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8-Hydroxy-5-nitroquinoline as a C-nucleophilic reagent in the reaction of C, C-coupling with quinazoline

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Abstract. The first example of the reaction of 5-nitro-8-hydroxyquinoline as a C-nucleophile with quinazoline is described. As a result of the reaction of C, C-coupling, a stable σ-adduct containing the drug nitroxalin on a heterocyclic carrier was obtained. The structure of the resulting adduct was confirmed by 2D ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and ^{1}H-^{15}N HMBC spectra.

Keywords: 5-nitro-8-hydroxyquinoline; quinazoline; C, C-coupling

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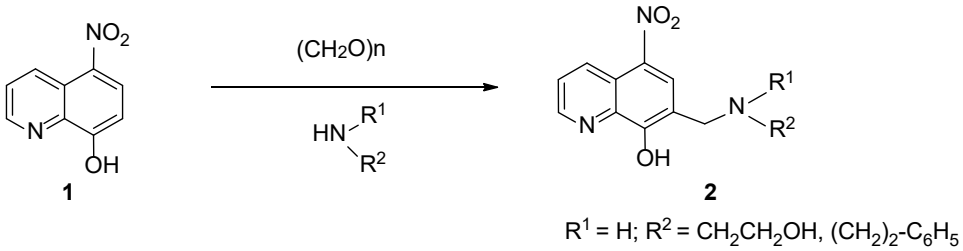
Introduction

5-nitro-8-hydroxyquinoline (nitroxaline) is an antimicrobial agent from the group of hydroxyquinolines. It has a wide spectrum of action, including selectively suppressing the synthesis of bacterial DNA, forms complexes with metal-containing enzymes of the microbial cell [1, 2].

Preparations containing 8-hydroxyquinoline are highly toxic. In this regard, the search for new derivatives of these compounds that are less toxic is urgent.

It seems promising to carry out the synthesis of new derivatives of 8-hydroxyquinolines by means of environmentally friendly C–C coupling reactions, during which the addition of a C-nucleophile to the 8-hydroxyquinoxaline molecule occurs, followed by the replacement of a hydrogen atom [3]. Theoretically, this type of transformation is waste-free and possible under conditions of acid activation of heterocyclic azines.

Reactions of nucleophilic substitution of hydrogen in 5-nitroquinolines have been described, which proceed in the ortho-position to the nitro group in interaction with nucleophiles containing a vicarious group (vicarious substitution) [4]. The reaction of amination of nitroquinolines with trimethylhydrazinium iodide occured in a solution of anhydrous DMSO in the presence of potassium tert-butylate [5]. Vicarious amination of nitroquinolones with 4-amino-1,2,4-triazole was carried out under similar conditions and occured at the C^{6} atom of nitroquinolone [6]. It was known that 5-nitro-8-hydroxyquinoline **1** reacted with formaldehyde in the presence of amines, to form 7-substituted aminomethyl derivatives of 5-nitroquinoline-8-ol **2** [7] (Scheme 1).



Scheme 1

Experimental

All reagents used were commercially available and were used without further purification (Sigma Aldrich, Merck).

The reaction progress and purity of the obtained compounds were controlled by TLC method on Sorbfil UV-254 plates, using visualization under UV light. Melting points were determined on a Stuart SMP10 melting point apparatus.

^{1}H, ^{13}C and ^{19}F NMR spectra were acquired on Bruker Bruker Avance NEO — 600 spectrometer in DMSO-d_6 solutions, using TMS as internal reference for ^{1}H and ^{13}C NMR or $CFCl_3$ for ^{19}F NMR. Mass-spectra (EI, 70eV) were recorded on MicrOTOF-Q instrument (Bruker Daltonics) at 250 °C.

Elemental analysis was performed using a Perkin-Elmer 2400 Series II CHNS / O analyzer.

To calculate molecular orbitals, we used the B3LYP exchange correlation functional in the 6-31G++ (d, p) basis set, in the framework of the Density Functional Theory. The energy of solvation in acetonitrile was taken into account when calculating. The calculations were performed using the GAUSSIAN09 package similarly to work [8].

4-(8-hydroxy-5-nitroquinolin-7-yl)-1,4-dihydroquinazolin-3-ium 2,2,2-trifluoroacetate 4

0.095 g (0.5 mmol) of quinazoline **3** is heated with 0.5 mmol of 5-nitro-8-hydroxyquinoline **1** in 2.0 ml of trifluoroacetic acid for 70 hours at 110 °C. The reaction mixture is evaporated under vacuum. The residue was treated with 3 ml of alcohol, the precipitate of product 4 was filtered off, washed with 2–3 ml of ethanol, 0.105 g (32%) was obtained, m.p. > 300 °C.

^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 6.93 (s, 1H), 6.94 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 8.23 (s, 1H), 8.30 (dd, J = 9.0, 5.4 Hz, 1H), 8.58 (s, 1H), 9.22 (d, J = 5.2 Hz, 1H), 10.00 (d, J = 8.9 Hz, 1H), 11.60 (s, 9H),

^{13}C NMR (151 MHz, DMSO-d_6, δ, ppm): 50.23, 111.39, 114.21 (q, J = 283.5 Hz, CF_3), 117.88, 123.80, 125.54, 127.59, 128.43, 129.14, 129.31, 130.60, 130.72, 136.63, 144.46, 144.68, 148.27, 151.08, 160.72 (q, J = 43.2 Hz, $COCF_3$), 180.20.

