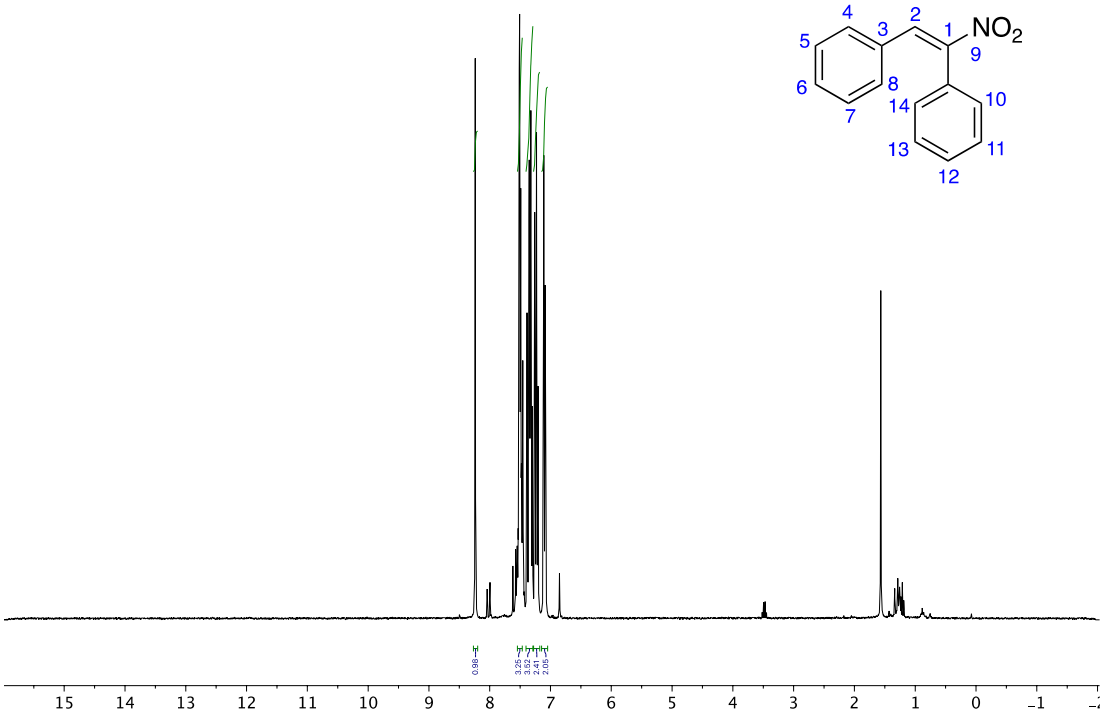
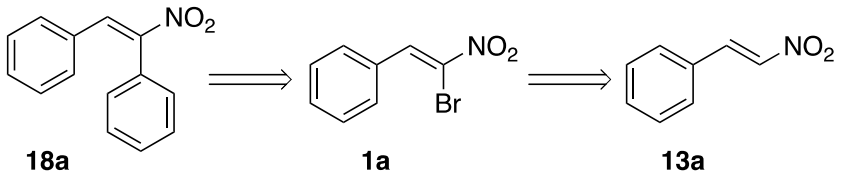


Figure 8: ^{1}H-NMR spectra of E-(1-nitroethene-1,2-diyl)dibenzene with some impurity.

4. RESULTS AND DISCUSSION

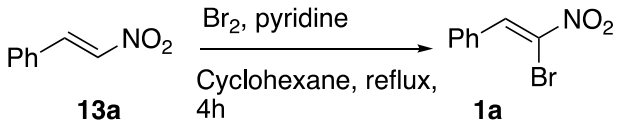
In this section, the chemistry of the reactions carried out is discussed, along with the spectroscopic data of the obtained intermediates and products.

As stated in the objectives, the main aim was the synthesis of *E*-(1-nitroethene-1,2-diyl)dibenzene **18a** from nitrostyrene **6a**. As depicted in Scheme 16, we envisioned a two-step synthetic procedure.



Scheme 16: Retrosynthetic pathway for the synthesis of E-(1-nitroethene-1,2-diyl)dibenzene.

The first step consisted of the bromination/dehydrobromination reaction. The reaction was carried out following the procedure showed in Scheme 17.



