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Synthesis of new 2,5-diaryl 4-azido-derivatives of 2H-1,2,3-triazoles

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Abstract

4-azido-2 H- 1,2,3-triazoles were synthesized by reaction of dichlorodiazadienes (which were synthesized from nitrobenzaldehyde) with NaN_3. It was established that during the reaction, unstable bis-azides are formed as a result of the replacement of geminal chlorine atoms at the double bond with azide anion. Then, the corresponding 1,2,3-triazoles were obtained as a result of elimination of nitrogen and intramolecular cyclization reaction. This method can be considered a highly effective method of synthesis for obtaining biologically active 4-azido-2H-1,2,3-triazoles. The structure of the synthesized compounds was confirmed by NMR and X-ray method.

***Keywords*:** Dichlorodiazadiene, triazole, NMR, X-ray, catalytic olefination.
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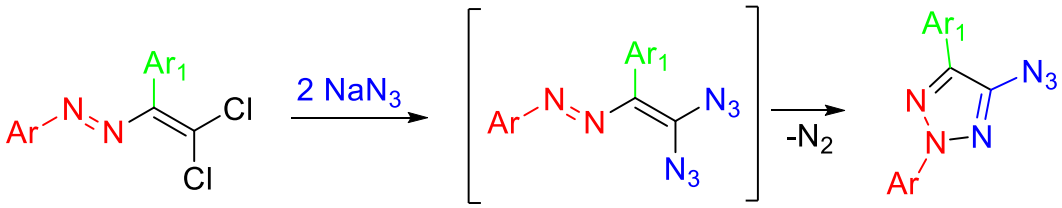
1. Introduction

In our previous research, 4-azido 1,2,3-triazoles were synthesized by the reaction of dichlorodiazadienes with sodium azide (scheme 1). During these reactions, 4-azido-2H-1,2,3 was obtained as a result of intramolecular cyclization of (E)-1-(2,2-diazido-1-arylvinyl)-2-aryldiazene, which was first obtained as an intermediate via nucleophilic substitution of chlorine atoms by azide groups [1-4]. The fact that the azide group is easily involved in substitution reactions in organic synthesis leads to their wide range of applications.



Scheme 1. Synthesis of 2,5-diaryl-4-azido 1,2,3 triazoles

1,2,3-Triazoles are widely utilized in treatment of diseases. For example, antifungal drugs with triazole rings, such as itraconazole, fluconazole, voriconazole, antiviral drug ribavirin and mubritinib (used in the treatment of breast, bladder, kidney and prostate cancer)

are known. Ribavirin is a drug used in the treatment of viral diseases such as cold sore and hepatitis. Among 2H-1,2,3-triazoles there are also drugs that have anesthetic and anti-tuberculosis properties. It should be noted that due to certain extent of complexity of the methods of synthesis of triazoles the possibilities of studying biological activity of these compounds, as well as using them as useful materials in other areas of science and technology is limited. Generally speaking, developing new methods of synthesis of 2H-1,2,3-triazoles' derivatives has always been in the center of attention of specialists in organic synthesis. 1,2,3-triazole rings are components of many drugs, which is why the number of scientific papers on the topic of researching their synthesis [5-8] and biological activities are always rising [9-16]. At the same time, triazoles are used as biologically active compounds against inflammation, thrombosis, viruses and other diseases [16, 17]. 2H-1,2,3- triazoles are also utilized in organic synthesis as effective catalysts [18] and find application as ionic liquids [19].

2. Materials and methods

The syntheses of compounds were carried out at the Organic Chemistry Department of Baku State University (Baku, Azerbaijan). Unless stated otherwise, all the reagents used in this study were obtained from the commercial sources (Aldrich, TCI-Europe, Strem, ABCR). NMR spectra were recorded on a Bruker Avance 300 (1H: 500 MHz, Karlsruhe, Germany); chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references ($CDCl_3$ δH = 7.26 ppm, δC = 77.16 pp). The X-ray analyses of compound was carried out using the Bruker APEX II CCD (T = 296 K, λ(MoKα) - radiation, graphite monochromator, φ- and ω-scan) diffractometer.

