Sonogashira Coupling: Synthesis of 1-Nitro-4-(phenylethynyl)benzene

Glenn Murray

11/18/2026

Department of Chemistry

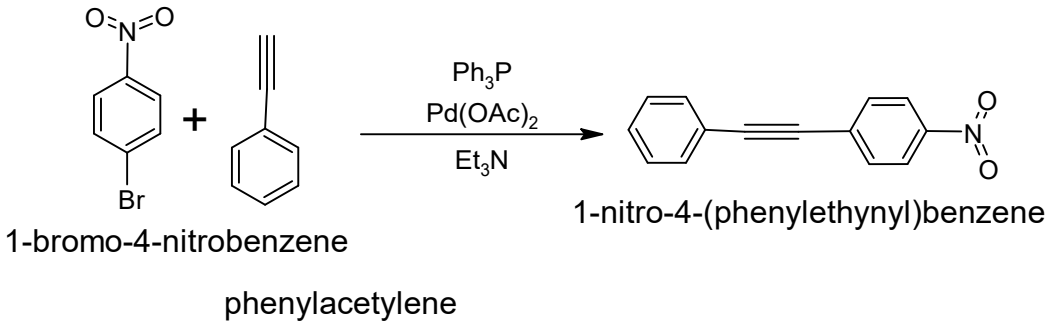
Georgia State University, Atlanta, GA

Fall Semester, 2026, Chem 6330

ABSTRACT

The purpose of this experiment was to perform a carbon–carbon coupling reaction using the Sonogashira reaction. Sonogashira coupling is a palladium-catalyzed carbon–carbon bond-forming reaction that typically proceeds under relatively mild conditions. The reaction generally involves a terminal alkyne and a copper salt co-catalyst; however, as demonstrated in this experiment, copper is not always required. In this experiment, 1-nitro-4-(phenylethynyl)benzene was synthesized from 4-bromonitrobenzene and phenylacetylene using palladium acetate, triphenylphosphine as a ligand, and triethylamine as a base. The

Scheme 1 Synthetic scheme used in this experiment



catalytic cycle used in this experiment was like the conventional Sonogashira mechanism, except that the CuX/copper acetylide portion of the cycle was omitted. Instead, the palladium intermediate, RX–L_2Pd, appears to have interacted directly with the acetylide anion during the transmetalation step. The proposed reaction scheme is shown in Scheme 1. A cleaner and faster procedure for this experiment utilizes microwave chemistry, allowing the synthesis to be completed in a fraction of the time of this procedure.

The crude product yield was 2.1 g, corresponding to a 92% yield. Sublimation of a 503 mg portion of the crude product yielded 284 mg of purified material, corresponding to a recovery of 56%. Based on this recovery, the projected amount of purified compound was 1.1 g, corresponding to a projected purified yield of 52%. The ^{1}H NMR and IR spectra were

consistent with the formation of 1-nitro-4-(phenylethynyl)benzene and showed little evidence of contamination.