Scheme 17: Reaction of bromination/dehydrobromination

Nitrostyrene **13a** was reacted with Br_2 and pyridine in cyclohexane to give a bright yellow solid with a 26% yield and total *Z* stereoselectivity. The compound was analyzed by ^{1}H-NMR, ^{13}C-NMR and ^{13}C-DEPT which confirmed the formation of the desired bromo nitroalkene **1a**.

The ^{1}H-NMR spectra (Figure 9) displays a singlet at 8.67 ppm corresponding to H-2. The low field is due to the electronegativity of the bromine atom. In the aromatic region, the multiplet at 7.94-7.90 ppm corresponds to equivalent H-4 and H-8 and the multiplet at 7.58-7.49 ppm is due to protons H-5, H-6 and H-7.

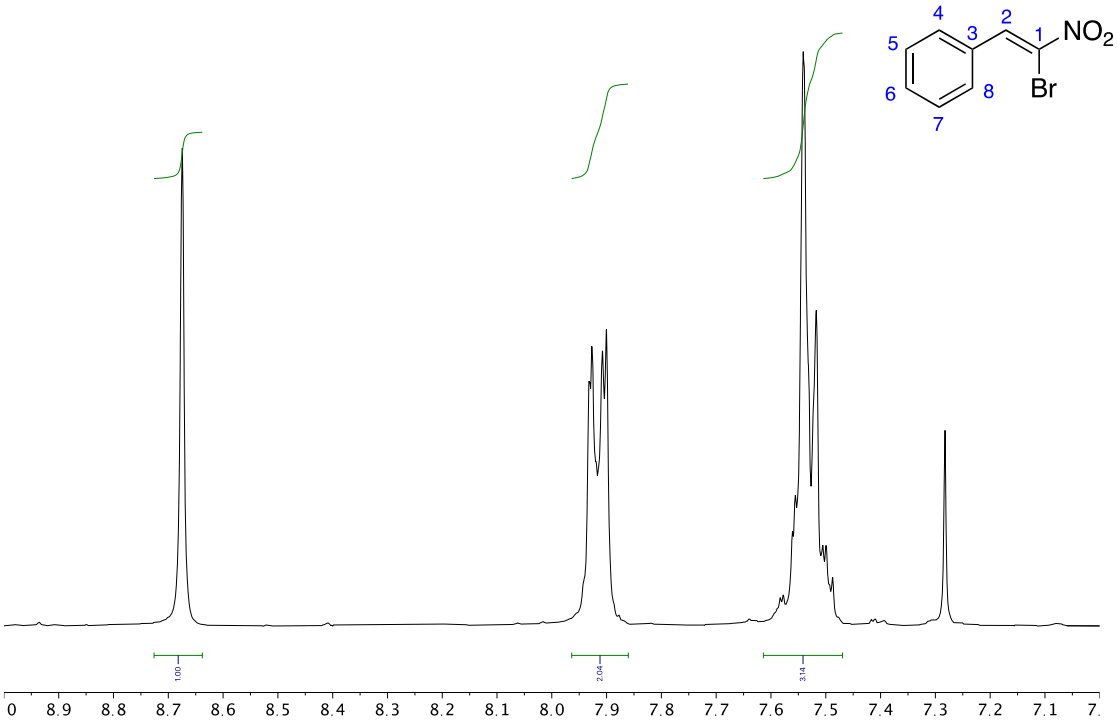
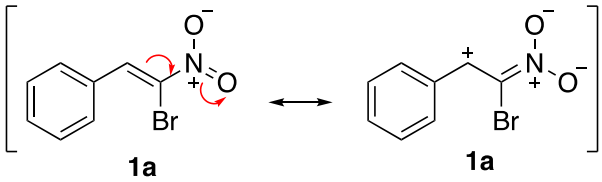


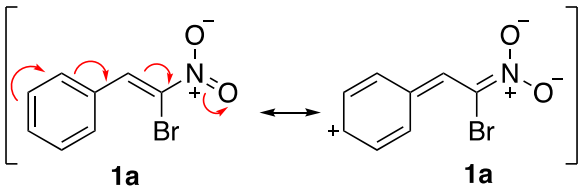
Figure 9: Region of interest in ^{1}H-NMR of Z-(2-bromo-2nitrovinyl)benzene to show the significant signals.

