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LETTERS TO THE EDITOR

Synthesis of 6-Chlorotetrazolo[1,5-*a*]quinazoline and 6-Chloro-4,5-dihydrotetrazolo[1,5-*a*]quinazoline

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Abstract—Reaction of 5-aminotetrazole triethylammonium salt and 2-fluoro-6-chlorobenzaldehyde resulted in the formation of 6-chlorotetrazolo[1,5-*a*]quinazoline instead of the expected azomethine. Hydrogenation of the obtained quinazoline afforded 6-chloro-4,5-dihydrotetrazolo[1,5-*a*]quinazoline.

Keywords: 5-aminotetrazole, 5-benzylaminotetrazoles, tetrazolo[1,5-*a*]quinazolines, 4,5-dihydrotetrazolo[1,5-*a*]quinazolines

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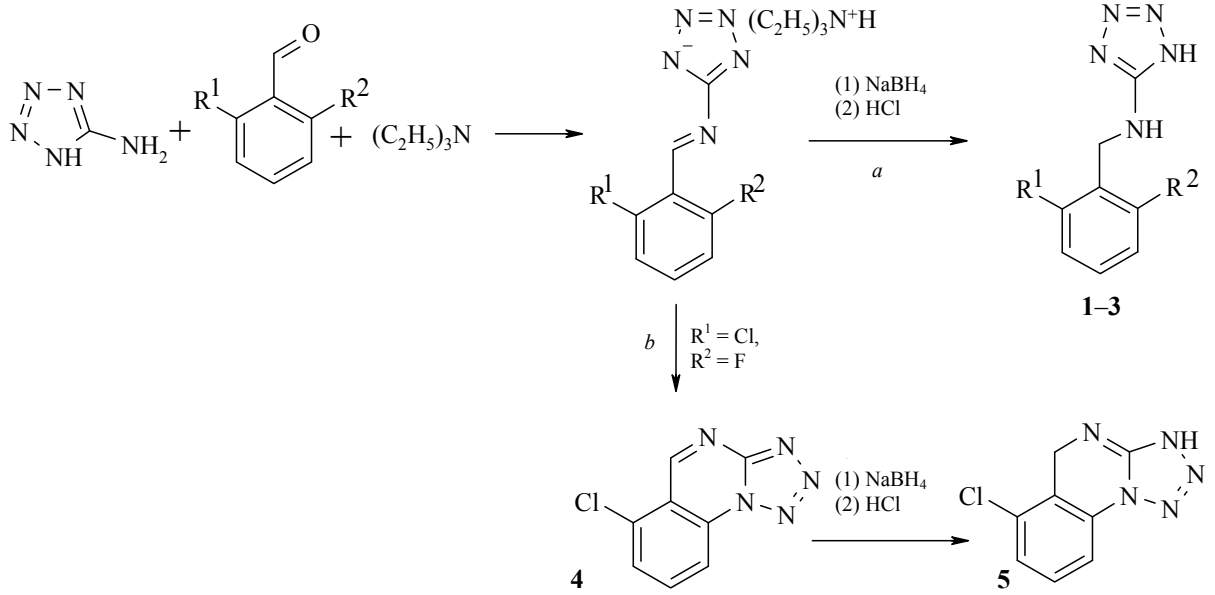
Tetrazolo[1,5-*a*]quinazolines and 4,5-dihydrotetrazolo[1,5-*a*]quinazolines exhibit various types of biological activity [1–4].

Condensation of 5-aminotetrazole with various benzaldehydes followed by hydrogenation of the azomethines formed is a convenient method for the synthesis of biologically active 5-benzylaminotetrazoles [5]. Thus, the reactions of 5-aminotetrazole with 2-chloro-, 2-fluoro, and 2,6-dichlorobenzaldehydes in the presence of triethylamine in DMF followed by reducing the formed intermediate azomethines with sodium borohydride furnished the corresponding *N*-benzyl-1*H*-terazole-5-amines **1–3** in yields of 61–81% (pathway *a*). However, in the case of 6-fluoro-2-chlorobenzaldehyde we found that the reaction product containing no fluorine atom (by mass spectrometry data) was obtained. In the ^{1}H NMR spectrum of this compound there were no signals characteristic of the protons of the benzylated amino group (7.2–7.6 ppm) and tetrazole ring (14.3–14.6 ppm). Additionally, the methylene group singlet was shifted upfield (~1 ppm) in comparison with the corresponding signals of 5-benzylaminotetrazoles. Furthermore, the spectrum contained a singlet signal at 10.99 ppm corresponding to the resonance of one proton. These data allowed us to assume that after the formation of azomethine the intramolecular cyclization unexpectedly took place due to the replacement of the fluorine atom in the benzene ring by the tetrazole nitrogen atom. Further hydrogenation of the resulting heterocycle led to the reduction of the C=N double bond of quinazoline moiety to form 6-chloro-4,5-dihydrotetrazolo[1,5-*a*]quinazoline **5**. To confirm this assumption, we stopped the process at the cyclization stage and isolated the intermediate 6-chlorotetrazolo [1,5-*a*]quinazoline **4** (pathway *b*). The structure of the latter was unambiguously confirmed by ^{1}H NMR spectroscopy and mass spectrometry (Scheme 1).

