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Synthesis and Ring-Chain Tautomerism of 1-(4-Ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic Acid: The First Representative of a 5-Formyl-1*H*-1,2,3-triazole-4-carboxylic Acids Series

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Abstract: Synthesis of the first representative of a 5-formyl-1*H*-1,2,3-triazole-4-carboxylic acids series – 1-(4-ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid was performed. The 1-azido-4-ethoxybenzene was chosen as a starting reagent in a two-step synthesis, which reacted with the ethyl 4,4-diethoxy-3-oxobutanoate under base catalysis to form ethyl 5-(diethoxymethyl)-1-(4-ethoxyphenyl)-1H-1,2,3-triazole-4-carboxylate with protected formyl and acid groups. By the subsequent saponification of the ester group and removing of acetal protection, the target 1-(4-ethoxyphenyl)-5-formyl-1H-1,2,3-triazole-4-carboxylic acid was obtained. It has been found that the free acid form predominated in the solution under its cyclic 6-hydroxy-1,6-dihydro-4*H*-furo[3,4-*d*][1,2,3]triazol-4-one tautomer. According to ^{1}H NMR, cyclic hemiacetal is about 20%.

Keywords: 5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid; furo[3,4-*d*][1,2,3]triazole; aryl azides; 1,2,3-triazoles; ortho-formyl (het)aromatic carboxylic acid; ring-chain tautomerism

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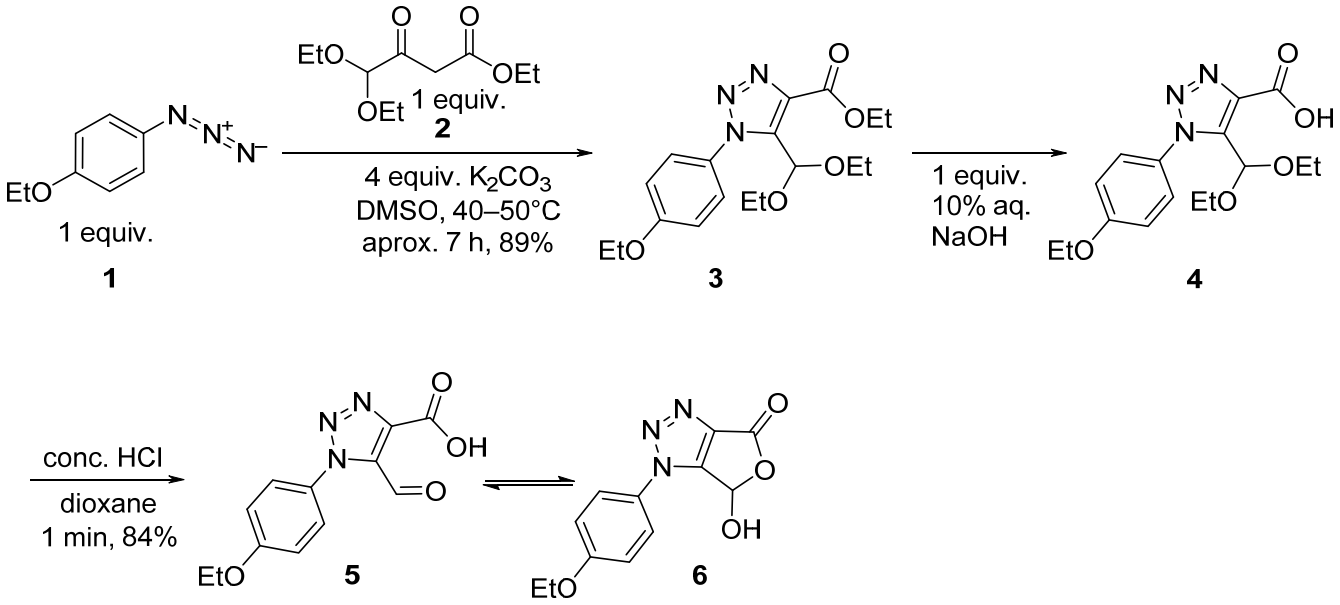
1. Introduction

Recently, we have developed a convenient synthetic route to ethyl 1-(het)aryl-5-formyl-1H-1,2,3-triazole-4-carboxylates [1–3]. Moreover, in our latest article in this journal [3], structural features of 5-formyl-1-(pyridin-3-yl)-1H-1,2,3-triazole-4-carboxylate as a representative of such series were set out, and a synthetic application of ortho-formyl (hetero)aromatic carboxylic acids in the synthesis of numerous classes of important molecules was emphasized (see ref. [3] and works cited therein). The wide synthetic application of ortho-formyl (hetero)aromatic carboxylic acids is still growing as confirmed by the newly published article [4]. Moreover, ortho-formyl aromatic carboxylic acids play a significant role in analytical chemistry, for preparing rhodamine-related dyes and as a metal-binding moiety [5]. In this regard, the synthesis of new ortho-formyl heteroaromatic carboxylic acids is an actual challenge. This paper describes the preparation, characterisation, and ring-chain tautomerism of the new ortho-formyl heteroaromatic carboxylic acid, the first derivative in the 1*H*-1,2,3-triazole series.

