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Short Note

N-(1-azido-2-(azidomethyl)butan-2-yl)-4-methylbenzenesulfonamide

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Abstract: A new bi-triazole precursor, *N*-(1-azido-2-(azidomethyl)butan-2-yl)-4-methylbenzenesulfonamide, was synthesized in two steps from 2-amino-2-ethyl-1,3-propanediol, with an overall yield of 80%. The chemical structures of the products obtained were established based on 1D and 2D NMR, IR spectroscopy, and elemental analysis.

Keywords: azide; nucleophilic substitution reaction; 2D NMR experiments

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1. Introduction

The synthesis of new molecular units with drug-like properties remains a major concern in the field of drug chemistry, particularly in the fight against cancer and infectious diseases. The preparation of bi-triazole systems constitutes a matter of urgency for researchers [1], mainly due to their broad spectrum of applications. Thus, in recent years, triazoles have increasingly been targeted due to their interesting antiproliferative [2], antifungal [3], antidiabetic [4], antibacterial [5], anticancer [6], antioxidants, and anti-inflammatory properties [7]. They are also used as corrosion inhibitors [8].

Given these observations and the continuity of our previous work concerning the synthesis of derivatives of heterocyclic amino acids and their precursors [9–15], we were interested in performing the synthesis and characterization of a new precursor of the bi-triazole systems.

We report, in this article, on the synthesis of a new precursor of bi-triazole compounds obtained in two steps: The first step included the tosylation of 2-amino-2-ethyl-1,3-propanediol (**1**) to obtain the di-O-tosyl compound, namely 2-ethyl-2-((4-methylphenyl) sulfonamido)propane-1,3-diylbis(4-methylbenzenesulfonate) (**2**). this was followed by the substitution of the O-tosyl groups of the latter with -N_3, which allowed us to obtain the desired compound (**3**) in a good yield. The compounds obtained were characterized by 1D and 2D NMR, IR, and elemental analysis (Supplementary Materials).

2. Results

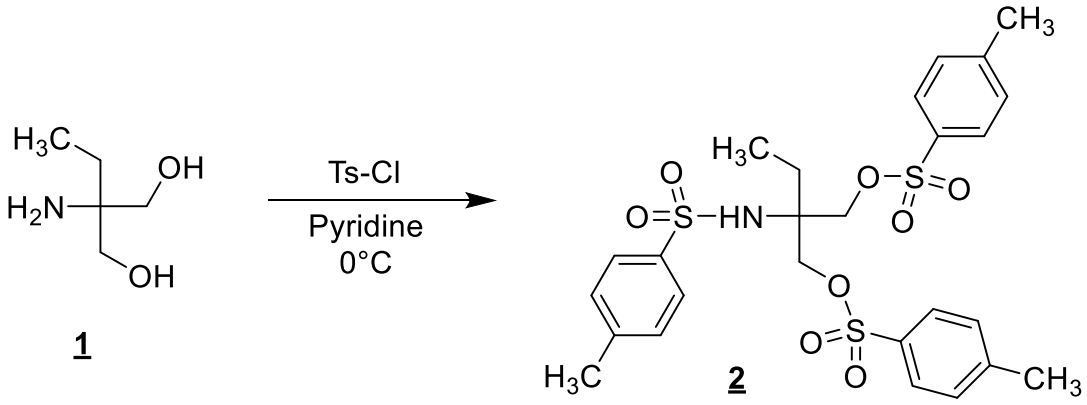
The action of tosyl chloride in pyridine on 2-amino-2-ethyl-1,3-propanediol (**1**) leads to the compound 2-ethyl-2-((4-methylphenyl)sulfonamido)propane-1,3-diyl bis(4-methylbenzenesulfonate) (**2**), with a yield of pure product of 60% (Scheme 1). Then, the obtained product is subjected to the action of sodium azide in acetonitrile (Scheme 2).