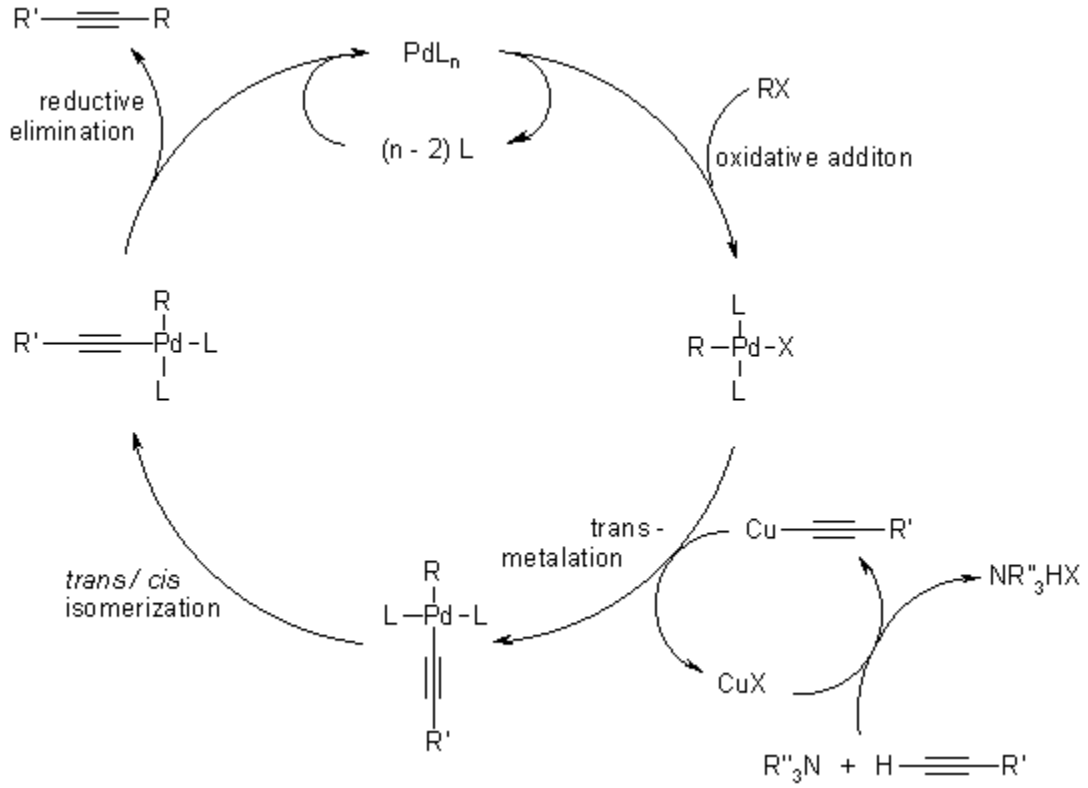
Keywords: Sonagashira reaction, palladium-catalyzed reactions, C-C coupling reactions, Sonohashira-Hagihara protocol, microwave-assisted chemistry.

1.0 INTRODUCTION

In the early 1960s, Charles Castro and R. D. Stephens developed a coupling reaction involving aryl iodides and copper(I) acetylides. However, the reaction required stoichiometric quantities of copper and elevated temperatures, typically under reflux in pyridine. This reaction became known as the Stephens–Castro cross-coupling reaction.[1] The harsh reaction conditions and hazards associated with copper acetylides limited its synthetic utility.

The Sonogashira–Hagihara protocol, commonly referred to as the Sonogashira coupling, has since become one of the most widely used methods for synthesizing substituted alkynes, particularly aryl alkynes. Its popularity stems from its relatively mild reaction conditions and tolerance of numerous functional groups. The development of this reaction was preceded by work from Heck and Dieck, who employed a palladium–triphenylphosphine catalyst system in an organic base, such as piperidine or triethylamine, at approximately 100 °C. Their approach, built upon earlier work by Cassar, who investigated palladium and nickel-catalyzed coupling reactions using inorganic bases.[2,3] The general Sonogashira coupling scheme is shown below in Scheme 2.

Scheme 2 Sonagashira Coupling Reprinted from Organic Chemistry Portal



Subsequent research has expanded the scope of Sonogashira coupling in several directions, including aqueous and copper-free procedures that can be conducted under ambient atmospheric conditions. One such development was reported by Ghiglietti, Incarbone, Mattiello, and Beverina, who published an efficient copper-free Sonogashira coupling in water under ambient atmosphere. Their approach utilized lipophilic, conjugated organic compounds containing molecular pockets within an aqueous environment, allowing the reaction to proceed without a copper co-catalyst.[4]

The present experiment deviated from the conventional Sonogashira coupling by omitting the copper salt co-catalyst while otherwise following the general Sonogashira reaction protocol. Under these conditions, the terminal alkyne was deprotonated to form an acetylide species, which subsequently participated in the palladium-catalyzed coupling reaction, replacing the bromide substituent with the alkynyl group.

This experiment introduced palladium-catalyzed carbon–carbon cross-coupling reactions. Specifically, 1-bromo-4-nitrobenzene was coupled with phenylacetylene to produce the substituted alkyne 1-nitro-4-(phenylethynyl)benzene. Palladium(II) acetate was employed as the catalyst, triphenylphosphine as the ligand, and triethylamine as the base. The experiment demonstrated the application of a copper-free Sonogashira coupling protocol for the formation of a carbon–carbon bond between an aromatic halide and a terminal alkyne.

