JOURNAL of the TURKISH CHEMICAL SOCIETY
SECTION: A
CHEMISTRY
TURKISH CHEMICAL SOCIETY

3- and 4-Arm Star Polymers (PEG_3 and PEG_4) via Metal-Free Azide-Alkyne Click Reaction

Ufuk Saim Gunay[1*]

[1]Istanbul Technical University, Department of Chemistry, İstanbul, 34469, Türkiye

Abstract: Star polymers are known for their different structural and functional properties. Depending on their structure, they may display a wide range of characteristics. Star polymers can be synthesized using either a core-first or arm-first strategy. Numerous synthetic approaches can be used in both cases. In this work, 3- and 4-arm star polymers were prepared via the metal-free azide-alkyne click reaction. Trifunctional and tetrafunctional propiolate (acetylenecarboxylate) ester-containing cores were prepared and then subjected to a metal-free azide-alkyne reaction with azide end-functionalized PEG ($PEG\text{-}N_3$) to yield A_3 and A_4-type star polymers, respectively. All the structures were characterized using ^1H and ^{13}C NMR spectroscopy and GPC.

Keywords: Star Polymers, metal-free click, azide-alkyne click reaction

Submitted: July 07, 2023. **Accepted:** August 01, 2023.

Cite this: Gunay US. 3- and 4-Arm Star Polymers (PEG_3 and PEG_4) via Metal-Free Azide-Alkyne Click Reaction. JOTCSA. 2023;10(3): 797-804.

DOI: https://doi.org/10.18596/jotcsa.1324025.

***Corresponding author. E-mail:** gunayuf@itu.edu.tr.

1. INTRODUCTION

A particular category of macromolecules known as star polymers displays distinct structural and functional characteristics. Star polymers are within the category of branched polymers with a single branching point. When compared to linear chains, the branching of a polymer chain produces a considerably more compact structure, altering the polymer's crystallographic, mechanical, and viscoelastic behavior as well as its physical properties and processability. Star polymers are distinguished from their linear or branched polymer analogs by their unique architecture, which gives them outstanding versatility and performance in a variety of applications, including drug delivery, polymeric coatings, electronics, and material science (1).

Either a core-first or an arm-first approach can be used to make star polymers. The multifunctional cores, also known as core molecules or core initiators, are used in the core-first approach to start the formation of the polymer arms. This technique allows for the synthesis of targeted star polymers with controlled molecular weights, tunable arms, and dispersites. The arm-first strategy, on the other hand, binds a multifunctional core to linear polymeric arms with reactive end groups. Both of the approaches used for the synthesis of star polymers can be carried out using a variety of techniques, such as anionic and cationic polymerization as well as controlled-living polymerization techniques like ATRP, NMP, and RAFT (1, 2).

The click chemistry term was introduced by Sharpless, which indicates key features for a reaction such as high yields, functional group tolerance, and stereoselectivity (3). Among these, the Cu(I)-catalyzed 1,3-cycloaddition reaction (or the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction) gained tremendous attention among polymer chemists (4-6). CuAAC has been used to synthesize various polymer topologies for a wide range of applications and maintains its interest in the development of new materials (7).

Yet, the use of Cu salt has also raised toxicity concerns and pushed polymer chemists to develop new metal-free methods in order to synthesize functional well-defined materials for tailored applications. One of the metal-free methods to overcome this toxicity issue is using activated alkynes, alkynes that contain electron-withdrawing groups (EWGs), in the azide-alkyne cycloaddition reaction (8). With this knowledge, we envisioned a strategy to synthesize 3- and 4-arm star polymers via the metal-free azide-alkyne click reaction. In this study, two core compounds with activated alkyne units, called propiolate esters, were designed to undergo the metal-free azide-alkyne click reaction with PEG-N_3 to yield A_3 and A_4-type star polymers (PEG_3 and PEG_4).

