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Cyclization Reactions of Non-Conjugate Ynones with Propargyl Amine in the Presence of a Catalyst

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Abstract: In this study, acetate derivatives were obtained from the reaction of acetophenones using diethyl carbonate. The acidic proton of CH_2 moiety was abstracted using a suitable base and α-propargyl-β-ketoester (non-conjugated ynone) derivatives **3a-c** were obtained from the reaction of the acetate derivatives with propargyl bromide. By removing the ester group of α propargyl-β-ketoester derivatives under suitable conditions, α-propargyl acetophenones (non-conjugated ynone) **4a-c** were obtained. In this study, 6 different unconjugated ynone derivatives were synthesized as starting material with yield in a range of 60-95%. Cyclization reactions with propargyl amine in the presence of three different unconjugated ynone derivatives, metal catalysts were investigated. The synthesis of propargyl pyrroles **7a-c** having substituents on C-2 and C-5 was completed.

Keywords: Cyclization, propargyl amine, pyrrole, unconjugated ynone.

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INTRODUCTION

Pyrrolic systems, which are in the class of five-membered heterocyclic compounds containing a single nitrogen atom, are bioactive compounds that can be synthesized both from natural products and by synthetic means (1-3). Pyrrole ring containing compounds are used in material chemistry (4), in natural products (5,6), dyes and as bioactive entity (7,8), it has antiallergic, cholesterol-lowering, antidepressant, anti-inflammatory (9), antidiabetic, antimicrobial (10), antifungal, antiviral, anticonvulsant, antihyperlipidemic, and antitumor (11) properties (12,13). Numerous methods have been developed and continue to be developed for the synthesis of nitrogen-containing heterocyclic compounds. In recent years, great importance has been given to the development of new methods for the synthesis of substituted pyrroles (14). We can cite alkyne groups among the most important groups because of their easy modifications and electronic properties (15). Alkynes allow the synthesis of molecules of different modifications with a wide variety of reactions such as oxidation (16), reduction (17), and nucleophilic addition (18,19).

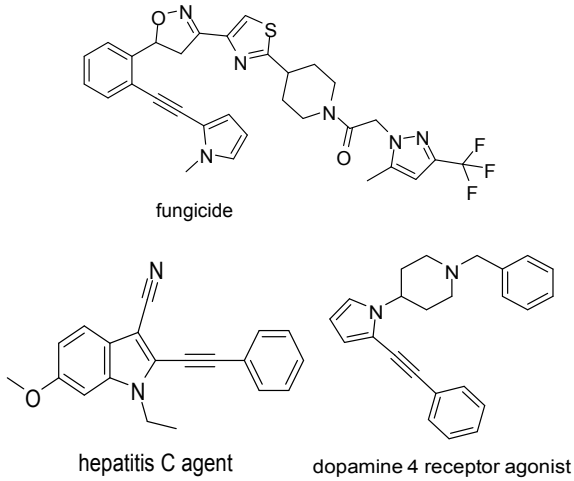


Figure 1: Activity of some compounds containing alkyne group attached to the pyrrole ring.

The presence of propargyl pyrrole compounds in structures such as dopamine 4 receptor agonist (20), fungicide, hepatitis C agent, as shown in Figure 1, increases the interest in new pyrrolic propargyl derivatives and in recent years, the production of metal-catalyzed alkylated pyrrolic systems has attracted a lot of attention (21,22). In the literature, generally, pyrrolic propargyl systems have been synthesized either by removing the NH proton with a base or by binding to the N-protected pyrrolic system at the propargyl ortho and/or meta position (23-26). In these studies, the synthesis of substituted pyrrolic derivatives was carried out, generally starting from the ynone derivative molecule. Recently, ynones, known as alkynones and also referred to as conjugated ynones, are attracting attention as important starting compounds. Ynones are compounds that contain an alkyne group directly attached to a carbonyl group in their structure (27,28). Although conjugated ynone compounds have been used as starting compounds in the synthesis of many heterocycles in the literature, α propargyl acetophenone compounds, which we can express as unconjugated ynone compounds, have not been studied much in the literature (29). In this study, the synthesis of pyrrole propargyl derivatives as a result of metal-catalyzed reaction of unconjugated ynone derivatives (α propargyl acetophenone) and propargyl amine compound as starting compound was investigated.

EXPERIMENTAL SECTION

Materials

All chemicals and solvents were commercially obtained from Sigma-Aldrich with analytical quality. The solutions were distilled and dried with suitable agents. All syntheses were carried out at normal atmospheric conditions. An Electrothermal Gallenkamp apparatus was used to determine the melting points. A Q Exactive High Performance Liquid Chromatography and High Resolution Mass Spectrometer (LC-MS/MS) was used to record the mass spectra of all compounds. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a 400 MHz Agilent using TMS (tetramethylsilane) as the internal standard. All experiments were followed by TLC (thin layer chromatography) using DC Alufolien Kieselgel 60 F254 and a Camag TLC lamp (254/366 nm).

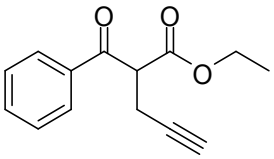
General Procedure for the Synthesis of Acetate Derivatives

1 mmol of 4-methoxyacetophenone derivative was added into a 50 mL balloon containing 10 mL of DMF and 5 mmol of NaH was added. After 45 minutes, 1.2 mmol diethyl carbonate was added and refluxed. With TLC method, the reaction was observed to end after 24 hours. The crude product was extracted (ethyl acetate/water) and the product was purified by column chromatography with ethyl acetate/n-hexane (1:5).

General procedure for the synthesis of (α-propargyl-β-ketoester)propargyl acetophenone ethyl ester (non-conjugated ynone) derivatives (3a-c)(29-31)

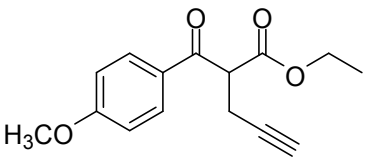
1 mmol (5 mL) ethylbenzoyl acetate was placed in a 50 mL flask, and 1.3 mmol (0.76 g) metallic sodium was added at 0 °C. After the sodium metal was finished in 10 minutes, 1.3 mmol (3.95 mL) of propargyl bromide was added and mixed. It was observed that the reaction ended after 24 hours by TLC method. The crude product was evaporated by filtration. Purification was done with ethyl acetate - n-hexane (1/5) as the mobile phase.

R/S ethyl 2-benzoylpent-4-ynoate (3a)



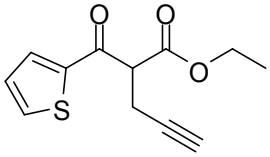
Yield; 85%, Color: Yellow, appearance: Liquid.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02-7.99 (m, 2H, Ar-H), 7.59-7.55 (m, 1H, Ar-H), 7.48-7.43 (m, 2H, Ar-H), 4.57-4.53 (t, J= 7.39 Hz, 1H, CH), 4.16-4.09 (qd, J=1.26, 7.10 Hz, 2H, OCH_2), 2.89-2.83 (ddd, J= 2.65, 7.39, 16.18 Hz, 2H, CH_2), 1.97-1.96 (t, J= 2.65 Hz, 1H, CH), 1.15-1.11 (td, J= 2.23, 7.10 Hz, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ= 193.6, 193.2, 170.4, 168.2, 135.8, 135.1, 133.8, 133.1, 129.5, 128.8, 128.7, 128.6, 128.3,128.0, 80.6, 78.3, 72.4, 70.5, 70.4, 62.3, 61.8, 59.8, 53.1, 23.5, 19.9, 18.3, 13.9, 13.8. LC-MS-MS Anal.Calcd. for $C_{14}H_{14}O_3$[M^+H]: 231.10157, Found 231.10162.

R/S ethyl 2-(4-methoxybenzoyl)pent-4-ynoate (3b)



Yield; 85%, Color: Yellow, appearance: liquid.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03-8.01 (m, A part of AA'BB' system, 2H, Ar-H), 6.96-6.94 (m, B part of AA'BB' system, 2H, Ar-H), 4.53-4.50 (m, 1H, CH), 4.18-4.13 (m, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 2.93-2.87 (m, 2H, CH_2), 1.97 (t, J= 2.67 Hz, 1H, CH), 1.20-1.16 (m, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ= 191.5, 168.5, 164.1, 131.3, 113.9, 80.8, 78.5, 72.2, 70.2, 61.7, 55.5, 52.9, 23.7, 18.4, 13.9. LC-MS-MS Anal.Calcd. for $C_{15}H_{17}O_4$ [M^+H]: 261.11214, Found 261.11282.

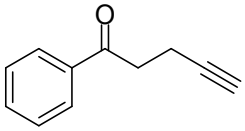
R/S ethyl 2-(thiophene-2-carbonyl)pent-4-ynoate (3c)



Yield; 90%, Color: Brown, appearance: Gel.
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.86 (d, J= 1.27, 3.62 Hz, 1H, Ar-H), 7.71-7.69 (m, 1H, Ar-H), 7.15-7.13 (m, 1H, Ar-H), 4.38 (t, J= 7.50 Hz, 1H, CH), 4.18-4.12 (m, 2H, OCH_2), 2.94-2.77 (m, 2H, CH_2), 1.97-1.96 (m, 1H, CH), 1.19-1.15 (m, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ= 185.7, 167.9, 142.9, 135.4, 133.7, 128.4, 80.4, 70.5, 61.9, 54.3, 18.3, 13.9.

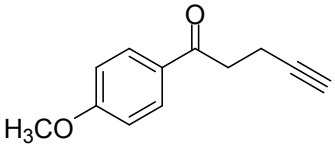
General Procedure for the Synthesis of Propargyl Acetophenone (Non-Conjugated Ynone) Derivatives (4a-c) (29-31)
12 mL of 10% NaOH solution by mass was added to the crude product and refluxed. It was observed that the reaction ended after 8 hours by TLC method. The crude product was brought to room temperature and the pH was arranged to 4 by adding HCl. It was extracted with diethyl ether and re-extracted with $NaHCO_3$ solution. It was dried with $MgSO_4$ and evaporated. The product was purified with ethyl acetate - n-hexane (1/5) as the mobile phase.

1-phenylpent-4-yn-1-one (4a)(26)



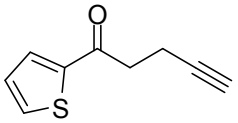
Yield; 60%, Color: White, appearance: Solid. M.P:72-75°C
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97-7.95 (m, 2H, Ar-H), 7.59-7.54 (m, 1H, Ar-H), 7.48-7.44 (m, 2H, Ar-H), 3.26-3.22 (m, 2H, CH_2), 2.65-2.60 (m, 2H, CH_2), 1.98 (t, J= 2.68 Hz, 1H, CH).^{13}C NMR (100 MHz, $CDCl_3$) δ= 197.6, 136.4, 133.3, 128.6, 128.0, 83.3, 68.8, 37.5, 13.2. LC-MS-MS Anal.Calcd. for $C_{11}H_{11}O$ [M^+H]: 159.08044, Found 159.08058.

