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Synthesis and Properties of Products of Nucleophilic Substitution of the Nitro Group in 1-Methyl-5-Nitro-3R-1,2,4-Triazoles with O-Nucleophiles

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Abstract

Modern medical science widely uses the following drugs that include 1,2,4-triazole structure: fluconazole, ribavirin, trazodone and, etc. In terms of fundamental research, the interest to 1,2,4-triazole derivatives is driven by great opportunities of structural design, which in turn opens up prospects to develop new generation functional materials with predetermined properties. Nucleophilic substitution may become one of the methods of functionalization of 1,2,4-triazole ring at a carbon atom. 1-Methyl-5-nitro-3R-1,2,4-triazoles enter into a substitution reaction of the nitro group (S_N^{ipso}) with mono- and dibasic alcohols (tyrosol, phenylethanol, resorcin, hydroquinone) producing conjugates in 63.0–83.0 % yields, as demonstrated. Interaction process monitoring of initial substrates with O-nucleophiles and analysis of the resulting reaction products are carried out using 1H NMR spectroscopy. The rate and direction of nucleophilic substitution reaction depend on both the structure of the initial substrate and the nature of the O-nucleophile, as established. The process is accompanied by competitive reactions of the substrate with hydroxide ion and triazolone formed in this reaction. Consequently, the same N–C triazolyltriazolone structure, *i.e.* 2,2′-dimethyl-2H,2′H-[3,4′]bis([1,2,4]triazolyl)-3′-one is recorded in reaction products, regardless of the alcohol used. Products of nucleophilic substitution of the nitro group in 1-methyl-5-nitro-3R-1,2,4-triazoles by mono- and dibasic alcohols show activity (antiischemic, antihypertensive, and antiarrhythmic) that is currently of high interest in Russia and abroad for treatment and prevention of cardiovascular diseases, as demonstrated using PASS Online computer program. By using the method of holes, it is experimentally found that 1,3-dimethyl-5-(2-phenylethoxy)-1H-1,2,4-triazole displays antimicrobial activity against phytopathogenic fungi of the *Fusarium oxysporum* species.

Keywords: 1-methyl-5-nitro-3R-1,2,4-triazoles, conjugates, aromatic alcohols, nucleophilic substitution, bifunctional O-nucleophile, biological activity

INTRODUCTION

The search for new highly efficient biologically active compounds is one of the main tasks of pharmaceutical chemistry. Derivatives of 1,2,4-triazole have an important place among synthetic drugs.

A number of pharmacophore fragments, the introduction of which into a drug molecule imparts the required bioactivity to it, *e.g.* synthons for 1,2,4-triazole derivatives and aromatic alcohols.

Modern medical science widely uses the following drugs that contain 1,2,4-triazole structure: fluconazole, ribavirin, trazodone, etc. Handbook [1] describes over 10 derivatives of 1,2,4-triazole that show antifungal, antibacterial, antiviral, hypotensive, analeptic, anti-depressant and other types of activity. Based on analysis of extensive material on chemistry and biological action of 1,2,4-triazole derivatives, they may be regarded as one of the promising classes of biologically active compounds with a wide range of action.

The introduction of the phenol group may impart antiseptic properties to a substance, and also improves water solubility of an organic molecule of a drug, changes its basicity or acidity and, consequently, enhances its effect [2].

Synthesis of new compounds combining two pharmacophore fragments may allow coming close to addressing the issue related to the development of new drugs with a wide range of action.

From the standpoint of fundamental research, the interest to 1,2,4-triazol derivatives is driven by broad opportunities of structural design, which in turn opens up good opportunities to develop a new generation of functional materials with predetermined properties. In this regard, research in the area of the development of synthesis methods for new promising materials based on 1,2,4-triazole that have a set of unique features, the study of characteristics of their behaviour in various chemical processes is of interest from both theoretical and practical viewpoints.