2. EXPERIMENTAL SECTION

2.1. Materials

1,1,1-Tris(hydroxymethyl)ethane (98%, Sigma-Aldrich), pentaerythritol (99%, Sigma-Aldrich), propiolic acid (prop-2-ynoic acid or acetylenecarboxylic acid) (95%, Sigma-Aldrich), *p*-toluenesulfonic acid monohydrate (pTsOH, 98.5%, Aldrich), anhydrous sodium sulfate (Na_2SO_4, ≥99.0%, Aldrich) were used as received. *N,N*-dime-thylformamide (DMF, 99.8%, Sigma-Aldrich) and dichloromethane (DCM, 99.8%, Aldrich) were anhydrous, and used without further purification. Other reagents were all purchased from Sigma Aldrich and used as received. Mono azide end-functionalized poly(ethylene glycol) (PEG-N_3) was synthesized by using poly(ethylene glycol) methyl ether (average M_n ~2,000, Sigma-Aldrich) according to a published procedure (9).

2.2. Instrumentation

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using an Agilent VNMRS 500 instrument in $CDCl_3$. Gel permeation chromatography (GPC) measurements were carried out with an Agilent Instrument (series 1100), using a refractive index detector, loaded with Waters Styragel columns (HR 5E, HR 4E, HR 3, HR 2, 4.6 mm internal diameter, 300 mm length, packed with 5 µm particles). The effective molecular weight ranges of the columns are 2,000−4,000,000; 50−100,000; 500−30,000; and 500−20,000 g/mol, respectively. THF was used as an eluent at a flow rate of 0.3 mL/min at 30 ºC, and 2,6-di-*tert*-butyl-4-methylphenol (BHT) was used as an internal standard. The number-average molecular weight (M_n), weight-average molecular weight (M_w), and polydispersity ($Đ$) of the polymers were calculated based on narrow linear polystyrene (PS) standards (Polymer Laboratories) ranging between 2300−3,050,000 g/mol.

2.3. Synthesis of 2-methyl-2-((propioloyloxy) methyl)propane-1,3-diyldipropiolate (1)

1,1,1-Tris(hydroxymethyl)ethane (1 g, 8.32 mmol), propiolic acid (3.5 mL, 49.93 mmol) and pTsOH (0.158 g, 0.83 mmol) were added to a round-bottomed flask and dissolved in 40 mL of benzene. The flask was attached to a Dean-Stark trap utilized with a condenser and placed in an oil bath at 105 °C for 24 h. After 24 h, benzene was removed by using a rotary evaporator, and the remaining yellow liquid was dissolved in DCM. The organic phase was washed three times with 50 mL of distilled water. The washed solution was dried with Na_2SO_4 and evaporated to obtain the pure product. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.17 (s, 6H, CCH_2), 2.95 (s, 3H, CC*H*), 1.11 (s, 4H, CCH_3).

2.4. Synthesis of 2,2-bis((propioloyloxy) methyl)propane-1,3-diyldipropiolate (2)

Pentaerythritol (1 g, 7.34 mmol), propiolic acid (4.11 mL, 58.76 mmol) and pTsOH (0.138 g, 0.73 mmol) were added to a round-bottomed flask and dissolved in 40 mL of benzene. The flask was attached to a Dean-Stark trap utilized with a condenser and placed in an oil bath at 105 °C for 24 h. After 24 h, benzene was removed by using a rotary evaporator, and the remaining yellow liquid was dissolved in DCM. The organic phase was washed three times with 50 mL of distilled water. The washed solution was dried with Na_2SO_4 and evaporated to obtain the pure product. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.31 (s, 8H, CCH_2), 2.99 (s, 4H, CC*H*).

2.5. Synthesis of 3-Arm Star Polymer (PEG_3)

To a 25 mL Schlenk flask, compound **1** (100 mg, 0.36 mmol) and PEG-N_3 (2.39 g, 1.19 mmol) were added and dissolved in 5 mL of DMF. After 3 freeze-pump-thaw cycles, the flask was placed in an oil bath at 80 °C for 48 h. At the end of 48 h, the solution was precipitated into diethyl ether. The dissolution-precipitation cycle was repeated twice. The purified product was dried in a vacuum oven for 24 h. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.43-8.11 (m, 3H, NC*H*), 4.61 (t, 6H, NCH_2), 3.91 (d, 6H, CCH_2), 4.47 (m, 6H, NCH_2CH_2), 3.91 ($COOCH_2$), 3.64 (m, 570H, OCH_2CH_2), 3.38 (s, 9H, OCH_3), 1.25 (s, 3H, CCH_3).