1-(4-methoxyphenyl)pent-4-yn-1-one (4b) (26)



Yield; 65%, Color: White, appearance: Solid. M.P:85-87°C
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94-7.91 (m, A part of AA'BB' system, 2H, Ar-H), 6.93-6.90 (m, B part of AA'BB' system, 2H, Ar-H), 3.84 (dd, J=3.00, 4.70 Hz, 3H, OCH_3), 3.19-3.15 (m, 2H, CH_2), 2.62-2.57 (m, 2H, CH_2), 2.01-1.96 (m, 1H, CH).^{13}C NMR (100 MHz, $CDCl_3$) δ= 196.1, 163.6, 130.3, 113.8, 83.5, 68.7, 55.4, 37.1, 13.3. LC-MS-MS Anal.Calcd. for $C_{12}H_{12}O_2Na$ [M^+Na]: 211.07295, Found 211.07208.

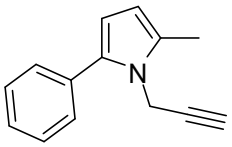
1-(thiophen-2-yl)pent-4-yn-1-one(4c) (26)



Yield; 60%, Color: Brown, appearance: Gel.
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.70-7.68 (m, 1H, Ar-H), 7.62-7.60 (m, 1H, Ar-H), 7.10-7.08 (m, 1H, Ar-H), 3.14-3.10 (m, 2H, CH_2), 2.59-2.54 (m, 2H, CH_2), 1.97-1.95 (m, 1H, CH).^{13}C NMR (100 MHz, $CDCl_3$) δ= 190.6, 143.6, 133.9, 132.1, 128.2, 83.0, 69.1, 38.0, 13.4.

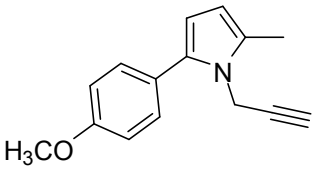
General Procedure for the Synthesis of Propargyl Pyrrole Derivatives (7a-c)
1 mmol of 4a-c compound was dissolved in 2 mL of ethanol and 3 mmol of propargyl amine was added. The mixture was refluxed after adding a catalytic amount of $AuCl_3$. It was observed that the reaction ended after 24 hours by TLC method. The crude product was evaporated by filtration. The reaction product was purified by column chromatography in which the mobile phase was ethyl acetate - n-hexane (1/5).

2-methyl-5-phenyl-1-(prop-2-yn-1-yl)-1H-pyrrole (7a)



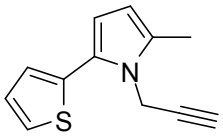
Yield; 85%, Color: Brown, appearance: Gel.
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.49-7.47 (m, 2H, Ar-H), 7.43-7.39 (m, 2H, Ar-H), 7.33-7.28 (m, 1H, Ar-H), 6.15 (t, J= 3.0 Hz, 1H, CH), 5.99 (s, 1H, CH), 4.56 (t, J=2.55 Hz, 2H, CH_2), 2.41(d, J=2.01 Hz, 3H, CH_3), 2.38(dd, J= 2.55, 5.31 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 128.6, 128.5, 126.8, 107.9, 107.2, 79.5, 72.6, 34.2, 12.4. LC-MS-MS Anal.Calcd. for $C_{14}H_{13}N$ [M^+H]: 196,11208, Found 196.11255.

2-(4-methoxyphenyl)-5-methyl-1-(prop-2-yn-1-yl)-1H-pyrrole(7b)



Yield; 50%, Color: White, appearance: Gel.
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.41-7.39 (m, A part of AA'BB' system, 2H, Ar-H), 6.97-6.94 (m, B part of AA'BB' system, 2H, Ar-H), 6.07-6.06 (m, 1H, CH), 5.96 (s, 1H, CH), 4.52 (d, J=2.24 Hz, 2H, CH_2), 3.84 (d, J=1.79 Hz, 3H, OCH_3), 2.39 (d, J= 1.40 Hz, 3H, CH_3), 2.36 (d, J= 2.24 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 158.7, 133.7, 130.1, 129.6, 126.0, 113.9, 107.2, 106.9, 79.6, 72.4, 55.3, 34.0, 12.4. LC-MS-MS Anal.Calcd. for $C_{15}H_{15}NO$ [M^+H]: 226.12264, Found 226,12415.

2-methyl-1-(prop-2-yn-1-yl)-5-(thiophen-2-yl)-1H-pyrrole(7c)



Yield; 60%, Color: Brown, appearance: Gel.
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.28-7.26 (m, 1H, Ar-H), 7.15-7.14 (m, 1H, Ar-H), 7.10-7.07 (m, 1H, Ar-H), 6.23 (d, J= 2.61 Hz, 1H, CH), 5.97 (d, J=1.38 Hz, 1H, CH), 4.64 (d, J=1.43 Hz, 2H, CH_2), 2.38(s, 3H, CH_3), 2.36-2.35 (m, 3H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 134.9, 130.7, 127.5, 125.8, 125.3, 124.9, 109.1, 107.4, 79.1, 72.6, 33.9, 12.4. LC-MS-MS Anal.Calcd. for $C_{12}H_{11}NS$ [M^+H]: 202,06850, Found 202.06989.

RESULTS AND DISCUSSION

Molecules 3 and 4, which are unconjugated ynone derivatives, were obtained in several steps (Figure 2).

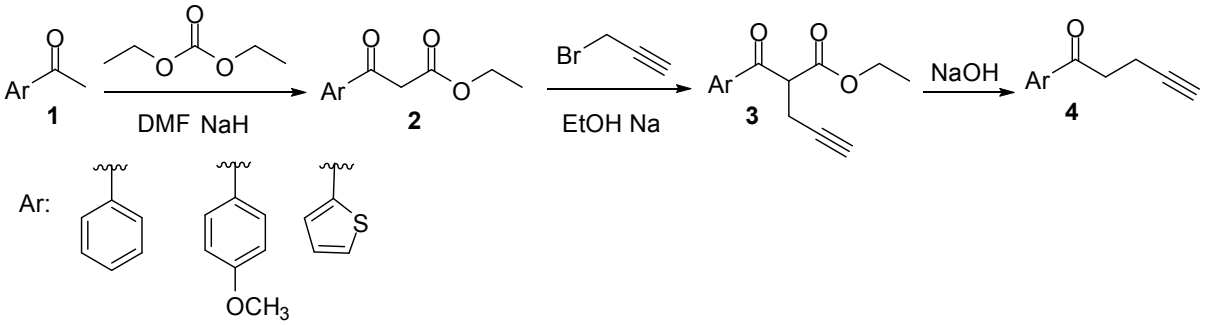


Figure 2: Synthesis of unconjugated ynone compounds.

Firstly, as shown in Figure 2, ethyl acetate derivatives 2 were obtained from acetophenone derivative compounds by removing one of the protons in the methyl carbon with sodium hydride (NaH) and reacting with diethyl carbonate. Then, α propargyl acetophenone ethyl esters 3 were obtained from the reaction of ethyl acetate derivatives with propargyl bromide by removing one of the acidic CH_2 protons in the presence of metallic sodium (Na). It is obvious that the synthesis of compounds **3a-c** give chiral molecules. However, the reaction will take place in a racemic mixture because of non-stereoselectivity. Finally, the synthesis of α propargyl acetophenone derivatives 4 was carried out by removing the ester part in the compound. Cyclization reactions of ynones 3 and 4 with propargyl amine with various metal catalysts in different solvent were investigated. Possible cyclization reactions are shown in Figure 3. As it is known, a wide research area has emerged in the literature regarding the formation of more than one possible product (endo-dig or exo-dig) or selective cyclization product in alkyne cyclizations (32-35). The reason for this is that the nucleophilic atom in the carbonyl group can attack both atoms of the alkyne group. In such cases, the metal catalyst chosen usually allows a regioselective reaction to proceed.

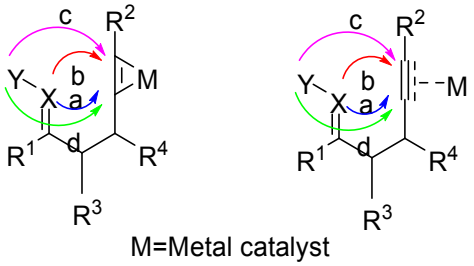
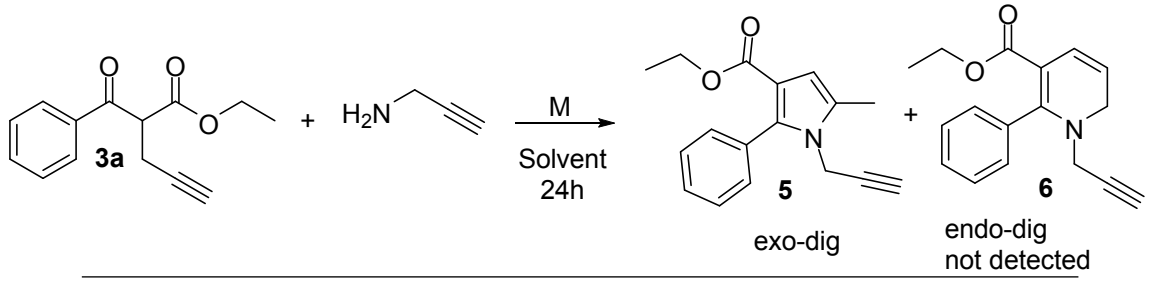


Figure 3: Cyclization of alkyne group compounds with metallic catalyst.

When the possible mechanism of the reaction is examined in the light of this information, X and/or Y atoms in the carbonyl group can attack the inner or outer carbon atom of the alkyne group in the presence of metal catalysts. If the X or Y atom attacks the inner carbon atom (path a and d), there will be exo-dig closure, and if it attacks the outer carbon atom (path b and c), there will be endo-dig closure (Figure 3) (36). Therefore, many different reactions are likely to occur. With both the examples in the literature and the experience we have gained from our studies, we can say that their regioselective properties will depend on the substituents in the ynone skeleton and/or metal catalysts. In this context, cyclization reactions of ynone 3 with propargyl amine in metals and solvent environments shown in Table 1 were investigated.

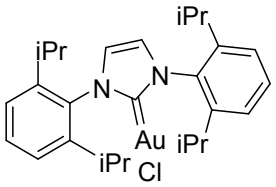
Table 1: Cyclization reactions of ethyl 2-benzoylpent-4-ynoate compound.



Compound		Solvent	Catalyst	Temperature	Result
1	3a	EtOH	$AuCl_3$	RT	nd
2	3a	EtOH	$AuCl_3$	Reflux	nd
3	3a	EtOH	p-toluenesulfonic acid	Reflux	nd
4	3a	PrOH	CuI	Reflux	nd
5	3a	PrOH	$AuCl_3$	Reflux	nd
6	3a	EtOH	AgOTf	Reflux	nd
7	3a	PrOH	Au(L)*	Reflux	nd
8	3a	PrOH	$Pd(OAc)_2$	Reflux	nd
9	3a	EtOH	$InCl_3$	Reflux	nd

nd: No reaction, the starting material was recovered.

