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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-(4-HYDROXYPHENYL)-3-(4-R-SULFONYLAMIDOPHENYL)-5-ETHYL-1,2,4-TRIAZOLES

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A handy method for the synthesis of 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole by the reduction of respective nitro compound is developed. The reactions of the R-sulfonylation of aminotriazole at the amino group by the methane sulfochloride and arylsulfochlorides are investigated. The 1-(4-hydroxyphenyl)-3-(4-R-sulfonylamidophenyl)-5-ethyl-1,2,4-triazoles have been synthesized, these compounds being not described previously. The structures of new synthesized compounds are proved by means of ^{1}H NMR spectroscopy. The spectra of a potential biological activity of the synthesized 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazoles and their derivatives are obtained by using the software «Prediction of Activity Spectra for Substances».

Keywords: 1,2,4-triazole, amino group, methane sulfochlorides, arylsulfochlorides.

Introduction

It is known that substituted 1,2,4-triazoles exhibited a broad spectrum of biological activity, in particular fungicidal, antibacterial and antiviral activity [1–3]. There are many methods of the synthesis of 1,2,4-triazoles, for example, the well-known Einhorn-Brunner [4] reaction and the Pellizzari reaction [5]. A convenient method to prepare these compounds is also the reaction of hydrazonoyl chloride condensation with nitriles in the presence of Lewis acids, ytterbium triflate being the most effective of these agents [6]. It has been also reported that 1,2,4-triazoles were formed when oxidative cyclization of triazenes took place [7]. However, multistage nature of the process, complexity of precursors and necessity of application of expensive catalysts limit the possibilities of such scheme of synthesis. Therefore, the search of new methods of synthesis of such class of compounds and research of their chemical features are important and promising task.

Results and discussion

We have previously developed a convenient method of the synthesis of 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (I) by reaction of 4-nitrophenilalazines 1,4-benzoquinone with n-propylamine [8]. The proposed method of synthesis has the advantage of the previously described methods since it requires no strict terms for reaction and there is no need for rare and costly reagents. Reactions of compound (I) with electrophilic agents have been examined and new derivatives with substituents in hydroxyphenyl moietys have been obtained [9].

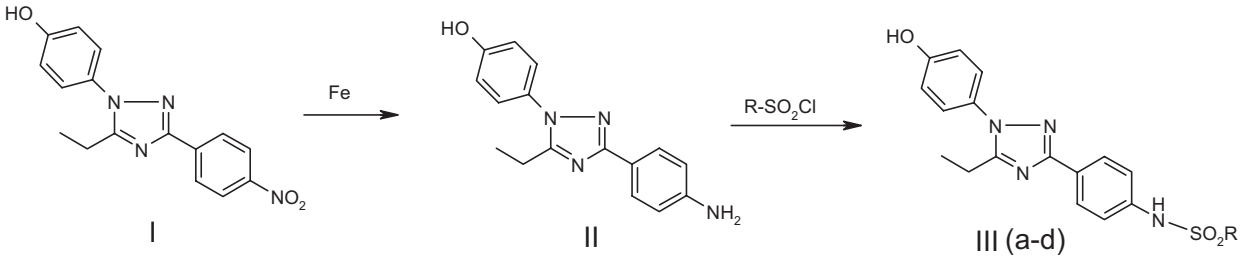
Using the Prediction of Activity Spectra for Substances program the spectra of potential biologic activity of initial triazole (II) and its derivatives have been obtained. It's probable (index Pa=0.63–0.60) that the triazole (II) and its derivatives (III b-d) are inhibitors of CYP_2C_8. The compound (III a) is aldehyde oxidase inhibitor (Pa=0.77) [9].

The purpose of this research is the development of convenient method of the synthesis 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole (II) and obtainment of derivatives at the amino group that are potential biologically active compounds.

For the nitro group reduction to amino group in triazole (I) the following reduction agents have been tested: zinc dust in acetic acid, hydrazine hydrate with Raney nickel and iron shavings with hydrochloric acid. It should be noted that the best reducing agent of nitro group in triazole (I) is iron shavings. Zinc dust does not make reduction at all cases. Hydrazine hydrate with activated Raney nickel reduces the triazole (I) nitro group, but the reduction occurs relatively slowly. The structure of synthesized 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole (II) is proved using ^{1}H NMR-spectroscopy.

We have researched the reactions of R-sulfonylation of aminotriazole at the amino group of compound (II) by the methane sulfochloride and arylsulfochlorides.

The structures of the synthesized compounds



Scheme

III: a) R=CH_3; b) R=4-$CH_3C_6H_4$; c) R=4-$NO_2C_6H_4$; d) R=C_6H_5.

have been confirmed by the data of ^{1}H NMR spectroscopy. The spectra revealed almost constant characteristic signals of pseudo-AB-systems of the two 1,4-substituted benzene ring which bonded with triazole ring in 6.62−7.95 triplet and quartet of ethyl group in the 1.21−2.70, as well as signals of substituents at nitrogen. The characteristics of ^{1}H NMR spectra are specified in Table 1.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 2000 spectradiometer (400 MHz) in DMSO-d_6. Kieselgel 60 F254 (Merck) and Sorbfil PTLC-AF-A-UV plates (Russia) have been used for the thin layer chromatography.

