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Synthesis of 1,2,3-triazole derivatives based on propargyl ester of a saturated single-basic carbonic acid and *para*-azidobenzoic acid

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ABSTRACT

The development of highly effective and low-toxicity nonsteroidal anti-inflammatory drugs (NSAIDs) is one of the important challenges facing modern pharmacology. To overcome this problem, many studies have been conducted on compounds containing a five-membered heterocycle containing three nitrogen atoms. The pharmacodynamics of these compounds are mainly due to their anti-inflammatory effect. Therefore, it is important to synthesize new derivatives of 1,2,3-triazoles, to determine their structure and to look for substances with anti-inflammatory activity on their basis. For the first time, the corresponding derivatives of 4-(4-(exchangeable)-1*H*-1,2,3-triazole-1-yl)-benzoic acid were synthesized by cycloaddition of propargyl esters of saturated carboxylic acids and *para*-azidobenzoic acid in the presence of copper (I) iodide. The structure of the obtained substances was analyzed by IR, ¹H NMR, and MS techniques. It is proved that under the action of the catalyst in the reaction, only 1,4-isomers are formed. Factors affecting the course of the reaction were identified. Only one isomer is formed in the reaction of cyclic addition under the action of a catalyst and the effect of temperature, duration of time, and nature of the solvent on the reaction yield was studied.

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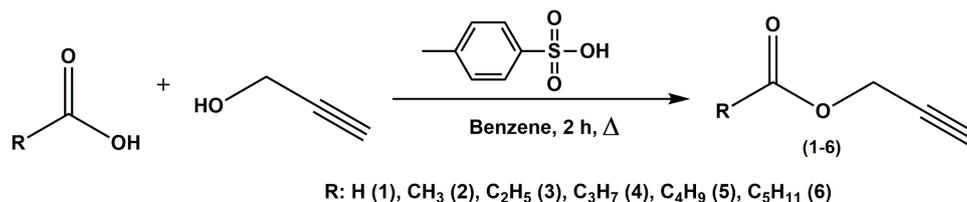
1. Introduction

The first alkyne, acetylene, was discovered by Edmund Devill in 1837, while in 1864 Griess synthesized organic azides and described it as a class of new compounds [1,2]. The first article on the preparation of 1,2,3-triazoles was published at the end of the 19th century [1,2]. In the first work on the synthesis of 1,2,3-triazole derivatives from alkynes and azides, the cyclization reaction of phenylazide dimethyl ester and acetylene dicarboxylic acid was studied under the influence of strong light or at a temperature of 100 °C in a metal ampoule for 8 hours [3]. One isomer is formed in this reaction due to the using of symmetrical alkynes [3]. In the early 1960s, Rolf Huisgen developed a general reaction mechanism for the 1,3-bipolar cycloaddition of alkynes and organic azides [4-15]. Over the past 50 years, this reaction has been actively studied. However, the formation of a mixture of two 1,4- and 1,5-isomeric triazoles (often difficult to separate) from the reaction of asymmetric or

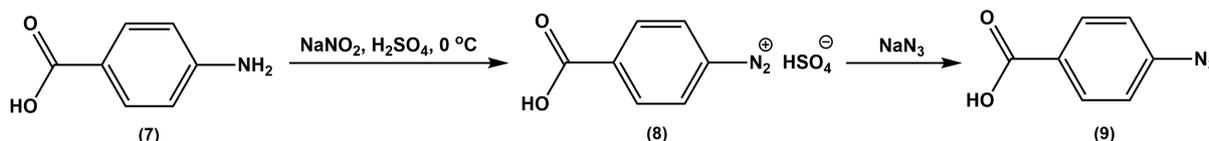
terminal alkynes with azides prevented the widespread development of this reaction [11-13].

At the beginning of the XXI century, in 2002, a group of scientists led by Rostovtsev *et al.* and Tornøe *et al.* discovered that the cycloaddition of terminal alkynes and organic azides in the presence of a catalyst of copper (I) salts forms only one 1,4-isomer [8,9,16,17]. In this reaction, the function of the Cu(I) salt and the related mechanism were fully justified. Later, the reaction of alkynes with azides became known as the Güssens-Meldal-Sharpless reaction. After this invention, the chemistry of 1,2,3-triazoles rapidly developed. After some time, it was determined that only 1,5-isomers were formed in the reaction under the catalyst of ruthenium salts [17,18].