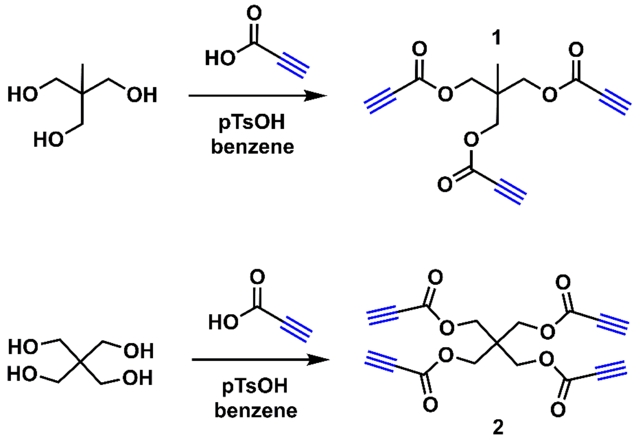
2.6. Synthesis of 4-Arm Star Polymer (PEG_4)

To a 25 mL Schlenk flask, compound **2** (100 mg, 0.29 mmol) and PEG-N_3 (2.55 g, 1.28 mmol) were added and dissolved in 5 mL of DMF. After 3 freeze-pump-thaw cycles, the flask was placed in an oil bath at 80 °C for 48 h. At the end of 48 h, the solution was precipitated into diethyl ether. The dissolution-precipitation cycle was repeated twice. The purified product was dried in a vacuum oven for 24 h. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.47-8.12 (m, 4H, NC*H*), 4.67 (s, 8H, NCH_2), 4.61 (t, 8H, NCH_2CH_2), 3.92 (t, 8H, CCH_2), 3.64(m, 744H, OCH_2CH_2), 3.38 (s, 12H, OCH_3).

3. RESULTS AND DISCUSSION

3-Arm and 4-arm star polymers, PEG_3 and PEG_4, respectively, were successfully synthesized using multifunctional propiolate ester containing cores along with PEG-N_3 via the metal-free azide-alkyne click reaction.

Firstly, Scheme 1 depicts the preparation of multifunctional cores by an esterification reaction of 1,1,1-tris(hydroxymethyl)ethane and pentaerythritol in the presence of propiolic acid using a catalytic amount of pTsOH to yield core compounds 1 and 2, respectively.



Scheme 1: Synthesis of the core compounds, **1** and **2**.