Although microwave chemistry was not employed in this experiment, the Sonogashira coupling reaction is a good candidate for microwave-assisted synthesis. Microwave heating occurs primarily through dipolar polarization, in which the alternating electric field causes molecules with a dipole moment to continually reorient, resulting in molecular motion and the generation of heat. Depending on the reaction system, microwave energy can produce bulk heating by heating the solvent or selective heating of specific reactants or catalysts.[5] Microwave heating can accelerate reactions by providing rapid and efficient energy transfer. Furthermore, reactions conducted in sealed vessels can be performed at elevated temperatures and pressures, potentially reducing reaction times and improving yields.[6] Microwave-assisted Sonogashira coupling has also been demonstrated under conditions consistent with green chemistry principles, including the use of water as a reaction medium.[7]

Due to their mild conditions and high yields, the Sonogashira coupling is widely used in pharmaceuticals and industry. It is crucial in synthesizing many complex molecules used in drug synthesis, and recent advances have led to new syntheses of pyrimidine-based compounds important in medicinal chemistry.[8,9]

2.0 RESULTS AND DISCUSSION

Except for phenylacetylene, all reagents were added to a dried flask that had been flushed with N_2. The flask was then assembled into a reflux apparatus. Phenylacetylene was added, the system was flushed again with N_2, and the reaction mixture was heated to reflux. After maintaining the reaction at 90 °C for 70 min, the flask was allowed to cool before the reaction mixture was acidified with 2 M HCl. Following neutralization, the resulting precipitate was collected by vacuum filtration, washed several times with deionized water, and allowed to dry for one week.

After drying, 2.1 g of crude product was obtained, corresponding to a crude yield of 92%. A 503 mg sample of the crude product was purified by sublimation, yielding 284 mg of purified product. This corresponds to a sublimation recovery of 56%. Based on this recovery, the projected mass of purified product was 1.1 g, corresponding to a projected purified yield of 52%.

The IR spectrum exhibits a sharp absorption band at 2214 cm^{-1}, consistent with a conjugated alkyne stretching vibration. Additional absorption bands include a peak at 1560 cm^{-1}, attributed to aromatic C=C stretching, and a peak at 1509 cm^{-1}, consistent with asymmetric NO_2 stretching. The peak at 1349 cm^{-1} is assigned to symmetric NO_2 stretching, while the absorption at 1266 cm^{-1} is consistent with C–N stretching. Finally, the peak at 1105 cm^{-1} is attributed to aromatic C–H in-plane bending. Overall, these absorptions are consistent with the expected functional groups of the nitrophenyl alkyne product. The ^1H NMR spectrum shows several signals corresponding to the aromatic protons of 1-nitro-4-(phenylethynyl)benzene.

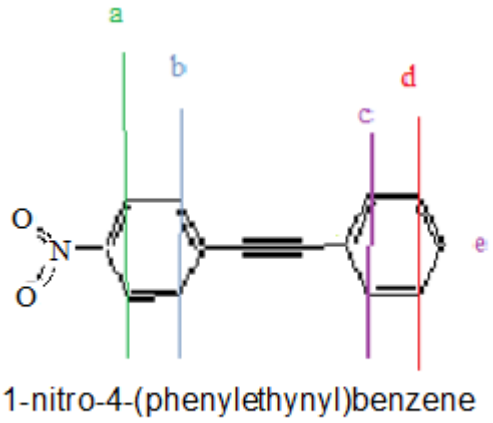


Figure 1 ^{1}H NMR hydrogen labels

The signals assigned to the ‘d’ and ‘e’ protons overlap, appearing as a complex multiplet between 7.38 and 7.42 ppm and integrating for three protons (one para and two meta to the acetylene substituent). The two ‘c’ protons, located ortho to the acetylene substituent on the phenyl ring, appear as a multiplet between 7.55 and 7.58 ppm. The ‘b’ protons, located meta to the nitro group, appear as a doublet between 7.66 and 7.68 ppm, with a coupling constant (J) of 5 Hz. This chemical shift is consistent with deshielding caused by the electron-withdrawing nitro and acetylene substituents. The greatest degree of deshielding is observed for the ‘a’ protons, which appear as a doublet between 8.21 and 8.24 ppm, with a coupling constant (J) of 6 Hz.

A signal not attributed to the product was observed at 7.26 ppm and may represent a triplet corresponding to residual $CHCl_3$ in the deuterated solvent.[10] The ^{1}H NMR spectrum is presented in figure S2 of the Supporting Information.