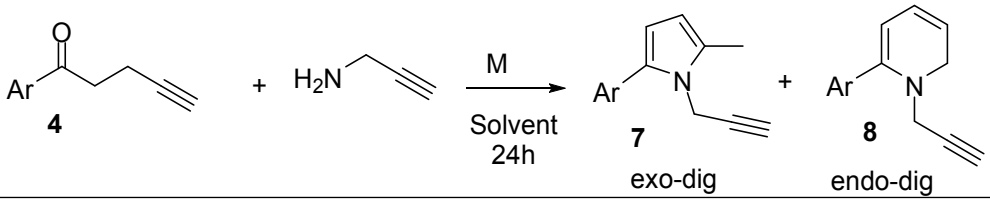
*



Au(L)

Reactions 1 to 9 were first carried out at room temperature. When it was understood that there was the starting product in the reactions controlled by TLC, no product was observed as a result of reacting the molecule 3a with different solvents in the presence of the catalyst for 24 hours in the reactions controlled by TLC again by increasing the temperature. When the reaction medium was examined, only the starting compound was obtained. In this case, it can be considered that the metal catalysts used form a complex with the 1,3-dicarbonyl structure in the starting compound and this complex is more dominant despite activating the alkyne group, therefore the reaction does not proceed. Then, the reactions of the other starting compound ɑ propargyl acetophenone derivative and propargyl amine were investigated. The pyrrole propargyl derivatives were obtained in the cyclization reactions performed with the starting compound ynone 4 under the reaction conditions shown in Table 2, under different reaction conditions.

Table 2: Preparation of 2-methyl-5-phenyl-1-(prop-2-yn-1-yl)-1H-pyrrole (**7a**).



Compound		Solvent	Catalyst	Temperature	Result
1	**4**	EtOH	$AuCl_3$	RT	nd
2	**4**	EtOH	$AuCl_3$	Reflux	**7a** 95%
3	**4**	EtOH	p-toluenesulfonic acid	Reflux	**7a** 80%
4	**4**	EtOH	$InCl_3$	Reflux	**7a** 15%
5	**4**	EtOH	CuI	Reflux	nd
6	**4**	EtOH	$Pd(OAc)_2$	Reflux	nd

nd: No reaction, the starting material was recovered.

Cyclization reactions of compound 4a-c using p-toluenesulfonic acid were screened. However, only compound 4a gave the cyclic product. So, we have decided to use $AuCl_3$ for further cyclization reactions. The pyrrole derivatives **7a-c** shown in Figure 4 were obtained with a good yield from the reaction of the starting compound **4a-c** and propargyl amine under the catalytic effect of $AuCl_3$. When we have checked the reaction media, we did not see any sign of endo-dig cyclization which is represented as compound **8** in Table 2.

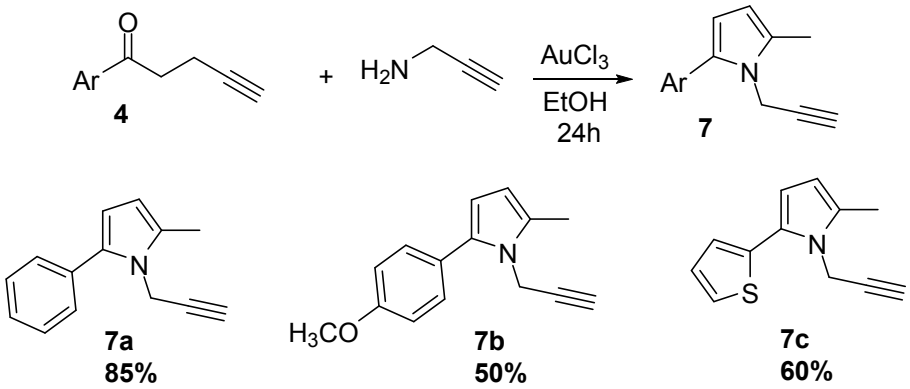


Figure 4: Obtained compounds **7a-c**.

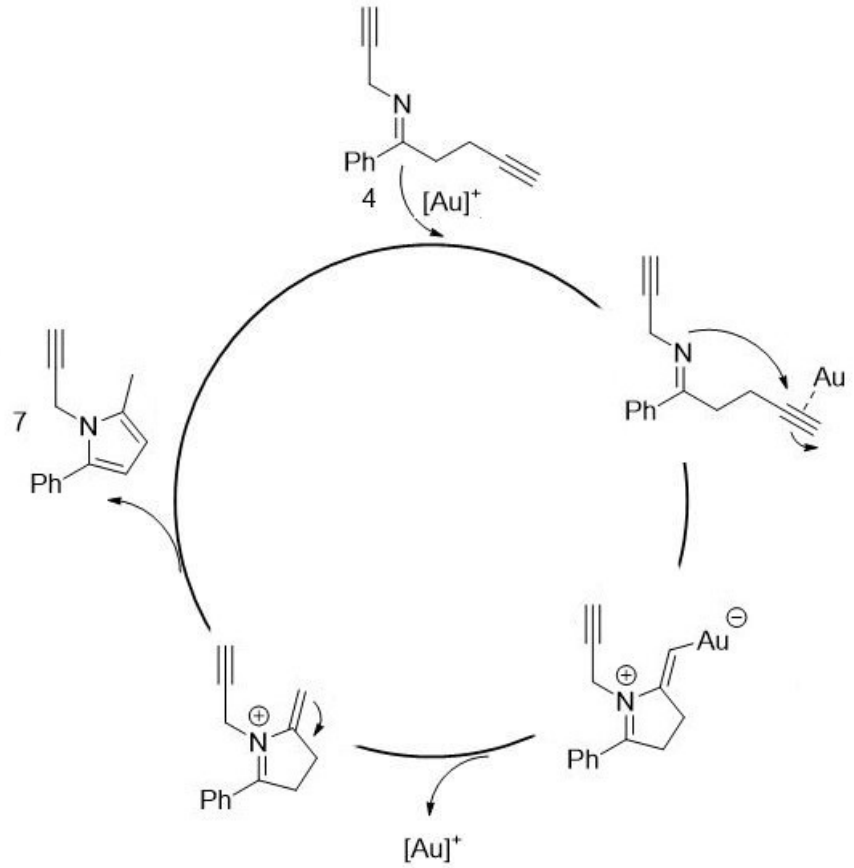


Figure 5: Proposed reaction mechanism of 2-methyl-5-phenyl-1-(prop-2-yn-1-yl)-1H-pyrrole (**7a**).

When the proposed reaction mechanism is examined in Figure 5, it can be said that the metal catalyst $AuCl_3$ activates the alkyne group, and the imine nitrogen in the imine propargyl group attached to the carbonyl group attacks the inner carbon atom of the activated alkyne group, and the reaction proceeds and becomes cyclic to pyrrole propargyl derivatives with a quintuple exo-dig closure. When the structure characterization of 2-methyl-5-phenyl-1-(prop-2-yn-1-yl)-1H-pyrrole (7a) is examined by NMR spectrum, protons resonating at 6.15 ppm and 5.99 ppm in the ^{1}H-NMR spectrum indicate pyrrole ring protons, -CH_2 protons coming as a triplet at 4.56 ppm and -CH protons resonating

as a doublet at 2.38 ppm indicate alkyne group protons and protons resonating at 2.41 ppm indicate pyrrole ring methyl protons. When the ^{13}C-NMR spectrum is examined, it is seen that the pyrrole C_3 and C_4 carbons resonate at 107.9 and 107.2 ppm, the alkyne group carbons resonate at 79.4, 72.6 and 34.2 ppm, respectively, and the methyl group attached to the pyrrole ring resonates at 12.4 ppm.

CONCLUSION

In this study, the synthesis of 1,3-diketo esters from acetophenone derivative compounds was carried out and from these derivatives, 6 different unconjugated ynone derivatives were synthesized as starting compounds. Cyclization reactions of unconjugated ynone derivatives were investigated using metal catalysts. In the presence of metal catalysts, 3 different pyrrole propargyl derivatives were obtained as a result of cyclization reactions of unconjugated ynone derivatives and propargyl amine compound in a single step.

CONFLICT OF INTEREST

There is no conflict of interest.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

^{1}H-NMR, ^{13}C-NMR, spectrum and HRMS data are provided in the Supplementary Material section of this article.

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Supplementary material

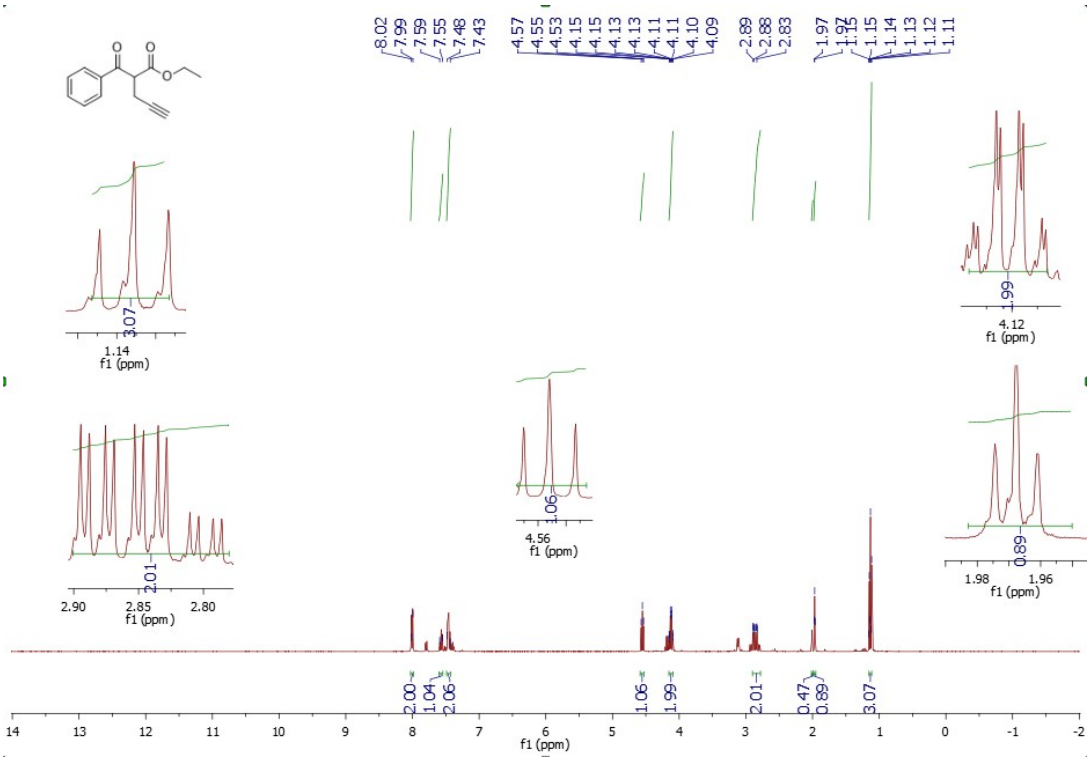
Cyclization Reactions of Non-Conjugate Ynones with Propargyl Amine in the Presence of a Catalyst