Regarding the ^{13}C {^{1}H}-NMR spectrum (Figure 10) there are six different signals. The less intense ones correspond to both quaternary carbons, signal at 128.1 ppm to C-1 and that at 130.2 ppm to the ipso carbon C-3. In the ^{13}C-DEPT (Figure 7) it can be observed that both signals disappear. The most deshielded signal, that at 136.5 ppm, corresponds to C-2. This chemical shift is explained by the following resonant forms:



Scheme 18: Resonant forms of that explain the deshielded in the C-2.

As there is a resonant form which presents a positive charge in that C-2, it is more deshielded in the ^{13}C-NMR spectra because less electron density is found in that carbon (Scheme 18). Signal at 132.0 ppm could be assigned to the other less electron dense carbon, which is found to be the *para* carbon (C-6) in the aromatic ring (Scheme 19). This can be explained with the following resonant forms:



Scheme 19: Resonant forms that explain the chemical shift of the para-carbon (C-6) in the ^{13}C-NMR.

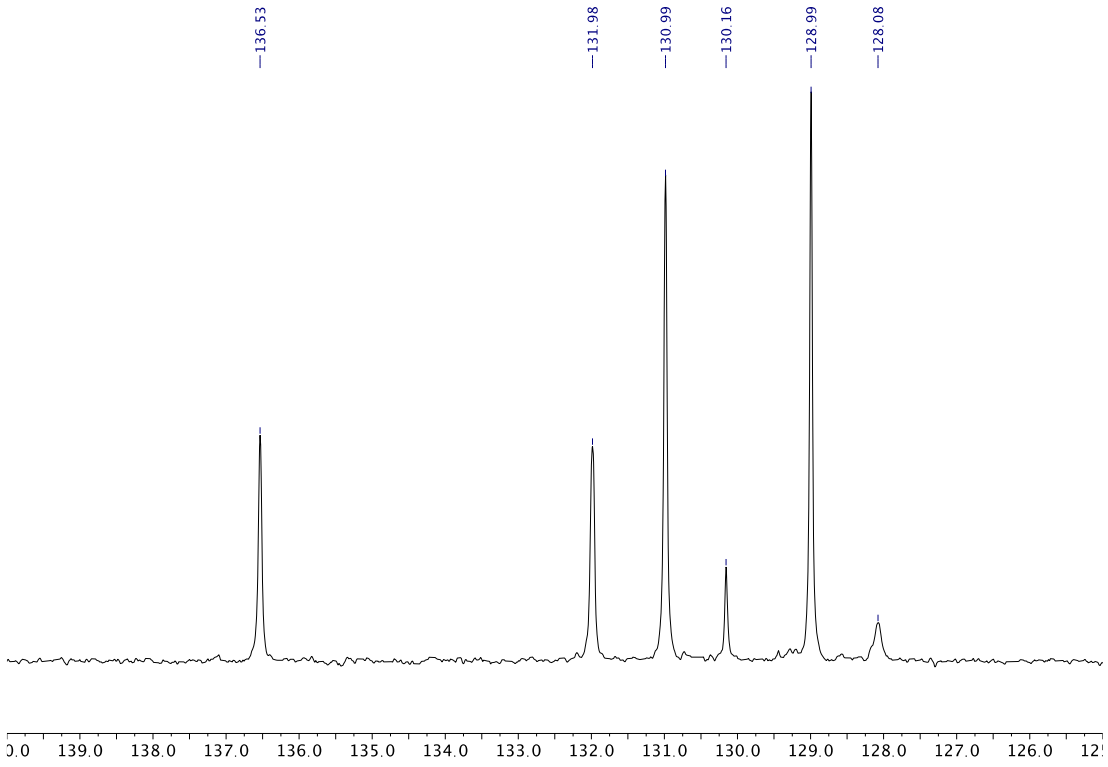
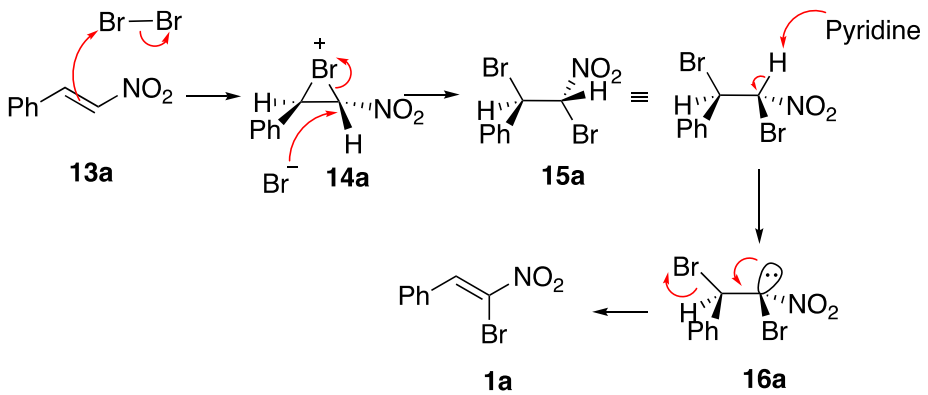