Synthesis of compounds 1–3, 5. To a solution of 10 mmol of anhydrous 5-aminotetrazole and 10 mmol of the corresponding benzaldehyde in 20 mL of DMF was added 20 mmol of triethylamine. The mixture was gradually brought to the boiling point for 10 min, and then boiled for another 10 min so that 15–20% of the solvent was evaporated. After the completion of the reaction, the mixture was cooled and 40 mL of methanol was added. Next, sodium borohydride (30 mmol) was added by portions to the solution. The reaction mixture was refluxed for 10 min, and then diluted with 100 mL of cold water. The cooled solution was acidified with concentrated hydrochloric acid to pH 2. The precipitate was filtered off and recrystallized from aqueous ethanol.

***N*-(2-Chlorobenzyl)-1*H*-tetrazole-5-amine (1).** Yield 74%, colorless solid, mp 215–216°C. ^{1}H NMR spectrum, d, ppm: 14.5 s (1H), 7.52 s (1H), 7.45–7.22 m (4H), 4.48 s (1H), 4.46 s (1H). Mass spectrum (HRMS-ESI), *m*/*z*: 232.0354 $[M + Na]^+$ (calculated for $C_8H_8ClN_5$: 232.0360).

Scheme 1.



R^1 = Cl, R^2 = H (**1**); R^1 = Cl, R^2 = Cl (**2**); R^1 = F, R^2 = H (**3**).

***N*-(2,6-Dichlorobenzyl)-1*H*-tetrazole-5-amine (2).** Yield 81%, colorless solid, mp 239–240°C. ^{1}H NMR spectrum, d, ppm: 14.34 s (1H), 7.48–7.31 m (4H), 7.21 s (1H), 4.61 s (1H), 4.60 s (1H). Mass spectrum (HRMS-ESI), *m*/*z*: 265.9965 $[M + Na]^+$ (calculated for $C_8H_7Cl_2N_5$: 265.9971).

***N*-(2-Fluorobenzyl)-1*H*-tetrazole-5-amine (3).** Yield 61%, colorless solid, mp 209–210°C. ^{1}H NMR spectrum, d, ppm: 14.46 s (1H), 7.46 s (1H), 7.39–7.08 m (4H), 4.45 s (1H), 4.44 s (1H). Mass spectrum (HRMS-ESI), *m*/*z*: 216.0651 $[M + Na]^+$ (calculated for $C_8H_8FN_5$: 216.0656).

6-Chloro-4,5-dihydrotetrazolo[1,5-*a*]quinazoline (5). Yield 69%, colorless amorphous precipitate, mp 293–294°C. ^{1}H NMR spectrum, d, ppm: 10.99 s (1H), 7.27–6.87 m (3H), 5.56 s (2H). Mass spectrum (HRMS-ESI), *m*/*z*: 208.0381 $[M + H]^+$ (calculated for $C_8H_6ClN_5$: 208.0384).

6-Chlorotetrazolo[1,5-*a*]quinazoline (4). To a solution of 10 mmol of anhydrous 5-aminotetrazole and 10 mmol of 2-fluoro-6-chlorobenzaldehyde in 20 mL of DMF was added 20 mmol of triethylamine. The mixture was gradually brought to the boiling point for 10 min, and then boiled for another 10 min so that 15–20% of the solvent was evaporated. The resulting solution was diluted with 100 mL of cold water. The precipitate was filtered off and recrystallized from aqueous ethanol. Yield 73%, pale yellow solid, mp 202–203°C. ^{1}H NMR spectrum, d, ppm: 9.77 s (1H), 8.72–7.87 m (3H). Mass spectrum (HRMS-ESI), *m*/*z*: 228.0055 $[M + Na]^+$ (calculated for $C_8H_4ClN_5$: 228.0047).

^{1}H NMR spectra (DMSO-d_6) were obtained on a Bruker AVANCE III 400 spectrometer operating at 400.13 MHz. High-resolution mass spectra (ESI) were registered on a Bruker micrOTOF spectrometer.

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