The structures of the compounds obtained were elucidated using standard spectroscopic analytical methods (1D and 2D NMR) and infrared spectroscopy. The ^{1}H NMR spectrum of compound (**2**) shows the presence of a singlet at 2.43 ppm, corresponding to the three methyl protons bound to -NHTs. In addition, the methyl group protons bonded to -OTs resonate at 2.46 ppm as a singlet. In addition, the 12 aromatic protons appear as four doublets at around 7.24–7.71 ppm (J = 8.1 Hz). Moreover, for the ^{13}C NMR spectrum,

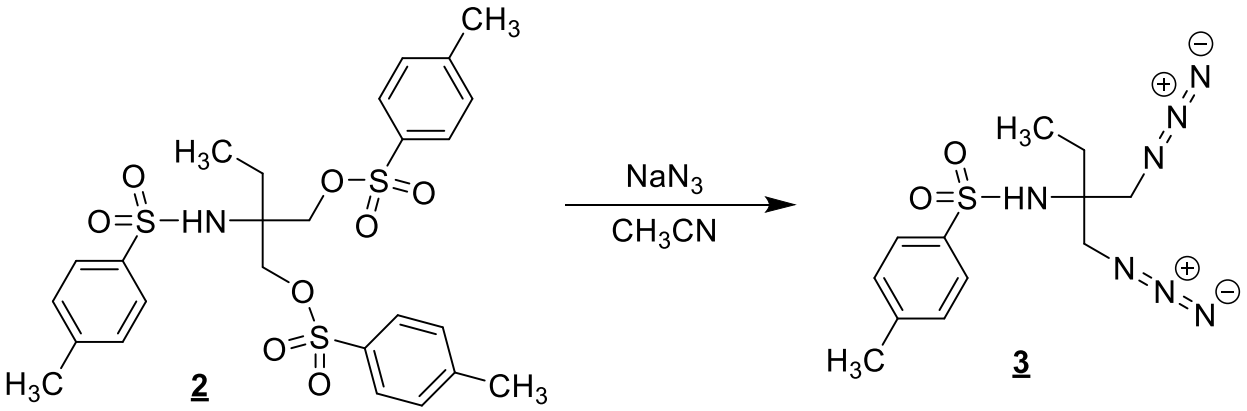
which shows the presence of a signal at 21.6 ppm, corresponding to the methyl carbon linked to -NHTs, there is a signal at 21.7 ppm relating to the two carbons of the methyl groups linked to -OTs.

Furthermore, the ^{1}H-NMR spectrum of compound (**3**) shows a singlet at 2.44 ppm, attributed to the three protons of the methyl group bonded to -NHTs. It also shows two doublets at 7.31–7.34 and 7.82–7.85 ppm, corresponding only to the four aromatic protons (J = 8.1 Hz). On the other hand, the ^{13}C NMR spectrum of this compound exhibits a signal at 21.5 ppm, attributed to the methyl group carbon bonded to -NHTs. The precise assignment of the chemical shifts of the protons and carbons is presented in Tables 1 and 2. The interpretation of the 2D HSQC NMR spectra (Figures 1 and 2) of the two compounds (**2**) and (**3**) showed a perfect correlation between proton–proton and proton–carbon 13.

The IR spectrum of compound (**3**) shows, inter alia, a high-intensity band at 2100 cm^{-1}, characteristic of the stretching vibrations of the azide group (-N_3). Thus, in the spectrum of compound (**2**), we note the absence of this last band, which shows that the substitution reaction of the leaving groups -OTs by the azide groups (-N_3) has taken place.



Scheme 1. Synthesis of compound (**2**).



Scheme 2. Synthesis of compound (**3**).

Table 1. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectral data for compound (**2**) in $CDCl_3$, including results obtained by homonuclear 2D-shift-correlated and heteronuclear 2D-shift-correlated HMBC. Chemical shifts (δ in ppm) and coupling constants (*J* in Hz).