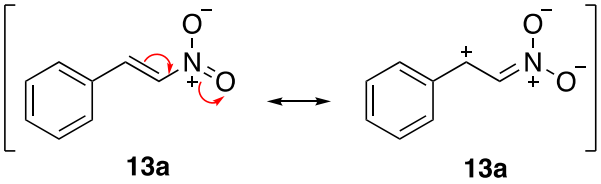
Figure 10: Region of interest in the ^{13}C-NMR of Z-(2-bromo-2nitrovinyl)benzene.

The reaction occurs through the mechanism depicted in Scheme 20.



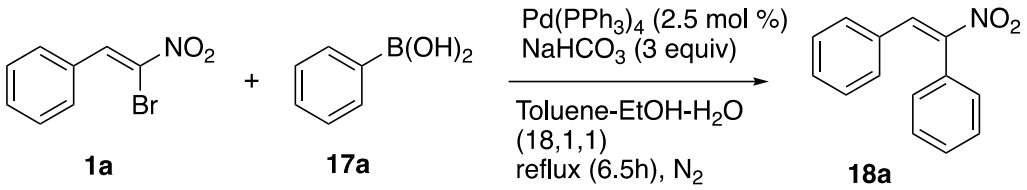
Scheme 20: Mechanism for the bromination/dehydrobromination.

The mechanism starts with the reaction of nucleophilic nitrostyrene **13a** (Scheme 21) to the polarizable bromine to afford intermediate cyclic bromonium **14a**. Then, attack of the released bromide over the electron deficient carbon forms dibrominated intermediate **15a**. From vicinal dibromide **15a**, an E1cb elimination, using pyridine as base, finally affords the desired *gem*-bromo nitroalkene **1a**.



*Scheme 21: Resonant forms of the nitro styrene **13a.***

Once the synthesis of pure *Z*-(2-bromo-2-nitrovinyl)benzene **1a** was achieved, the Suzuki-Miyaura cross-coupling reaction was carried out next, as depicted in the Scheme 22.



*Scheme 22: Cross-coupling reaction for the obtention of E-(1-nitroethene-1,2-diyl)dibenzene **18a**.*

For the performance of this reaction, bromo nitroalkene **1a** was reacted with boronic acid **17a**, $NaHCO_3$ and a catalytic amount of $Pd(PPh_3)_4$ in a mixture of toluene, EtOH and H_2O to yield pure *E*-(1-nitroethene-1,2-diyl)dibenzene with a moderate yield (32%).
The use of aqueous reaction media is due to the enhanced reactivity of the borate in the presence of water. [25]
The formation of the desired product was confirmed by the ^{1}H-NMR (Figure 11) data. Thus, the singlet at 8.24 ppm corresponds to H-1. When compared to the starting *gem*-bromo nitroalkene **1a**, this proton is shifted to a higher field because of the effect of the electronegative bromine atom present in **1a**. In the aromatic region, the multiplets at 7.54-7.46 ppm and 7.40-7.29 ppm integrate together for 6H and correspond to H-5, H-6, H-7, H-11, H-12 and H-13. The triplet at 7.23 ppm is due to H-4 and H-8 and the doublet at 7.10 ppm corresponds to H-10 and H-14.

