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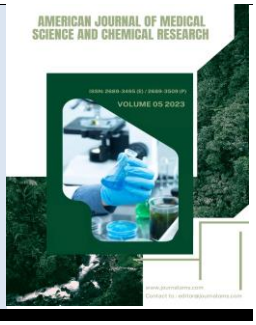

Effect of Electron Withdrawing Group on Phenyl Boronic Acid for the Synthesis of Indole by Nickle Catalyst

Sidra Ghafoor[1a *], Ammara Fatima[2b], Mahendra Singh Kushwah[3c]

[1,2]Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan. 3[2]Researcher Scholar Department of Pharmaceutical science, Rajiv Gandhi University M.P. India

***Corresponding Contact, Orcid Id**: [a]sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562 / [b]ammrafatima97@gmail.com, https://orcid.org/3450139040382 / [c]mahendrasingh.9276@gmail.com, https://orcid.org/0000-0002-6634-3757*

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ABSTRACT

Indole is a major heterocyclic system that is indestructible due to its significance biochemical importance, for example as a component of tryptophan. Indole derivatives have been identified in the literature as having a wide variety of biological characteristics and the immense potential to be used for novel treatments. One of the most proven and trustworthy methods for producing substitute indole is Fischer indole synthesis, which was developed in 1883. Since then a huge number of synthetic methods have been developed, and there a very few methods that can be used to add unsaturation at 3-position of indole. Furthermore, previous methods either required harsh reaction conditions or required the use challenging substrates to synthesis indole by these conventional methods. In this work, we designed an approach synthesis indole by using Nickle-catalyzed arylatic cyclization for alkenyl substitution at 3-position. Furthermore, the effect of electron –withdrawing groups on phenylboronic acid for the synthesis of indole by a nickel catalysis was explored. A suitable substrate was synthesized by a three steps short synthesis involving N-methylation of 2-iodoaniline group at 2-position of derivatized aniline. In the presence of Ni (OAc) 2.4H2O as a catalyst, pyphos as a ligand the 2-alkinylanilid was allowed to react with electron deficient phenylboronic acid in trifluoroethanol at 800C to give the desired 3-alkyneylindole derivatives. Reaction progress was monitored by TLC and products were purified by column chromatography. The synthesized product was characterized through techniques including infrared spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. This synthesized indole derivatives can be tested to explore its potential as a biologically active agent.

INTRODUCTION

1.1 Introduction of the study:

Heterocyclic chemistry is one of the most valuable sources of novel mainly because of the unique ability of the resulting compounds to imitate the structure of peptides and to bind reversibly to proteins. To medicinal chemists, the true utility of heterocyclic structures is the ability to synthesize one library based on one core scaffold and to screen it against variety of different receptors, yielding several active compounds. Almost unlimited combinations of

fused heterocyclic structures can be designed, resulting in novel polycyclic frameworks with the most diverse physical, chemical and biological properties. Compounds with heterocyclic rings are inextricably woven into the most basic biochemical processes of life. If one were to choose a step in a biochemical pathway at random there would be a very good chance that one of the reactants or products would be a heterocyclic compound. Even if this were untrue, the presence of heterocyclic in the process in issue would almost certainly occur given that enzymes catalyze all biochemical changes and that three of the twenty amino acids found in enzymes include heterocyclic rings. Furthermore, a lot of enzymes required the presence of specific tiny, non-amino acid molecules known as co-enzymes (or co-factor), which are typically heterocyclic compounds. But even if the questioned enzymes did not have any of this effect the heterocyclic bases present in DNA.

These are all uses of heterocyclic compounds, which have a particular chemical reactivity. A significant number of synthetic therapeutic compounds contain indole derivatives which have provided hopeful therapy suggestions and are highly efficiency bond to a variety of receptors, assisting in the development of new functional derivatives. A significant homocycle system, indole provides the structural framework for plant-derived alkaloids like strychnine. A significant heterocyclic broad- spectrum biological activity was created by the addition of the indole nucleus to pharmaceutical compounds that are physiologically active pharmacophores. For instance, indole serves as a parent nucleus of numerous natural substances, including tryptophan. Indole -3 acetic acid, a plant hormone, is produced when tryptophan is broken down taller plants. Derivatives of indole are particularly intriguing and have demonstrated many pharmacological properties including anti-viral, antiatrophic and anti-inflammatory due to their diverse biological and therapeutic functions. Researchers are interesting in creating indole – containing anti-cancer, anti-HIV, anti-oxidant, anti-microbial, anti-bacterial, anti-viral and anti-diabetic medicines as results of the discovery of numerous indole derivatives. (Kumar 2020)).

RESEARCH METHODOLOGY

All the research work reported here was carried out at chemistry lab of university of Sialkot. All commercially available reagents were purchased from Sigma Scientific (Pvt) Limited and used without further purification.

3.1 General Reagent Information

All commercially available reagents including Ni (OAc) 2·4H2O, 3- (diphenyl-phosphaneyl) propan-1-amine, arylboronic acid derivatives, and 2, 2, 2-trifluoroethanol was purchased from Sigma-Aldrich, Alfa Aesar, TCI or Strem Chemicals. All other reagents required for the synthesis of 2,2,2-trifluoro-N-methyl-N-(2-(prop-1-yn-1-yl) phenyl) acetamide derivative 1 were purchased from Sigma Aldrich, Alfa Aesar, or TCI chemical companies. Flash column chromatography was performed using Zeochem silica gel 60 (60−200 mesh).