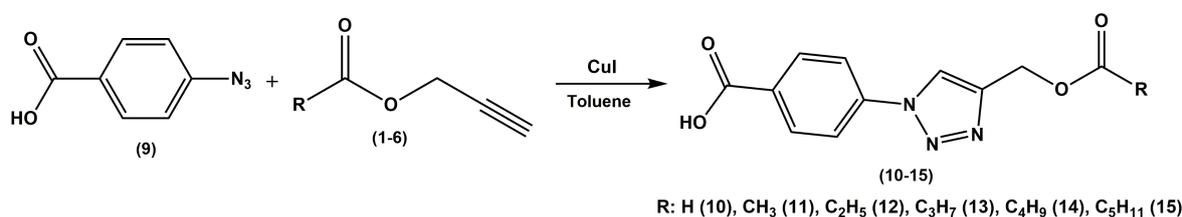
Currently, the worldwide synthesis and biological activity of 1,2,3-triazoles are being studied rapidly. This is also evident from articles in prestigious magazines published in recent years [19-23].



Scheme 1



Scheme 2



Scheme 3

Among the 1,2,3-triazole derivatives, various drugs with anti-tuberculosis, antiviral, antibacterial, anti-diabetic, anti-leishmaniasis, anti-inflammatory activities were found, and research in these areas is still ongoing [24-39]. Earlier, Uzbek scientists (Makhsumov A.G, Madikhanov N.) also synthesized and modified 1,2,3-triazoles and found a positive anti-inflammatory effect of some of the obtained substances [35,36]. We have studied the interaction of bipolar cycloaddition of the obtained esters and azides under the action of a catalyst. As a result, we were able to obtain 1,4-isomeric derivatives of the corresponding 1,2,3-triazoles. Factors affecting the yield of the reaction were determined, and the optimal reaction conditions were found.

2. Experimental

2.1. Materials and apparatus

The used solvents (Toluene, acetone, hexane, benzene, ethyl alcohol, and chloroform) were dried and purified, as shown in the literature [40]. Fourier transform infrared spectroscopy (FTIR) analysis was done by scanning pressed tablets of 0.5 mg of powder sample mixed with pure KBr (300 mg) using a Perkin Elmer System 2000 Fourier Transform Infrared Spectrometer. Mass spectra were recorded on Kratos MS-30 mass spectrometer (Shimadzu, Japan, EI, 70 eV). The NMR spectra were recorded on a Varian Unity-400 Plus (¹H: 400 MHz, ¹³C: 100 MHz). CD₃OD or CD₃COOD were used as a solvent. The chemical shifts are expressed in δ (ppm) and the coupling constants, J, are reported in hertz (Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet and br, broad. The melting point of the synthesized compounds was determined on a Boetius device (Germany).

2.2. Synthesis

The propargyl esters (Propargyl formate (1), propargyl acetate (2), propargyl propionate (3), propargyl butyrate (4), propargyl valerate (5) and propargyl capronate (6)) (Scheme

1) and *para*-azidobenzoic acid (9) (Scheme 2) were synthesized according to literature [24,35,36,38].

2.2.1. Synthesis of 4-(4-((formyloxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (10)

0.815 g (0.005 mol) of *para*-azidobenzoic acid (9), 0.8 mL of propargyl formate (0.001 mol) (1), 0.10 g of copper (I) iodide and 40 mL toluene was poured into a 100 mL round bottom flask. The flask was placed in an oil bath and combined with a reflux condenser, where toluene was heated to the boiling point (110 °C) for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography. Over time, a white precipitate began to form in the reaction mixture. After 6 hours, the reaction was stopped and left overnight at room temperature. The precipitate formed was filtered off, dried and recrystallized from ethanol (Scheme 3). Color: Colorless. Yield: 75%. M.p.: 240-241 °C. FT-IR (KBr, ν, cm⁻¹): 3417 (OH), 2923 (CH), 1726 (C=O), 1683 (C=O), 1608 (C=C), 1519 (N=N), 1322 (CO), 1220 (CN). ¹H NMR (400 MHz, CD₃OD, δ, ppm): 5.31 (s, 2H, OCH₂), 7.95 (d, 2H, J = 7.7 Hz, Ar-H-2',6'), 8.12 (s, 1H, CHO), 8.15 (d, 2H, J = 8.4 Hz, Ar-H-3'5'), 8.65 (s, 1H, CH). MS (EI, m/z (%)): 248 ([M]⁺, 2.3), 237 (3.3), 219 (5.17), 174 (3.48), 149 (1.96), 130 (5.81), 103 (60.46), 77 (79.07). R_f (Benzene:methanol, 5:1): 0.33.