The ^{13}C NMR spectrum provided clear evidence of the expected product, although several additional signals suggested the presence of a contaminant. Three minor signals at 129.2, 132.5, and 137.2 ppm are consistent with the ortho and ipso carbons of triphenylphosphine.

Other triphenylphosphine signals may be obscured by overlapping product resonances.[11] The spectrum is presented in figure S3 of the Supporting Information.

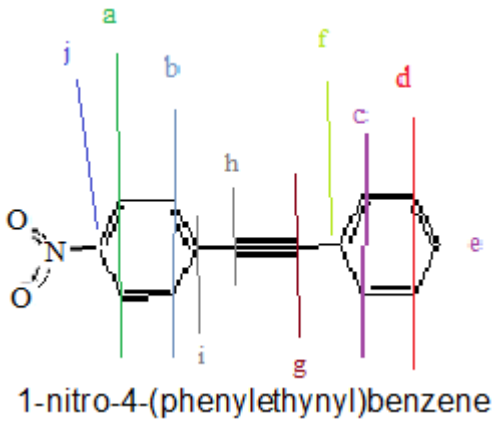


Figure 2 ^{13}C NMR carbon labeling

Among the signals assigned to the product, the ‘g’ and ‘h’ carbons appear at 87.6 and 94.7 ppm, respectively, while the ‘f’ and ‘a’ carbons appear at 122.1 and 122.7 ppm, respectively. The ‘d’, ‘e’, and ‘i’ carbons correspond to signals at 128.5, 129.3, and 130.3 ppm, respectively. The ‘c’ carbons are assigned to the signal at 131.9 ppm, while the ‘b’ carbons correspond to the signal at 132.3 ppm. Finally, the ‘j’ carbon exhibits the most downfield signal at 147.0 ppm. Overall, these chemical shifts are consistent with the expected structure of 1-nitro-4-(phenylethynyl)benzene.

3.0 EXPERIMENTAL

3.1 Chemicals

Reagents used were; tetrahydrofuran – certified, Fisher Chemical, Fair Lawn, NJ. CAS# 109-99-9; hexanes – mixture of isomers, 99.9%, Fisher Chemical, Fair Lawn, NJ. CAS# 92112-69-1; dichloromethane – 99.9%, ACS certified, Fisher Chemical, Fair Lawn, NJ. CAS# 75-09-2; Nitrogen – UHP – Pure gas, AirGas, Radnor PA. CAS# 7727-37-9; Silica gel for chromatotron – 60PF_{254} containing gypsum, EMScience, NJ. And Silica gel for column

chromatography = ultrapure, 60-200 micron, 60 Å, Acros Organics, NJ. CAS# 7631-86-9. Also used were TLC glass plates – Silica Gel 60 PF_{254}, Merch KGaD, Darmstad, Germany.

3.2 Equipment

The equipment used included rotary evaporator, Rotavap R-114, manufactured by Büchi Labortechnik AG, Meierseggstrasse 40, 9230 Flawil, Switzerland; and Bruker NMR, Bruker Avance, manufactured by Bruker BioSpin, 40 Manning Road, Billerica, MA 01821; CEM Discover microwave reactor, manufactured by CEM Corporation, Matthews, NC, USA; Nicolet iS10 FTIR spectrometer, manufactured by Thermo Fisher Scientific, 2797 Peterson Pt NW, Norcross, GA 30071.

3.3 Procedures

Triphenylphosphine (6.8 ,g), 4-bromonitrobenzene (2.01 g), palladium acetate (2.8 mg/0.12 mol%), and triethylamine (20 mL), was placed into a dried, N_2 flushed flask, with two septums, and a reflux condenser was inserted. It was placed over a stirrer and heating mantle, and the setup reflushed. Phenylacetylene (1.65 mL/1.53 g) was added, and the mixture was

Table 1 – Reagents and quantities

Reactants	Mole ratio	MW	Molarity (mols)	mass (g)	volume (mL)	density (g/mL)
4-bromonitrobenzene	1	202.0	0.010	2.02		
phenylacetylene	1.5	102.1	0.015	1.53	1.65	0.93
triphenylphosphine	2.5E-03	262.3	2.59E-05	6.80E-03		
palladium acetate	1.2E-03	224.5	1.25E-05	2.80E-03		
triethylamine				14.5	20	0.73

stirred and heated to 90 °C for the next 70 mins. As the reaction progressed, material was thrown onto the sides of the flask, which was washed back into the mixture with extra triethyl amine.The mixture was allowed to cool and HCl solution (2 M) was added with mixing

The precipitate was filtered using vacuum filteration, washing with several aliquots of distilled water. Air was drawn through the precipitate for a few minutes to remove excess water, then the previpitate placed on a watch glass to dry over the next week.