3.2 General Analytical Information

The synthesized compounds were characterized by 1H NMR, 13C NMR, and FT-IR spectroscopies, as well as mass spectrometry. NMR spectra were recorded on a Varian 600 MHz instrument (600 MHz for 1H NMR and 151 MHz for 13C NMR). Copies of 1H NMR and 13C NMR spectra can be found in the result and discussion section. 1H NMR chemical shifts are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) in the deuterated solvent. 13C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm) and all were obtained with 1H decoupling. Coupling constants were reported in Hz. FT-IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer (Thermo Fisher). Reactions were monitored by thin layer chromatography

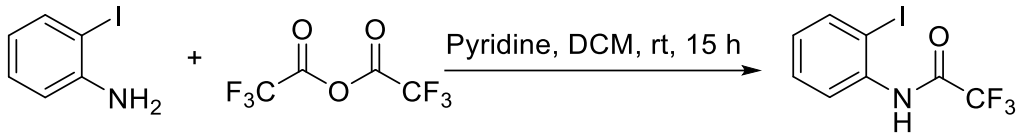
***Sidra Ghafoor**, Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan, Email/ Orcid Id: sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562*

METHODS

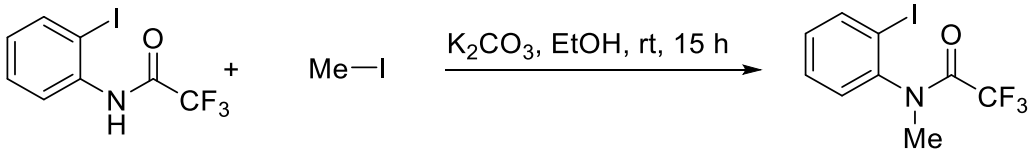
First step to synthesize indole for terminal alkenyl substitution at 3-position is preparation of starting material. There are three steps to synthesize starting material.

1) N-Acylation
2) Sonogashira coupling
3) N-Methylation

PROCEDURE



N-Acylation: An oven-dried 100-mL round-bottom flask equipped with a magnetic stir bar was charged with the 2-iodoaniline (10 mmol), pyridine (1.5 equiv., 15 mmol) and CH2Cl2 (0.5 M, 20 mL). The solution was then cooled to 0 °C with the use of an ice bath, and acetic anhydride (1.5 equiv., 15 mmol) was added drop wise to the reaction mixture. The reaction mixture was then taken out of the ice bath, and then allowed to warm to room temperature and stirred. After 16 hours, the reaction mixture was diluted with CH2Cl2 and washed with brine. The combined organic layer was dried over anhydrous MgSO4 and concentrated in vacuum. The crude N-(2-iodophenyl) acetamide was used without further purification as a starting material of the following step.



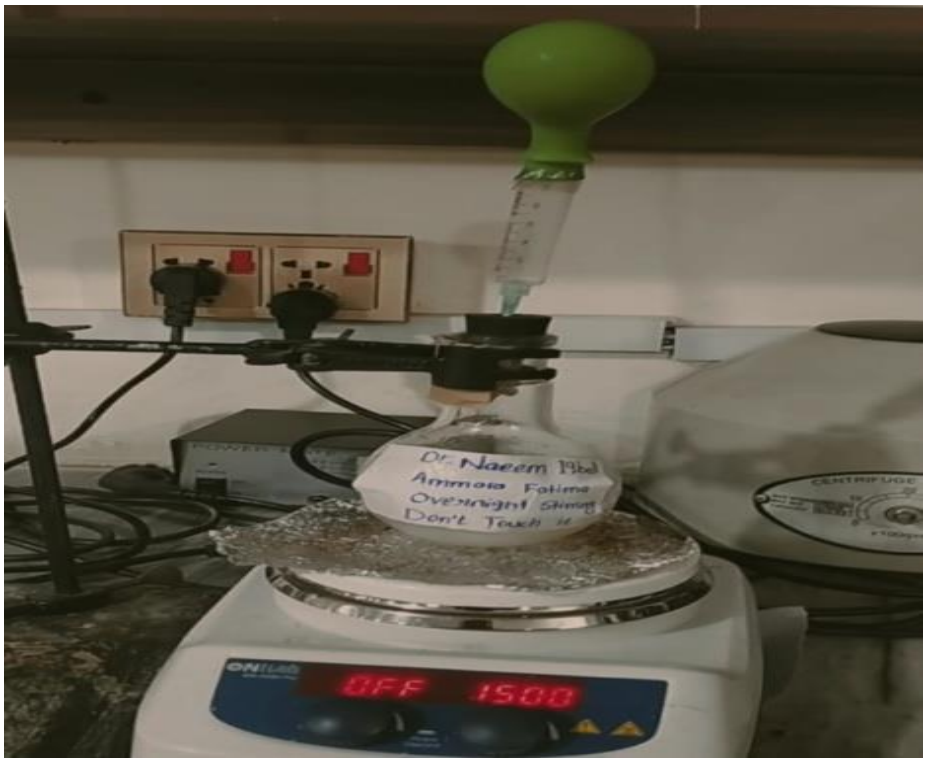


Figure 3.1. Stirring of reaction mixture

***Sidra Ghafoor**, Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan, Email/ Orcid Id: sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562*
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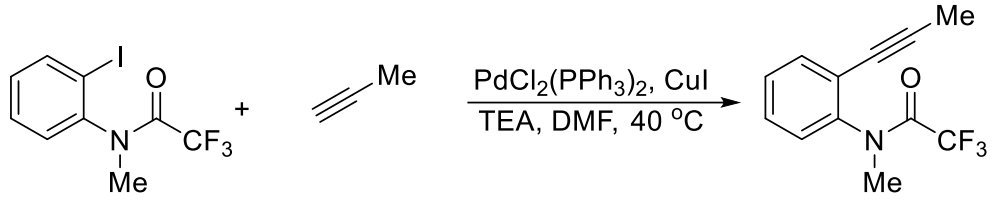
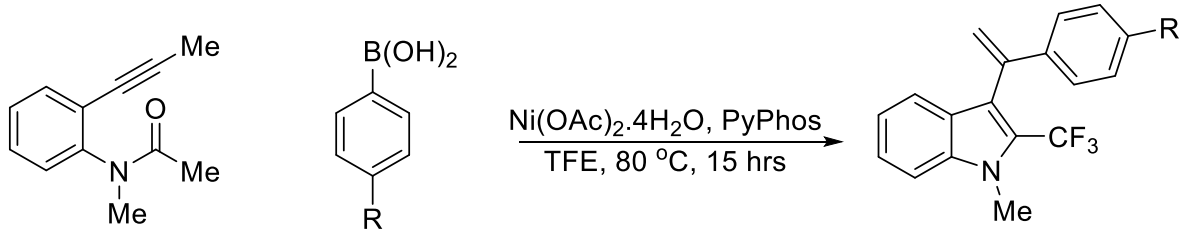
N-methylation an oven-dried 100-mL round-bottom flask equipped with a magnetic stir bar was charged with the N-(2-iodophenyl) acetamide (crude, ca. 10 mmol), potassium carbonate (3.0 equiv., 30 mmol), Methyl iodide (3.0 equiv., 30 mmol), and EtOH (0.5 M, 20 mL). The reaction mixture was stirred at room temperature (20–22 °C). After 12 hours, the reaction mixture was diluted with CH2Cl2 and washed with brine. The organic layer was dried over anhydrous MgSO4 and concentrated in vacuum. The crude product was purified by flash column chromatography using hexane/Et OAc as the eluent to afford the N-(2-iodophenyl)-N-alkyl acetamide.