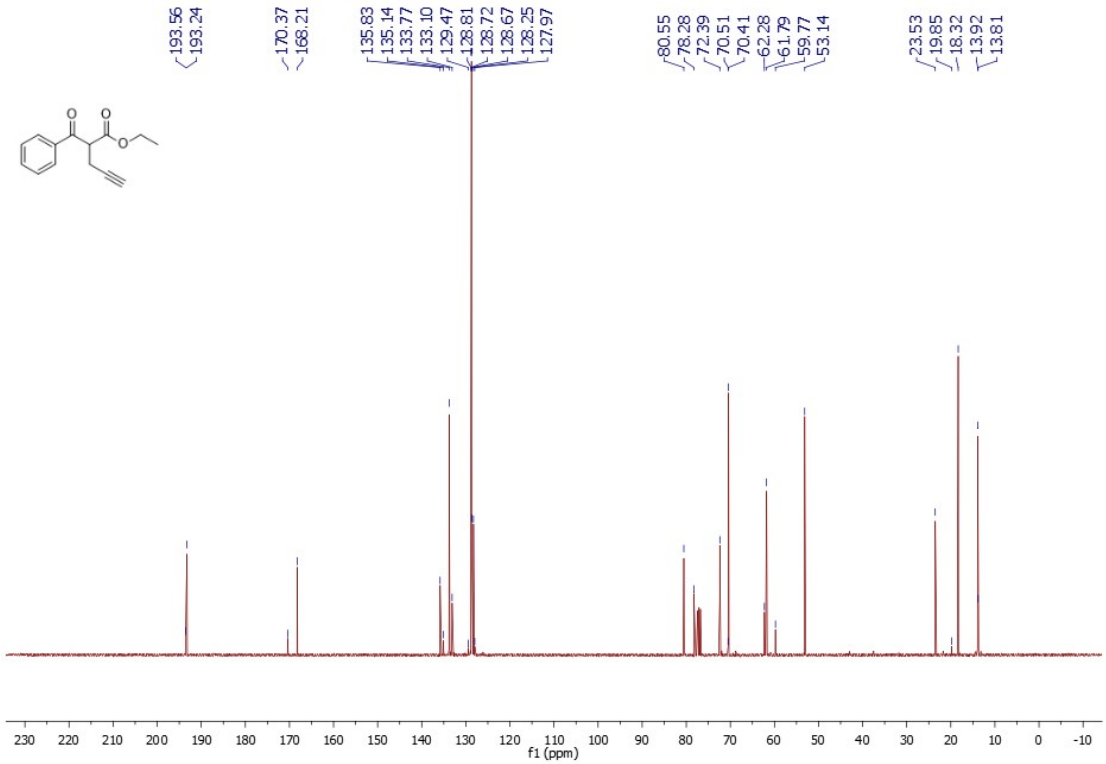
Volkan TAŞDEMİR[1*]

Spectra

^{1}H-NMR, ^{13}C-NMR spectra were taken with an Agilent 400 MHz (^{13}C-NMR: 100 MHz) and mass spectra were taken by a Thermoscientific brand LC-MS / MS.

Ethyl 2-benzoylpent-4-ynoate (3a)





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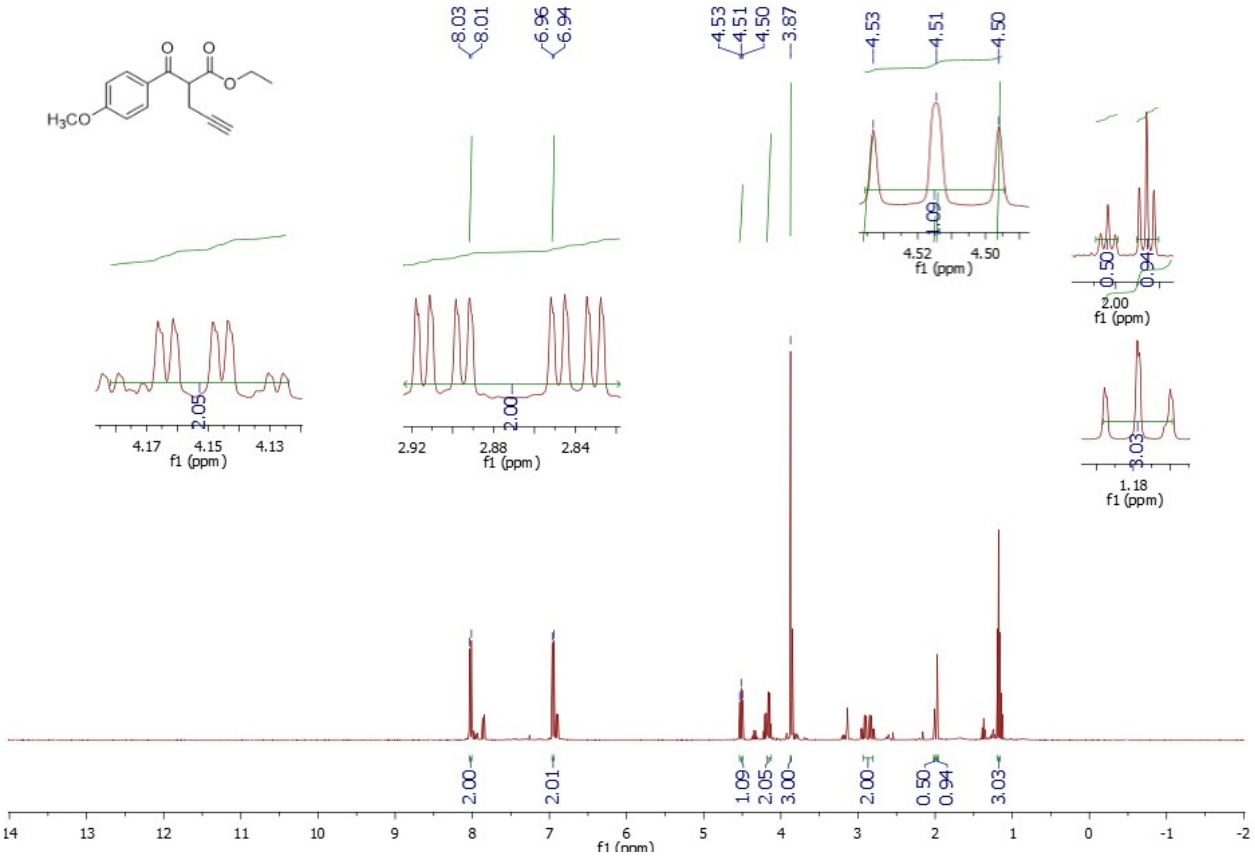
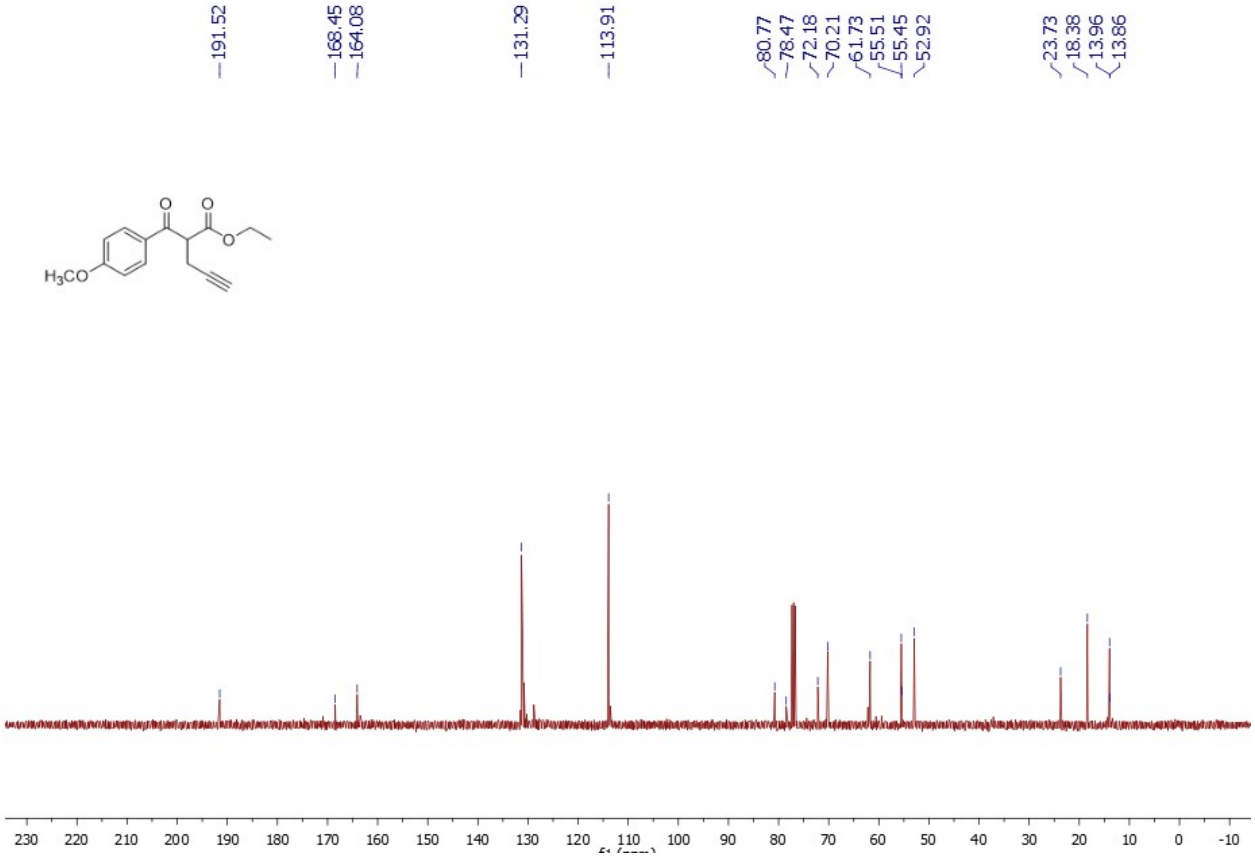
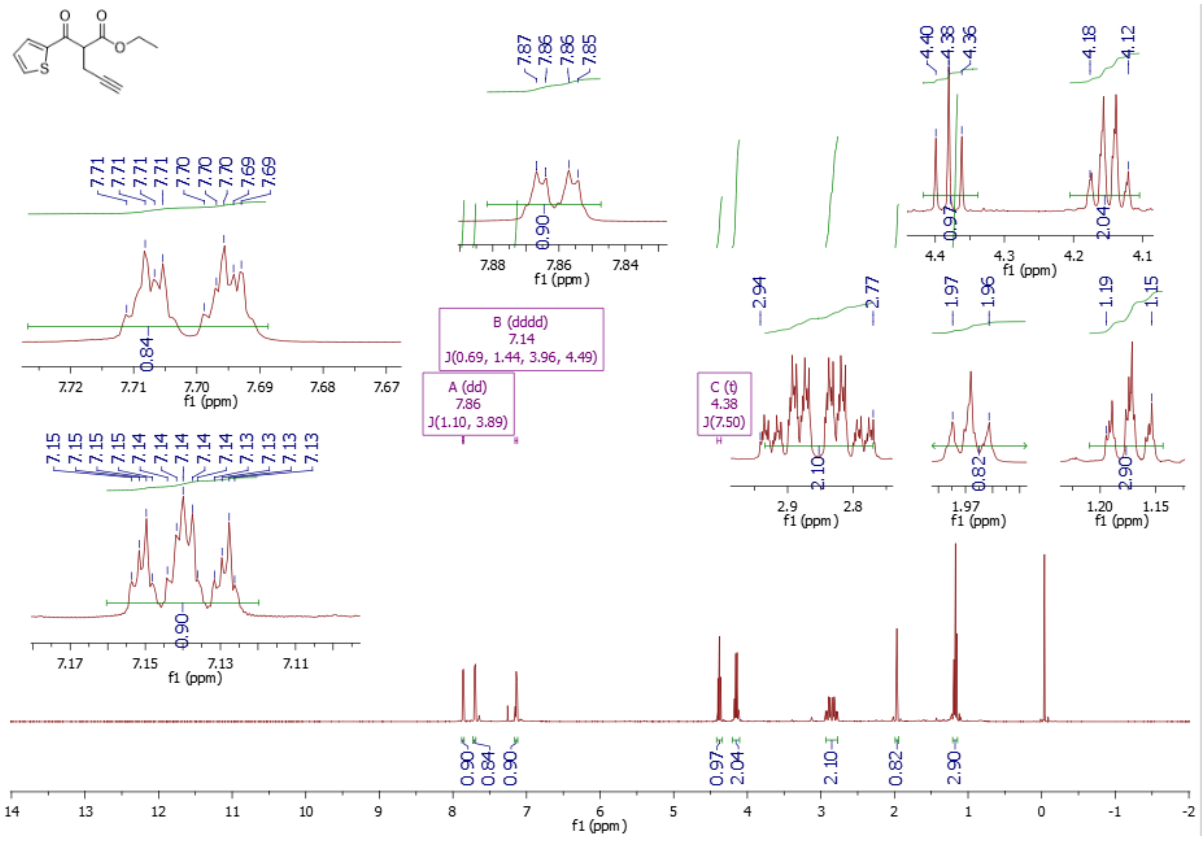
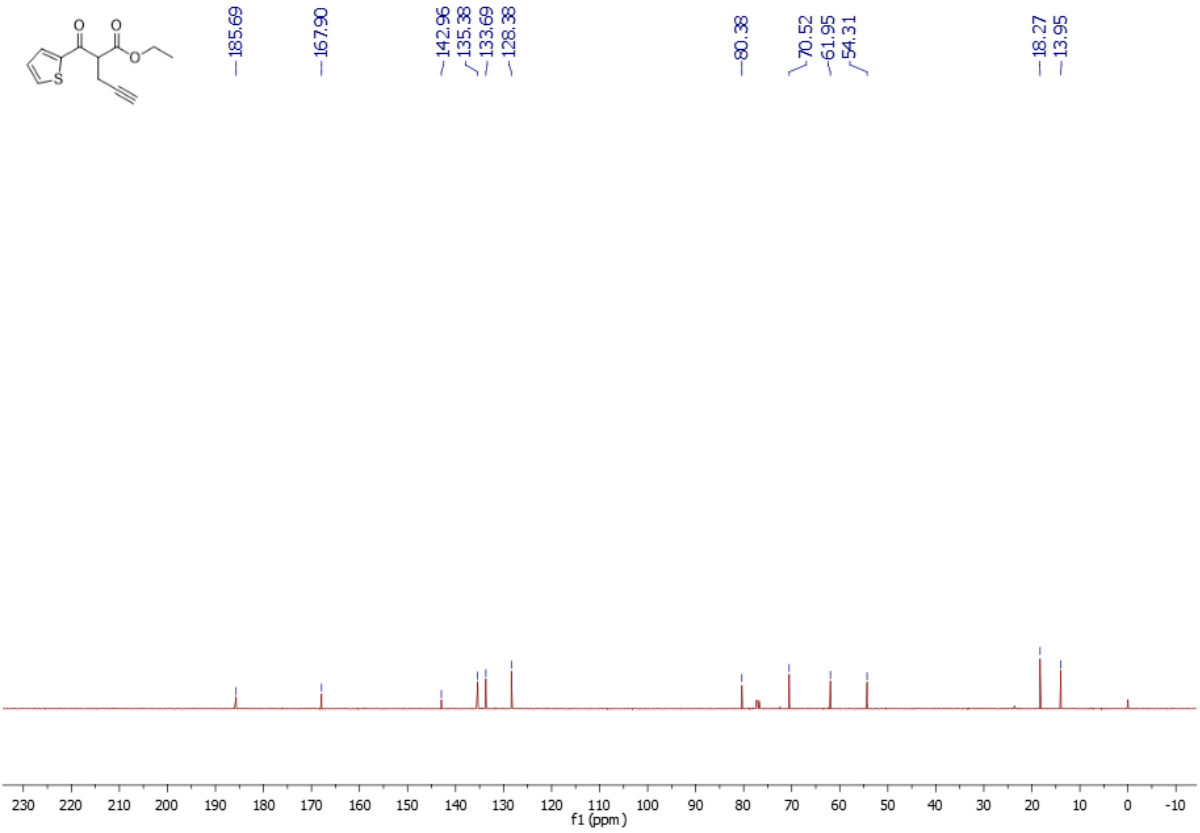