2.2.2. Synthesis of 4-(4-(acetoxymethyl)-1H-1,2,3-triazol-1-yl)benzoic acid (11)

0.815 g (0.005 mol) of *para*-azidobenzoic acid (9), 0.8 mL of propargyl acetate (0.008 mol) (2), 0.10 g of copper (I) iodide and 40 mL toluene was poured into a 100 mL round bottom flask. The flask was placed in an oil bath and combined with a reflux condenser, where toluene was heated to the boiling point (110 °C) for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography. Over time, a white precipitate began to form in the reaction mixture. After 6 hours, the reaction was stopped and left overnight at room temperature. The precipitate formed was filtered off, dried and

recrystallized from ethanol (Scheme 3). Color: Orange. Yield: 77%. M.p.: 238-239 °C. FT-IR (KBr, ν , cm^{-1}): 3415 (OH), 2921 (CH), 1750 (C=O), 1686 (C=O), 1607 (C=C), 1519 (N=N), 1367 (CO), 1238 (CN). ^1H NMR (400 MHz, CD_3COOD , δ , ppm): 1.96 (s, 3H, CH_3), 5.28 (s, 2H, OCH_2), 7.95 (d, 2H, $J = 7.8$ Hz, Ar-H-2',6'), 8.20 (d, 2H, $J = 7.4$ Hz, Ar-H-3',5'), 8.47 (s, 1H, CH). MS (EI, m/z (%)): 262 ([M]⁺, 2.2), 220 (2.2), 174 (3.46), 130 (5.86), 103 (61.21), 77 (81.88). R_f (Benzene:methanol system, 5:1): 0.37.

2.2.3. Synthesis of 4-(4-((propionyloxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (12)

0.815 g (0.005 mol) of *para*-azidobenzoic acid (9), 0.8 mL of propargyl propionate (0.007 mol) (3), 0.10 g of copper (I) iodide and 40 mL toluene was poured into a 100 mL round bottom flask. The flask was placed in an oil bath and combined with a reflux condenser, where toluene was heated to the boiling point (110 °C) for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography. Over time, a white precipitate began to form in the reaction mixture. After 6 hours, the reaction was stopped and left overnight at room temperature. The precipitate formed was filtered off, dried and recrystallized from ethanol (Scheme 3). Color: Colorless. Yield: 80 %. M.p.: 237-238 °C. FT-IR (KBr, ν , cm^{-1}): 3481 (OH), 2924 (CH), 1748 (C=O), 1681 (C=O), 1605 (C=C), 1518 (N=N), 1351 (CO), 1235 (CN). ^1H NMR (400 MHz, CD_3OD , δ , ppm): 1.07 (t, 3H, $J = 7.6$ Hz, CH_3), 2.33 (m, 2H, $J = 6.4$ Hz, CH_2CH_3), 5.22 (s, 2H, OCH_2), 7.94 (d, 2H, $J = 7.8$ Hz, Ar-H-2,6), 8.16 (d, 2H, Ar-H-3,5), 8.61 (s, 1H, CH). MS (EI, m/z (%)): 276 ([M]⁺, 2.2), 275 ([M], 3.1), 274 ([M-H], 1.5), 247 (5.2), 220 (2.2) 192 (3.2), 174 (3.5), 130 (5.9), 103 (61.4), 77 (81.9). R_f (Benzene:methanol system, 5:1): 0.41.