Sonogashira coupling An oven-dried 100-mL round-bottom flask equipped with a magnetic stir bar was charged with the N-(2-iodophenyl)-N-alkyl acetamide (5 mmol), Pd(PPh3)2Cl2 (4 mol%), CuI (8 mol%), DMF (3.2 equiv., 2.5 mL) and Et3N (1.0 M, 10 mL). S-6 Argon was bubbled through the reaction mixture for 15 min, and alkyne (1.5 equiv., 15 mmol) was added. The reaction flask was placed into a preheated oil bath at 40 °C while stirring. After 16 h, saturated aqueous NH4Cl/NH3 was added and was diluted with CH2Cl2 and washed with brine. The organic layer was dried over anhydrous MgSO4 and concentrated in vacuum. The crude product was purified by flash column chromatography using hexane/Et OAc as the eluent to afford the derivative.

After the synthesis of substrate, it was subject to nickel catalyzed arylative cyclization conditions.



Nickel Catalyzed arylative cyclization's an oven-dried 20-mL resalable reaction tube equipped with a magnetic stir bar was charged with 2-alkynylphenyl acetamide derivative (0.5 mmol), arylboronic acid, (2.0 equiv., 1 mmol), Ni (OAc) 2.4H2O (3 mol %), PyPhos (4 mol %), and TFE (0.1 M, 5 mL). The reaction tube was then sealed with a screw-cap, and placed into a preheated oil bath at 80 °C with stirring. After 15 hrs. the tube was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was concentrated in vacuum, and purified by flash column chromatography using hexane/Et OAc as the eluent to afford the corresponding indole product derivative.

RESULTS AND DISCUSSION

Indoles are among the most privileged structural motifs due to their diverse applications in pharmaceuticals, agrochemicals, and materials science.[1] The systematic installation of selective functional groups such as trifluoromethyl group can further enhance the performance of indole molecules, as the trifluoromethyl (CF3) group is commonly employed to manipulate the pharmacokinetic and pharmacodynamics properties of bioactive molecules, such as the metabolic stability, lipophilicity, bioavailability, binding selectivity, and cell membrane permeability.[2] Therefore, methods for synthesizing CF3-substituted indoles have received wide attention. Therefore, the synthesis

***Sidra Ghafoor**, Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan, Email/ Orcid Id: sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562*
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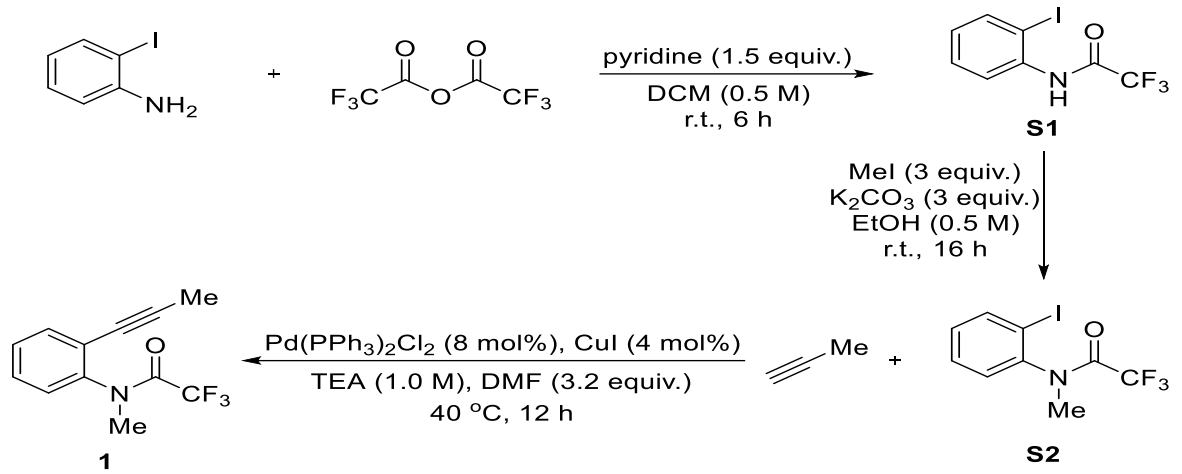
of trifluoro-methylated indoles requires serious attention from synthetic organic chemists.

Nickel-catalyzed arylative cyclization of internal alkynes has become an attractive strategy for synthesizing complex heterocycles through nucleophilic attack of alkenyl-Ni intermediates by various internal electrophiles. [5] we have employed this approach for the synthesis of indoles. Furthermore, effect of electron withdrawing groups on this reaction is also figured out in this research.

Synthesis of Substrate: Following the three steps, N-acylation, alkylation and sonogashira coupling starting material ((2,2,2-trifluoro-N-methyl-N-(2-(prop-1-yn-1-yl) phenyl) acetamide) was synthesized.



The synthesized starting material was confirmed by different analytical techniques such as 1H and 13C NMR and IR analysis. As shown in figure 4.1 there are four protons in the aromatic region, 1 proton signal between δ7.49 and δ7.45, two proton peaks between δ7.34-7.32 one proton doublet at δ7.21. These signals indicate the presence of aniline ring in the desired starting material. Furthermore, two singlet peaks in the up-field region of NMR spectra showed the presence of methyl groups attached to nitrogen (at δ 3.33) and alkyne group (at δ 2.04). Next, we took the carbon NMR of this compound to confirm the number and types of carbons in the synthesized compound. A quartet at δ 157.40 (J = 35.7 Hz) showed that a carbonyl group is present in the compound, and it is attached to the trifluoromethyl group. Six different carbon peaks at δ 141.91, 133.30, 129.18, 128.62, 128.25 (q, J = 1.5 Hz), 123.78 showed the presence of aromatic ring in the compound. A browd quartet at δ 116.48 (q, J = 288.2 Hz) represents the CF3 group in the molecule. Peaks at □92.39, 75.07 represents the presence of alkyne group. Methyl groups attached to the aminde nitrogen appears at □38.39 while the one attached to the alkyne group showed a peak at □4.61. Although these spectral characterizations confirmed the structure of our synthesized compounds but the IR analysis showed the presence of alkyne and carbonyl functional groups as well.IR νmax = 2922, 2235, 1701, 1491, 1199, 1153, 753 cm-1.