Moreover, the ^{1}H-NMR clearly indicates that the desired product is contaminated with other minor compound, ratio product/impurity 12:1, displaying doublets at 8.03 ppm and a singlet at 7.6 ppm.

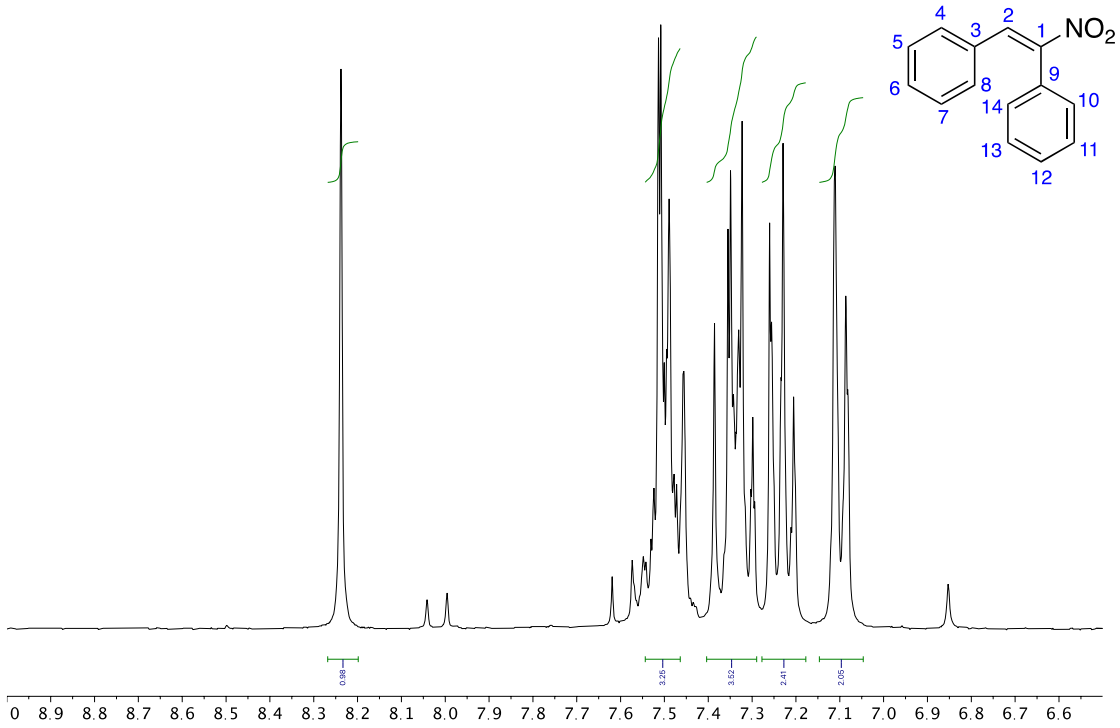


Figure 11: Region of interest of the ^{1}H-NMR spectra of the E-(1-nitroethene-1,2-diyl)dibenzene.

The possible compound that can be formed during this reaction is nitrostyrene **13a** itself. To confirm this hypothesis, the signals in (Figure 12) are compared with those in the literature. ^{1}H-NMR of nitrostyrene in the literature shows: 8.02-7.98 (d, 1H), 7.61-7.57 (d, 1H), 7.56–7.53 (m, 2H), 7.50-7.43 (m, 3H).[21] Some signals described in the literature cannot be appreciated in Figure 12 because they are mixed with that from the cross-coupling product **18a.** However, it clearly shows a coincidence between both spectra in the signals at 8.00 ppm and that at 7.50 ppm, confirming the presence of nitrostyrene **13a**. A possible explanation is that the bromine was substituted by a hydrogen atom. When the palladium catalyst got inserted into the alkenyl halide, there could occur a normal metal hydrolysis in which, in presence of water, the metal is lost and replaced by a proton, forming a metal hydroxide and the nitrostyrene **13a**.[22] Similar reactions have been reported in the bibliography.[23,24] That would also explain some unreacted boronic acid **17a** was also recovered. Thus, the ^{1}H-NMR of one fraction of the column displays the signals corresponding to the phenyl boronic acid **17a**: two triplets integrating for 1H

(*para* hydrogen) and 2H (*meta* hydrogens) and one doublet integrating for another 2H (*ortho* hydrogens). (Figure 13)