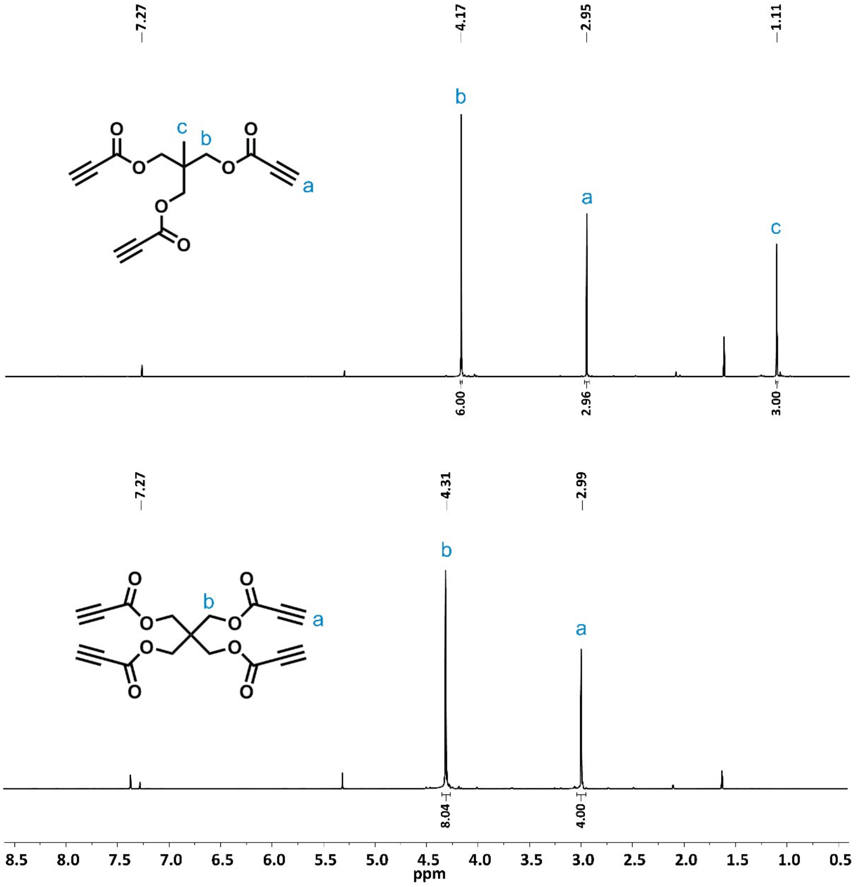


Figure 1: ^{1}H NMR spectra of **1** (top) and **2** (bottom) in $CDCl_3$ (500 MHz).

The structures of **1** and **2** were confirmed by using both ^{1}H and ^{13}C NMR. From the ^{1}H NMR spectra of **1** and **2** (Figure 1), methylene protons regarding the propiolate ester resonated at δ 4.17 ppm for **1** (top) and δ 4.35 ppm for **2** (bottom). In addition, the methine proton of the propiolate groups in **1** and **2** resonated at 2.95 and 2.99 ppm, respectively, showing that the alkyne group was still intact after the esterification. It should also be noted here that the integral values of the resulting structures were found to be consistent with the resulting structures. Also, from the ^{13}C NMR spectra (Figure 2), the peaks regarding propiolate units resonated at δ 75.80 ppm for **1** (top) and 76.41 ppm for **2** (bottom), further validating the structures.

3- and 4-arm star polymers were prepared by the metal-free azide-alkyne click reaction, as depicted in

Scheme 2. To this end, **1** and **2** were used as the core structures, and PEG-N_3 was used as the arms in the reactions to yield PEG_3 and PEG_4, respect-ively. Briefly, to perform the reactions, PEG-N_3 was intentionally used in excess with respect to **1** and **2** and carried out in DMF at 80 °C for 48 h. The resulting PEG_3 and PEG_4 star polymers were then characterized by ^1H and ^{13}C NMR spectroscopy and GPC.