2. Results and Discussion

In the current work, we focus on the synthesis of the first representative of a 5-formyl-1*H*-1,2,3-triazole-4-carboxylic acids series–1-(4-ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid (Scheme 1). At the first step of the synthesis, a convenient and variable reaction of the triazole formation *via* the base catalysis reaction of azide with β-ketoesters [1] was used. By the reaction of 4-ethoxyphenyl azide **1** and ethyl 4,4-diethoxy-3-oxobutanoate **2** under K_2CO_3 catalysis in DMSO, the ethyl 5-(diethoxymethyl)-1-(4-ethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylate **3** was formed and after saponification

in situ 5-(diethoxymethyl)-1-(4-ethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid **4** was prepared. Deprotection of acetal with HCl led to target 1-(4-ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid **4** and its ring-chain tautomer 1-(4-ethoxyphenyl)-6-hydroxy-1,6-dihydro-4*H*-furo[3,4-*d*][1,2,3]triazol-4-one according to the NMR data. It is noteworthy that such ring-chain tautomerism is well known for 2-formylbenzoic acids series [6] and cyclic hemiacetal 3-hydroxyisobenzofuran-1(3*H*)-one form predominated [7–11]. In the case of ortho-formyl heteroaromatic carboxylic acids, such a ring-chain tautomerism is least studied. As an example, the rare transformation of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles with hydrohalic acids involves the formation of 4-halo-3-hydroxyfuro[3,4-*c*]pyridin-1(3*H*)-ones capable of the ring-chain tautomerism, but the formation of the open form was not observed. [12]. According to the NMR data, cyclic hemiacetal structure of 4-halo-3-hydroxyfuro[3,4-*c*]pyridin-1(3*H*)-ones predominates in the solution [13]. On the contrary, in the case of 1-(4-ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid, open aldehyde form predominated (see Figure 1). The characteristic high-intensity signals of the aldehyde group and the acid exchange signal are clearly observed in the spectra. Instead, signal of CH has a much lower intensity and was found in a stronger field at 9.26 ppm. The position of the signals is well correlated with the previously described similar tautomers of 2-formylbenzoic acids [14]. In the ^{13}C NMR spectrum, the intense signal of the aldehyde group at 180.7 ppm is clearly visible. In addition to intense signals of the main tautomer in the spectrum, there are weak signals of the 6-hydroxy-1,6-dihydro-4*H*-furo[3,4-*d*][1,2,3]triazol-4-one tautomer (see the figure in the Supplementary Materials).



Scheme 1. Synthesis of 1-(4-ethoxyphenyl)-5-formyl-1H-1,2,3-triazole-4-carboxylic acid **5**.

Also, evidence of the dominance of the open form is indirectly indicated by the fact that when the compound is heated to 175 °C, its decomposition process is very similar to decarboxylation, which is characteristic of 1,2,3-triazole-4-carboxylic acids [15].