Position	δ_H	δ_C	Correlation H-H	Correlation C-H
1	-	60.4	-	-
2	1.65 (2H, q, *J* = 7.5)	24.5	$2H^2$-$2H^2$	C^2-$2H^2$
3	0.59 (3H, t, *J* = 7.5)	6.8	$3H^3$-$3H^3$	C^3-$3H^3$
4; 4′	3.97 (2 × 2H, s)	69.0	$2H^4$-$2H^4$ $2H^{4'}$-$2H^{4'}$	C^4-$2H^4$ $C^{4'}$-$2H^{4'}$
5	5.08 (1H, s)	-	-	-
6	-	143.7	-	-
7; 7′; 8; 8′	7.24–7.27; 7.66–7.69 (4 × -CH_{arom}, 2d, *J* = 8.1)	126.8–130.0	$1H^7$-$1H^8$ $1H^{7'}$-$1H^{8'}$	C^7-$1H^7$; C^7-$1H^7$ $C^{7'}$-$1H^{7'}$; $C^{8'}$-$1H^{8'}$
9	-	139.1	-	-
10	2.42 (3H, s)	21.6	$3H^{10}$-$3H^{10}$	C^{10}-$3H^{10}$
11; 11′	-	145.4	-	-
12–15; 12′–15′	7.33–7.36; 7.68–7.71 (8 × -CH_{arom}, 2d, *J* = 8.1)	126.8–130.0	$1H^{12}$-$1H^{13}$ $1H^{12'}$-$1H^{13'}$ $1H^{14}$-$1H^{15}$ $1H^{14'}$-$1H^{15'}$	C^{12}-$1H^{12}$; C^{13}-$1H^{13}$ C^{14}-$1H^{14}$; C^{15}-$1H^{15}$ $C^{12'}$-$1H^{12'}$; $C^{13'}$-$1H^{13'}$ $C^{14'}$-$1H^{14'}$; $C^{15'}$-$1H^{15'}$
16–16′	-	131.9	-	-
17–17′	2.46 (2 × 3H, s)	21.7	$3H^{17}$-$3H^{17}$ $3H^{17'}$-$3H^{17'}$	C^{17}-$3H^{17}$ $C^{17'}$-$3H^{17'}$

Table 2. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectral data for compound (**3**) in $CDCl_3$, including results obtained by homonuclear 2D-shift-correlated and heteronuclear 2D-shift-correlated HMBC. Chemical shifts (δ in ppm) and coupling constants (*J* in Hz).

Position	δ_H	δ_C	Correlation H-H	Correlation C-H
1	-	62.0	-	-
2	1.64 (2H, q, *J* = 7.5)	25.9	$2H^2$-$2H^2$	C^2-$2H^2$
3	0.74 (3H, t, *J* = 7.5)	7.1	$3H^3$-$3H^3$	C^3-$3H^3$
4; 4′	3.45 (2 × 2H, s)	53.9	$2H^4$-$2H^4$ $2H^{4'}$-$2H^{4'}$	C^4-$2H^4$ $C^{4'}$-$2H^{4'}$
5	5.39 (1H, s)	-	-	-
6	-	143.7	-	-
7; 7′	7.82–7.85 (2 × -CH_{arom}, d, *J* = 8.1)	126.8	$1H^7$-$1H^8$ $1H^{7'}$-$1H^{8'}$	C^7-$1H^7$ $C^{7'}$-$1H^{7'}$
8; 8′	7.31–7.34 (2 × -CH_{arom}, d, *J* = 8.1)	129.8	$1H^8$-$1H^7$ $1H^{8'}$-$1H^{7'}$	C^8-$1H^8$ $C^{8'}$-$1H^{8'}$
9	-	139.6	-	-
10	2.44 (3H, s)	21.5	$3H^{10}$-$3H^{10}$	C^{10}-$3H^{10}$