The predicted yield, computed from the above amounts, is 2.23 g. The crude yield was 2.1 g, or a crude percent yield of 92 %. A portion (503 mg) was purified using sublimation. This yielded 284 mg of purified product for a purification percentage of 56%. Based on the crude yield, the projected purified yield calculates to 1.1 g and a 52% yield.

This synthesis was performed in the laboratory utilizing the microwave for 20-25 min, at 200 °C, under a pressure of 65 bar during the synthesis.

An IR spectrum was run and a 50 mg sample was sent for ^{1}H NMR and ^{13}C NMR.

3.4 Product Characterization

1. *1-nitro-4-(phenylethynyl)benzene: white-yellow crystals*, MP 117 – 122 °C, projected yield 1.1 g, percent yield 52%; IR (neat) υ_{max} 1560, 1509, 1346, 1266, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.40 (m, 3H), 7.55-7.58 (m, 2H), 7.66-7.68 (d, $J \approx 5$ Hz, 2H), 8.23 ppm (d, $J \approx 6$ Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 87.6, 94.7, 122.1, 123.7, 128.5, 129.3, 130.3, 131.9, 132.2, 132.5, 132.3, 137.2, 147.0.

4.0 CONCLUSIONS

This experiment successfully coupled two compounds using the Sonogashira reaction under mild conditions and without a copper co-catalyst. The reaction produced 2.1 g of crude product, corresponding to a 92% yield. Based on the sublimation of a portion of the crude product, the projected purified yield was approximately 52%. Improving the recovery during

purification would be a worthwhile goal for future experiments and appears feasible with additional time for optimization.

The ^{1}H NMR, ^{13}C NMR, and IR spectra were consistent with the formation of 1-nitro-4-(phenylethynyl)benzene. The ^{1}H NMR and IR spectra showed little evidence of contamination from residual solvents, unreacted starting materials, or other impurities. Although the ^{13}C NMR spectrum showed signals potentially attributable to triphenylphosphine contamination, that spectrum was obtained from a sample associated with a separate experiment rather than the product batch characterized in this experiment.

5.0 REFERENCES

[1] Ahmed, N. Advances and Emerging Trends in Mechanistic Insights of Sonogashira-Type Coupling Reactions Towards Green Protocols for Sustainable Organic Transformations. Journal of Organometallic Chemistry 2024, 1016, 123243. https://doi.org/10.1016/j.jorganchem.2024.123243.

[2] Ibid

[3] Dieck, H. A.; Heck, F. R. Palladium Catalyzed Synthesis of Aryl, Heterocyclic and Vinylic Acetylene Derivatives. Journal of Organometallic Chemistry 1975, 93 (2), 259–263. https://doi.org/10.1016/s0022-328x(00)94049-x.

[4] Ghiglietti, E.; Incarbone, E. A.; Mattiello, S.; Beverina, L. Efficient Copper-Free Sonogashira Coupling in Water and Under Ambient Atmosphere. European Journal of Organic Chemistry 2024, 27 (21). https://doi.org/10.1002/ejoc.202400223.

[5] Ziad Alsudairy; Campbell, A.; Zheng, Q.; Harrod, C.; Brown, N.; Saintlima, A.; Raghu Vamsy Maligal-Ganesh; Ingram, C.; Li, X. Microwave-Assisted One-Step Synthesis of Palladium-Encapsulated Covalent Organic Frameworks for Heterogeneous Catalysis. Chemistry - A European Journal 2024. https://doi.org/10.1002/chem.202402513.

[6] Arcudi, F.; Sartorel, A.; Fortunato, A.; Marangoni, T.; Demitri, N.; Maggini, M.; Đorđević, L. Efficient Synthesis and Microwave-Assisted Sonogashira Reactions of Triflate-Substituted Porphyrin. European Journal of Organic Chemistry 2023, 26 (43). https://doi.org/10.1002/ejoc.202300772.