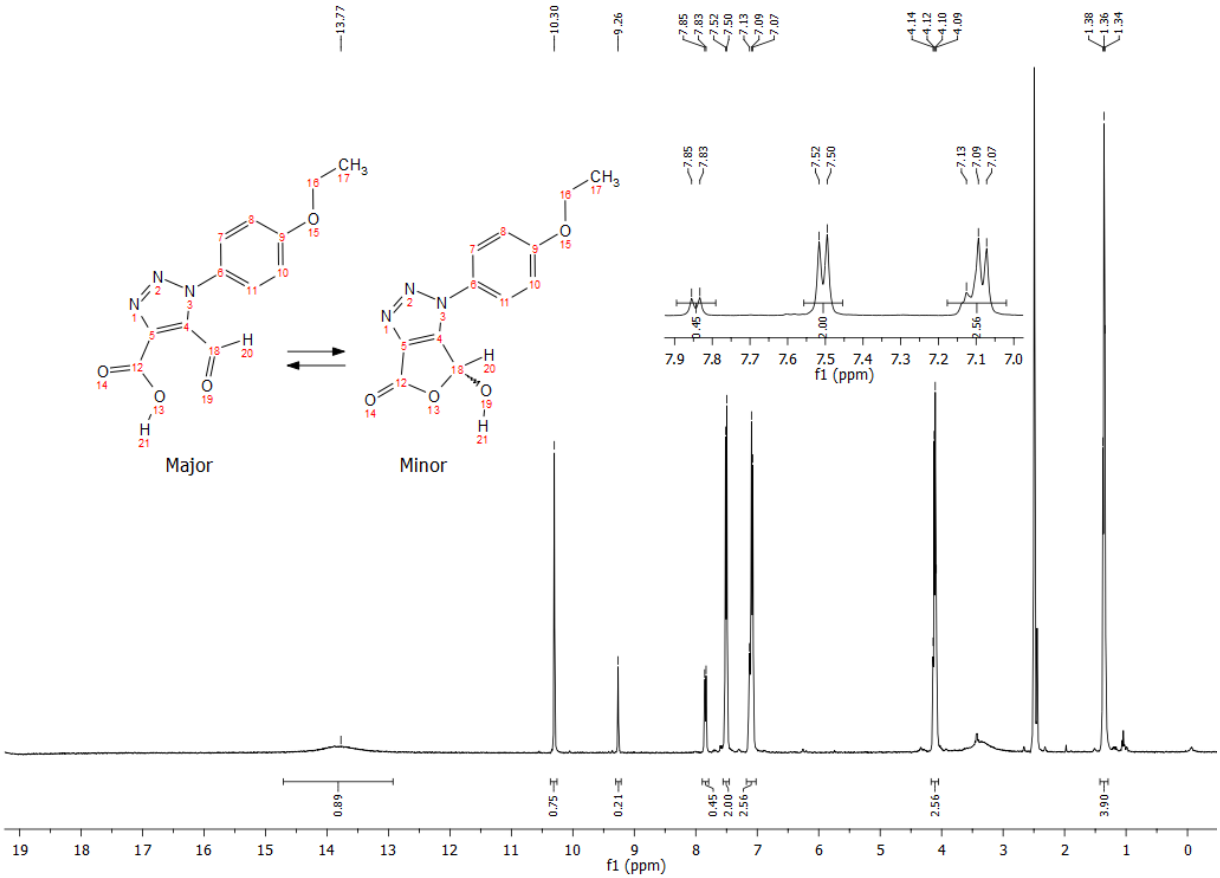


Figure 1. ^{1}H NMR spectrum of 1-(4-ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid **5** and its tautomer 1-(4-ethoxyphenyl)-6-hydroxy-1,6-dihydro-4*H*-furo[3,4-*d*][1,2,3]triazol-4-one.

3. Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 (500 and 126 MHz, respectively) spectrometers in DMSO-d_6 solutions using the solvent line as internal reference. Mass spectral analyses were performed using an Agilent 1100 series LC/MSD with API-ES/APCI mode (200 eV) instrument. Elemental analyses were accomplished using a Carlo Erba 1106 instrument. Melting points were determined on a Boetius melting point apparatus. The progress of reactions and the purity of the synthesized compounds were examined by TLC on Silufol UV-254 plates, and visualization was performed using UV lamp (254 nm). The 4,4-diethoxy-3-oxobutanoate **2** [16] and 1-azido-4-ethoxybenzene **1** [17] were prepared according to literature procedures.

3.1. Synthesis of 5-(Diethoxymethyl)-1-(4-Ethoxyphenyl)-1H-1,2,3-Triazole-4-Carboxylic Acid 4

Anhydrous K_2CO_3 (5.53 g, 40 mmol) and ethyl 4,4-diethoxy-3-oxobutanoate **2** (2.18 g, 10 mmol) were added to a solution of 1-azido-4-ethoxybenzene **1** (1.2 g, 10 mmol) in DMSO (4 mL). The suspension was stirred at 40–50 °C until TLC (eluent hexane–EtOAc, *v/v* 5:1) indicated that all starting materials were consumed (approximately 7 h). The reaction mixture was cooled to 5 °C, diluted with H_2O (15 mL) then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were concentrated under reduced pressure. The oil residue was dissolved in ethanol (10 mL) and 4 mL 10% aq. NaOH was added. The solution was left at room temperature for 10 h. After the solution became neutral the solvent was removed under reduced pressure Acid sodium salt was dissolved in a minimum amount of water (approx. 20 mL). The solution was washed with TBME (10 mL) and acetic acid (0.66 mL, 11 mmol) was added. The formed solid 1*H*-1,2,3-triazole-4-carboxylic acid **4** was collected by the filtration and dried in air. Yield 79%; white solid; mp 145–147 °C; ^{1}H