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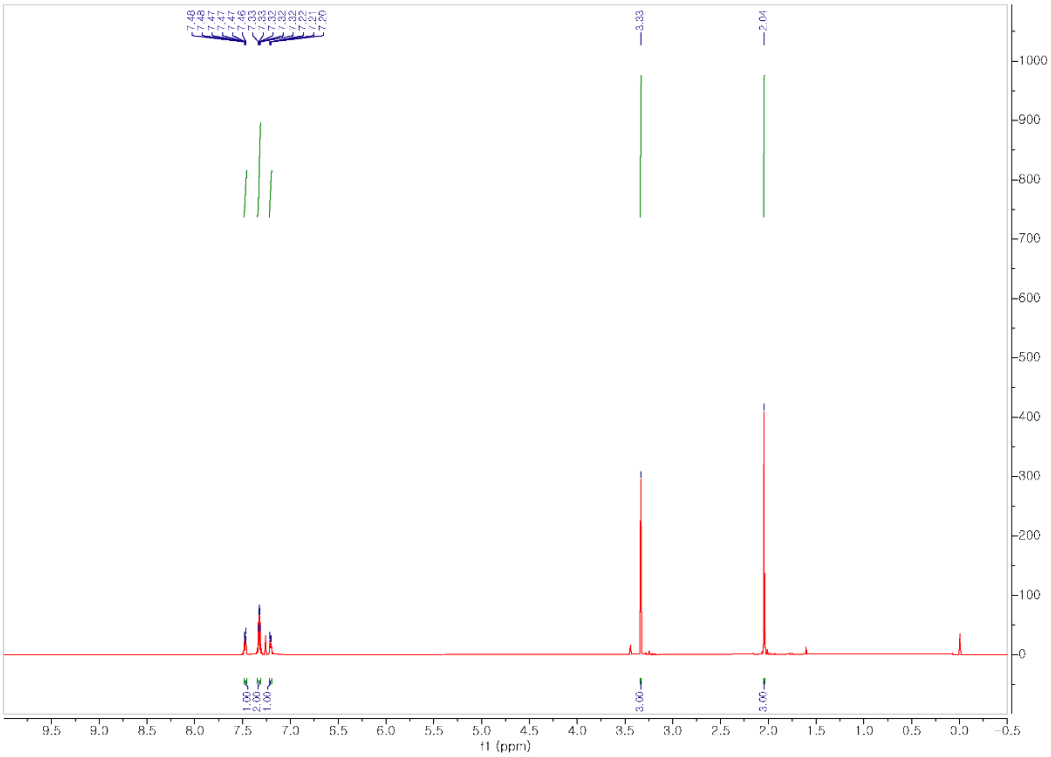

Figure 4.1. 1H NMR Spectra of Starting material

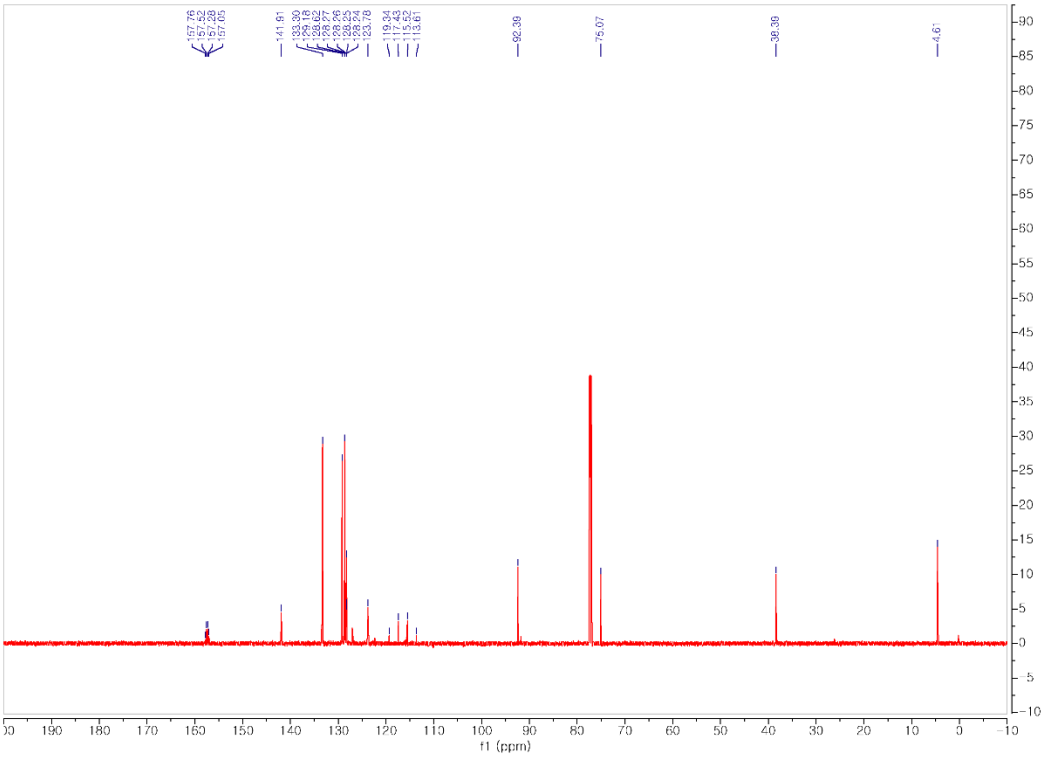

Figure 4.2. 13C NMR Spectra of Starting material

Once successfully synthesizing the starting material next, we tried to investigate the impact of electron donating groups on phenyl boronic acids on nickel catalyzed arylative cyclization of our

