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TRANSFORMATION OF 5-HALOGEN-3-ARIL-2,1-BENZISOXAZOLES INTO QUINAZOLINES

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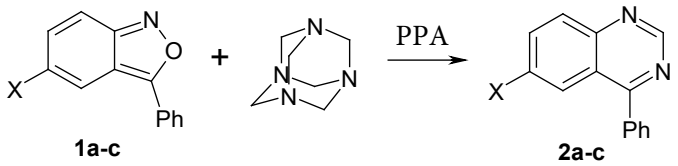
The article considers the new method of producing 4-aryl-6-haloquinazolines by transforming 5-halogen-3-aryl-2,1-benzisoxazoles by reacting them with urotropin in a polyphosphoric acid medium.

Introduction

Increasing interest of researchers to 2,1-benzisoxazoles is connected not only with their diverse biological activity [1, 2], but also with ability to act as versatile synthetics in fine organic synthesis, intermediates in production of monomers and bioactive substances [3-10].

The chemical transformations of 2,1-benzisoxazoles include both processes involving the preservation of the anthranilic cycle [13, 14] and reactions involving the opening of the heterocycle ring, often accompanied by annelation with other heterocyclic fragments [15, 16]. Thus the development of new methods for the transformation of 2,1-benzizoxazoles is very actual.

In order to study the reactivity and modification ways of 2,1-benzizoxazoles we investigated their interaction with urotropine. We discover the following scheme of 5-halogen-3-phenyl-2,1-benzizoxazoles reactions with urotropine in polyphosphoric acid medium leading to the formation of 4-phenyl-6-halogenquinazolines:



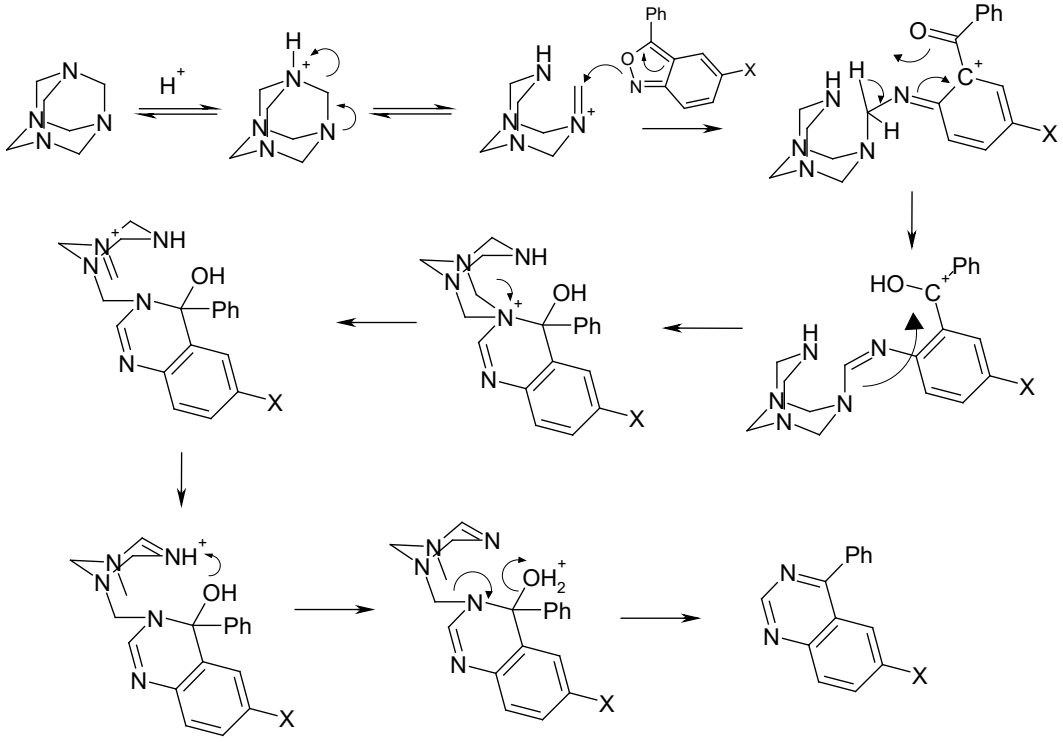
1a-c **2a-c**

a - X=Cl; **b** - X=Br; **c** - X=I

The structures of the obtained compounds were confirmed by analysis methods and results of the previous experiments [17]. All the isolated products mass spectra differ from the mass spectra of the original 2,1-benzisoxazoles and agree with the structures of the 4-phenyl-6-halogenquinazolines. The main signals in the obtained compounds mass spectra correspond to the molecular ion and fragment of the $[M\text{-}Hal]^+$ fragment ion (m/z 205). We observed the absorption bands of C=N bonds in the region of 1664-1670 cm^{-1} in IR spectra. By ^1H NMR spectra only the signals of aromatic protons of quinazoline and phenyl fragments are present in the

region of 7.20-8.30 ppm. The integral values and nature of spin-spin interaction of proton signals in ^{1}H NMR spectra and the number of carbon atom signals in ^{13}C NMR spectra for the compounds obtained clearly indicate the formation of 4-phenyl-6-halogenquinazolines in the reaction. The resulting compounds belong to the class of quinazolines and their biological activity is widely studied [18].

