Synthesis of ethynyl-3-hydroxyquinoline-4-carboxylic acids

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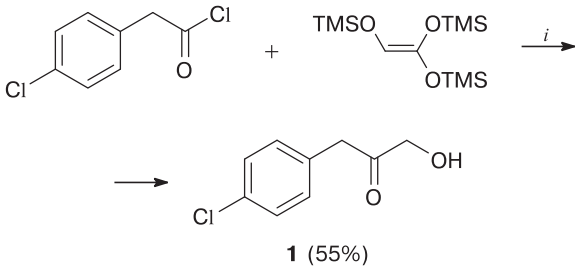
3-Hydroxyquinoline-4-carboxylic acids containing ethynyl moiety in the 6th and 8th positions were obtained for the first time. A synthetic approach to aforementioned compounds based on the Sonogashira cross-coupling and the Pfitzinger reaction was developed. Physicochemical properties of the newly synthesized structures were investigated.

Key words: 3-hydroxyquinoline-4-carboxylic acids, Sonogashira reaction, Pfitzinger reaction.

Currently, a number of quinoline-4-carboxylic acid derivatives with a hydroxyl group in position 3, which have biological activity (anti-inflammatory and antithrombotic), are known.[1—3] At the same time, the methods for the synthesis of 3-hydroxyquinoline-4-carboxylic acids substituted with halogen, alkyl, and heteroaryl substituents in the positions 5—8 have been well studied,[1—3] while their alkynyl analogs have not been described in the literature. In this regard, the purpose of this work was to develop a synthetic approaches to such compounds with a triple bond in positions 6 or 8.

The main step in the synthesis of target compounds was the Pfitzinger reaction.[4,5] 1-(4-Chlorophenyl)-3-hydroxyprop-2-one (**1**) was used as a model carbonyl compound, which allowed us to introduce the hydroxyl group at position 3 of the quinoline. α-Hydroxyketone was prepared according to known procedure[3] from 2-(chlorophenyl)acetyl chloride using 1,1,2-*tris*(trimethylsilyloxy)-ethylene to build up the carbon skeleton (Scheme 1).

Scheme 1

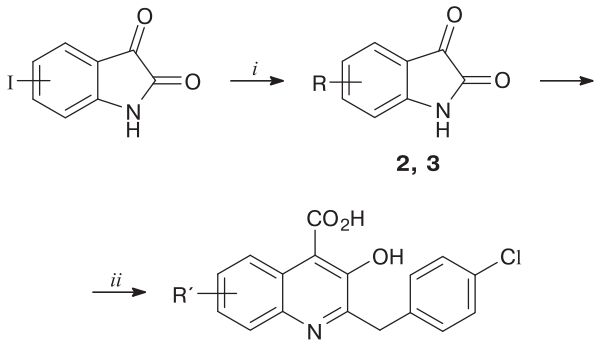


1 (55%)

i, 1) 100 °C, 2) HCl, dioxane, Δ.

Sandmeyer reaction[1,2] was used for the synthesis of halogenated isatin derivatives from the corresponding iodo-substituted anilines. Obtained isatins were introduced into Sonogashira reaction in the standard for this cross-coupling reaction conditions, namely, $Pd(Ph_3P)_4$ and copper(I) iodide were used as catalysts (Scheme 2).

Scheme 2



Compound	R	Yield (%)	Compound	R′	Yield (%)
2	7-C≡C-TMS	48	**4**	8-C≡CH	16
3	5-C≡C-TMS	22	**5**	6-C≡CH	14

i. ≡—TMS, $Pd(Ph_3P)_4$, CuI, Et_3N, DMF; *ii*. 1) **1**, KOH, H_2O—EtOH, 2) HCl.

Note that in the literature the synthesis of compound **2** is mentioned only once, while the authors managed to isolate the product in 5% yield (see Ref. 6). Physicochemical properties of isatins **2** and **3** were not described.

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In our case, the yield of the target product of cross-coupling **2** was 48% and compounds **2** and **3** were characterized by a complex of physico-chemical methods of analysis.

In order to synthesize the target quinolines, α-hydroxyketone **1** was introduced into the Pfitzinger reaction with isatin **2** and **3** containing triple bonds (see Scheme 2). The trimethylsilyl group was removed under alkaline conditions. Therefore, no additional step was required to obtain a free terminal alkyne.

3-Hydroxyquinoline-4-carboxylic acids containing ethynyl moiety in positions 6 and 8, were obtained for the first time. Their composition was confirmed using high-resolution mass spectrometry, and their structures were confirmed by ^{1}H and ^{13}C NMR and IR spectroscopy.

Experimental

^{1}H and ^{13}C NMR spectra were registered using a Bruker Avance 400 spectrometer with working frequencies 400 and 100 MHz. High-resolution mass spectra were recorded using a Orbitrap Elite spectrometer (Thermo Fischer Scientific). The solutions of the samples in acetonitrile with the addition of 1% of formic acid were introduced into the ionization source by the electrospray method. IR spectra were recorded using an IR200 FTIR spectrometer (TermoNicolet, USA) with resolution of 4 cm^{-1}.

Synthesis of indoline-2,3-diones 2 and 3 (general procedure). 5-Iodo- or 7-iodoisatine (550 mg, 2.0 mmol), $Pd(PPh_3)_4$ (50 mg, 0.04 mmol), CuI (40 mg, 0.2 mmol) were dissolved in DMF (5 mL), then Et_3N (700 μL, 5.0 mmol) was added, and the mixture was stirred under inert atmosphere (N_2) for 1 h. Trimethylsilylacetylene (430 μL, 3.0 mmol) was added and the reaction mixture was stirred at 80 °C for 4 h, then cooled down, and filtered *via* Celite® layer. Then EtOAc was added, the mixture was washed with water and saturated NaCl solution, dried with Na_2SO_4. The solvent was removed under reduced pressure, and product was purified by column chromatography ($CHCl_3$).