^{15}N NMR (61 MHz, DMSO-d_6, δ, ppm): 118.48, 125.63, 184.09, 364.34.

Mass spectrum (EI), 321 (20), 320 (100) $[M]^+$, 301(20), 288 (24), 272 (56), 271 (59).

Found, %: C 52.54; H 3.02; N 12.90. $C_{19}H_{13}N_4O_5F_3$ Calculated, %: C 52.68; H 3.08; N 13.01.

Results and discussion

The data presented in the literature confirm the presence of an electrophilic center on the C^6 atom and a nucleophilic center on the C^7 atom in the 5-nitro-8-hydroxyquinoline molecule.

It is obvious that the oxygen-containing substituents (8-hydroxy and 5-nitro group) cause a polarization of the electron density in the aromatic nucleus that is higher than that in the heterocyclic part of the nitroxaline molecule. This has been confirmed using quantum chemical calculations.

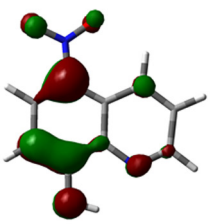
The electron density in the high occupied molecular orbital (HOMO, Fig. 1a) is most localized on the C^5, C^7, and C^8 atoms of the aromatic nucleus. In this case, due to the absence of steric hindrances, the C^7 atom of the nitroxaline can be the most effective nucleophilic center.

The lowest unoccupied molecular orbital (LUMO, Fig. 1b) are localized on the nitrogen atoms of the nitro group, C^6 and C^8 atoms of nitroxaline. These positions of molecule **1** are characterized by increased electrophilic properties. Taking into account the absence of steric hindrances to the formation of a stable C–C bond at the C^6 position of nitroxaline, it can be assumed that this electrophilic center is the most active when interacting with nucleophiles, which is confirmed by data from the literature [4–6].

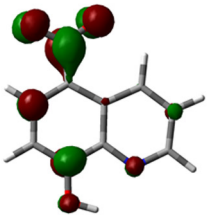
In this work, it was found that 5-nitro-8-hydroxyquinoline **1** interacts with quinazoline **3** in the presence of trifluoroacetic acid to form a stable σ-adduct **4** (Scheme 2).

An ion peak corresponding to the molecular weight of compound **4** was observed in the mass spectrum of electron impact. In the ^{1}H NMR spectrum of adduct **4**, the signal of the $H^{4'}$ atom of the quinazoline nucleus was found at 6.93 ppm, and the signal of the corresponding sp^3-hybridized $C^{4'}$ atom in the ^{13}C NMR spectrum was observed at 50.23 ppm.

The assignment of signals from ^{1}H, ^{13}C, and ^{15}N atoms of adduct **4** was carried out in the analysis of 2D ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and ^{1}H-^{15}N HMBC spectra. 2D

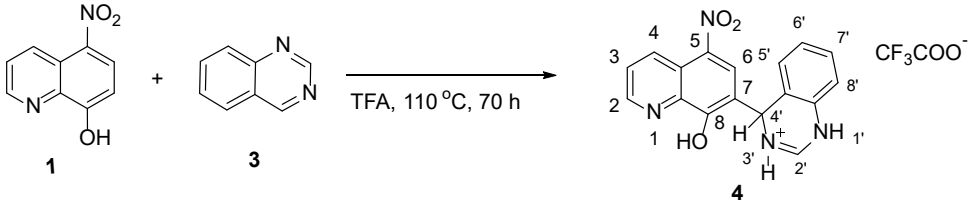


a



b

Fig. 1. Distribution of electron density in the nitroxoline 1: (*a*) HOMO, (*b*) LUMO.



Scheme 2

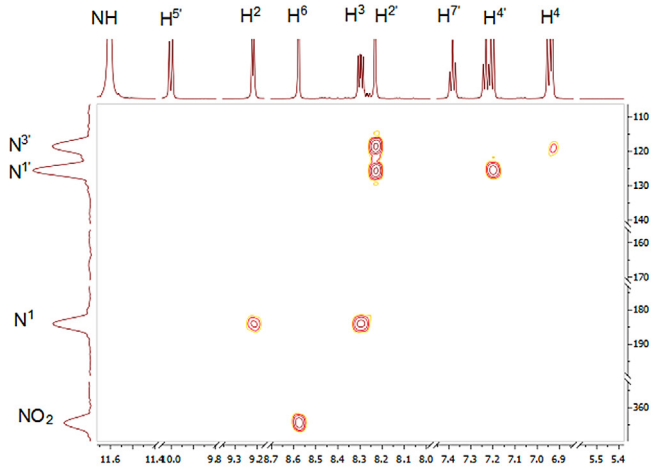


Fig. 2. ^{1}H-^{15}N HMBC spectrum of adduct **4**

^{1}H-^{15}N HMBC spectrum with assignment of signals of ^{1}H and ^{15}N atoms is shown in Fig. 2.

Apparently, 5-nitro-8-hydroxyquinoline **1** reacted as a C-nucleophile at the C^{7} position of the molecule to form a stable adduct under conditions of acid activation of the quinazoline nucleus.

Conclusions

In conclusion, it should be noted that a stable σ-adduct consisting of a biologically active drug (nitroxaline) on a heterocyclic quinazoline carrier was obtained for the first time by means of the C,C-coupling reaction under the conditions of acid catalysis.

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