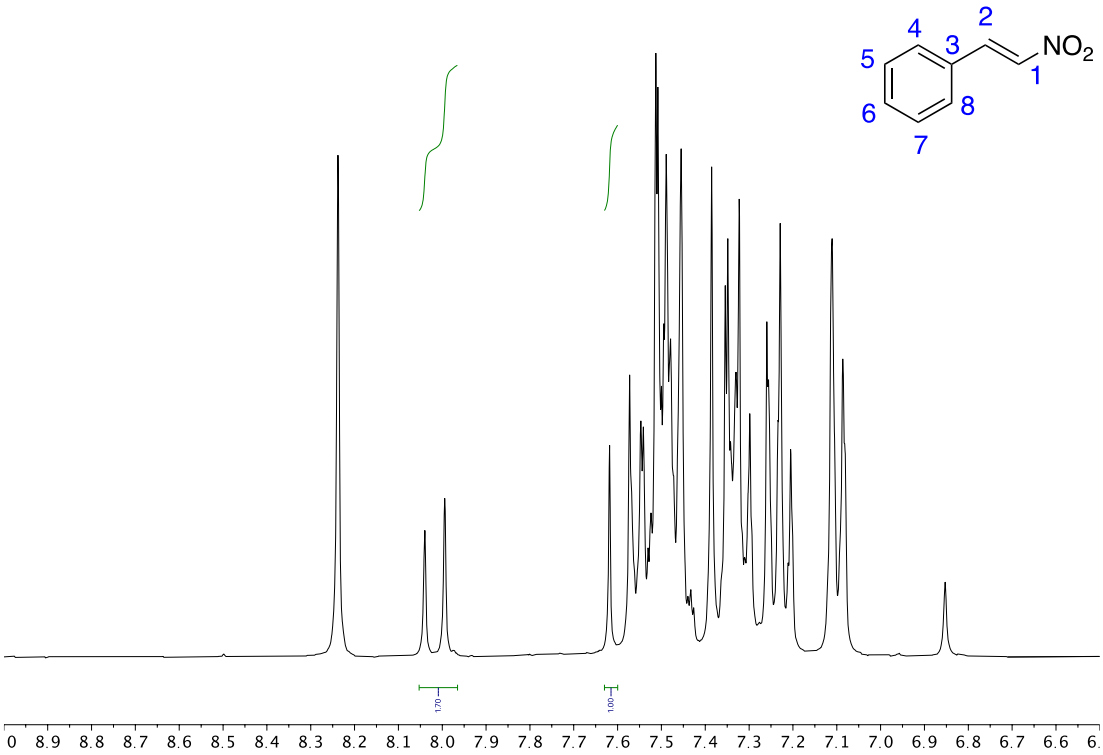


Figure 12: Region of interest of the 1H-NMR of E-(1-nitroethene-1,2-diyl)dibenzene where the signals for the impurity are clearly inferred.