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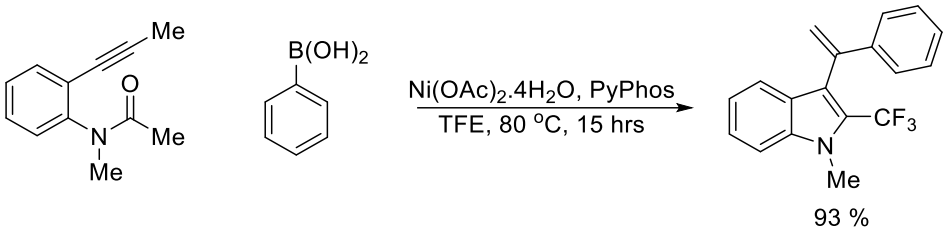
syntheses 2-alkynylamide. We aim to test 5 different phenyl boronic aids however; unfortunately, we just manage to test the impact of 2 functional groups. First reaction was conducted with simple unsubstituted phenyl boronic acid in order to compare its yield with the substrates having electron donating groups. As shown in scheme 4.1 the desired cyclized indole product (1-methyl-3-(1-phenylvinyl)-2-(trifluoromethyl)-1H-indole) was obtained with an isolated yield of 93%.



Scheme 4.1. Nickel catalyzed arylative cyclization with phenyl boronic acid.

This compound was characterized by NMR analysis. The product showed total 9 protons in the aromatic region (d 7.54-7.19) of proton NMR spectra (Figure 4.3) which are from phenyl group coming from phenyl boronic acid and four protons coming from indole ring. Two singlets at d 6.05 (s, 1H), and d 5.45 (s, 1H), showed the presence geminal protons of alkene and a singlet of three protons at d 3.94 refers to the N-Me group in the product. Next the 13C nmr analysis was carrier out to confirm the desired product formation. Abscence of any peak in the carbonyl region confirms that there is no starting material left. Ten signals in the downfield aromatic region of carbon nmr (Figure 4.4) δ 141.01 (q, 4JC-F = 1.2 Hz), 140.23, 137.80, 128.46, 127.87, 127.01, 126.54, 125.08, 123.50 (q, 2JC-F = 35.1 Hz), 121.66 showed the presence of two aromatic rings. A CF3 representative signals appears at 122.02 as a quarted withe J coupling constant of 270.2 showed the presence of this functional group in the product. Four peaks in the alkens region with peaks overlaping with the aromatic region indicated the indole ring and presene of alkene functional group (120.92, 119.83 (q, 3JC-F = 3.0 Hz), 117.63 (q, 4JC-F = 1.6 Hz), 109.82) a peak at 31.26 (q, 4JC-F = 2.6 Hz) refers to the N-Methyl group. IR signals also confirmed the presenf of alkens moity in the product (IR (neat): vmax = 3059, 3030, 2953, 1469, 1420, 1253, 1230, 1172, 1158, 1103, 1076, 745 cm-1;).

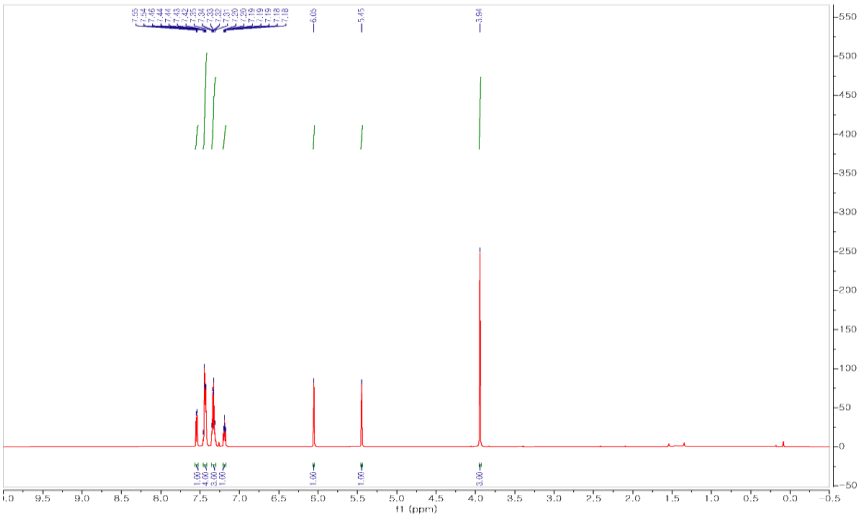


Figure 4.3. 1H NMR spectra of 1-methyl-3-(1-phenylvinyl)-2-(trifluoromethyl)-1H-indole.

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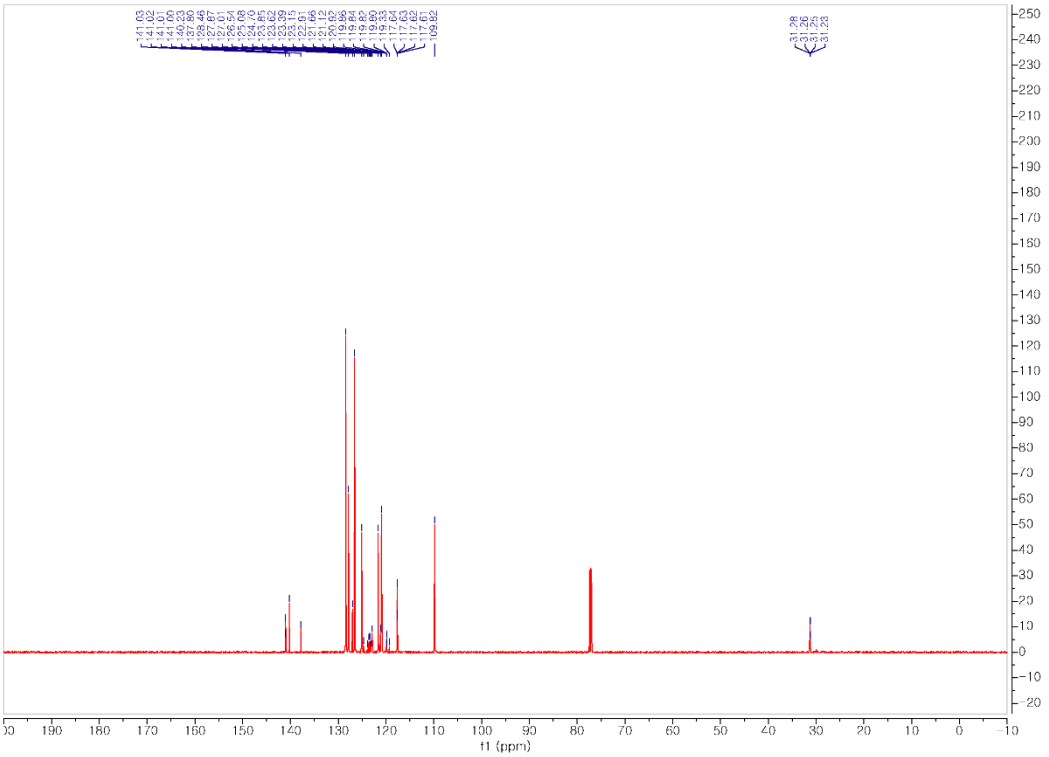
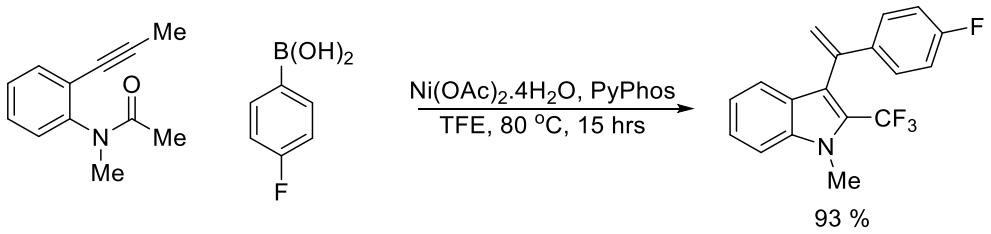