Synthetic part

The title compound was synthesized according to a literature protocol [4]. A 20 ml screw-neck vial was charged with DMSO (20 ml), dichlorodiazadiene (350 mg, 1 mmol) and sodium azide (NaN3; 390 mq; 3 mmol). After 1–3 h (until TLC analysis showed complete consumption of the corresponding triazole), the reaction mixture was poured into a 0.01 M solution of HCl (100 ml, pH = 2–3), and extracted with dichloromethane (3 x 20 ml). The combined organic phase was washed with water (3 x 50 ml), brine (30 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo using a rotary evaporator. The residue was purified by column chromatography on silica gel using appropriate mixtures of hexane and dichloromethane (v/v: 3/1–1/1).

4-Azido-5-(3-nitrophenyl)-2-(p-tolyl)-2H-1,2,3-triazole (1). Yield 68%, M.p. 153 ^{0}C, pale-yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.64 (t, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 7.6, Hz, 1H), 8.12 (d, *J* = 7.6, Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.22 (d, *J* = 7.2, Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 158.7, 149.9, 146.6, 138.6, 135.6, 130.4, 130.5, 130.2, 129.7, 126.4, 125.7, 121.5, 20.6.

4-Azido-2-(4-methoxyphenyl)-5-(3-nitrophenyl)-2H-1,2,3-triazole (2). Yield 65%, M.p. 149 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.67 (t, *J* = 2.0 Hz, 1H), 8.32 (d, *J* = 7.5, Hz, 1H), 8.12 (d, *J* = 7.4, Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.75 – 7.64 (m, 2H), 6.97 – 6.92 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 159.3, 157.2, 148.5, 145.7, 137.4, 130.6, 130.3, 129.5, 126.6, 126.3, 120.7, 115.6, 54.7.

4-Azido-2-(4-chlorophenyl)-5-(3-nitrophenyl)-2H-1,2,3-triazole (3). Yield 70%, M.p. 151 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.64 (t, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 7.6, Hz, 1H), 8.18 (d, *J* = 7.5, Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.40 – 7.34 (m, 2H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 161.3, 150.3, 147.6, 141.7, 135.7, 132.8, 132.5, 132.1, 129.7, 128.4, 126.9, 122.4.

4-Azido-2-(4-fluorophenyl)-5-(3-nitrophenyl)-2H-1,2,3-triazole (4). Yield 63%, M.p. 139 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.73 (t, *J* = 1.9 Hz, 1H), 8.43 (d,

J = 7.5, Hz, 1H), 8.22 (d, *J* = 7.6, Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.21 – 7.15 (m, 2H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 162.5, 159.3, 150.2, 147.6, 139.6, 132.5, 131.2, 128.4, 126.4, 125.5, 123.6, 115.4.

4-Azido-2-(4-bromophenyl)-5-(3-nitrophenyl)-2H-1,2,3-triazole (5). Yield 72%, M.p. 104 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.86 (t, *J* = 2.0 Hz, 1H), 8.45 (d, *J* = 7.6, Hz, 1H), 8.34 (d, *J* = 7.5 Hz, 1H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.67 – 7.57 (m, 4H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 160.3, 150.2, 147.6, 141.4, 137.9, 134.5, 132.7, 132.4, 128.4, 128.1, 124.7, 120.5.

4-(4-Azido-5-(3-nitrophenyl)-2H-1,2,3-triazol-2-yl)benzonitrile (6). Yield 64%, M.p. 168 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.79 (t, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.92 – 7.78 (m, 5H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 162.3, 152.2, 149.6, 147.9, 139.5, 135.6, 134.9, 134.6, 134.4, 132.1, 124.5, 122.6, 114.4.