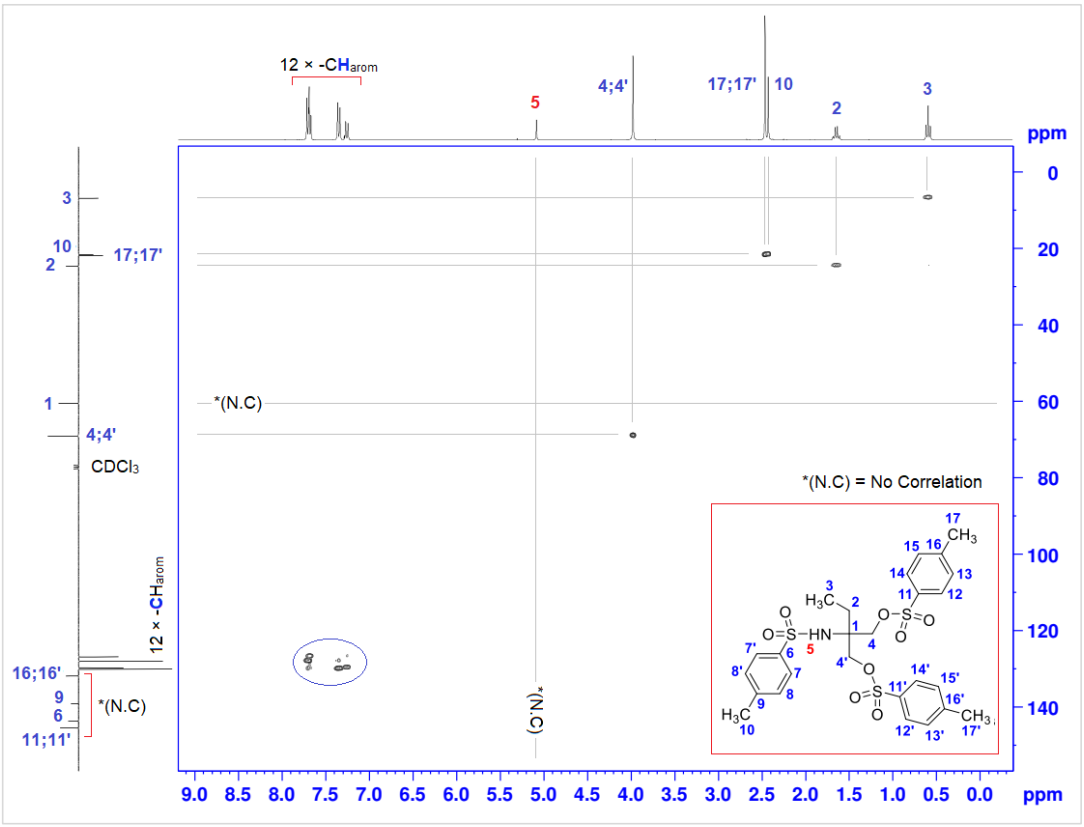


Figure 1. 2D HSQC spectrum of compound (**2**). "*": No correlation.