Nucleophilic substitution may be one of the methods for functionalization of 1,2,4-triazole ring. Nucleophilic substitution reactions have been relatively thoroughly investigated for a series of aromatic compounds [3] and to a lesser extent − for heteroaromatic [4−9]. Substitution reactions of the nitro group (S_N^{ipso}) in a series of N-substituted 3-nitro-1,2,4-triazoles have been scarcely explored and are limited by papers of the Institute for Problems of Chemical and Energetic Technologies of Siberian Branch of Russian Academy of Science (IPCET SB RAS, Biysk, Russia) [10−14] and other authors [15, 16]. Examples of using polyatomic phenols as O-nucleophiles in substitution reactions of the nitro group of 5-nitro-3R-1,2,4-triazoles have not been found in the literature.

The work goal is the development of conjugates for two structural blocks (derivatives of 1,2,4-triazole and aromatic alcohols) containing functional groups that specify the required biological activity to the resulting compound.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered in DMSO-d6 using Bruker Avance 200 AM 400 MHz FT NMR spectrometer with an operating frequency of 400.13 and 100.61 MHz for ^{1}H and ^{13}C nuclei, respectively.

1-Methyl-5-nitro-3R-1,2,4-triazoles (1, 2). They were obtained by alkylation of appropriate 5-nitro-3R-1,2,4-triazole with DMSO in alkaline medium followed by isolation of N_2-isomer from product mixture by the known technique [17].

A general method for preparation of conjugates (7−12). A 0.01 M solution of 1-methyl 1-methyl-5-nitro-3R-1,2,4-triazole (**1** or **2**) and 0.005 M of appropriate alcohol (**3–6**) in 6 mL of *tert*-butanol are heated with intense stirring. A 0.01 M solution NaOH add in portions to the boiling solution. Upon completion of aging, the reaction mass is cooled to room temperature; the precipitate is filtered off. The organic solution is evaporated to dryness under reduced pressure. The residue is treated with CH_2Cl_2 and the precipitate is filtered off. Product solution in methylene chloride is rinsed with an aqueous solution ºof sodium carbonate and water until the neutral reaction of rinsing water, dried over anhydrous $MgSO_4$ and the solvent is distilled off at reduced pressure.

1-Methyl-5-(4-{2-[(1-methyl-1H-1,2,4-triazole-5-yl)oxy]ethyl}phenoxy)-1H-1,2,4-triazole (7). Yield 83.6 %. T_m = 85−86 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.56−7.67 (dd, 8H, J = 8.78, $(CH_2)_4$); 7.35 (s, 1H, C5−H); 7,27 (s, 1H, C_5−H′); 4.54 (t, 2H, J = 6.65, −O−CH_2−); 3.72 (s, 3H, N−CH_3); 3.50 (s, 3H, N′−CH3); 3.08 (t, 2H, J = 6.65, −O−CH_2−CH_2−). NMR ^{13}C (100 MHz, DMSO-d_6), δ, ppm: 153.00 (−C−O−CH_2−); 135.23 (C_5−H); 130.72 (−C−CH_2−); 119.61 ($(CH_2)_2$); 71.78 ($(CH_2)_2$); 34.26 (−C−O−CH_2−); 33.75 (−C−CH_2−); 33.01 (N−CH_3).

5-(4-{2-[(1,3-Dimethyl-1H-1,2,4-triazole-5-yl)oxy]ethyl}phenoxy)-1,3-dimethyl-1H-1,2,4-triazole (8). Yield 82.3 %. T_m = 134−135 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.24−7.33 (dd, 8H, J = 8.71, $(CH_2)_4$); 4.50 (t, 2H, J = 6.66, −O−CH_2−); 3.05 (t, 2H, J = 6.66, −O−CH_2−CH_2−); 3.63 (s, 3H, N−CH_3); 3.41 (s, 3H, N′−CH_3); 2.09 (s, 6H, C−CH_3). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 158.63 (CH_3−C′−); 157.03 (CH_3−C−); 156.29 (−CH_2−); 155.79 (−C−O−CH_2−); 153.00 ($(CH_2)_2$); 135.26 (−C−CH_2−); 130.69 ($(CH_2)_2$); 119.74 ($(CH_2)_2$); 71.66 (−C−O−CH_2−); 34.31 (−CH_2−C−); 33.38 (N−CH_3); 32.66 (CH_3−C′−); 14.68 (CH_3−C−).