4-Azido-2-(3,4-dimethylphenyl)-5-(3-nitrophenyl)-2H-1,2,3-triazole (7). Yield 72%, M.p. 115 ^{0}C, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.75 (t, *J* = 2.0 Hz, 1H), 8.32 (d, *J* = 7.6, Hz, 1H), 8.18 (d, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.42 (s, 1H), 7.09 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 159.3, 148.2, 145.6, 141.0, 138.6, 130.4, 130.2, 130.2, 129.4, 128.8, 126.4, 126.1, 119. 8, 119.1, 20.6, 19.4.

4-Azido-5-(3-nitrophenyl)-2-(m-tolyl)-2H-1,2,3-triazole (8). Yield 63%, M.p. 112 ^{0}C, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.68 (t, *J* = 2.0 Hz, 1H), 8.31 (t, *J* = 7.5, Hz, 1H), 8.28 (d, *J* = 7.5, Hz, 1H), 7.78 (d, *J* = 7.1, Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 2.0, 1.1 Hz, 1H), 7.21 – 7.16 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 161.3, 153.2, 148.6, 145.5, 110.6, 135.4, 134.1, 130.3, 128.2, 127.4, 127.1, 124.0, 120.8, 118.5, 20.4.

4-Azido-5-(4-nitrophenyl)-2-(p-tolyl)-2H-1,2,3-triazole (9). Yield 62%, M.p. 163 ^{0}C, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.29 – 8.23 (m, 2H), 7.93 – 7.87 (m, 2H), 7.59 – 7.52 (m, 2H), 7.19 (d, *J* = 7.5, Hz, 2H) 2.42 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 161.3, 150.2, 147.6, 140.6, 136.4, 134.2, 133.4, 130.3, 127.4, 123.6, 20.6.

4-Azido-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (10). Yield 72%, M.p. 164 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.37 – 8.29 (m, 2H), 7.98 – 7.92 (m, 2H), 7.62 – 7.56 (m, 2H), 6.98 – 6.89 (m, 2H), 3.79 (s, 3H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 162.4, 159.4, 150.9, 147.3, 139.9, 136.0, 129.9, 127.9, 122.8, 117.8, 53.6.

4-Azido-2-(4-chlorophenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (11). Yield 70%, M.p. 107 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.29 – 8.23 (m, 2H), 7.93 – 7.87 (m, 2H), 7.59 – 7.52 (m, 2H), 7.41 – 7.35 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 159.29, 148.19, 145.63, 139.61, 133.70, 132.20, 130.94, 128.19, 125.19, 123.40.

4-Azido-2-(4-fluorophenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (12). Yield 68%, M.p. 132 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.39 – 8.33 (m, 2H), 7.83 – 7.77 (m, 2H), 7.74 – 7.65 (m, 2H), 7.26 – 7.20 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 161.3, 159.9, 148.9, 145.3, 138.6, 132.0, 128.9, 125.9, 121.3, 116.8.

4-Azido-2-(4-bromophenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (13). Yield 71%, M.p. 89 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.7 – 8.20 (m, 2H), 7.87 – 7.76 (m, 2H), 7.50 – 7.40 (m, 2H), 7.25 – 7.21 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 162.4, 148.5, 145.8, 139.5, 133.8, 132.3, 128.4, 125.3, 121.9, 120.6.

4-(4-Azido-5-(4-nitrophenyl)-2H-1,2,3-triazol-2-yl)benzonitrile (14). Yield 73%, M.p. 172 ^{0}C, yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.32 – 8.28 (m, 2H), 7.87 – 7.79 (m, 2H), 7.82 – 7.79 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 161.2, 150.1, 148.6, 140.9, 135.2, 131.9, 130.1, 127.2, 123.4, 118.6, 113.3.