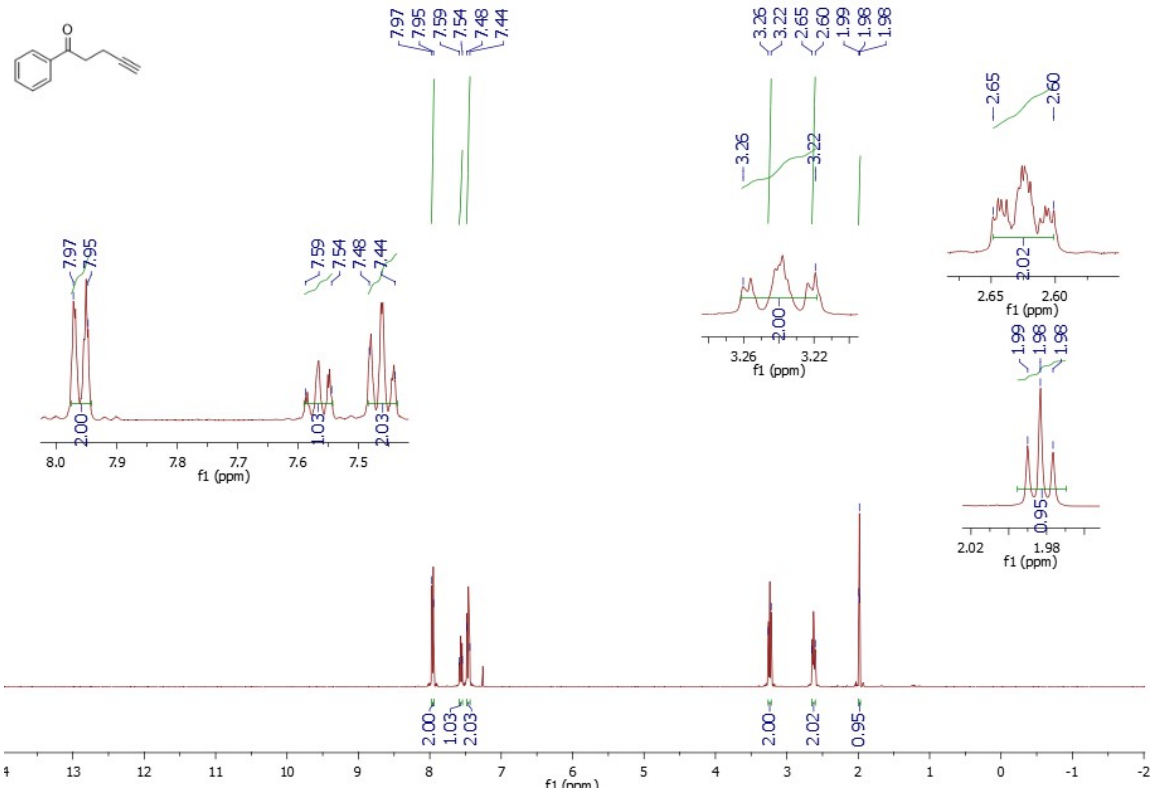


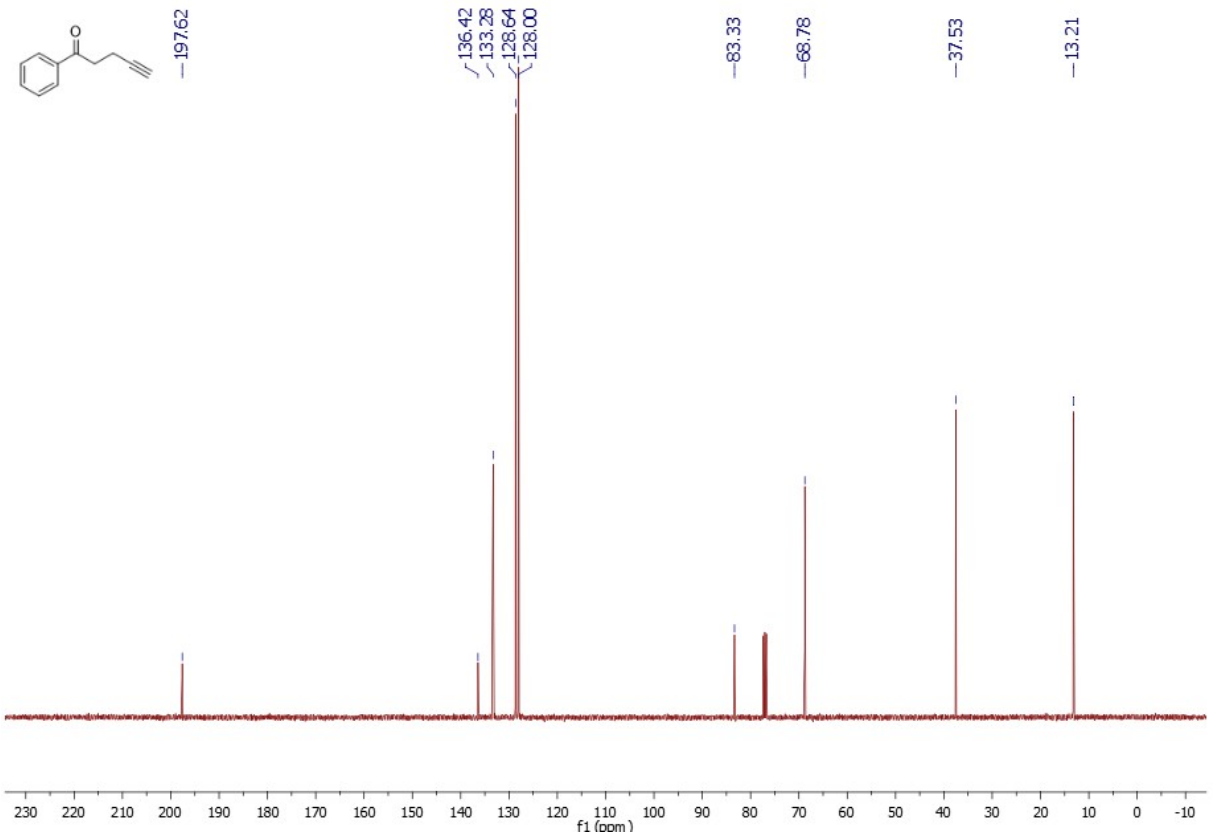
Ethyl 2-(thiophene-2-carbonyl)pent-4-ynoate(3c)





1-Phenylpent-4-yn-1-one (4a)