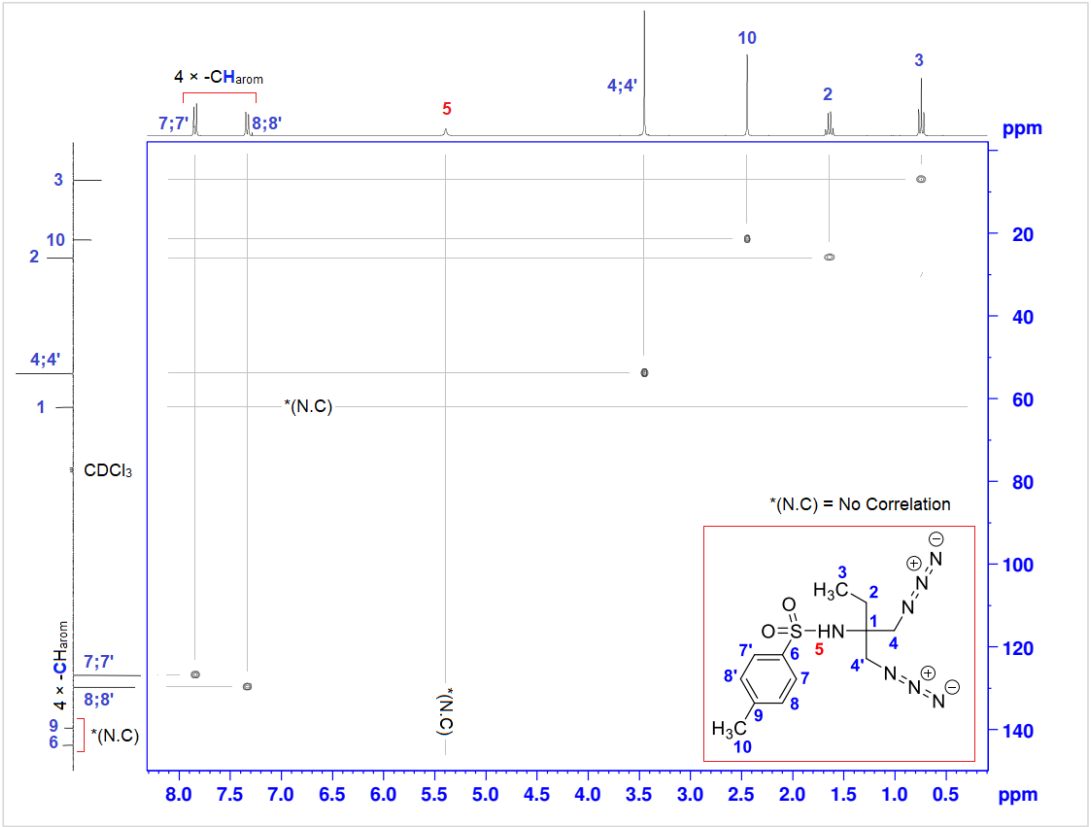


Figure 2. 2D HSQC spectrum of compound (**3**). "*": No correlation.

3. Materials and Methods

All solvents were purified following the standard techniques, and commercial reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). The melting point was determined using an electrothermal melting point apparatus and was uncorrected. The NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AM 300 spectrometer (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) (Bruker Analytische Messtechnik & GmbH, Rheinstetten, Germany). NMR data are listed in ppm and are reported relative to tetramethylsilane (^{1}H, ^{13}C). NMR spectroscopic data were recorded in $CDCl_3$ using, as internal standards, the residual non-deuterated signal (δ = 7.26 ppm) for ^{1}H NMR and the deuterated solvent signal (δ = 77.16 ppm) for the ^{13}C NMR spectroscopy. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are given in Hz. The following abbreviations are used for the multiplicities: s = singlet, d = doublet, t = triplet, and q = quartet. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm-thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F_{254}), and spots were visualized under UV light or by exposure to vaporized iodine. The FT-IR spectrum was recorded using a KBr pellet on a Bruker Vertex 70 FTIR spectrometer. The elemental analysis was performed using a Flash 2000 EA 1112 Thermo Fisher Scientific-Elemental Analyzer (CNRST, Rabat, Morocco).

*3.1. Synthesis of 2-Ethyl-2-((4-methylphenyl)sulfonamido)propane-1,3-diyl bis(4-methylbenzenesulfonate) (**2**)*

To 42 mmol (5 g) of 2-amino-2-ethyl-1,3-propanediol, 10 mL of pyridine is added under stirring at 0 °C, followed by 0.21 mol (39.9 g, 5 eq) of 4-methylbenzenesulfonyl chloride (Ts-Cl), which is added in small portions. After stirring overnight, acidified water (pH between 3–4) is added to the pasty solution formed. The reaction crude is extracted with methylene chloride (3 × 30 mL). The organic phase is washed with acidified water (6 × 30 mL) and then dried and concentrated.

Yield = 75% (white solid); m.p = 132 °C; R_f = 0.36 (ethyl acetate/hexane: 1/4). ^{1}H NMR ($CDCl_3$, δ_H ppm, 300 MHz): 0.59 (3H, -CH_2-C**H$_3$**, t, *J* = 7.5 Hz); 1.65 (2H, -C**H$_2$**-CH_3, q, *J* = 7.5 Hz); 2.42 (3H, -NHTs-C**H$_3$**, s); 2.46 (6H, 2 × (-OTs-C**H$_3$**), s); 3.97 (4H, 2 × (-C**H$_2$**-OTs), s); 5.08 (1H, -N**H**Ts-CH_3, s); 7.24–7.27; 7.66–7.69 (4 × -C**H**$_{arom}$, 2d, *J* = 8.1 Hz); 7.33–7.36; 7.68–7.71 (8 × -C**H**$_{arom}$, 2d, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, δ_C ppm, 75 MHz): 6.8 (1C, -CH_2-**C**H_3); 21.6 (1C, -NHTs-**C**H_3); 21.7 (2C, 2 × (-OTs-**C**H_3); 24.5 (1C, -**C**H_2-CH_3); 60.4 (1C, **C$_q$**$_{(sp3)}$); 69.0 (2C, 2 × (-**C**H_2-OTs)); 126.84–130.07 (12C, -**C**H$_{arom}$); 131.85 (1C, -**C$_q$**$_{(arom)}$-CH_3); 139.12 (2C, -**C$_q$**$_{(arom)}$-CH_3); 143.7 (1C, -**C$_q$**$_{(arom)}$-Ts-NH-); 145.4 (2C, -**C$_q$**$_{(arom)}$-TsO-). IR (ν (cm^{-1})): 3240 (N-H(stretching)); 2960 (=CH(stretching)); 1600 (N-H(bending)); 1350–1450 (S=O(stretching)); 800–850 (=CH(bending)).