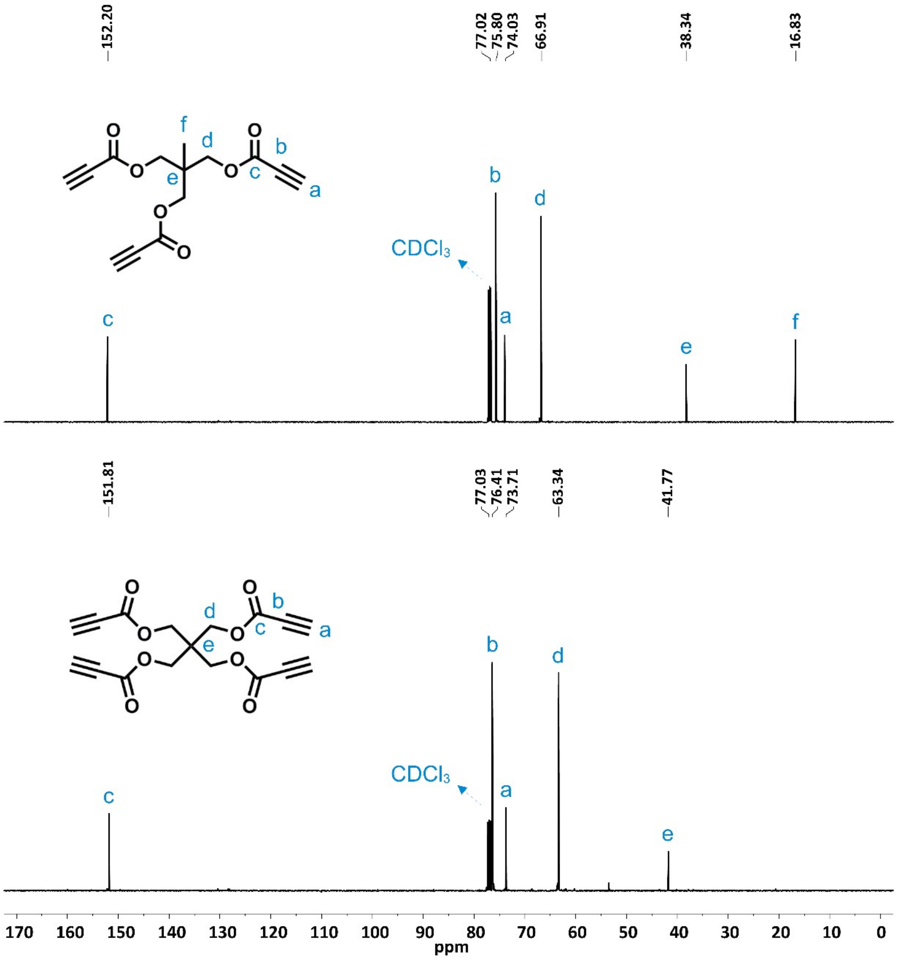
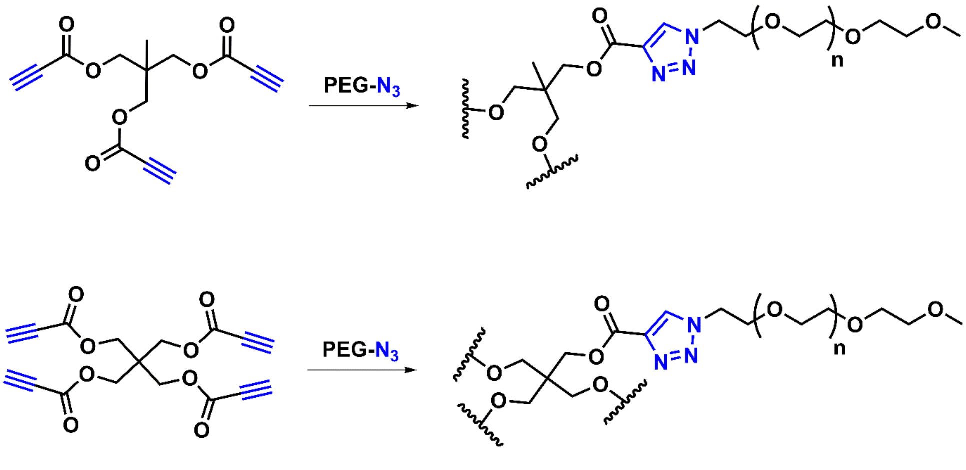


Figure 2: ^{13}C NMR spectra of **1** (top) and **2** (bottom) in $CDCl_3$ (125 MHz).



Scheme 2: Synthesis of the PEG_3 and PEG_4 star polymers (only one arm was shown for clarity).