1-Methyl-5-(2-phenylethoxy)-1H-1,2,4-triazole (9). Yield of 72.7 %. ^{1}H NMR (400 MHz,

DMSO-d_6), δ, ppm: 7.57 (s, 1H, C_5–H); 7.30 (m, 10H, J = 8.63, $(CH_2)_5$); 4.54 (t, 2H, J = 6.83, –O–CH_2–); 3.48 (s, 3H, N–CH_3); 3.06 (t, 2H, J = 6.83, –O–CH_2–CH_2–). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 158.75 (–C–O–CH_2–); 147.81 (C_5–H); 138.04 (–CH_2–); 129.37 ($(CH_2)_2$); 128.84 ($(CH_2)_2$); 126.91 (–CH_2–); 71.82 (–C–O–CH_2–); 35.02 (–C–O–CH_2–CH_2–); 32.94 (N–CH_3).

1,3-Dimethyl-5-(2-phenylethoxy)-1H-1,2,4-triazole (10). Yield of 68.6 %. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.29 (m, 10H, J = 6.58, $(CH_2)_5$); 4.50 (t, 2H, J = 6.75, –O–CH_2–); 3.40 (s, 3H, N–CH_3); 3.04 (t, 2H, J = 6.75, –O–CH_2–CH_2–); 2.11 (s, 3H, C–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 158.63 (C–CH_3); 155.83 (–C–O–CH_2–); 138.09 (–C–CH_2–); 129.33 ($(CH_2)_2$); 128.81 ($(CH_2)_2$); 126.87 (CH_2); 71.71 (–C–O–CH_2–); 35.04 (–C–CH_2–); 32.53 (N–CH_3); 14.57 (C–CH_3).

5,5'-[Benzene-1,3-diylbis(oxy)]bis(1-methyl-1H-1,2,4-triazole) (11). Yield of 63.5 %. T_m = 119–120 °C. ^{1}H NMR (400 МГц, DMSO-d_6), δ, ppm: 7.69 (s, 2H, C_5–H); 7.26–7.51 (m, 8H, J = 8.53, $(CH_2)_4$); 3.73 (s, 6H, N–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 154.83 (–C–O–CH_2–); 150.70 (–C–O–CH_2–); 148.27 (C_5–H); 131.18 (–CH_2–); 116.45 ($(CH_2)_2$); 110.99 (–CH_2–); 33.86 (N–CH_3).

5,5'-[benzene-1,4-diylbis(oxy)]bis(1-methyl-1H-1,2,4-triazole) (12). Yield of 63.7 %. T_m = 183–184 °C. 1H NMR (400 МГц, ДМСО-d_6), δ, ppm: 7.68 (s, 2H, C_5–H); 7.42 (s, 8H, $(CH_2)_4$); 3.75 (s, 6H, N–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 157.22 (–C–O–CH_2–); 151.18 (–C–O–CH_2–); 148.14 (C_5–H); 121.20 ($(CH_2)_4$); 33.76 (N–CH_3).

Antimicrobial activity of the resulting compounds **7**–**12** was determined using the method of holes. For this purpose, fungal test objects were grown in potato-glucose broth at 24 °C for 48 h; bacterial test objects – in Hottinger broth at 28 °C for 24 h. Disks with a diameter of 10 mm were cut from inoculated test objects using agar plates. Two symmetrically located holes were received for each Petri dish; the substances under study by 0.1 cm^3 were introduced therein. After liquid introduction into holes, the dishes were carefully set in the fridge at 10 єC and after 5 h, transferred in a thermostat with temperature (24±2) °C for fungal test objects and (28±2) °C for bacterial. The diameter for zones of suppression of growth inhibition for test-cultures of the fungus formed around holes was measured after 48 h.

