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SYNTHESIS AND HYDROLYTIC CLEAVAGE OF TETRAZOLO[1,5-*c*]QUINAZOLINES

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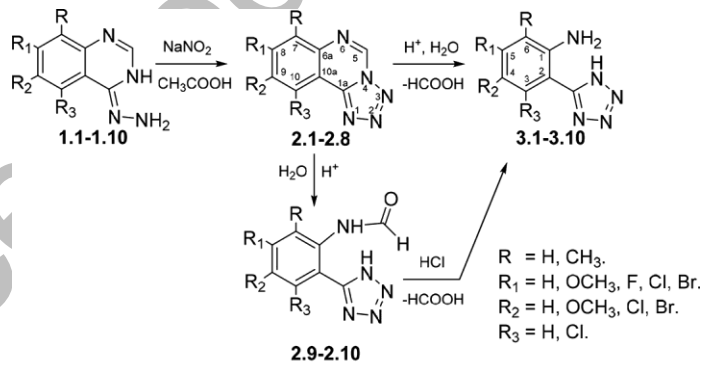
Abstract

A series of tetrazolo[1,5-*c*]quinazolines were synthesized by [4+1]-cyclocondensation of 4-hydrazinoquinazolines with sodium nitrite with good yields. Peculiarities of this reaction were discussed, namely, the influence of halogen on the reaction yield. Hydrolytic cleavage of tetrazolo[1,5-*c*]quinozoline cycle was studied, in order to obtain 2-(1*H*-tetrazolo-5-yl)anilines. The structures of the compounds were elucidated by ^{1}H, ^{13}C NMR, IR-, MS-(EI) – spectrometry, and elemental analysis data.



Tetrazolo[1,5-*c*]quinazolines synthesis.

KEYWORDS: Tetrazolo[1,5-*c*]quinazolines; 2-(1*H*-tetrazolo-5-yl)anilines; hydrolytic cleavage

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INTRODUCTION

Substituted tetrazolo[1,5-*c*]quinazolines exhibit various biological activities. In particular, their cytostatic[1,2], anticancer[3,4], hypoglycemic[5], actoprotective[6], antimicrobial and bioluminescence-inhibitory potential[4,7] was studied. In addition, patents confirm bronchodilator[8,9] and fibrinolytic activity[10]. Other condensed tetrazoloquinazolines also showed high biological activity[11-13]. However, 7, 8, 9 and 10 substituted tetrazolo[1,5-*c*]quinazolines were insufficiently studied. Therefore, it was decided to synthesize a range of tetrazolo[1,5-*c*]quinazolines (**2.1-2.8**) and to study their behavior in hydrolytic cleavage reactions of the pyrimidine ring, which lead to the formation of 2-(1*H*-tetrazol-5-yl)anilines (**3.1-3.10**). As the latter were promising 1,5-binucleophiles, they could be used for [5+1]-cyclocondensation with electrophiles.

RESULTS AND DISCUSSION

tetrazolo[1,5-*c*]quinazolines (**2.1-2.8**) were synthesized according to a known method, namely, by reaction of 4-hydrazinoquinazoline with sodium nitrite[14] (Scheme 1). It was found, that the presence of electron withdrawing substituent, such as halogen in position 8 or 10, resulted in spontaneous cleavage of pyrimidine ring of formed tetrazolo[1,5-*c*]quinazoline and formation of *N*-(3(5)-halogen-2-(1*H*-tetrazolo-5-yl)phenyl)formamides. What should be noted, in case of fluorine, according to LC-MS and ^{1}H NMR data, *N*-(3-fluoro-2-(1*H*-tetrazol-5-yl)phenyl)formamide **2.9** and *N*-(5-fluoro-2-(1*H*-tetrazolo-5-yl)phenyl)formamide **2.10** were isolated as the main products. In contrast, in the spectra of 8-chloro- **2.4**, 8-bromo- **2.7** and 10-chlorotetrazolo[1,5-

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c]quinazoline **2.6**, only low-intensity signals of impurities corresponding to formamide derivatives were present.

The possible mechanism of this reaction is most likely implemented by the following. The first step is the protonation of N1 pyrimidine ring with formation of intermediate A, that contributes further steps [14-16] (Scheme 2). Then, formation of carbocation (intermediate B) is followed by the nucleophilic attack of water at position 5 with formation of intermediate C. The next step is the cleavage of the N(4)-C(5) bond with formation of formamide derivative (**2.9-2.10**). The electrophilic properties of carbon at position 5 of triazolo[1,5-*c*]quinazoline significantly affect the course of this reaction.