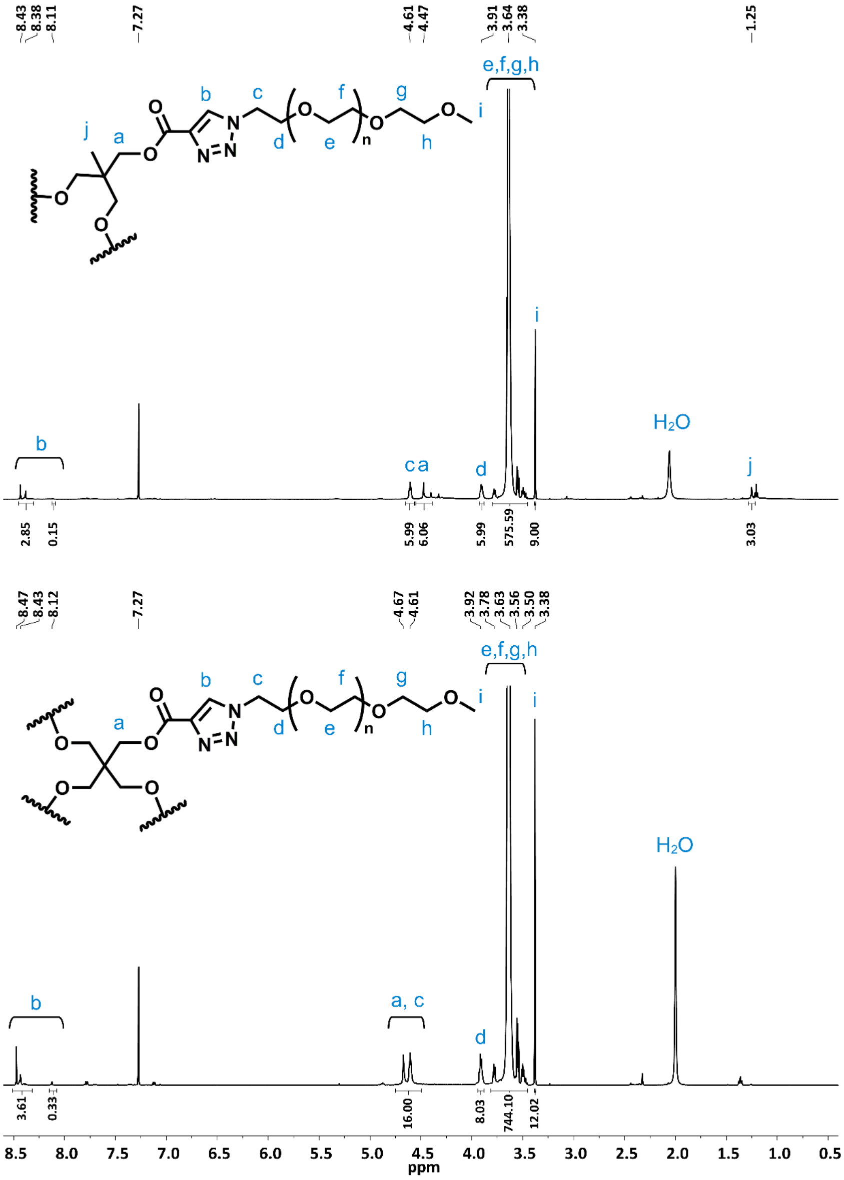


Figure 3: ^{1}H NMR spectra of PEG_3 (top) and PEG_4 (bottom) in $CDCl_3$ (500 MHz).

From the ^{1}H NMR spectra of the resulting structures (Figure 3), the ester methylene protons were found to shift to δ 4.47 for PEG3 (top) and 4.67 ppm for PEG4 (bottom) after the click reaction. Also, for both star polymers, the aromatic proton of the triazole unit resonated between δ 8.40 and 8.10 ppm, and the methylene group next to the triazole unit was found around δ 4.61 ppm, which clearly indicated a smooth reaction. In addition, it is important to notice that the integral values of the protons align with the star polymers that were obtained.

^{13}C NMR spectra of the star polymers (Figure 4) showed the successful synthesis of PEG_3 and PEG_4 star polymers as well. The disappearance of the alkyne carbons and the appearance of the aromatic carbons regarding the triazole unit resonated between δ 140 and 130 ppm, which was indicative of the star polymers.