Bacteria (*Escherichia coli, Pseudomonas brassicacearum*, and *Bacillus amyloliquefaciens*) and phytopathogenic fungi (*Fusarium oxysporum* and *Botrytis cinerea*) were used as test objects to determine antimicrobial activity of the compounds under study.

RESULTS AND DISCUSSION

In order to make conjugates, the method of S_N^{ipso}-substitution of the nitro group in 1-methyl-5-nitro-3R-1,2,4-triaxoles **1**, **2** was used in this work. The following alcohols were utilised as nucleophilic reagents: tyrosol **3**, phenylethanol **4**, resorcin **5**, and hydroquinone **6**.

Nucleophilic substitution of the nitro group in nitrotriazoles **1**, **2** with tyrosol **3** containing two hydroxyl groups with different reactivities proceeds stepwise and in the beginning, leads to the consecutive formation of incomplete substitution product, and then the target one (**7** and **8**, respectively) [12]. Monosubstitution products were not detected in the present work when using alcohols **4**–**6** under similar conditions due to a high reaction rate (Fig. 1). The data on reaction times and product yields are given in Table 1.

Increased reaction time for the use of alcohol **3** is likely to be related to its functionality and the presence of the linker which binds the ring to the hydroxyl group in the structure.

A competing reaction yielding reactive triazolone [7, 11] proceeds upon nucleophilic substitution reactions of the nitro group of 3-nitro-1,2,4-triazole derivatives in addition to the desired (target) substitution reaction of the nitro group in 1-methyl-5-nitro-3R-1,2,4-triazoles with O-nucleophiles due to dosing alkaline agents. The resulting highly reactive species for the reaction of heterylation, 1-methyl-1,2,4-triazol-5-one (see Fig. 1) reacts with the initial substrate 1 to form the same 2,2′-dimethyl-2H,2′ H-[3,4′]bis(1,2,4-triazolyl)-3′-one (13) regardless of the alcohol used [18, 19]. The yield of competing product **13** is increased from 0.5 to 10.0 % (see Table 1) because of longer reaction time for alcohol **3** compared