4-Azido-2-(3,4-dimethylphenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (15). Yield 62%, M.p. 158 ^{0}C, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.42 – 8.39 (m, 2H), 7.89 – 7.79 (m, 2H), 7.63 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.6, Hz, 1H),

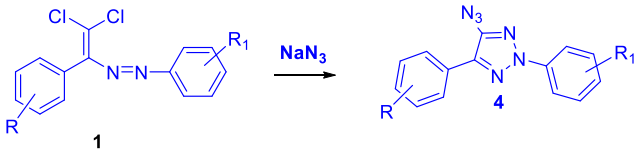
2.45 (s, 3H), 2.42 (s,3H). ^{13}C NMR (75 MHz, Chloroform-d_6) δ 161.7, 150.4, 147.6, 145.0, 140.4, 136.2, 134.2, 130.8, 130.3, 127.1, 121.5, 120.2, 20.6, 19.4.

4-Azido-5-(4-nitrophenyl)-2-(m-tolyl)-2H-1,2,3-triazole (16). Yield 65%, M.p. 119 ^{0}C, pale-yellow solid. ^{1}H NMR (300 MHz, Chloroform-d_6) δ 8.45 – 8.40 (m, 2H), 7.87 – 7.80 (m, 2H), 7.60 (*s*, 1H), 7.40 (d, *J* = 7.5, Hz, 1H), 7.25(d, *J* = 7.5,Hz, 1H), 7.10 (t, *J* = 7.6,Hz, 1H), 2.43 (s, 3H).^{13}C NMR (75 MHz, Chloroform-d_6) δ 162.2, 150.19, 147.63, 145.51, 141.67, 137.2, 136.6, 130.20, 128.3, 127.0, 120.8, 119.9, 20.4.

4-Azido -2-(4-methoxyphenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole (17). Yield 63%, M.p. 112 ^{0}C, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.92 (t, *J* = 7.3 Hz, 3H), 7.75 – 7.62 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 148.4, 143.6, 132.9, 132.6, 131.6, 129.7, 124.8, 124.5, 119.7, 115.1, 114.3, 55.5.

3. Results and discussion

We synthesized dichlorodiazadienes in the catalytic olefination reaction conditions and studied their different reactions with nucleophiles [26]. Continuing research in this direction, transformation reactions involving NaN_3 were carried out and new 2,5-diaryl 4-azido derivatives of 2H-1,2,3-triazoles were synthesized [1-4].



1

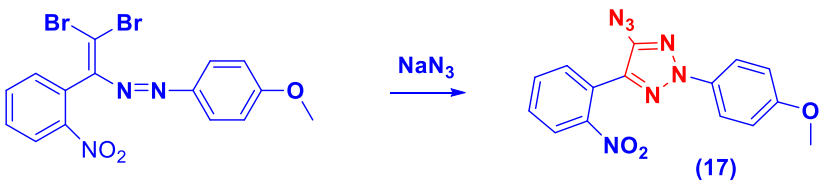
R= 3-NO_2, R_1= 4-CH_3(1), 4-OCH_3(2), 4-Cl (3), 4-F(4), 4-Br(5), 4-CN (6), 3,4-CH_3(7), 3-CH_3(8),

R= 4-NO_2, R_1= 4-CH_3(9), 4-OCH_3(10), 4-Cl (11), 4-F(12), 4-Br(13), 4-CN (14), 3,4-CH_3(15), 3-CH_3(16),

Scheme 2. Synthesis of new 2,5-diaryl 4-azido-derivatives of 2H-1,2,3-triazoles

Triazole fragment is considered to be the most important pharmacophor unit, and many drugs containing this heterocycle are known. It bears mentioning that up until now, structures containing 1,2,4-triazole fragment were used more often for this purpose. At the same time, 1H-1,2,3- and 2H-1,2,3-triazoles are more actively studied as an important class of heterocyclic compounds. Among 2H-1,2,3-triazoles there are drugs with anesthetic and anti-tuberculosis properties. Several patents have recently been issued that describe incorporation of compounds containing 2H-1,2,3-triazole nucleus in the pharmaceuticals that can be used in the treatment of several diseases, including asthma. It is from this perspective that the synthesis of 4-azido derivatives of 2H-1,2,3-triazoles attracts great interest.