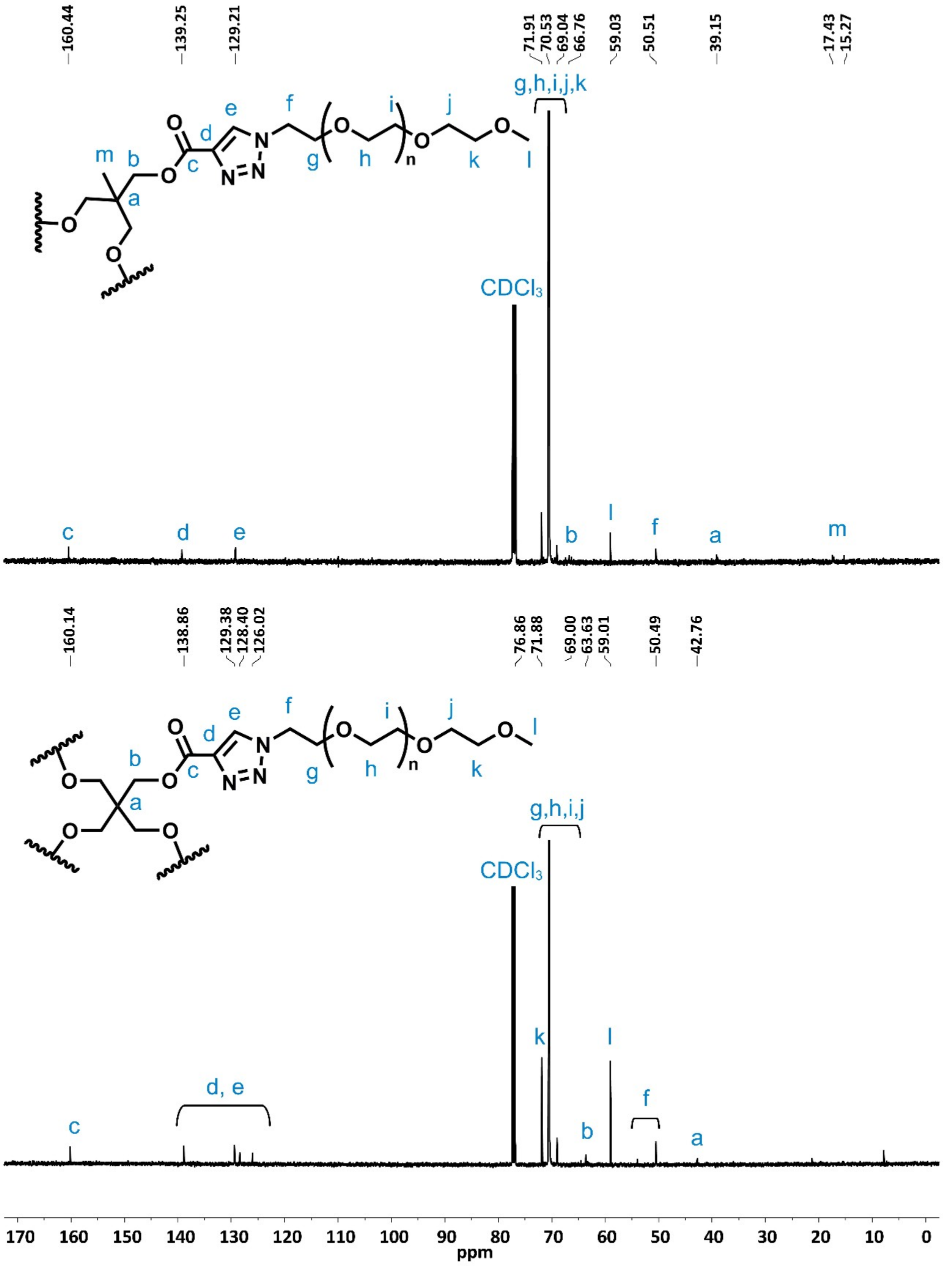


Figure 4: ^{13}C NMR spectra of PEG$_3$ (top) and PEG$_4$ (bottom) in CDCl$_3$ (125 MHz).

Finally, GPC traces of the star polymers showed a monomodal distribution with relatively narrow polydispersities. Also, as expected, PEG$_4$ was found to be in a relatively higher molecular weight region when compared to PEG$_3$, and both showed a shift to the higher molecular weight region when compared with PEG-N$_3$.