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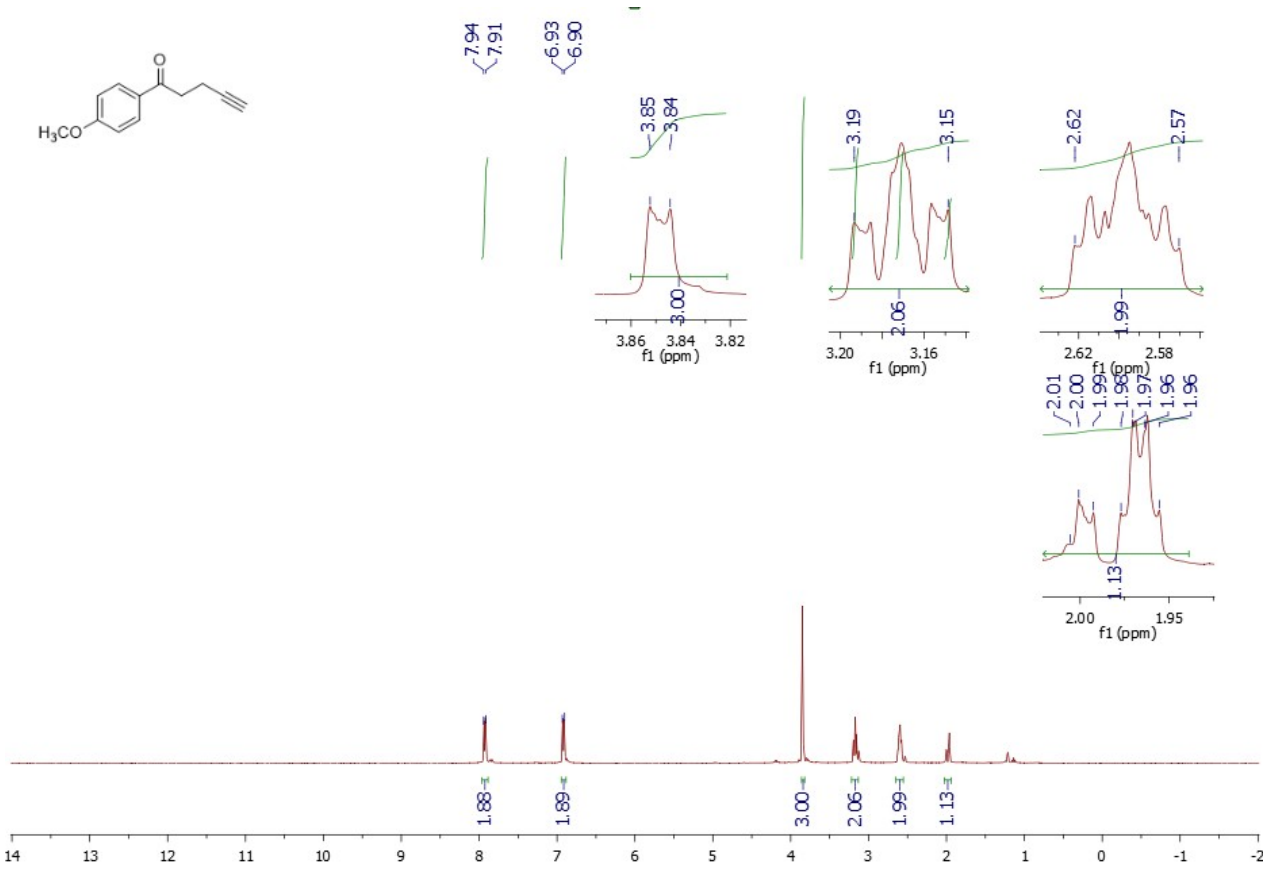
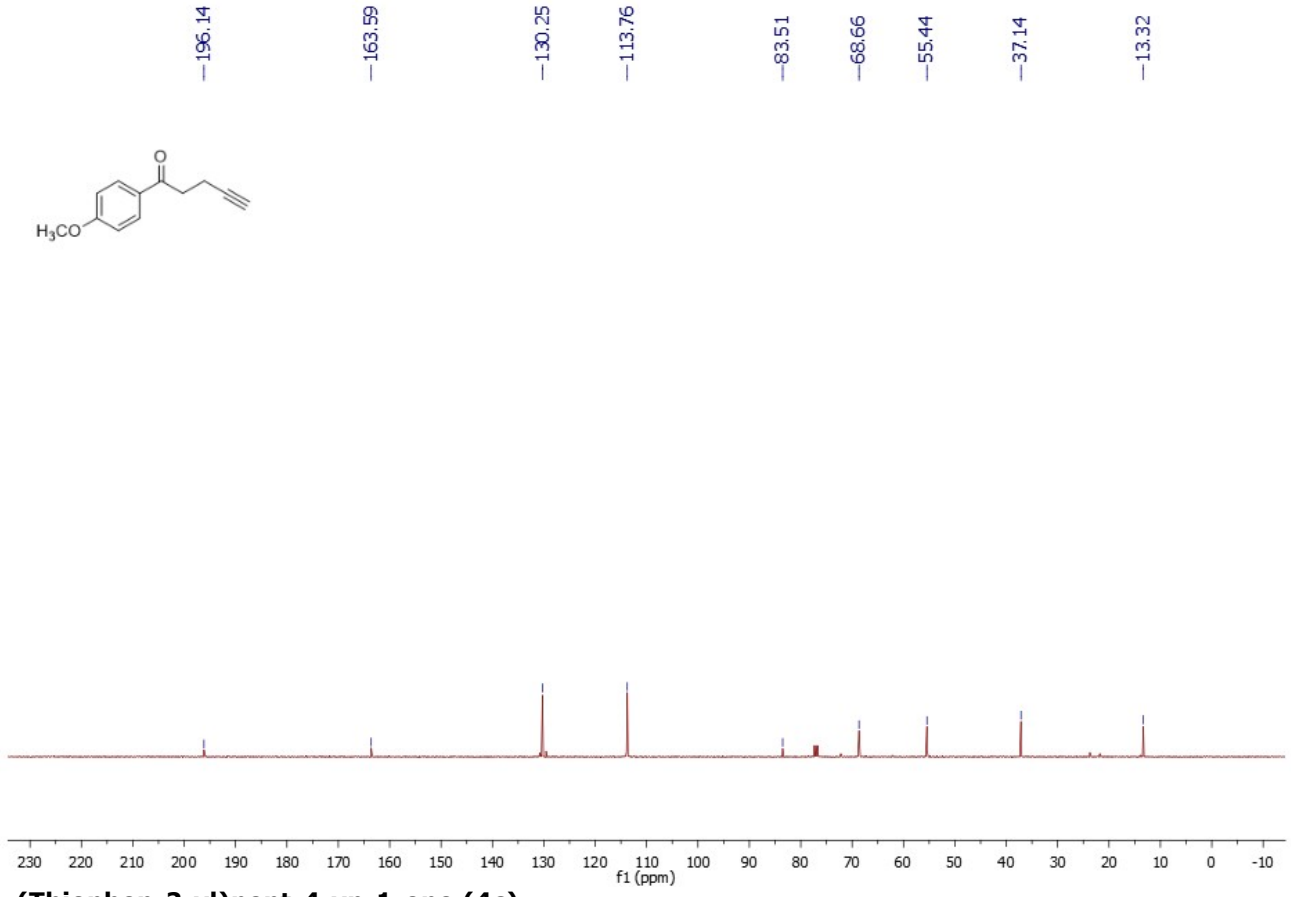
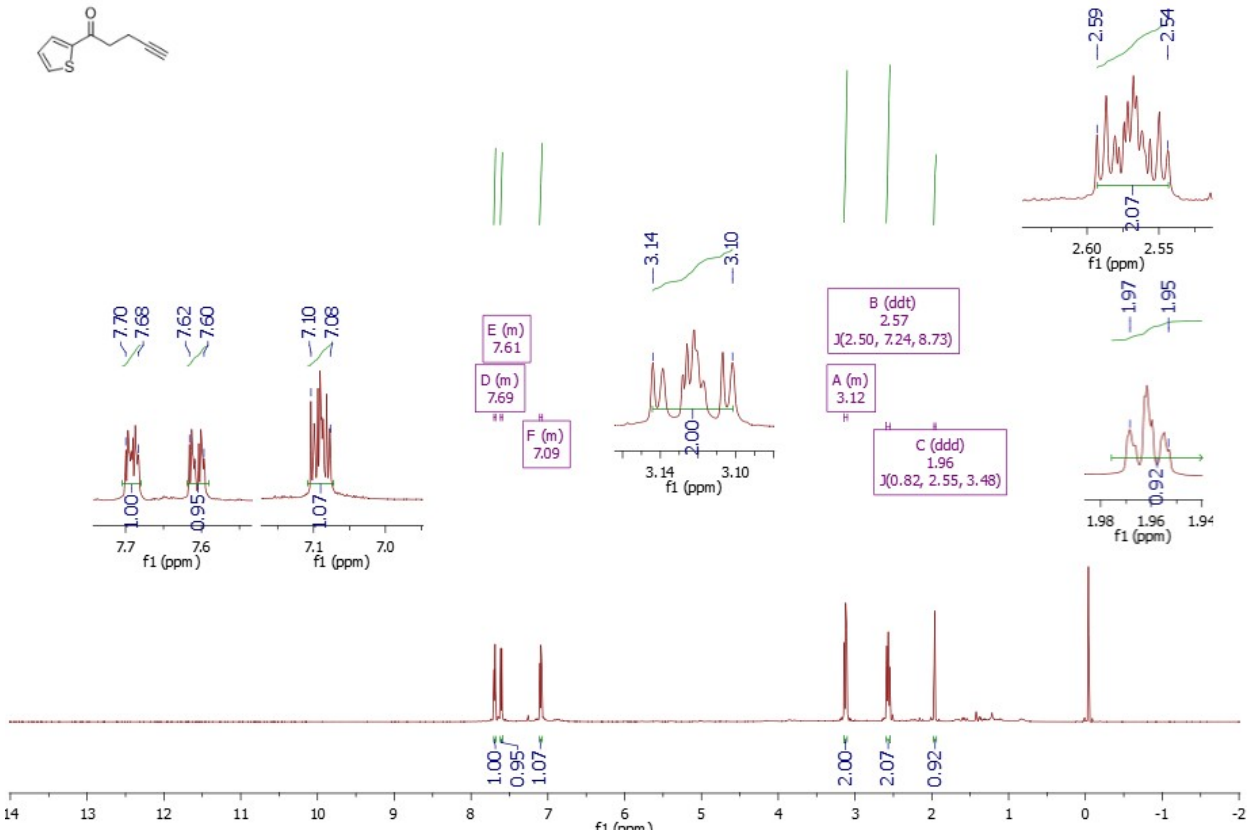
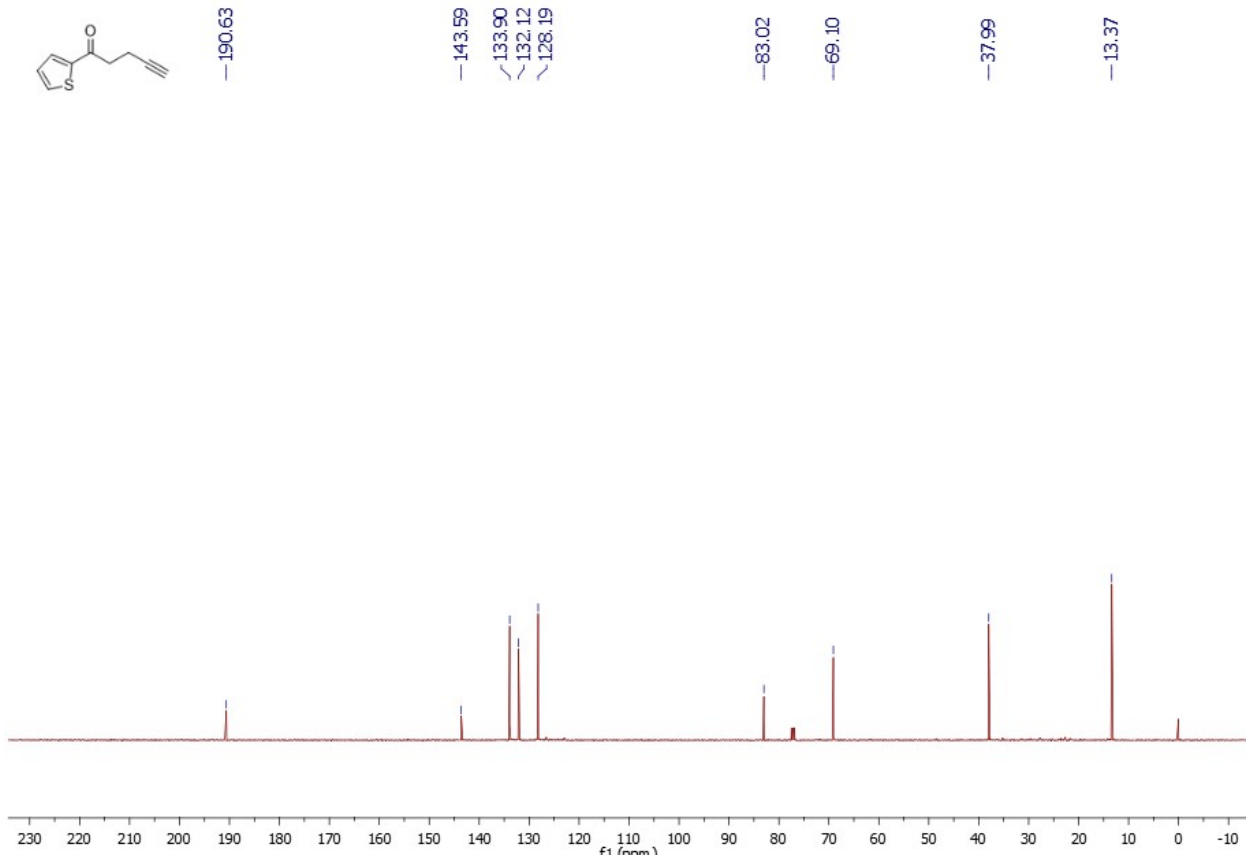