[7] Tian, Y.; Wang, J.; Cheng, X.; Liu, K.; Wu, T.; Qiu, X.; Kuang, Z.; Li, Z.; Bian, J. Microwave-Assisted Unprotected Sonogashira Reaction in Water for the Synthesis of Polysubstituted Aromatic Acetylene Compounds. Green Chemistry 2020, 22 (4), 1338–1344. https://doi.org/10.1039/c9gc04051j.

[8] Rezaeimanesh, F.; Bakherad, M.; Nasr-Isfahani, H. Sonogashira Coupling Reactions: Synthesis of 4-Substituted-6-Methyl-2-(Methylthio)Pyrimidines Catalyzed by Pd–Cu. Journal of Chemical Research 2019, 43 (9–10), 431–436. https://doi.org/10.1177/1747519819868920.

[9] Petricci, E.; Radi, M.; Corelli, F.; Botta, M. Microwave-Enhanced Sonogashira Coupling Reaction of Substituted Pyrimidinones and Pyrimidine Nucleosides. Tetrahedron Letters 2003, 44 (51), 9181–9184. https://doi.org/10.1016/j.tetlet.2003.10.028.

[10] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. The Journal of Organic Chemistry 1997, 62 (21), 7512–7515. https://doi.org/10.1021/jo971176v.

[11] JEOL Ltd. Case Study of Samples Containing Phenylphosphine Using ROYALPROBETM P+ NMR Experiments; Technical application note; JEOL Ltd., 2024. https://www.jeol.com/solutions/applications/assets/pdf/nm240009.pdf (accessed 2026-11-09).

6.0 SUPPLEMENTAL INFORMATION

6.1 Formulas

Yield calculations

Product moles as determined by moles of limiting reagent = moles of limiting reagent *x* ratio of product moles to moles of the limiting reagent

Theoretical yield = Product MW *x* (product moles as determined by moles of limiting reagent)

Percent yield = yield / theoretical yield

J coupling constant calculations

J coupling constant = difference in ppm, between two adjacent signals (of a tuplet) *x* operating frequency

Moles calculated from concentration and volume

molarity = moles / liters

moles = liters *x* molarity

6.2 Significant Figures

Significant figures used were the significant figures of the raw data plus one, for all calculation results.

6.3 Acknowledgements

6.3.1 Acknowledged use of AI in this paper

AI was used to check tense, wording, spelling, and grammar. All work in this paper is the author's original work.

6.3.2 Acknowledged use of figures, schemes, and tables

Scheme 2 – Reprinted from Organic Chemistry Portal

6.4 Raw Data

Available on request.