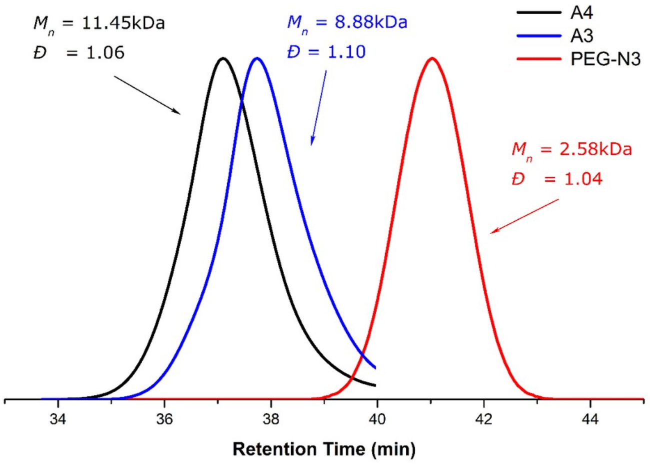


Figure 5: GPC curves (in THF) of PEG-N_3 (red), PEG_3 (blue) and PEG_4 (black).

4. CONCLUSION

The metal-free azide-alkyne click reaction was utilized in the synthesis of 3- and 4-arm star polymers using propiolate esters. Multifunctional cores were specifically designed to carry out a metal-free azide-alkyne cycloaddition reaction using PEG-N_3 as the arms. The reaction was conducted at 80 °C for 48 h to yield PEG_3 and PEG_4 star polymers. Both the cores and the star polymers were characterized by ^1H and ^{13}C NMR spectroscopy, indicating the success of the strategy. In addition, the resulting polymers were also analyzed by GPC, resulting in a monomodal distribution with relatively narrow dispersities, further showing the smooth transition. It is believed that the metal-free approach for the synthesis of well-defined star polymers with this proposed method can be a very efficient tool for synthesizing functional polymers for polymer chemists and can be extended to a wide range of applications.

5. CONFLICT OF INTEREST

No potential conflict of interest was reported by the author.

6. ACKNOWLEDGMENTS

This work was supported by the Research Fund of Istanbul Technical University.

7. REFERENCES

1. Ren JM, McKenzie TG, Fu Q, Wong EHH, Xu J, An Z, Shanmugam S, Davis TP, Boyer C, Qiao GG. Star Polymers. Chem Rev. 2016;116(12):6743–6836. Available from: <DOI>.

2. Dag A, Durmaz H, Hizal G, Tunca U. Preparation of 3-arm star polymers (A3) via Diels–Alder click reaction. J Polym Sci Part A: Polym Chem. 2008;46(1):302-313. Available from: <DOI>.

3. Kolb HC, Finn MG, Sharpless KB. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. Angew Chem Int Ed. 2001;40(11):2004–2021. Available from: <DOI>.

4. Tornoe CW, Christensen C, Meldal M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. J Org Chem. 2002;67(9):3057-3064. Available from: <DOI>.

5. Demko ZP, Sharpless KB. A Click Chemistry Approach to Tetrazoles by Huisgen 1,3-Dipolar Cycloaddition: Synthesis of 5-Sulfonyl Tetrazoles from Azides and Sulfonyl Cyanides. Angew Chem Int Ed. 2002;41(12):2110–2113. Available from: <DOI>.

6. Rostovtsev VV, Green G, Fokin VV, Sharpless KB. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes. Angew Chem Int Ed. 2002;41(14):2596–2599. Available from: <DOI>.

7. Neumann S, Biewend M, Rana S, Binder WH. The CuAAC: Principles, Homogeneous and Heterogeneous Catalysts, and Novel Developments and Applications. Macromol Rapid Commun. 2020;41(1):1900359. Available from: <DOI>.

8. Cetin M, Esen C, Daglar O, Luleburgaz S, Hizal G, Durmaz H, Tunca U. 1, 3-Dipolar and Diels–Alder cycloaddition reactions on polyester backbones possessing internal electron-deficient alkyne moieties. Polym Chem. 2016;7(46):7094-7100. Available from: <DOI>.

9. Jia H, Li Q, Bayaguud A, She S, Huang Y, Chen K, Wei Y. Tosylation of alcohols: an effective strategy for the functional group transformation of organic derivatives of polyoxometalates. Scientific Reports. 2017;7:12523. Available from: <DOI>.