*3.2. Synthesis of N-(1-azido-2-(azidomethyl)butan-2-yl)-4-methylbenzenesulfonamide (**3**)*

To 90 mL of acetonitrile, 28 mmol (10g) of the product (**2**) is added with 98 mmol (6.37 g, 3.5 eq) of sodium azide. Then, the mixture is brought to reflux by stirring for 24 h at 80 °C. After the reaction, the mixture is filtered and concentrated in a vacuum. The residue obtained is washed with water (3 × 30 mL). The organic phase is dried and then concentrated. The crude reaction is purified by chromatography on a silica gel column (eluent: 10 % methylene chloride/5% ethyl acetate/85% hexane).

Yield = 80% (white solid); m.p = 159 °C; R_f = 0,08 (ethyl acetate /hexane: 1/4). ^{1}H NMR ($CDCl_3$, δ_H ppm, 300 MHz): 0.74 (3H, -CH_2-C**H$_3$**, t, *J* = 7.5 Hz); 1.64 (2H, -C**H$_2$**-CH_3, q, *J* = 7.5 Hz); 2.44 (3H, -NHTs-C**H$_3$**, s); 3.45 (4H, 2 × (-C**H$_2$**-N_3), s); 5.39 (1H, -N**H**Ts-CH_3, s); 7.31–7.34 (2 × -CH_{arom}, d, *J* = 8.1 Hz); 7.82–7.85 (2 × -CH_{arom}, d, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, δ_C ppm, 75 Hz): 7.1 (1C, -CH_2-**C**H_3); 21.5 (1C, -NHTs-**C**H_3); 25.9 (1C, -**C**H_2-CH_3); 53.9 (2C, 2 × (-**C**H_2-N_3)); 62.0 (1C, $C_{q(sp3)}$); 126.8 and 129.8 (4C, -**C**H$_{arom}$); 139.6 and 143.7 (2C, -**C$_q$**$_{(arom)}$). IR (ν (cm^{-1})): 3250 (N-H(stretching)); 2950 (=CH(stretching)); 2100 (-N_3); 1600 (N-H(bending)); 1300–1350 (S=O(stretching)); 820 (=CH(bending)). Anal. Calcd. for $C_{12}H_{17}N_7O_2S$ (%): C, 44.57; H, 5.30; N, 30.32; found (%): C, 44.68; H, 5.42; N, 30.17.

4. Conclusions

The synthesis of the title compound, *N*-(1-azido-2-(azidomethyl)butan-2-yl)-4-methylbenzenesulfonamide, was carried out with a good yield via the substitution reaction of the O-tosyl groups of 2-ethyl-2-((4-methylphenyl)sulfonamido)propane-1,3-diylbis(4-methylbenzenesulfonate) with the azide group ($-N_3$). The characterization of the structures of the two products obtained (**2**) and (**3**) was carried out by 1D and 2D NMR spectroscopy, as well as IR.

Supplementary Materials: The following materials are available online, Figure S1: ^{1}H-NMR spectrum of compound (**2**); Figure S2: ^{13}C-NMR spectrum of compound (**2**); Figure S3: 2D-HSQC spectrum of compound (**2**); Figure S4: IR spectrum of compound (**2**); Figure S5: ^{1}H-NMR spectrum of compound (**3**); Figure S6: ^{13}C-NMR spectrum of compound (**3**); Figure S7: 2D-HSQC spectrum of compound (**3**); Figure S8: IR spectrum of compound (**3**).

Author Contributions: S.H. performed the experiments; H.F. and A.A. conceived and designed the experiments; Y.A. and A.A. analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in the Supplementary Materials.

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Conflicts of Interest: The authors declare no conflict of interest.

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