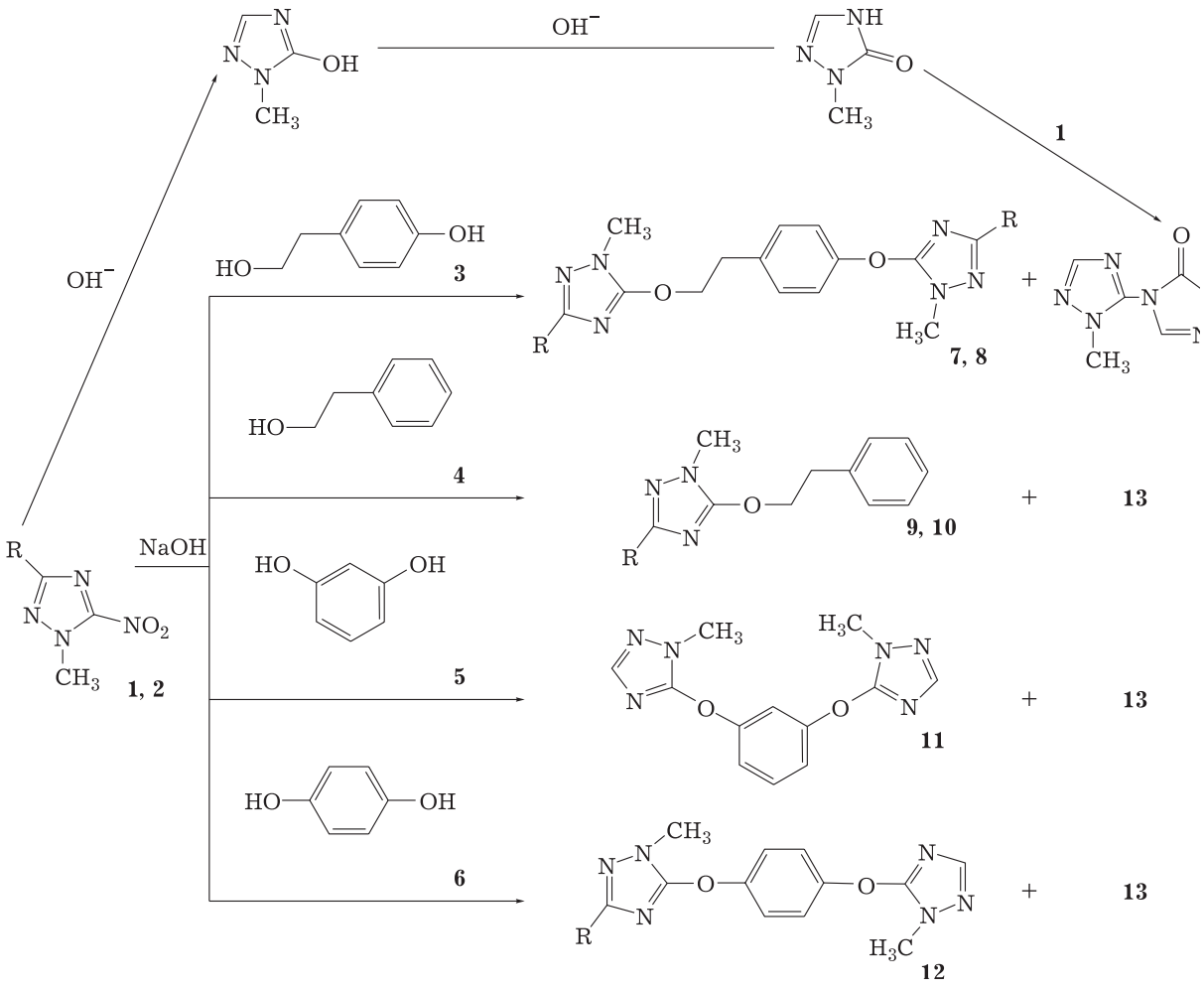

Fig. 1. Reaction scheme for nucleophilic substitution of the nitro group in 1-methyl-5-nitro-3R-1,2,4-triazoles **1**, **2** with aromatic alcohols.

to other alcohols 4–6. Product **13** content in the reaction mass was determined by ^{1}H NMR spectroscopy.

The monitoring of the interaction process for 1-methyl-3R-5-nitro-1,2,4-triazoles with mono- and diatomic alcohols was carried out using ^{1}H NMR-spectroscopy until the complete consumption of nitrotriazoles **1** and **2** in the

TABLE 1

Time and product yield in nucleophilic substitution reactions of the nitro group in 1-methyl-5-nitro-3R-1,2,4-triazoles **1**, **2** with appropriate alcohols

Substrates	Alcohols	Time, h	Yield, %	Bicycle **13** fraction, %
1	**3**	95.0	83.6	10.0
2	**3**	98.0	82.3	–
1	**4**	11.5	72.7	3.8
2	**4**	15.5	68.6	–
1	**5**	6.0	63.5	0.9
1	**6**	6.5	63.7	0.5

reaction mass. The resulting compounds **7–13** were analysed by ^{1}H NMR.

The prediction of the biology activities for the resulting conjugates **7–12** was carried out using PASS Software (Prediction of Activity Spectra for Substances). The latter enables to assess probable characteristics of an organic compound according to its structural form. The assessment is premised on the analysis of structure–activity interrelationships for extensive research sampling. The latter includes drugs, preparation candidates that are found at various steps of clinical and preclinical research, pharmacological matter and biochemical reagents, and also compounds, for which there is information regarding specific toxicity [20].