The detailed mechanism of the reaction is not clear yet. But the probable conversion of 2,1-benzisoxazoles into quinazolines consists of the following sequence of steps:



Interaction with urotropine in PPA of some other derivatives of 2. 1-benzisoxazole, such as 5-bromo-3-(4-chlorophenyl)-2,1-benzisoxazole, 5-chloro-3-(3,4-dimethoxyphenyl)-2,1-benzisoxazole, 5-[3'(3'-phenyl-2',1'-benzisoxazole-5'-iloxy)phenoxy]-3-phenyl-2,1-benzisoxazole, 3-phenyl-2,1-benzisoxazole-5-carbaldehyde, oxy-bis-3-phenyl-2,1-benzizoxazole, thio-bis-3-phenyl-2,1-benzizoxazole, proceeds not so definitely and leads to formation of alternative products, non-separable mixtures of substances or to separation of the starting compounds. The use of other solvents or acids instead of polyphosphoric acid also does not lead to the formation of the corresponding quinazolines.

Experimental part

We recorded IR spectra by apparatus Perkin Elmer Spectrum 65 FT-IR Spectrometer on a Universal ATR Sampling Accessory using Attenuation Total Reflection method (ATRM). NMR spectra were recorded on the apparatus Varian XL-400 for solutions in DMSO-d_6 at 25 °C. Solvent residual proton signals in 1H NMR (δ_H 2.50 m.d.) or in 13C NMR (δ_C 39.5 m.d.) were the reference for the chemical shift readout, tetramethylsilane signal was used as the marker. Mass spectra were recorded on a Perkin Elmer Clarus 680 (GC) + Clarus SQ 8T (MS) chromatography mass spectrometer, using an ELITE-5ms 30 m×0.25 mm×0.25 um capillary

column. The sample was dissolved in DMF and injected into a 1 μl manual chromatograph, flow division 1:30, $T_{injector}$ = 230–280 °C, carrier gas speed 1 ml/min, carrier gas helium (cp). The column was kept at a temperature between 200 and 220 °C. The strength of the ionising shock was 70 eV. Elemental analysis was carried out on a Perkin Elmer 2400. The melting point was determined by Büchi M-560 melting point and boiling point apparatus.

The methodology of the compounds **2 (a-c)** synthesis. We add 5 mmol of urotropine to a solution of 1 mmol of compound 1 **(a-c)** in 10 g polyphosphoric acid. We heated the reaction mixture at 80–100 °C for 4-8 h. The reaction was monitored by TLC on *Silufol UV-254* plates, eluent chloroform-methanol 10:1. The chromatograms were screened under UV light. At the end of the reaction, the flask contents were poured into a beaker with ten times the excess of iced water. The resulting crystalline precipitate was filtered off, recrystallised from ethyl alcohol and dried in air.

4-phenyl-6-chloroquinazoline **(2a)**

Grey powder 190 mg (79%), m.p. 124-127 °C. IR (υ_{max}, sm^{-1}): 1668 (C=N), 1600 (Ar), 1536, MS (EI, 70 eV): *m/z* (%): 240 $[M]^+$ (49), 239 $[M\text{-}H]^+$ (100), 205 $[M\text{-}Cl]^+$ (97), 177 $[M\text{-}Cl\text{-}N_2]^+$ (16), 75 (21). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.59-7.63 (m, 3 H), 7.75-7.79 (m, 2H), 7.85-7.87 (m, 1 H), 8.07-8.13 (m, 2 H), 9.38 (c, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 123.8, 125.9, 128.9, 130.0, 130.5, 130.7, 133.6, 134.8, 136.6, 149.6, 154.9, 167.9. Total, %: C, 69.63; H, 3.88; N, 11.61. $C_{14}H_9ClN_2$. Calculated, %: C, 69.86; H, 3.77; N, 11.64.

6-bromo-4-phenylquinazoline **(2b)**

Brownish powder 193 mg (68%), m.p. 129-132 °C. IR (υ_{max}, sm^{-1}): 1670 (C=N), 1596 (Ar), 1520. MS (EI, 70 eV): *m/z* (%): 285 $[M]^+$ (98), 205 $[M\text{-}Br]^+$ (100), 177 $[M\text{-}Br\text{-}N_2]^+$ (14), 75 (24). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.58-7.62 (m, 3H), 7.74-7.79 (m, 2H), 7.96-8.0 (m, 2H), 8.28 (d, 1H, *J*=1.2 Hz), 9.39 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 121.7, 124.2, 128.9, 129.2, 129.9, 130.5, 130.7, 136.5, 137.3, 149.8, 154.9, 167.6. Total, %: C 58.88; H 3.28; N 9.86. $C_{14}H_9BrN_2$. Calculated, %: C, 58.97; H, 3.18; N, 9.82.

6-iodo-4-phenylquinazoline **(2c)**

Brownish powder 203 mg (61%), m.p. 125-128 °C. IR (υ_{max}, sm^{-1}): 1664 (C=N), 1594 (Ar), 1531. MS (EI, 70 eV): *m/z* (%): 332 $[M]^+$ (96), 205 $[M\text{-}I]^+$ (100), 177 $[M\text{-}I\text{-}N_2]^+$ (21), 151 $[M\text{-}I\text{-}N_2\text{-}C_2H_2]^+$ (18), 128 (17), 75 (26). ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 7.58-7.63 (m, 3H), 7.75-7.78 (m, 2H), 7.85(d, 1H, *J*=8.8 Hz), 8.15 (dd, 1H, *J*=8.8 Hz, *J*=2.2 Hz), 8.49 (d, 1H, *J*=2.2 Hz), 9.39 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 93.3, 124.8, 129.0, 130.0, 130.5, 130.8, 135.9, 136.7, 142.6, 150.3, 155.1, 167.3. Total, %: C 50.76; H 2.84; N, 8.49. $C_{14}H_9IN_2$. Calculated, %: C 50.63; H 2.73; N 8.43.

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