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New approaches to the synthesis of selected hydroxyquinolines and their hydroxyquinoline carboxylic acid analogues

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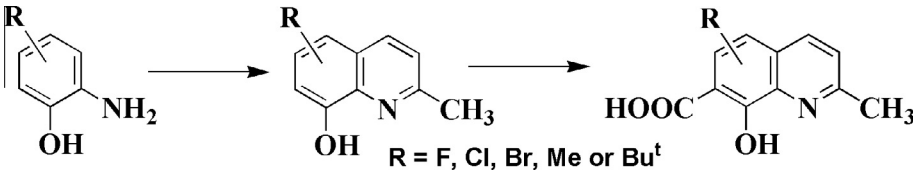
HIGHLIGHTS

- Three hydroxyquinolines have been characterized by X-ray diffraction method.
- The X-ray structure of 5-chloro-8-hydroxy-2-methylquinoline-7-carboxylic acid.
- New approaches to the Skraup synthesis of selected hydroxyquinolines.

GRAPHICAL ABSTRACT



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ABSTRACT

New approaches to the synthesis of selected crystalline hydroxyquinolines and their carboxylic acid analogues were elaborated in this paper with the auxiliary of computational and spectroscopic characterization, such as FTIR, NMR and single crystal X-ray measurements. The experimental data were further rationalized based on a DFT calculation method with B3LYP functional, which reflected the impact of electron donating or withdrawing groups on the energy level of HOMO orbitals and the reactivity of the substituted hydroxyquinolines.

Introduction

Quinolines were first discovered from coal tar by Friedlieb Ferdinand Runge in 1834 [1]. After half century Skraup-Doebner–Miller successfully synthesized the quinolines in laboratory [2–5]. For 180 years many synthetic protocols and applications have been developed based on the Skraup transformation because of its simplicity and the importance of the quinoline itself [6–18].

We are particularly interested in the functionalization of benzene (or phenol) ring in quinoline (or hydroxyquinoline) constitution from both theoretical and practical point view. Recently derivatives of quinoline with both hydroxyl and carboxylic acid groups on benzene ring have attracted increased attention due to their analogy to the precursor of a promising HIV-1 integrase inhibitor, 2-[(*E*)-2-(3,4-dihydroxy-5-methoxyphenyl)ethenyl]-8-hydroxyquinoline-7-carboxylic acid (FZ-41) which has been demonstrated to block the replication of HIV-1 in cell cultures at nontoxic concentrations [19,20]. The modifications of quinoline moiety through introducing carboxylic acid function increased their acidity and water solubility. In consequence this could increase their bioavailability and biological activity, and could trigger searches on new biological applications of the compounds.

In this paper, we reported new approaches to the synthesis of the aforementioned compounds with in-depth spectroscopic characterization. Computational and spectroscopic studies were carried out to compare selected hydroxyquinolines and hydroxyquinoline carboxylic acid, which have not been reported by previous studies according to our best knowledge.

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Experimental

General

NMR spectra were obtained with Bruker Avance 400 and 500 operating at 400.13 MHz (^{1}H) and 100.5 MHz (^{13}C) at 21 °C; chemical shifts referenced to ext. TMS (^{1}H, ^{13}C); coupling constants are given in Hz. The ^{1}H and ^{13}C NMR calculations were performed with the ACD Labs NMR Predictor v.8 program. For GC/MS, a Gas Chromatograph TRACE 2000 with MS Finnigan TRACE (ThermoQuest) with autosampler Combi PAL (CTC) with capillary column DB-5 MS 30 m × 0.25 μm × 0.5 μm was used. Mass spectra were obtained with a Varian 500 MS with applied ESI technique. FTIR spectra were recorded on a Perkin Elmer spectrophotometer in the spectral range 4000–450 cm^{-1} with the samples in the form of KBr pellets. Electronic spectra were measured on a spectrophotometer Lab. Chromatography was carried out on Silica Gel 60 (0.15–0.3 mm) Machery Nagel. Melting points were determined on MPA100 OptiMelt melting point apparatus and uncorrected. 2-Amino-4-*tert*-butylphenol (**1a**), 2-amino-5-methylphenol (**1b**), 2-amino-4-bromophenol (**1c**), 2-amino-4-chlorophenol (**1d**) and 2-amino-4-fluorophenol (**1e**) were purchased from Sigma–Aldrich, and were used without further purification.

The synthesis of quinolines **2a**, **2b**, **2c**, **3a**, **3b** and **3c** followed our procedure described in the literature [6,7]:

*5-tertButyl-2-methyl-quinolin-8-ol (**2a**)*

16%; mp = 54.5 °C; IR (KBr; cm^{-1}): 3344 ν_{OH}; 2994, 2955, 2913, 2874 $\nu_{CH3;t\text{-}Bu}$; 1576 $\nu_{C=N}$; ^{1}H NMR ($CDCl_3$; 500.18 MHz) δ = 1.55 (s, 9H, Bu^t), 2.72 (s, 3H, CH_3), 7.05 (d, J = 8.1 Hz, 1H, aromatic), 7.30 (d, J = 8.9 Hz, 1H, aromatic), 7.37 (d, J = 8.1 Hz, 1H, aromatic), 8.66 (d, J = 8.9 Hz, 1H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$; 125.78 MHz) δ = 24.51, 32.08, 35.55, 108.78, 121.11, 123.53, 124.92, 135.83, 136.59, 138.83, 150.16, 155.32; t_r = 6.98 min, GC/MS: (EI) M^+ = 215 (65%), $(M+H)^+$ = 216 (10%), $(M\text{-}CH_3)^+$ = 200 (100%); CCDC 963546.