7-[(Trimethylsilyl)ethynyl]indoline-2,3-dione (2). Orange crystalline compound was obtained, the yield was 236 mg (48%), m.p. 189—190 °C. IR ($CDCl_3$), ν/cm^{-1}: 3181 (N—H); 2166 (C≡C); 1747 (overlapping contour of two C=O). ^{1}H NMR ($CDCl_3$), δ: 8.31 (br.s, 1 H, NH); 7.60 (dd, 1 H, H_{arom}, J = 7.8 Hz, J = 1.2 Hz); 7.56 (d, 1 H, H_{arom}, J = 7.5 Hz); 7.08 (t, 1 H, H_{arom}, J = 7.7 Hz); 0.30 (s, 9 H, $Si(CH_3)_3$). ^{13}C NMR (DMSO-d_6), δ: 183.7, 159.9, 152.0, 140.0, 131.4, 124.9, 122.7, 118.3, 106.7, 98.0, −0.2. MS: found m/z 242.0633 $[M - H]^-$; $C_{13}H_{12}NO_2Si$; calculated: 242.0643.

5-[(Trimethylsilyl)ethynyl]indoline-2,3-dione (3). Orange crystalline compound was obtained, the yield was 108 mg (22%), m.p. 216—218 °C. IR ($CDCl_3$), ν/cm^{-1}: 3222 (N—H); 2150 (C≡C); 1763, 1745 (C=O). ^{1}H NMR ($CDCl_3$), δ: 8.04 (br.s, 1 H, NH); 7.72 (d, 1 H, H_{arom}, J = 1.7 Hz); 7.66 (dd, 1 H, H_{arom}, J = 8.2 Hz, J = 1.7 Hz); 6.88 (d, 1 H, H_{arom}, J = 8.2 Hz); 0.26 (s, 9 H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$+CD_3OD), δ: 183.3, 159.3, 149.8, 141.5, 128.3, 118.2, 117.3, 112.2, 102.7, 94.6, −0.65. MS: found m/z 242.0643 $[M - H]^-$; $C_{13}H_{12}NO_2Si$; calculated: 242.0643.

Synthesis of 3-hydroxyquinoline-4-carboxylic acids 4 and 5 (general procedure). The corresponding indolin-2,3-dione (75 mg, 0.30 mmol) in 6 *M* KOH aqueous solution (2 mL) was placed in a two-neck round-bottomed flask equipped with a reflux condenser and heated to 100 °C. 3-(4-Chlorophenyl)-1-hydroxypropan-2-one (**1**) (65 mg, 0.35 mmol) was dissolved in ethanol (2 mL) and added in two portions to the solution. The reaction mixture was heated to reflux for 4 h, then cooled down to room temperature, and the solvents were removed under reduced pressure. The residue was dissolved in water and filtered. The filtrate was acidified to pH 1 with 1 *M* HCl solution. The precipitate was filtered and washed with water. Purification was performed using column chromatography (EtOAc—CH_3CN—MeOH, 70/5/2.5 + 0.5% Et_3N, v/v). The isolated fraction was dissolved in acetonitrile—water mixture, 1 *M* HCl solution was added to pH 1, and the product was collected by filtration, washed with water, and dried.

2-(4-Chlorobenzyl)-8-ethynyl-3-hydroxyquinoline-4-carboxylic acid (4). Brown crystalline compound was obtained, the yield was 16 mg (16%), m.p. 110—112 °C. IR (KBr), ν/cm^{-1}: 3560 (O—H); 3276 (≡C—H); 1658 (C=O). ^{1}H NMR (DMSO-d_6), δ: 8.58 (d, 1 H, H_{arom}, J = 8.6 Hz); 7.73 (d, 1 H, H_{arom}, J = 7.4 Hz); 7.53 (td, 1 H, H_{arom}, J = 8.6 Hz, J = 2.0 Hz); 7.32 (s, 4 H, H_{arom}); 4.41 (s, 1 H, C≡CH); 4.30 (s, 2 H, CH_2). ^{13}C NMR (DMSO-d_6), δ: 171.2, 155.5, 152.5, 141.8, 137.7, 131.5, 131.3, 131.2, 128.7, 127.7, 125.9, 125.4, 122.2, 115.2, 86.3, 82.3, 38.9. MS: found m/z 336.0430 $[M - H]^-$; $C_{19}H_{11}ClNO_3$; calculated: 336.0433.

2-(4-Chlorobenzyl)-6-ethynyl-3-hydroxyquinoline-4-carboxylic acid (5). Brown crystalline compound was obtained, the yield was 14 mg (14%). IR (KBr), ν/cm^{-1}: 3298 (O—H); 2917 (≡C—H); 1658 (C=O). ^{1}H NMR (DMSO-d_6), δ: 8.87 (s, 1 H, H_{arom}); 7.90 (d, 1 H, H_{arom}, J = 8.6 Hz); 7.56 (dd, 1 H, H_{arom}, J = 8.6 Hz, J = 1.7 Hz); 7.33 (s, 4 H, H_{arom}); 4.34 (s, 1 H, C≡CH); 4.32 (s, 2 H, CH_2). ^{13}C NMR (DMSO-d_6), δ: 171.2, 156.4, 151.8, 141.5, 137.3, 131.5, 131.3, 129.1, 128.9, 128.8, 128.7, 124.3, 121.4, 111.7, 84.2, 82.3, 38.4. MS: found m/z 336.0436 $[M - H]^-$; $C_{19}H_{11}ClNO_3$; calculated: 336.0433.

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