6.5 Tables, Graphs, and Plots

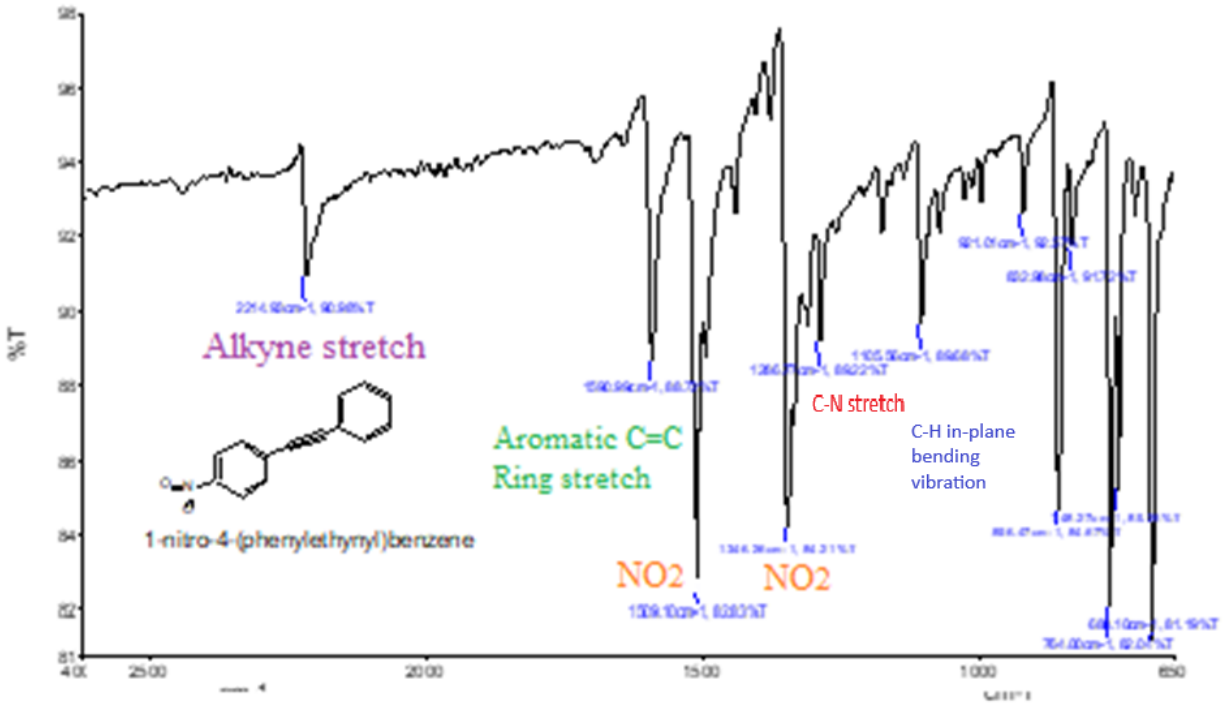


Figure S1 – IR of product

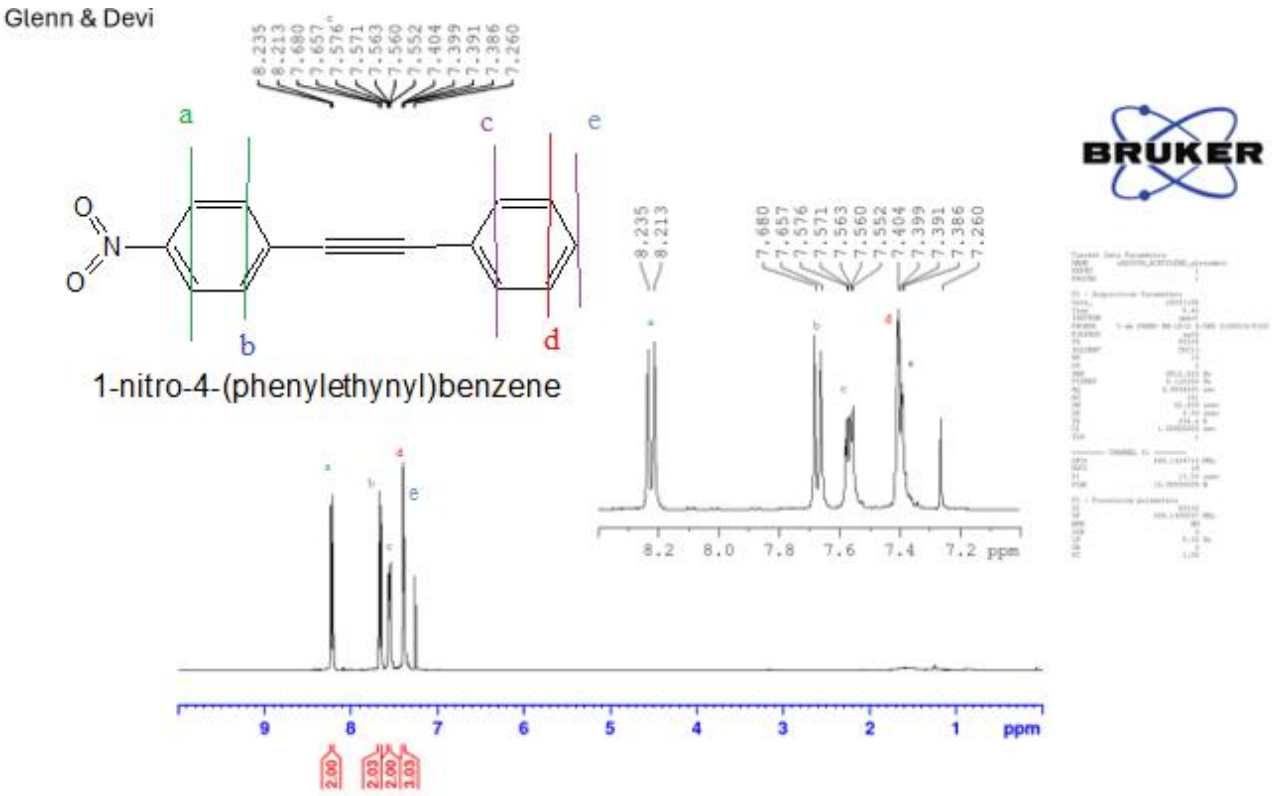