The prediction is carried out by comparing the structure of the chemical compound predicted with the database available in the package of the programme itself. The combined use of the Logical Framework Approach towards generating structure using PASS software ensures the higher accuracy and reliability of preliminary data [21]. The use of PASS software is extremely important on the initial step of the molecular design of bioactive compounds that enables to assess the advisability of the synthesis of target compounds from the standpoint of their probable pharmacological activity [22].

Prediction results for various bioactivities are presented as an ordered list of names of activity with assessments of probabilities. Table 2 reports predicted data on the activity of compounds **7–12**.

As it is known, they display activity (anti-ischemic, antihypertensive, and antiarrhythmic), which is currently increasingly interesting for

TABLE 2

Biological activity of conjugates **7–12** according to PASS Online program

Activity level	Property
1-Methyl-5-(4-{2-[(1-methyl-1H-1,2,4-triazole-5-yl)oxy]ethyl}phenoxy)-1H-1,2,4-triazole **7**	
0.540	Deceleration of cholesterol formation
0.485	Platelet aggregation stimulator
0.412	Anti-ischemic drug
5-(4-{2-[(1,3-dimethyl-1H-1,2,4-triazole-5-yl)oxy]ethyl}phenoxy)-1,3-dimethyl-1H-1,2,4-triazole **8**	
0.516	Antihypertensive drug
0.485	Platelet aggregation stimulator
0.496	Deceleration of cholesterol formation
1-methyl-5-(2-phenylethoxy)-1H-1,2,4-triazole **9**	
0.595	Deceleration of cholesterol formation
0.534	Platelet aggregation stimulator
0.521	Phospholipid translocation ATPase Inhibitor
1,3-dimethyl-5-(2-phenylethoxy)-1H-1,2,4-triazole **10**	
0.597	Antihypertensive drug
0.535	Platelet aggregation stimulator
0.552	Deceleration of cholesterol formation
5,5'-[benzene-1,3-diylbis(oxy)]bis(1-methyl-1H-1,2,4-triazole) **11**	
0.623	Renal function stimulator
0.661	Deceleration of cholesterol formation
0.581	Chymosin inhibitor
5,5'-[benzene-1,4-diylbis(oxy)]bis(1-methyl-1H-1,2,4-triazole) **12**	
0.580	Antimitotic drug
0.598	Phospholipid translocation ATPase inhibitor
0.510	Antiarrhythmic agent

the treatment and prevention of cardiovascular diseases [23].

As can be seen from the data in Table 2, 5,5′-[benzene-1,3-diylbis(oxy)bis(1-methyl-1H-1,2,4-triazol) **11** that is the conjugate of 1-methyl-5-nitro-1,2,4-triazol and resorcinol possesses the highest activity. According to the software, this compound has activity, *i.e.* slowing down cholesterol formation, with probability of 0.661.

PASS software does not determine whether a specific compound would become a drug, as that depends on a number of factors. However, biological activity types, on which the analysed compound should be primarily tested, may be determined using the acquired prediction. Revealing compounds that possess the activity of the required types is also likely.

The resulting compounds **7–12** have been tested as bioactive compounds. It has been found that 1,3-dimethyl-5-(2-phenylethoxy)-1H-1,2,4-triazol **10** shows minor activity against phytopathogenic fungi Fusarium oxysporum.

CONCLUSION

The present research presents a method of synthesis of conjugates consisting in nucleophilic substitution of the nitro group of 1-methyl-5-nitro-3R-1,2,4-triazoles with mono- and diatomic alcohols in the tert-butanol medium. The technique enables to obtain various bioactive compounds.

As ascertained, the nucleophilic substitution reaction rate and direction depend on both the composition of the initial substrate and the nature of the O-nucleophile. The process is accompanied by competing reactions of the substrate with the hydroxide anion and triazoline formed in this reaction. As a consequence, the same N-C-triazol-triazoline compound that is 2,2-dimethyl-2H,2H′-[3,4′](bis[1,2,4]triazolyl)-3′-one has been detected in the reaction products regardless of the alcohol used.

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