NMR (500 MHz, DMSO-d_6) δ_H 13.52 (br.s, 1H, COOH), 7.51 (d, $^3J_{H,H}$ = 8.4 Hz, 2H, H_{Ar}-2,6), 7.05 (d, $^3J_{H,H}$ = 8.4 Hz, 2H, H_{Ar}-3,5), 6.22 (s, 1H, CH), 4.10 (q, *J* = 6.7 Hz, 2H, CH_2O), 3.59 (dq, $^{2,3}J_{H,H}$ = 13.6, 6.8 Hz, 2H, CH_2O), 3.40 (dq, $^{2,3}J_{H,H}$ = 13.6, 6.8 Hz, 2H, CH_2O), 1.35 (t, *J* = 6.7 Hz, 3H, CH_3), 0.98 (t, *J* = 6.8 Hz, 6H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 162.68 (O=*C*-O), 159.70 (C_{Ar}-4), 138.88 ($C_{Triazole}$-5), 137.76 ($C_{Triazole}$-4), 130.30 (C_{Ar}-1), 127.73 (2 × CH_{Ar}-2,6), 114.52 (2 × CH_{Ar}-3,5), 94.82 (CH), 63.97 (CH_2O), 63.88 (2 × CH_2O), 15.23 (2 × CH_3), 15.02 (CH_3); MS (CI, 200 eV), *m/z*: 336 (M^+ + 1). Found, %: C, 57.22; H, 6.27; N, 12.58. $C_{16}H_{21}N_3O_5$ (335.3600). Calculated, %: C, 57.30; H, 6.31; N, 12.53.

3.2. Synthesis of 1-(4-Ethoxyphenyl)-5-Formyl-1H-1,2,3-Triazole-4-Carboxylic Acid 5

Concentrated HCl (0.5 mL) was added to a solution of compound **4** 671 mg (2 mmol) in 1,4-dioxane (5 mL). The mixture was heated under reflux for 1 min and cooled to room temperature. Water (approx. 15 mL) was added until the precipitate was formed. The solid was collected by the filtration, dissolved in 1N NaOH (5 mL, 5 mmol) and acidified with 1N HCl at 0 °C. The obtained precipitate collected by the filtration and washed with an excess amount of H_2O was then dried in air. Yield 84%; light yellow solid; mp 175 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 13.77 (br.s, 1H, COOH), 10.30 (s, 1H, CHO), 7.53 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 7.08 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 4.11 (d, $^3J_{H,H}$ = 6.7 Hz, 2H), 1.36 (t, $^3J_{H,H}$ = 6.7 Hz, 3H); Signals of the corresponding ring-chain tautomer (1-(4-ethoxyphenyl)-6-hydroxy-1,6-dihydro-4*H*-furo[3,4-d][1,2,3]triazol-4-one **6**, ca. 22%): δ_H 9.26 (s, 1H), 7.84 (d, $^3J_{H,H}$ = 8.8 Hz, 2H), 7.08 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 4.11 (d, $^3J_{H,H}$ = 6.7 Hz, 2H), 1.36 (t, $^3J_{H,H}$ = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 180.70 (COH), 161.40, 159.71, 142.3, 135.01, 128.68, 127.12, 114.54, 63.63, 14.54; Signals of the corresponding ring-chain tautomer (1-(4-ethoxyphenyl)-6-hydroxy-1,6-dihydro-4*H*-furo[3,4-d][1,2,3]triazol-4-one) **6**: 161.40, 158.93, 140.45, 129.40, 126.97, 122.18, 115.30, 115.12, 63.63, 14.54; MS (CI, 200 eV): 262 (M^+ + 1), 244 (M^+-OH); Found, %: C, 55.03; H, 4.17; N, 16.25. $C_{12}H_{11}N_3O_4$ (261.2370). Calculated, %: C, 55.17; H, 4.24; N, 16.09.

4. Conclusions

The first representative of a 5-formyl-1*H*-1,2,3-triazole-4-carboxylic acids series – 1-(4-ethoxyphenyl)-5-formyl-1*H*-1,2,3-triazole-4-carboxylic acid was prepared and characterized. Further work will emphasize incorporating this compound in the synthesis of new triazole condensed heterocyclic systems.

Supplementary Materials: The following are available online, containing NMR spectra of newly synthesized compounds.

Author Contributions: N.T.P. designed the experiments, performed syntheses, obtained the NMR spectra and wrote the draft; M.D.O. analysed the data and finalized the draft. All authors have read and agreed to the published version of the manuscript.

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Sample Availability: Samples of the compounds **1**–**6** are available from the authors.

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