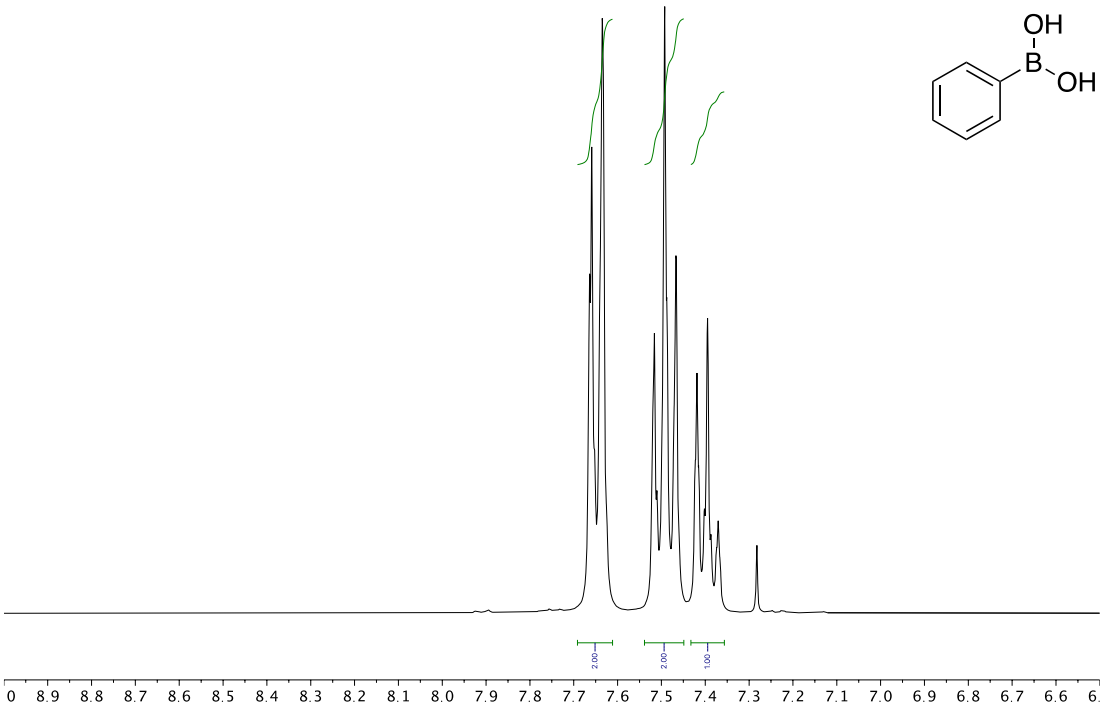
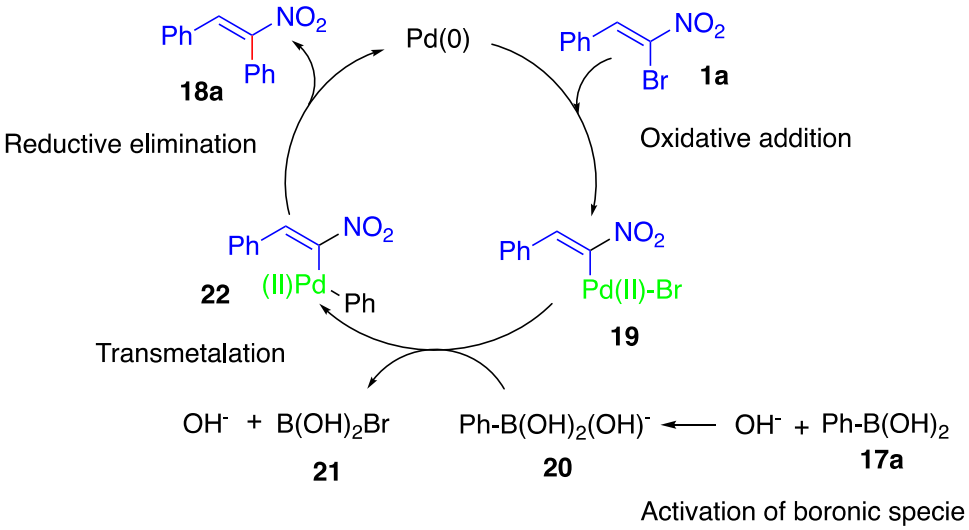


Figure 13: ^{1}H-NMR of phenylboronic acid.

The mechanism for the Suzuki cross-coupling reaction is depicted in Scheme 23.



Scheme 23: Mechanism of the Suzuki-Miyaura cross-coupling reaction.

Three fundamental steps are involved in this catalytic cycle. In the first one, the Pd(0) complex gets inserted in the C-Br bond of the alkenyl halide **1a**, to give the intermediate **19**. This step occurs with retention of configuration. The following reaction is the transmetalation, in which the phenyl group of the boronic specie gets transferred to the alkenyl one to form the intermediate **22**. The role of the base in this type of reactions is to convert the boronic acid **17a** into the more reactive organoborate species **20**, which facilitates transmetalation with the Pd-halide intermediate.[25] In the previously depicted reaction, the boronic specie **17a** is activated by the base to form a more reactive specie that can transfer the Ph substituent to the palladium complex. The halogen and the boronic specie combined with the base it lost and the product of the transmetalation **22** is formed. Finally, the last step is the reductive elimination in which the Pd(0) catalyst is regenerated to start the cycle again and the desired cross-coupling product **18a** is formed.