The same reaction was carried out with dibromodiazadiene synthesized from 2-nitrobenzaldehyde, and the structure of the synthesized triazole was confirmed by NMR and X-ray structural analysis (scheme 3).



(17)

Scheme 3. Synthesis of 4-azido -2-(4-methoxyphenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole 17

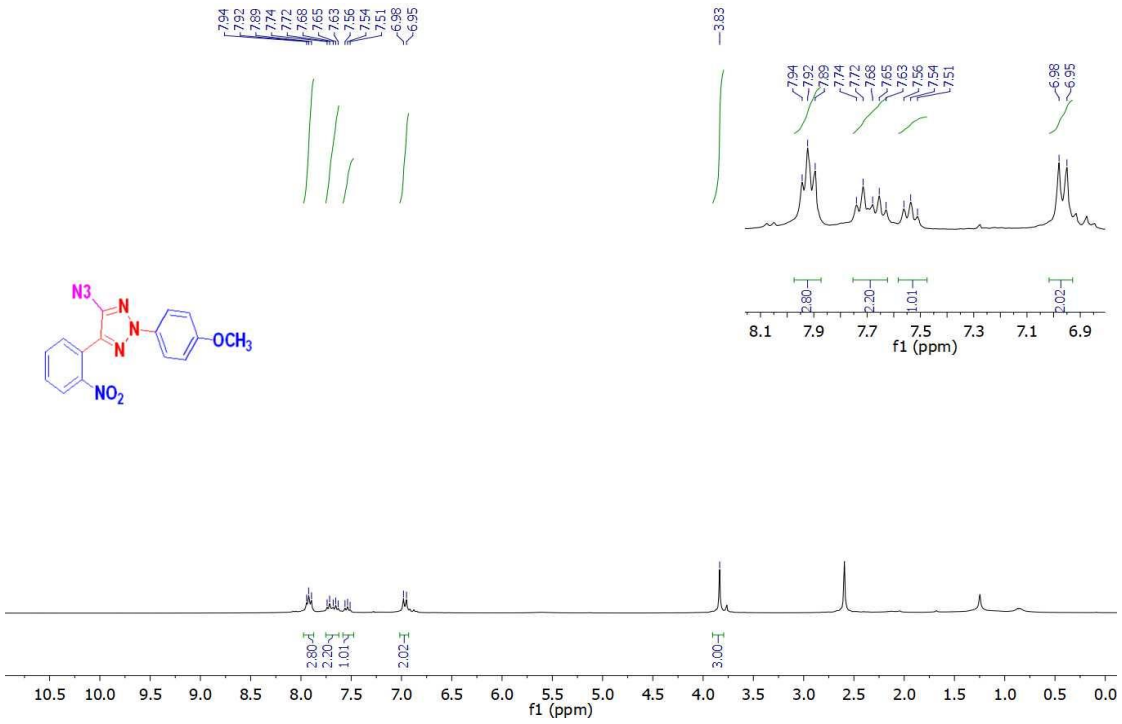


Figure 1. The ^{1}H NMR spectrum of 4-azido -2-(4-methoxyphenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole.