Refluxing compounds **2.1-2.10** with hydrochloric acid led to cleavage of the pyrimidine ring with elimination of formic acid and the formation of 2-(1*H*-tetrazolo-5-yl)anilines **3.1-3.10**.

The structure of the synthesized compounds was confirmed by IR, LC-, EI-MS, ^{1}H, ^{13}C NMR, and elemental analysis. LC-MS in a "soft" ionization (chemical ionization at atmospheric pressure) allowed to register the molecular ion peaks [M+1] in high intensity.

The signals in the IR spectra of primary aromatic amine NH_2 group were attributed to associated symmetric and asymmetric stretchings at 3462 cm^{-1} and 3373 cm^{-1}, for instance, for compound **3.6**. Secondary amines (**3.1-3.10**) exhibited stretching vibrations

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at 3477-3445 cm^{-1}. While bending vibrations of secondary amines were registered as broad wagging absorption at 695-881 cm^{-1}. Stretching vibrations of C-N group of tertiary amine group were found at 1365-1344 cm^{-1}[17] The intensive stretching vibration at 1660 to 1651 cm^{-1} of compounds **2.9**-**2.10** prove the presence of the carbonyl group in their structure.

^{1}H NMR spectra served as the confirmation for formation of tetrazolo[1,5-*c*]quinazoline system. Signal in a low field of H-5 was characteristic, which was found at 9.79-10.91 ppm, and proved the formation of an electron-deficient system. Other aromatic protons of ABC-system were registered with the following values: H-10 at 7.89-8.59 ppm, H-7 at 7.60-8.56 ppm, H-8 at 7.83-8.12-ppm, H-9 at 7.42-8.05 ppm. For compounds **2.9** and **2.10** characteristic H-5 was absent, instead, the signal of the tetrazole NH proton was recorded in a much weaker field at 16.69-16.87 ppm, confirming the hydrolytic opening of the pyrimidine ring. The same signal was described in our previously published work for 1-(2-(1*H*-tetrazol-5-yl)-R_1-phenyl)-3-R_2-phenyl(ethyl)ureas and was found at 16.18-16.85 ppm[5]. Furthermore, formamide moiety of compounds **2.9** and **2.10** was recorded as one-proton singlet at 10.45-11.02 ppm for NH and at 8.41-8.58 ppm for C(O)H.

For compounds **3.1**-**3.10** aromatic protons were recorded as following: H-3 at 7.08-7.89, H-6 at 6.51-7.12, H-5 at 7.09-7.58, H-4 at 6.37-6.84. Thus, proton shifts in a high field could be clearly seen, for compounds **3.1**-**3.10** compared with signals positions of electron-deficient tetrazolo[1,5-*c*]quinazolines **2.1**-**2.8**.

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Protons of group -NH_2 of 2-(1*H*-tetrazol-5-yl)aniline **3.1** were recorded as low-intensity very broad singlet at 8.86-10.46 ppm. For other compounds, exchange protons were not recorded, due to prototropic azole tautomerism[13,18,19].

Signals of C-6a, C-1a and C-5 were characteristic for tetrazolo[1,5-*c*]quinazoline skeleton in the ^{13}C NMR spectra, which were registered in the lowest field and were recorded for the substance **2.1** at 148.8 ppm, 143.0 ppm and 137.2 ppm respectively. Signals of C-1 and C-2 were characteristic for 2-(1*H*-tetrazol-5-yl)anilines, which were respectively detected at 147.9-152.8 ppm and at 94.4-107.3 ppm. Confirmation of azole tautomerism was the signal of C-5 with low intensity, that was registered for substances **3.1** and **3.4**, also in low field at 149.3-155.2 ppm[20,21].

It should be noted, that splitting of the signal, due to the presence of fluorine was observed in the ^{13}C NMR spectra of 3-fluoro-2-(1*H*-tetrazolo-5-yl)aniline: C-3 was found at 160.8 ppm as a doublet with a coupling constant of 246.2 *Hz*. As well, signals of the C-1,2,4,5 were registered as doublets with constants given in the experimental part.

$M^{+\bullet}$ characteristic peak was observed in the IE-MS spectra, with appropriate intensity, for compound **2.1** - *m/z* 171 (35.6%), **3.1** - *m/z* 161 (5.1%). Fragmentation of $M^{+\bullet}$ was associated with the cleavage of the N1-N2 and N3-N4 of tetrazol ring and the emission of N_2 (**2.1** - *m/z* 142 (100%), **3.1** - *m/z* 133 (13.9)).