The stereochemistry of the product can be explained in terms of the mechanism depicted in Scheme 23. In the oxidative addition step, the Pd inserts in the carbon-halogen bond. After the transmetalation, the Pd ends up substituted with the phenyl ligand. Eventually, during the reductive elimination the Pd catalyst is removed, thus forming the C-C presenting the retained configuration. Therefore, giving only the *E*-product.

5. CONCLUSIONS

In conclusion, a method for the synthesis of *gem*-bromo nitroalkenes **1** from β-nitrostyrene based on a one-pot bromination/dehydrobromination sequence was developed. The corresponding *gem*-bromo nitroalkene was isolated with moderate yield and total *Z* selectivity and was then employed in a Suzuki reaction with phenyl boronic acid. The cross-coupling reaction afforded the desired functionalized alkene with retention of configuration. When analyzing the ^{1}H-NMR, it was appreciated the formation not only of the desired compound but also some β-nitrostyrene as side product.

This work highlights the relevance of *gem*-bromo nitroalkenes as synthetic intermediates and the potential of palladium in catalyzed cross-coupling reactions to form C-C bonds. Moreover, the importance of NMR spectroscopy for compound characterization was also demonstrated.

6. REFERENCES

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APPENDIX

In this Appendix, the appearance of the relevant TLCs will be shown as well as the aspect of the products obtained.

Figure 14: Image of TLC after completion of the bromination/ dehydrobromination.

*Figure 15: Image of the crude product **1a**.*

Figure 16: Aspect of the column for the purification of Z-(2-bromo-2nitrovinyl)benzene.

Figure 17: Pure crystals of Z-(2-bromo-2nitrovinyl)benzene.

Figure 18: Sticky solid (mainly salts) after decanting the clear solution.

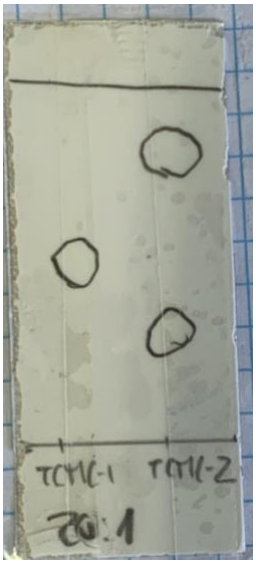

Figure 19: TLC after completion of the Suzuki-Miyaura cross-coupling reaction.

Figure 20: Column for the purification of E-(1-nitroethene-1,2-diyl)dibenzene.

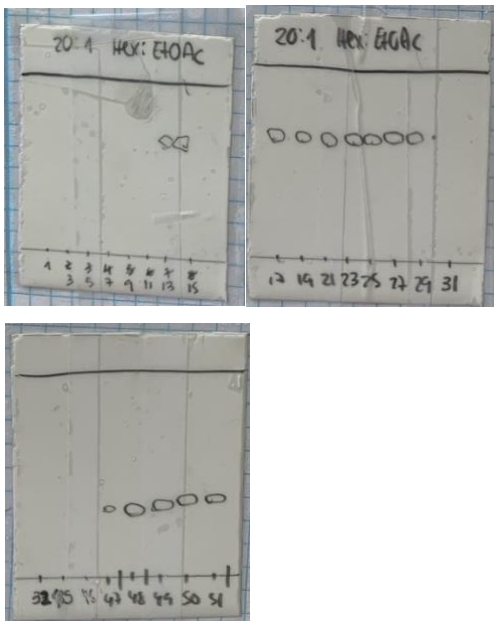

Figure 21: Images of the TLC obtained from the column.

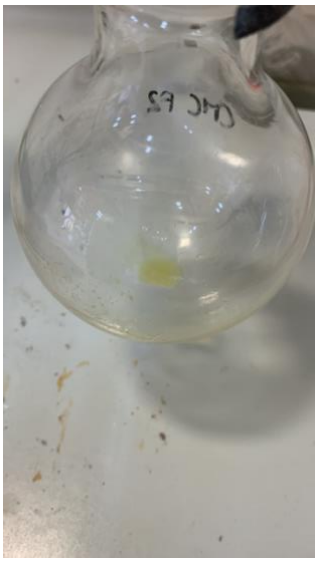

Figure 22: Fraction obtained from the column where the product should be. Mixture of two products was obtained.

Figure 23: Image of the boronic acid purified in the column.