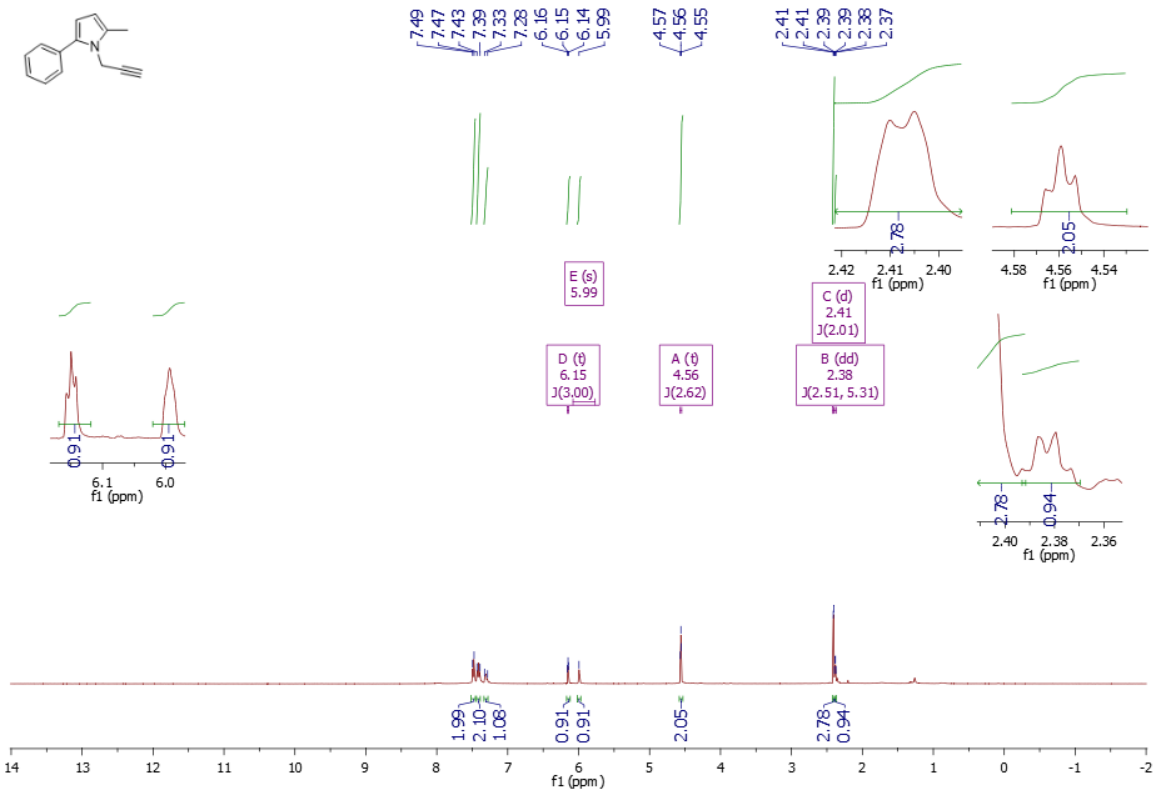


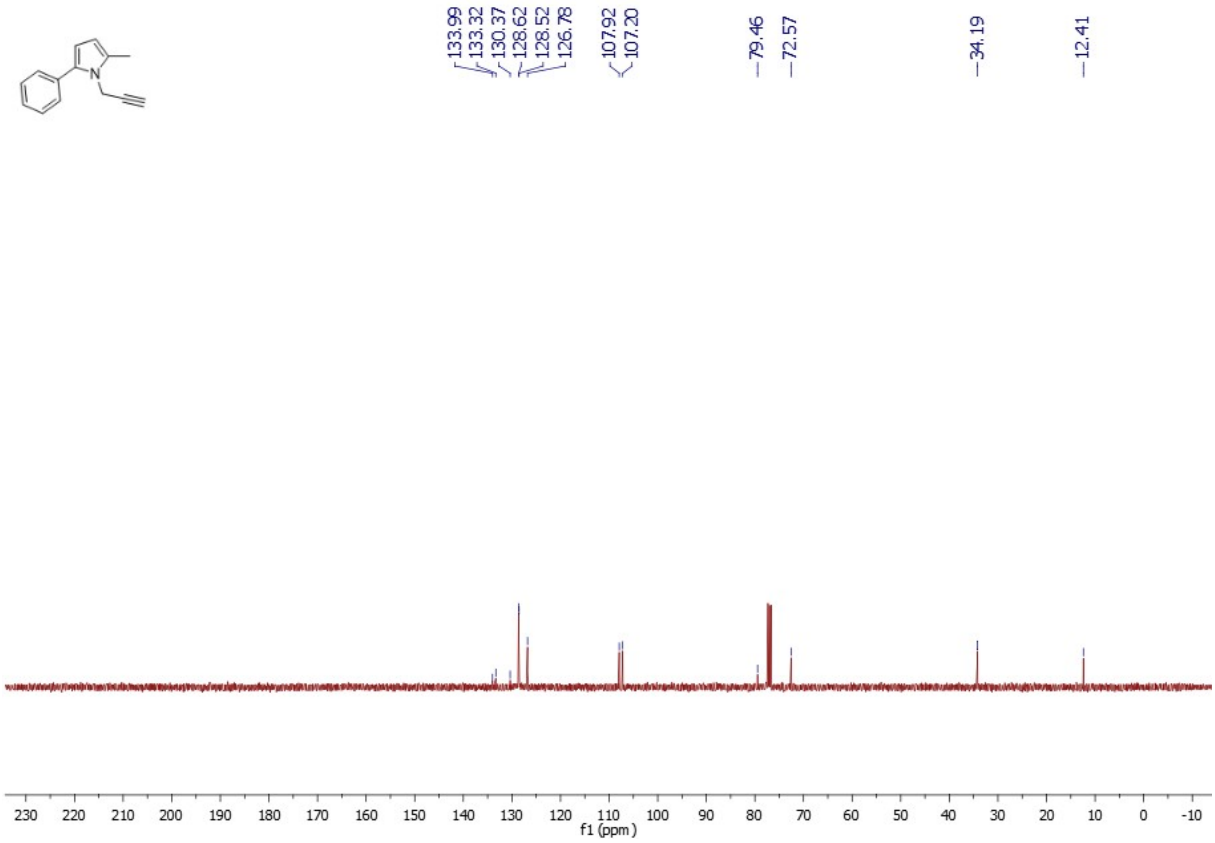
1-(Thiophen-2-yl)pent-4-yn-1-one (4c)