2.2.4. Synthesis of 4-(4-((butyryloxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (13)

0.815 g (0.005 mol) of *para*-azidobenzoic acid (9), 0.9 mL of propargylbutyrate (0.007 mol) (4), 0.10 g of copper (I) iodide and 40 mL toluene was poured into a 100 mL round bottom flask. The flask was placed in an oil bath and combined with a reflux condenser, where toluene was heated to the boiling point (110 °C) for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography. Over time, a white precipitate began to form in the reaction mixture. After 6 hours, the reaction was stopped and left overnight at room temperature. The precipitate formed was filtered off, dried and recrystallized from ethanol (Scheme 3). Color: Colorless. Yield: 81%. M.p.: 235-236 °C. FT-IR (KBr, ν , cm^{-1}): 3417 (OH), 2929 (CH), 1738 (C=O), 1684 (C=O), 1607 (C=C), 1520 (N=N), 1385 (CO), 1238 (CN). ^1H NMR (400 MHz, CD_3OD , δ , ppm): 1.10 (t, 3H, $J = 5.6$ Hz, CH_3), 1.72 (m, 2H, $J = 2.8$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.54 (t, 2H, $J = 6.4$ Hz, $-\text{CH}_2\text{CH}_2\text{CH}_3$), 5.22 (s, 2H, OCH_2), 7.93 (d, 2H, $J = 8.6$, Ar-H-2,6), 8.15 (d, 2H, $J = 7.5$, Ar-H-3,5), 8.61 (s, 1H, CH). MS (EI, m/z (%)): 290 ([M+H], 2.3), 289 ([M], 3.4), 288 ([M-H], 1.4), 261 (5.2), 220 (2.3), 192 (3.3), 174 (3.5), 130 (5.7), 103 (59.7), 77 (80.4). R_f (Benzene:methanol system, 5:1): 0.44.

2.2.5. Synthesis of 4-(4-((pentanoyloxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (14)

0.815 g (0.005 mol) of *para*-azidobenzoic acid (9), 1.1 mL of propargyl valerate (0.007 mol) (5), 0.10 g of copper (I) iodide and 40 mL toluene was poured into a 100 mL round bottom flask. The flask was placed in an oil bath and combined with a reflux condenser, where toluene was heated to the boiling point (110 °C) for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography. Over time, a white precipitate began to form in the reaction mixture. After 6 hours, the reaction was stopped and left overnight at room temperature. The precipitate formed was filtered off, dried and

recrystallized from ethanol (Scheme 3). Color: White. Yield: 83%. M.p.: 233-234 °C. FT-IR (KBr, ν , cm^{-1}): 3426 (OH), 2929 (CH), 1739 (C=O), 1681 (C=O), 1608 (C=C), 1520 (N=N), 1323 (CO), 1238 (CN). ^1H NMR (400 MHz, CD_3OD , δ , ppm): 0.85 (t, 3H, $J = 2.8$, CH_3), 1.29 (m, 2H, $J = 5.6$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.55 (m, 2H, $J = 6.4$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.32 (t, 2H, $J = 2.8$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 5.23 (s, 2H, OCH_2), 7.92 (d, 2H, $J = 7.2$ Hz, Ar-H-2,6), 8.15 (d, 2H, $J = 8.4$ Hz, Ar-H-3,5'), 8.58 (s, 1H, CH). MS (EI, m/z (%)): 304 ([M+H], 2.3), 297 (3.4), 281 (1.5), 192 (3.1), 174 (3.4), 130 (5.9), 103 (61.2), 77 (82.4). R_f (Benzene:methanol system, 5:1): 0.50.

2.2.6. Synthesis of 4-(4-((hexanoyloxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (15)

0.815 g (0.005 mol) of *para*-azidobenzoic acid (9), 1.2 mL of propargyl capronate (0.007 mol) (6), 0.10 g of copper (I) iodide and 40 mL toluene was poured into a 100 mL round bottom flask. The flask was placed in an oil bath and combined with a reflux condenser, where toluene was heated to the boiling point (110 °C) for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography. Over time, a white precipitate began to form in the reaction mixture. After 6 hours, the reaction was stopped and left overnight at room temperature. The precipitate formed was filtered off, dried, and recrystallized from ethanol (Scheme 3). Color: Colorless. Yield: 87%. M.p.: 229-230 °C. FT-IR (KBr, ν , cm^{-1}): 3477 (OH), 2924 (CH), 1739 (C=O), 1682 (C=O), 1607 (C=C), 1520 (N=N), 1317 (CO), 1244 (CN). ^1H NMR (400 MHz, CD_3OD , δ , ppm): 0.82 (t, 3H, $J = 2.8$, CH_3), 1.24 (m, 4H, $J = 2.61$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.56 (m, 2H, $J = 5.6$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.30 (t, 2H, $J = 7.6$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 5.22 (s, 2H, OCH_2), 7.98 (d, 2H, $J = 5.6$ Hz, Ar-H-2,6), 8.13 (d, 2H, $J = 8.2$ Hz, Ar-H-3,5), 8.61 (s, 1H, CH). MS (EI, m/z (%)): 318 ([M+H], 2.3), 317 ([M], 3.3), 316 ([M-H], 1.7), 289 (5.22), 219 (2.14), 174 (3.48), 130 (5.81), 103 (60.46), 77 (79.07). R_f (Benzene:methanol system, 5:1): 0.53.