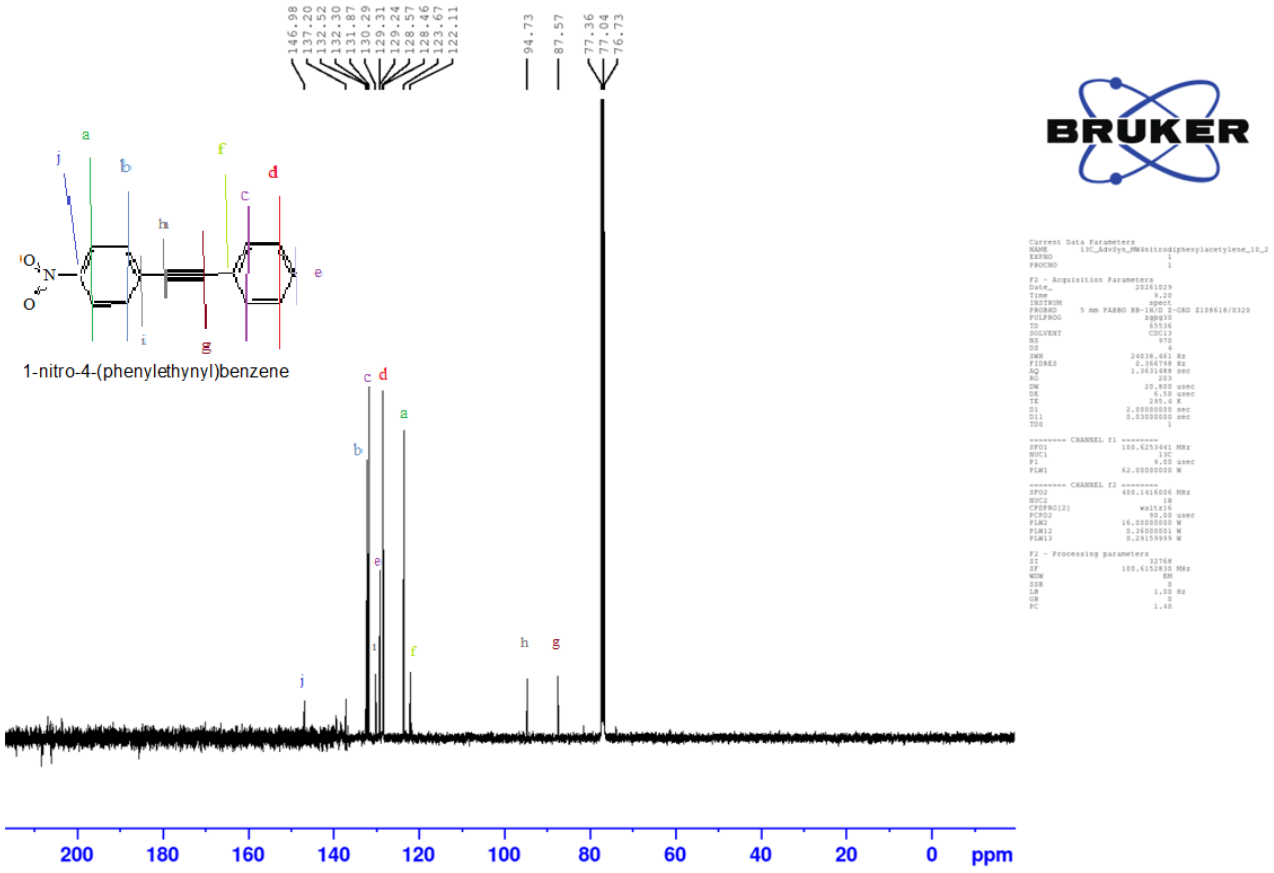


Figure S2 ^{1}H NMR of product



S3 – ^{13}C NMR of product