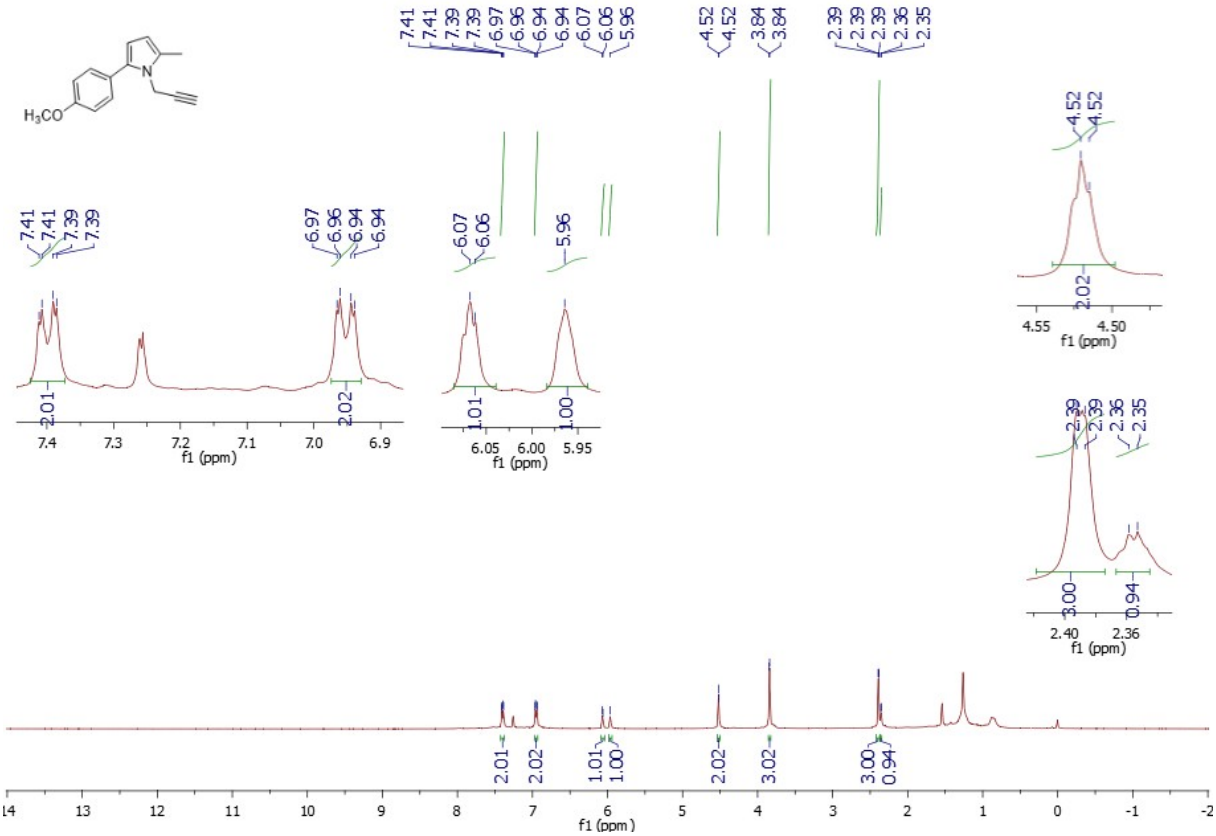


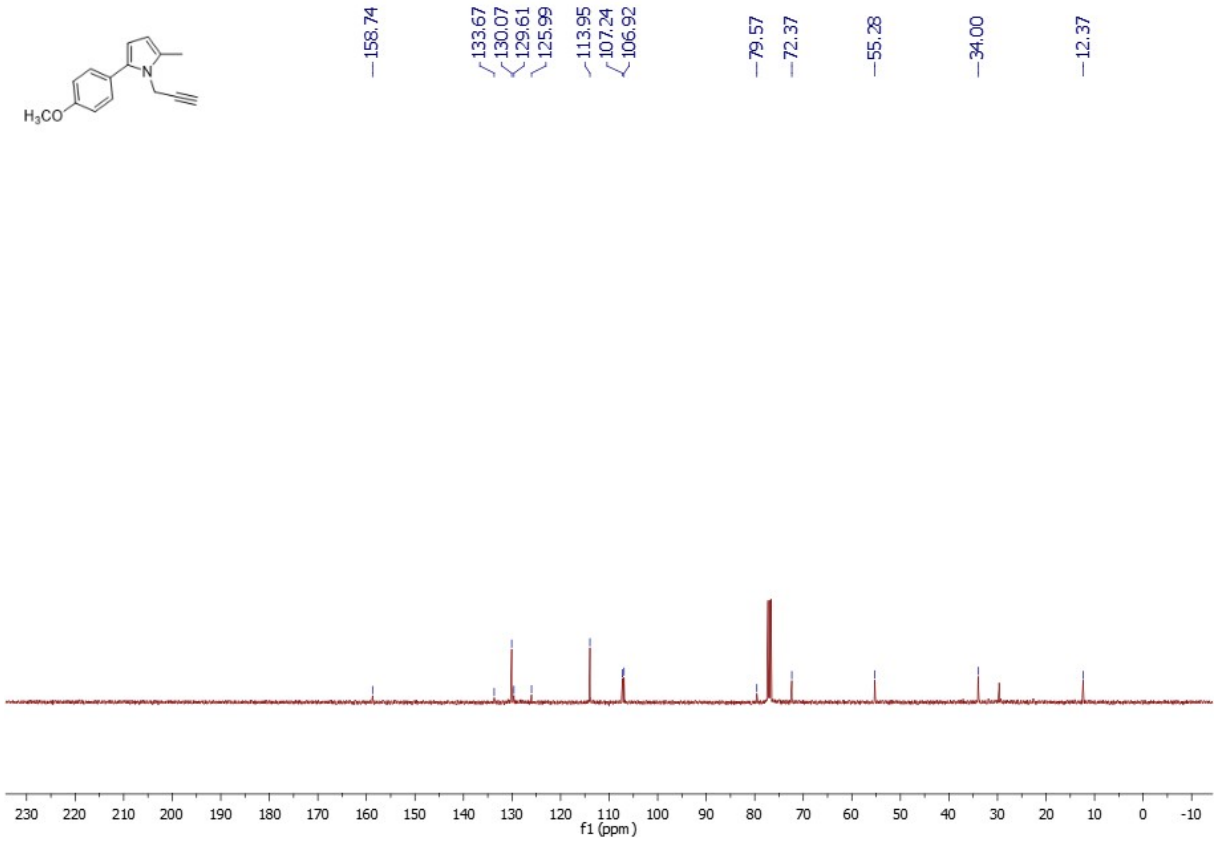
2-Methyl-5-phenyl-1-(prop-2-yn-1-yl)-1H-pyrrole (7a)



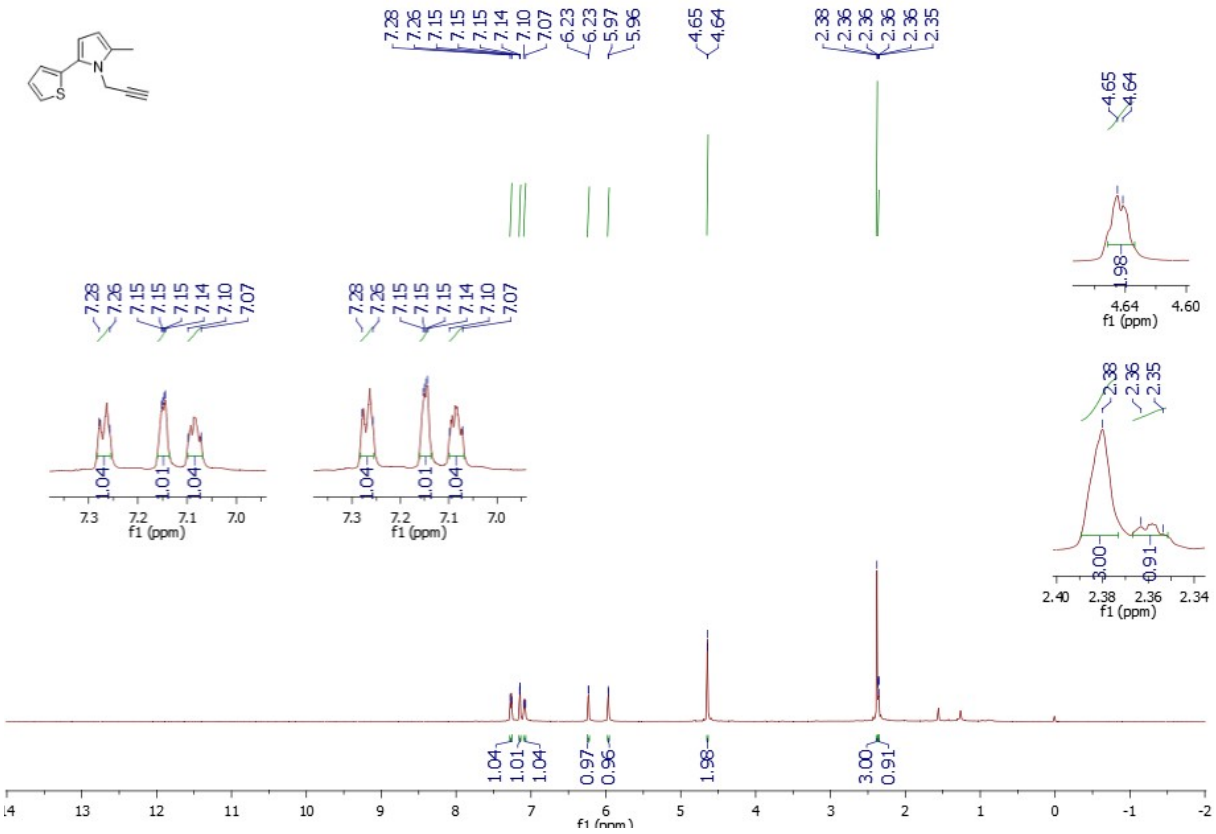


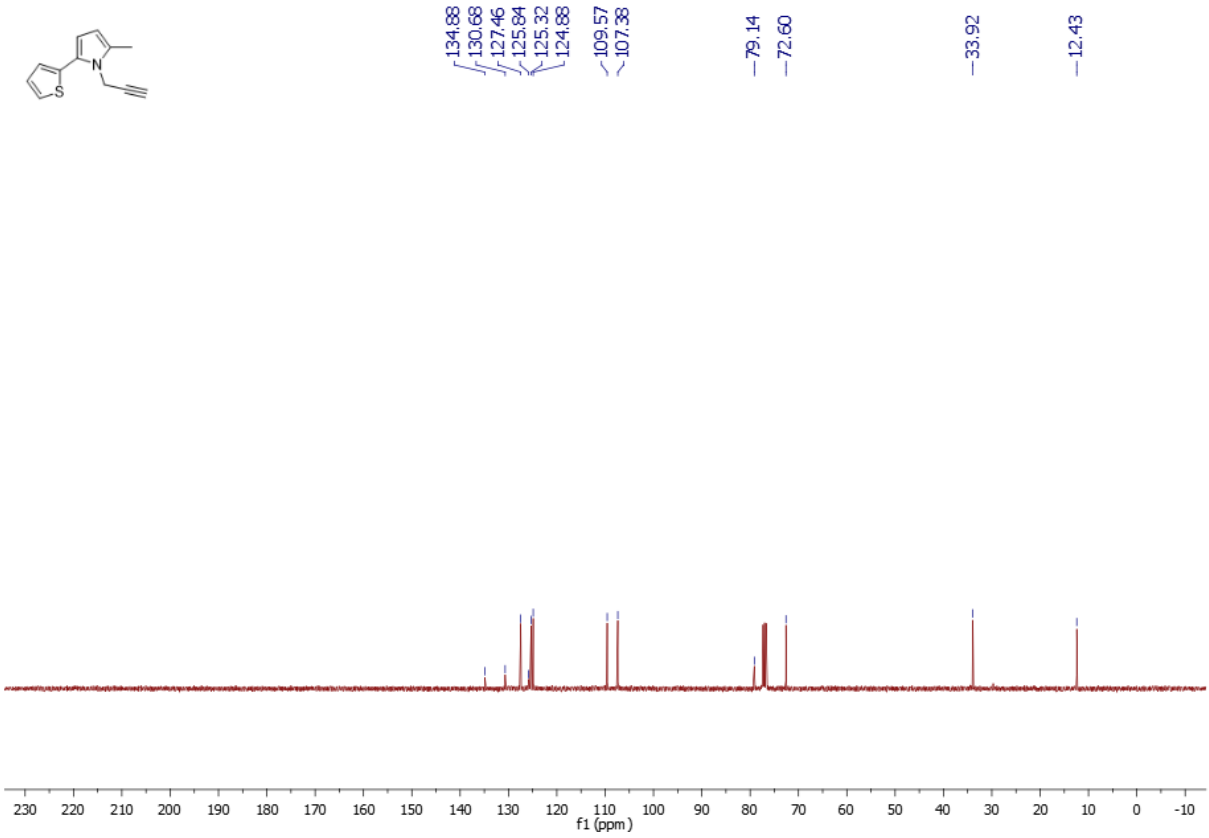
2-(4-Methoxyphenyl)-5-methyl-1-(prop-2-yn-1-yl)-1H-pyrrole (7b)





2-Methyl-1-(prop-2-yn-1-yl)-5-(thiophen-2-yl)-1H-pyrrole (7c)

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130.68
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125.32
124.88
109.57
107.38
79.14
72.60
33.92
12.43
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)