3. Results and discussion

The propargyl esters (Propargyl formate (1), propargyl acetate (2), propargyl propionate (3), propargyl butyrate (4), propargyl valerate (5) and propargyl capronate (6)) of lower monobasic carboxylic acids were synthesized with a 1:1 mixture of carboxylic acid and propargyl alcohols by the esterification reaction in the presence of *para*-toluenesulfonic acid in benzene (Scheme 1). The reaction was carried out on a Dean-Stark apparatus until the drops of water stopped falling (2 hours). Monobasic carboxylic acids (Formic acid, acetic acid, propionic acid, butyric acid, valeric acid and caproic acid) with carbon atoms from 1 to 6 were used in the reaction. The obtained products were purified by distillation using a vacuum pump at 12 mm Hg and propargyl ethers were synthesized in high yields [24,35,36,37].

para-Azidobenzoic acid (9) was synthesized by adding a drop of sodium azide solution to the diazonium salt (8) formed by the diazotization reaction of *para*-aminobenzoic acid (7) the yield of the product is 85% (Scheme 2). The melting point is 124 °C and is consistent with literature data [22,35,36,37].

We continued our research, studying the mutual cycloaddition of the synthesized esters of propargyl and *para*-azidobenzoic acid. The cyclic addition of organic azides with three acetylene-type bonds has been studied in the literature [38,39]. The synthesis of 1,2,3-triazole derivatives is mainly carried out by this reaction. The reaction mainly gives a mixture of 1,4- and 1,5-isomers (Scheme 4) [14]. However, it has recently been discovered that only one isomer is formed in the reaction in the presence of catalysts. According to the analysis of the literature, 1,4-isomers are formed using copper salts as catalysts, and only 1,5-isomers are formed using ruthenium salts [14,38,39].

range δ 1.96-0.82 ppm, a triplet signal observed for CH₃ protons of compounds 11-15. The OH protons are not observed in the ¹H NMR spectrum. In CD₃OD/ CD₃COOD, this is the result of the exchange of protons with deuterium so that the averaged signal is broadened in to the baseline. Satisfactory mass spectral data corresponding to a particular molecular ion peak of all cyclized products confirmed the formation of compounds 10-15.

The IR data of compounds 11-15 showed a strong absorption at the range 1750-1681 cm⁻¹ indicating the presence of CO group confirmed the synthesis of target compounds. In the IR spectrum of the studied compounds, the band of the carbonyl group of the ester group is found in the high-frequency region relative to the C=O carboxylic acid group. The presence of OH groups in compounds 10-15 is indicated by the absorption bands in the range 3481-3415 cm⁻¹. In the IR spectrum of the studied compounds, absorption bands are observed in the region of 2500-2600 cm⁻¹, which is characteristic of the dimeric form of carboxylic acids.

4. Conclusion

The reaction of esterification of the lower representatives of monobasic aliphatic monocarboxylic acids with propargyl alcohol was carried out. As a result, the corresponding propargyl esters were obtained. Para-azidobenzoic acid was synthesized based on para-aminobenzoic acid in the presence of sodium azide. The reactions of 1,3-bipolar cycloaddition of the obtained esters with para-azidobenzoic acid were carried out. The reaction was carried out in the presence of a catalyst - copper (I) iodide. As a result, it was found that 1,4-isomers of 1,2,3-triazole derivatives were formed. The structure of the obtained substances was thoroughly analyzed and confirmed using IR, ¹H NMR, and mass spectra. It was found that in the synthesis of 1,2,3-triazoles, the reaction yield increases with an increase in the homologous series of acids.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.

Author contributions: All authors contributed equally to this work.

Ethical approval: All ethical guidelines have been adhered.

Sample availability: Samples of the compounds are available from the author.

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