Figure 4.4. 13C NMR Spectra of 1-methyl-3-(1-phenylvinyl)-2-(trifluoromethyl)-1H-indole

Next, we tried to investigate the affect of electron donating group over the nickel catalysed arylative cyclization of 2-alkynylamides. For that purpose, 2-methoxyphenylboronic acid was employed. It was observed that reaction gave the lower yield as compared to the standared phenyl boronic acid (scheme 4.2). This low yield me be attributed to the slower transmetalation step of phenylbornic acid with nickel catalyst due to the electron rich nature of this compound. Another possible reason could be the stric hinderance as methoxy group is located next to boronic acid it might hinder the transmetllation step.



Scheme 4.2. Nickel catalyzed arylative cyclization with 4-fluorophenyl boronic acid.

The synthesized compound (3-(1-(4-fluorophenyl) vinyl)-1-methyl-2-(trifluoromethyl)-1H-indole) was next again confirmed by the NMR spectroscopy. The signals of eight protons from 7.55 to 7.13 showed the presence of aromatic region (δ7.54 (d, J = 8.0 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.39 (dd, J = 8.8, 3JH-F = 5.4 Hz, 2H), 7.20 (ddd, J = 8.0, 5.9, 2.0 Hz, 1H), 7.02 (dd, zJH-F = 9.0, J = 8.8 Hz, 2H). The two peaks with very low J coupling (5.98 (d, J = 1.2 Hz, 1H), 5.43 (d, J = 1.2 Hz, 1H) showed the presence of two geminal alkenyl protons. Single t at 3.95 (s, 3H) are reffered to N-Methyl groups. The carbon NMR specta showed the presence of 16 carbon peaks refers to our product. Twelve carbon nmr signals in the aromatic region showed the presence of

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multisubstituted aromatic rings (δ 162.70 (d, 1JC-F = 246.8 Hz), 139.25, 137.24 (q, J = 1.4 Hz), 128.21 (d, 3JC-F = 8.0 Hz), 126.86, 125.19, 123.51 (q, 2JC-F = 35.2 Hz), 121.53, 121.03, 119.60 (q, J = 3.1 Hz), 117.40, 117.40 (d, 4JC-F = 2.7 Hz). A peak with large J-coupling (121.99 (q, 1JC-F = 270.2 Hz),) referes to the CF3-groups is also found in the spectra. Two alkens signals at □115.31 (d, 2JC-F = 21.5 Hz), 109.90, are also present. N-Methyl was found at □31.26 (q, J = 2.7 Hz).

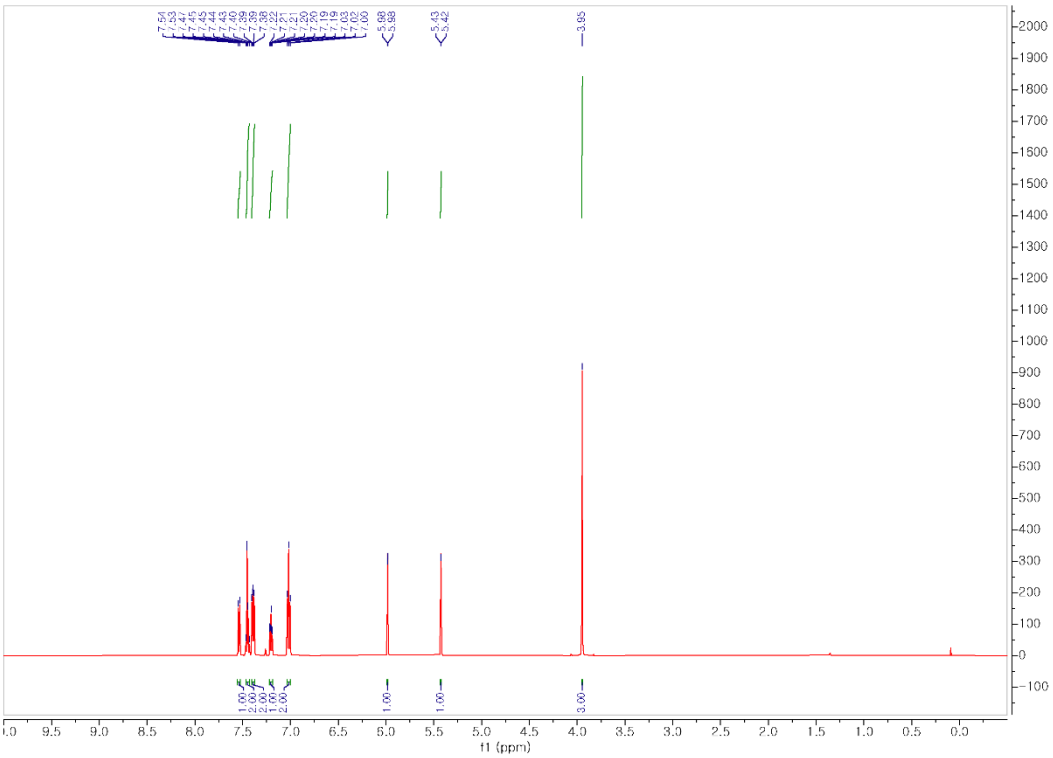

Figure 4.5. 1H NMR spectrum of 3-(1-(4-fluorophenyl) vinyl)-1-methyl-2-(trifluoromethyl)-1H-indole