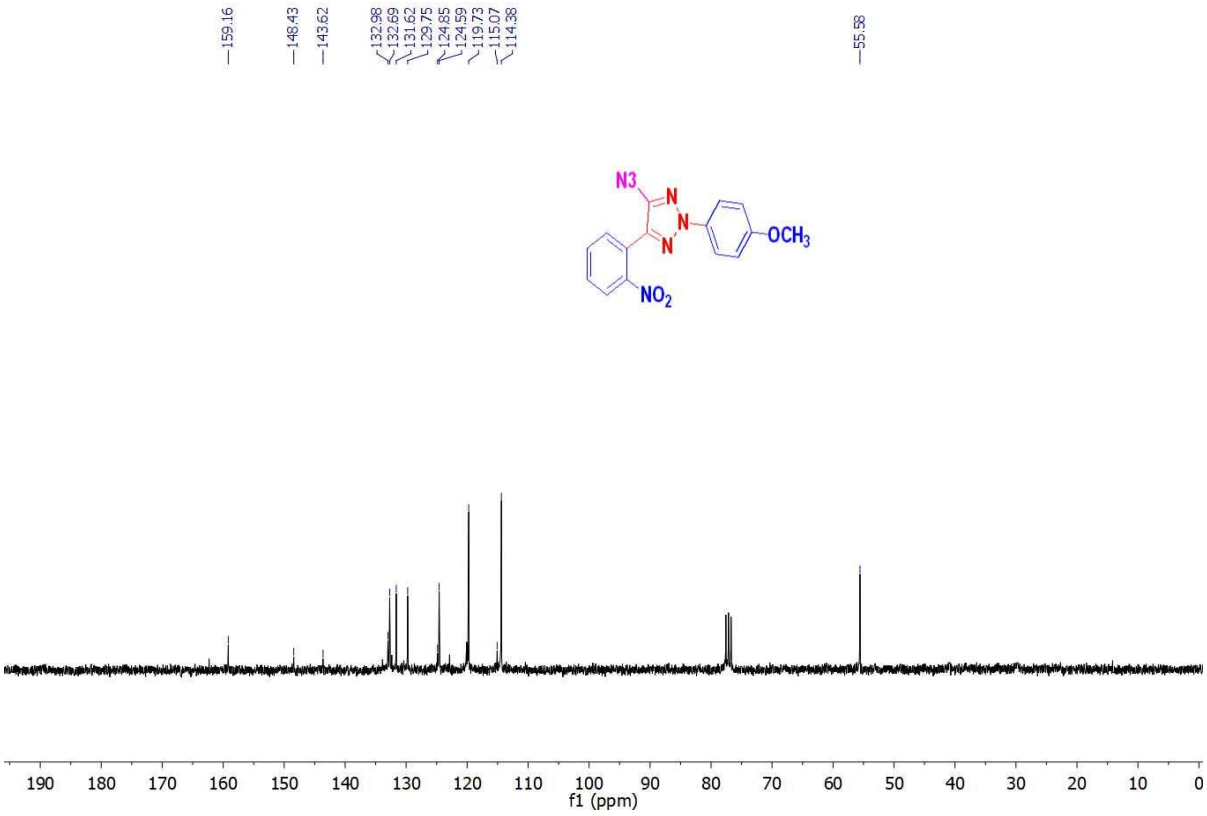


Figure 2. The ^{13}C NMR spectrum of 4-azido-2-(4-methoxyphenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole

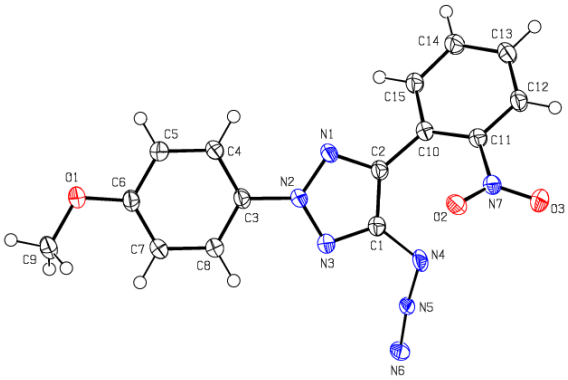


Figure 3. Molecular structure of 4-azido -2-(4-methoxyphenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole

4. Conclusion

Thus, derivatives of 4-azido-2,5-diaryl-2H-1,2,3-triazole were synthesized by reaction of dichlorodizadienes (synthesized from m, p-nitro-benzaldehydes) with NaN_3. The structures of some triazoles were confirmed by X-ray analysis. Due to the fact that compounds containing triazole ring find applications in medicine against various diseases, and also in organic cathalysis, ionic liquids, it is possible to say that the synthesis of these new triazole derivatives by this method is very important.

Authors' Declaration

The authors declare no conflict of interests regarding the publication of this article.

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