Synthesis of 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole (II):

a round bottom flask is put on a bath and charged with 10 mmol of iron shavings and 20 ml of water and 4 ml of 32% hydrochloric acid and stirred in a mixer. Then, 1 mmol of triazole (I) is dissolved in 100 ml of propanol-2 and added dropwise to the reaction mixture. The mixture is stirred during 12 hours under pH 7 control. The reaction mixture is filtered from salts of Fe, the solvent (propanol-2) was evaporated, and the residue was dried yielding compound (II). The yields, and the physical and analytical data of the synthesized compounds are given in Table 2.

Synthesis of 1-(4-hydroxyphenyl)-3-(4-R-sulfonilamidofenil)-5-ethyl-1,2,4-triazole (III a-d):

in a flask, 1 mmol of triazole (II) is suspended in 25 ml of pyridine and then 1 mmol of the appropriate RSO_2Cl is added, the reaction mixture is stirred for 1 hour and then is kept at room temperature during 1 day. Then the reaction mixture is poured onto mixture of 100 g of ice with 10 ml of 32%

Table 1

^{1}H NMR spectra of compounds (II, III a-d)

Compound	1H NMR spectrum (Varian Gemini 2000 spectrometer, 400 MHz), δ, ppm. (J, Hz)
II	1.21 (3H, t, J=7.6, CH_2Me); 2.70 (2H, q, J=7.6, CH_2); 5.34 (2H, s, NH_2);6.62 (2H, d, J=8.8, Ar); 6.92 (2H, d, J=8.8, Ar); 7.35 (2H, d, J=8.7, $C_6H_4NH_2$); 7.70 (2H, d, J=8.7, $C_6H_4NH_2$); 9.91 (1H, s, OH).
III a	1.24 (3H, t, J=7.6, CH_2Me); 2.78 (2H, q, J=7.6, CH_2); 3.35 (3H, s, Me); 3.90 (1H, s, NH); 6.93 (2H, d, J=8.5, Ar); 7.25-7.40 (4H, dd, J=8.6, $C_6H_4NH_2$); 7.95 (2H, d, J=8.5, Ar), 10.00 (2H, s, NH, OH).
III b	1.24 (3H, t, J=7.6, CH_2Me); 2.34 (1H, s, Me); 2.70 (2H, q, J=7.6, CH_2); 7.05 (2H, d, J=8.3, Ar); 7.20 (2H, d, J=8.0, C_6H_4NH); 7.35 (4H, s, C_6H_4Me); 7.70 (2H, d, J=8.0, C_6H_4NH); 7.85 (4H, d, J=8.3, Ar); 10.00 (1H, s, OH); 10.50 (1H, s, NH).DC
III c	1.21 (3H, t, J=7.6, CH_2Me); 2.70 (2H, q, J=7.6, CH_2); 6.90 (2H, d, J=8.3, Ar); 7.20 (4H, d J=8.3, Ar); 7.35 (2H, d, J=8.8, C_6H_4NH); 8.05 (2H, d, J=8.8, C_6H_4NH); 7.90 (2H, d, J=8.6, $C_6H_4NO_2$); 8.60 (2H, d, J=8.6, $C_6H_4NO_2$); 10.00 (2H, s, NH, OH).
III d	1.21 (3H, t, J=7.6, CH_2Me); 2.70 (2H, q, J=7.6, CH_2); 7.90 (2H, d, J=8.3, Ar); 7.20 (4H, d, J=8.3, Ar); 7.35 (2H, d, J=7.6, C_6H_4NH); 7.55 (2H, d, J=8.8, C_6H_4NH); 7.76-7.90 (5H, m, Ph); 10.00 (1H, s, OH); 10.50 (1H, s, NH).

Table 2

The yields, physical and analytical data of the synthesized compounds (II, III a-d)

Compound	Yield, %	Appearance	The melting point, ^{0}C	Elemental analysis						
				Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
II	80	light yellow crystals	111–114	68.55	5.75	19.99	$C_{16}H_{16}N_4O$	68.48	5.72	19.95
III a	50	beige crystals	97–100	70.11	6.54	18.17	$C_{17}H_{18}N_4O_3S$	70.05	6.50	18.19
III b	60	yellow crystals	84–87	74.97	6.29	14.57	$C_{23}H_{22}N_4O_3S$	74.89	6.22	14.60
III c	45	brown crystals	92–95	66.49	5.09	16.86	$C_{22}H_{19}N_5O_5S$	66.39	5.11	16.91
III d	65	light-brown crystals	83–86	74.57	5.99	15.12	$C_{22}H_{20}N_4O_3S$	74.53	5.95	15.17

hydrochloric acid. Crystallization of the product occurs during cooling. The precipitate is filtered off and dried. The yields, physical and analytical data of the synthesized compounds are shown in Table 2.

Conclusions

The method for synthesis of 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole (II) by reduction of nitro group in amino group in 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (I) has been developed. It is showed that amino group in 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole (II) demonstrates its features in the reaction of R-sulfonylation of aminotriazole by the methane sulfochloride and arylsulfochlorides. The synthesized 1-(4-hydroxyphenyl)-3-(4-aminophenyl)-5-ethyl-1,2,4-triazole (II) and its derivatives are potential biologically active compounds. The research of properties of this class compounds should be continued.

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