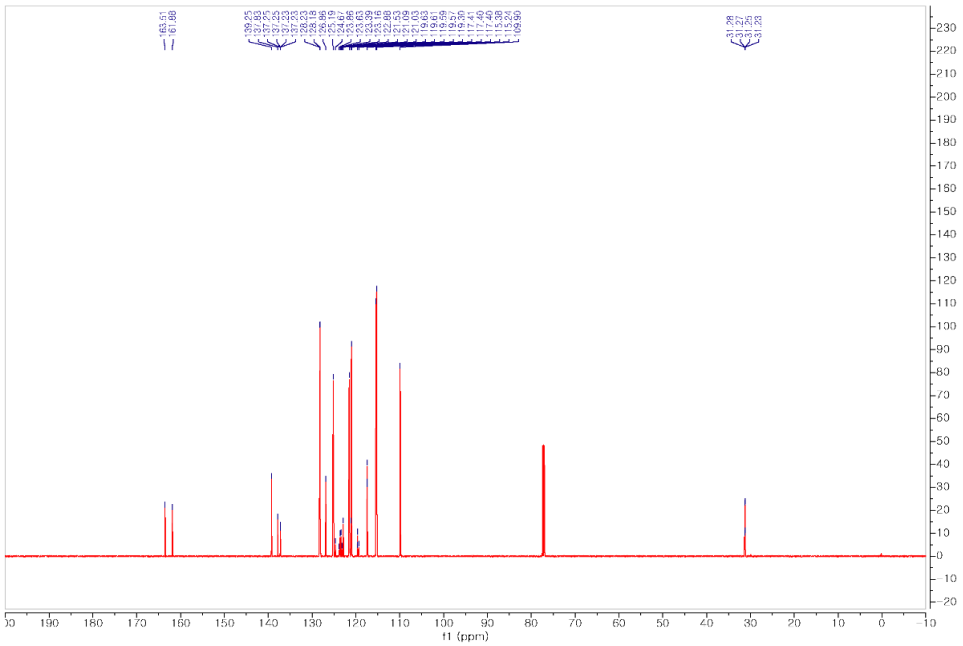

Figure 4.6. 13C NMR spectrum of 3-(1-(4-fluorophenyl) vinyl)-1-methyl-2-(trifluoromethyl)-1H-indole

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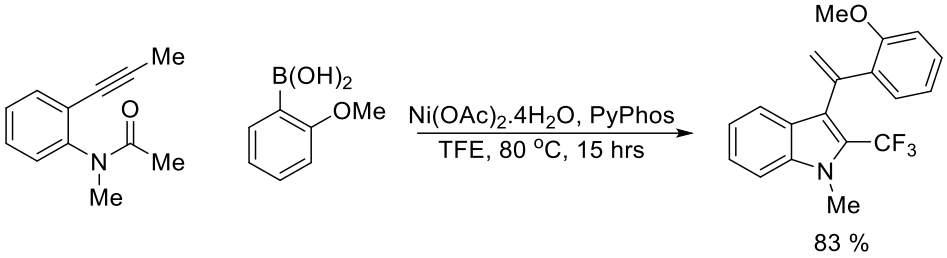

Scheme 4.2. Nickel catalyzed arylative cyclization with 2-methoxyphenyl boronic acid.

The synthesized compound (3-(1-(2-methoxyphenyl) vinyl)-1-methyl-2-(trifluoromethyl)-1H-indole) was next again confirmed by the NMR spectroscopy. The signals of six protons from 7.55 to 7.13 showed the presence of aromatic region. The additional two protons being located at slightly upfiled region □6.92 – 6.89 (m, 2H), showed the presence of electron donatic group onto the phenyl group. The two peaks with very low J coupling (6.01 (d, J = 2.1 Hz, 1H), 5.56 (d, J = 2.1 Hz, 1H)) showed the presence of two geminal alkenyl protons two singlets at 3.89 (s, 3H), and 3.71 (s, 3H) are reffered to the O-Methyl and N-Methyl groups repectively. The carbon NMR specta showed the presence of 19 carbon peaks refers to our product. Fourteen carbon nmr signals in the aromatic region showed the presence of multisubstituted aromatic rings (δ157.44, 137.62, 137.51, 130.93, 130.48, 128.82, 126.94, 124.73, 122.72 (q, 2JC-F = 35.1 Hz), 121.86, 121.70 (q, 3JC-F = 2.8 Hz), 121.61 (q, 4JC-F = 1.7 Hz), 120.59, 120.56,). A peak with large J-coupling (122.19 (q, 1JC-F = 270.1 Hz) referes to the CF3-groups is also found in the spectra. Two alkens signals at □111.67, 109.61are also present. O-Methyl and N-Methyl peaks are found at □55.63, and □ 31.19 respectively.