EXPERIMENTAL SECTION

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General Methods

Melting points were determined in open capillary tubes in a «Stuart SMP30» apparatus and were uncorrected. The elemental analyses (C, H, N, O) were performed using the ELEMENTAR vario EL cube analyzer. IR spectra (4000-600 cm^{-1}) were recorded on a Bruker ALPHA FT-IR spectrometer using a module ATR eco ZnSe. ^{1}H NMR spectra (400 M*Hz*), and ^{13}C NMR spectra (100 M*Hz*) were recorded on a Varian-Mercury 400 and Bruker Avance DRX-500 spectrometers with $SiMe_4$ as internal standard in DMSO-d_6 solution. LC–MS were recorded using chromatography/mass spectrometric system which consisted of high-performance liquid chromatograph «Agilent 1100 Series» equipped with diode-matrix and mass-selective detector «Agilent LC/MSD SL» (atmospheric pressure chemical ionization – APCI). Electron impact mass spectra (EI-MS) were recorded on a Varian 1200 L instrument at 70 eV.

General Procedure For The Synthesis Of Tetrazolo[1,5-C]Quinazolines (2.1-2.8).

4-Hydrazinoquinazoline 5.0 g (0.031 mol) was dissolved in 240 ml mixture of glacial acetic acid:water (1:1), then it was cooled to 5 C°. Then a solution of 2.15 g of sodium nitrite in the minimum amount of water was added dropwise. The mixture was stirred for 1 h. Formed precipitate was filtered off and washed with water.

General Procedure For The Synthesis Of 2-(1H-Tetrazol-5-Yl)Anilines (3.1-3.10).

Tetrazolo[1,5-*c*]quinazoline 3.0 g (0.018 mol) was dissolved in 100 ml of water. Then 10 ml of concentrated hydrochloric acid was added. The mixture was refluxed for 1 h and

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cooled down. To neutralize excess of hydrochloric acid, sodium hydroxide was added to pH=7. Formed precipitate was filtered off and washed with water.

CONCLUSIONS

A method for synthesis of tetrazolo[1,5-*c*]quinazolines was developed. The important role of electron withdrawing substituents on the products yield was discussed. The structure of the synthesized compounds was confirmed by IR, LC-, EI-MS, ^{1}H, ^{13}C NMR, and elemental analysis. A possible mechanism of pyrimidine ring cleavage of tetrazolo[1,5-*c*]quinazolines was proposed. The exceptions were *N*-(3-fluoro-2-(1*H*-tetrazol-5-yl)phenyl)formamide **2.9** and *N*-(5-fluoro-2-(1*H*-tetrazolo-5-yl)phenyl)formamide **2.10**. 2-(1*H*-Tetrazolo-5-yl)anilines **3.1-3.10** can be used as binucleophiles for further [5+1]-cyclocondensations with electrophiles.

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AUTHORS' STATEMENT

Competing Interests

The authors declare no conflict of interest.

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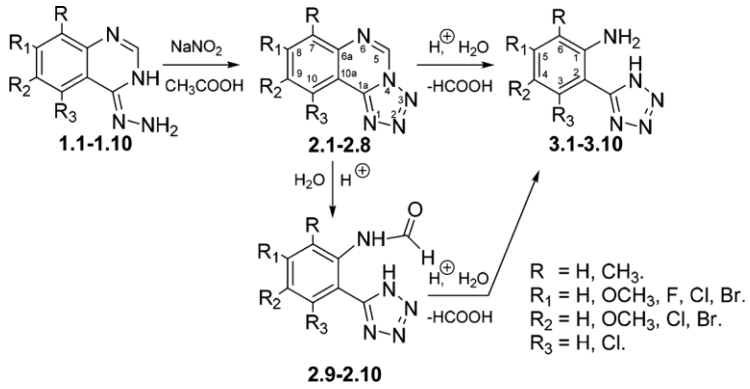
Scheme 1. Tetrazolo[1,5-*c*]quinazolines synthesis.



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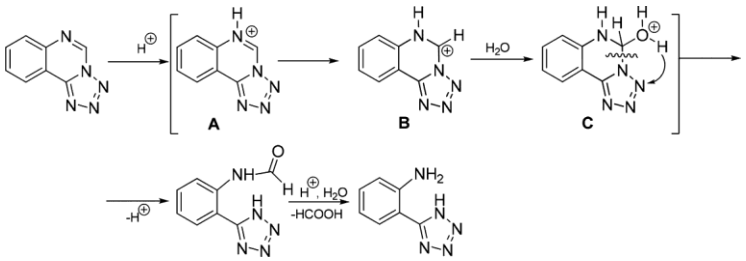
Scheme 2. The pyrimidine ring hydrolytic cleavage mechanism.



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