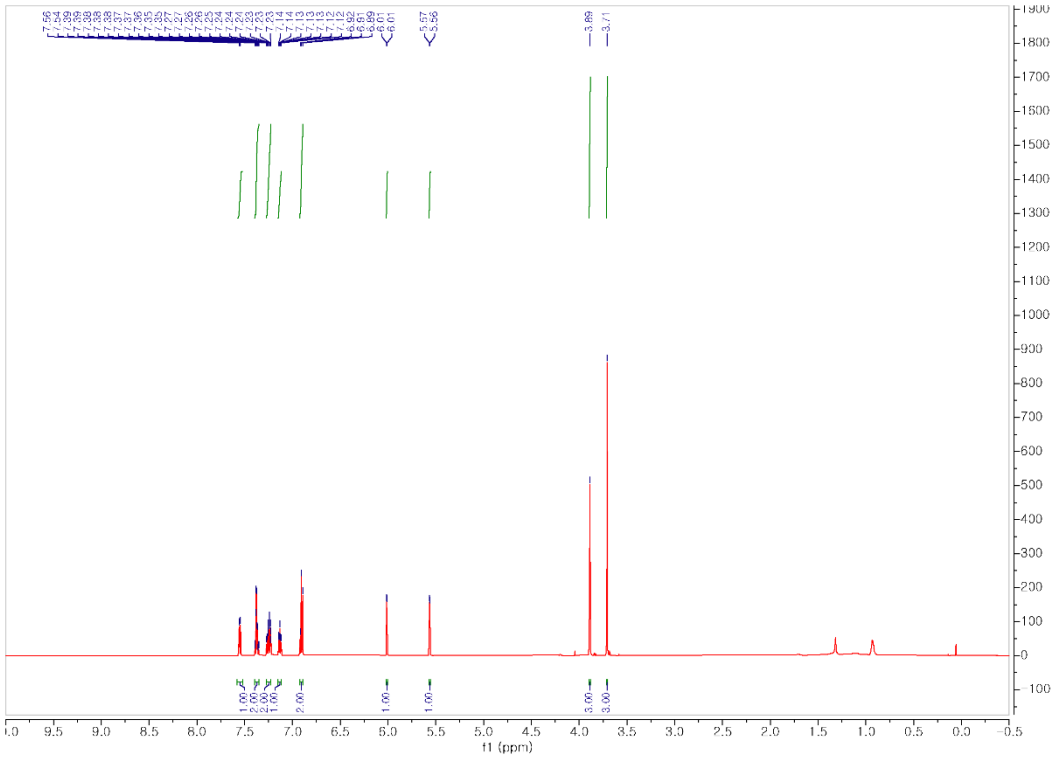

Figure 4.7. 1H NMR Spectra of 3-(1-(2-methoxyphenyl) vinyl)-1-methyl-2-(trifluoromethyl)-1H-indole

Sidra Ghafoor, *Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan, Email/ Orcid Id: sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562*
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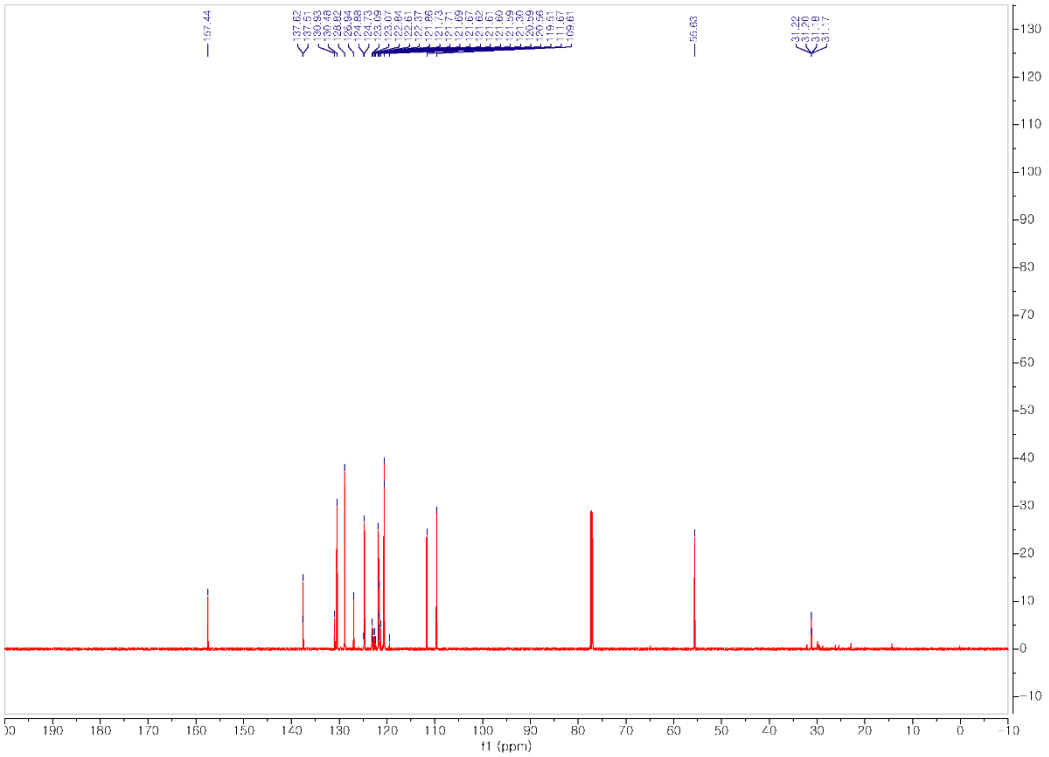

Abbildung8. 13C NMR Spectra of 3-(1-(2-methoxyphenyl) vinyl)-1-methyl-2-(trifluoromethyl)-1

CONCLUSION

In this work, we designed an approach to synthesize indole using nickel-catalyzed arylative cyclization for alkenyl substitution at 3-position. Furthermore, the effect of electron-withdrawing groups on phenylboronic acid for the synthesis of indole by nickel catalysis was explored. A suitable substrate was synthesized by a three-step short synthesis involving N-methylation of 2-iodoaniline followed by N-acylation. Sononogashira coupling was performed to introduce the alkyne group at 2-position of derivatized aniline. In the presence of Ni (OAc) 2.4H2O as a catalyst, PyPhos as a ligand the 2-alkynylanilid was allowed to react with electron deficient phenylboronic acid in trifluoroethanol at 800C to give the desired 3-alkyneylindole derivatives. Reaction progress was monitored by TLC and products were purified by column chromatography. The synthesized product will be characterized through techniques including infrared spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. It was observed that electron withdrawing group has shown no effect on the reaction outcome.

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***Sidra Ghafoor**, Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan, Email/ Orcid Id: sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562*

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***Sidra Ghafoor**, Research Scholar department of Chemistry, University of Sialkot Punjab, Pakistan, Email/ Orcid Id: sidraghafoorofficial@gmail.com, https://orcid.org/3450182449562*

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