*2,6-Dimethylquinolin-8-ol (**2b**)*

26%; mp = 136.6 °C; IR (KBr; cm^{-1}): 3347 ν_{OH}; 2916, 2849 ν_{CH3}; 1570 $\nu_{C=N}$; ^{1}H NMR ($CDCl_3$; 500.18 MHz) δ = 2.47 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.01 (d, J = 1.3 Hz, 1H, aromatic), 7.05 (bs, 1H, aromatic), 7.24 (d, J = 8.4 Hz, 1H, aromatic), 7.93 (d, J = 8.4 Hz, 1H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$; 125.78 MHz) δ = 22.19, 24.79, 112.17, 116.78, 122.83, 126.71, 135.78, 136.21, 137.02, 151.31, 155.93; t_r = 12.01 min, GC/MS: (EI) M^+ = 173 (100%), $(M+H)^+$ = 174 (12%); CCDC 973848.

*5-Bromo-2-methylquinolin-8-ol (**2c**)*

34%; mp = 66.1 °C (lit. 69 °C [32]); IR (KBr; cm^{-1}): 3373 ν_{OH}; 2920, 2874 ν_{CH3}; 1595 $\nu_{C=N}$; 1500, 1256; (IR (KBr): 3375, 1500, 1390, 1255 cm^{-1} [32])); ^{1}H NMR ($CDCl_3$; 500.18 MHz) δ = 2.78 (s, 3H, CH_3), 7.05 (d, J = 8.2 Hz, 1H, aromatic), 7.42 (d, J = 8.6 Hz, 1H, aromatic), 7.64 (d, J = 8.2 Hz, 1H, aromatic), 8.38 (d, J = 8.6 Hz, 1H, aromatic) (lit. ^{1}H NMR ($CDCl_3$) δ = 2.73 (s, 3H), 7.01 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 8.6 Hz, 1H) [32]); ^{13}C{^{1}H} NMR ($CDCl_3$; 125.78 MHz) δ = 24.76, 109.77, 110.76, 123.92, 126.00, 130.14, 136.04, 138.46, 151.71, 157.80 (^{13}C NMR ($CDCl_3$) δ = 24.7, 109.6, 110.5, 123.8, 125.7, 129.9, 135.7, 138.3, 151.5, 157.6 [32]); t_r = 6.82 min, GC/MS: (EI) M^+ = 237 (100%), 239 (96%), $(M+H)^+$ = 238 (15%), 240 (14%).

*5-Chloro-8-hydroxy-2-methylquinoline-7-carboxylic acid (**3a**)*

43%; IR (KBr; cm^{-1}): 3355 ν_{OH}; 2919 ν_{CH3}; 1597 $\nu_{as(COO)}$; 1570 $\nu_{C=N}$; 1330 $\nu_{s(COO)}$; CCDC 969571.

*5-Bromo-8-hydroxy-2-methylquinoline-7-carboxylic acid (**3b**)*

<1%; $mp_{dec.}$ = 214.2 °C; IR (KBr; cm^{-1}): 3416 ν_{OH}; 2831 ν_{CH3}; 1598 $\nu_{as(COO)}$; 1363 $\nu_{s(COO)}$; ^{1}H NMR (KOD/D_2O/DMSO-*d6*; 500.18 MHz) δ = 2.91 (s, 3H, CH_3), 6.89 (d, J = 8.4 Hz, 1H, aromatic), 7.71 (d, J = 8.5 Hz, 1H, aromatic), 8.20 (s, 1H, aromatic); MS: (ESI) (DMSO) $(M\text{-}H+Na)^+$ = 302 (100%), 304 (96%).

The isolated yield of acids **3a** and **3c** have been improved:

5-Fluoro-8-hydroxy-2-methylquinoline-7-carboxylic acid (**3c**) 70% [6].

Crystallization

The crystals suitable for X-ray analysis were obtained from hexane solution at room temperature for **2a**, **2b** and from AcOEt solution for **3a**.

DFT calculations

The calculations were carried out by using Gaussian09 program [21]. Molecular geometries of the singlet ground state of compounds **2a**, **2b** and **3a** were fully optimized in the gas phase at the B3LYP level of theory [22,23]. For each compound a frequency calculation was carried out, verifying that the optimized molecular structure obtained corresponded to an energy minimum, thus only positive frequencies were expected. The calculations were performed using the 6–31G** functions for all atoms.

Crystal structure determination and refinement

The crystals of the compounds were mounted in turn on a Gemini A ultra Oxford Diffraction automatic diffractometer equipped with a CCD detector for data collection. X-ray intensity data were collected with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at temperature of 295(2) K, with ω scan mode. Ewald sphere reflections were collected up to 2θ = 50.10. Lorentz, polarization and empirical absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm were applied [24]. The structures were solved by the direct method and subsequently completed by the difference of Fourier recycling. All the non-hydrogen atoms were refined anisotropically using a full-matrix least-squares technique. The Olex2 and SHELXS, SHELXL programs were used for all the calculations [25,26]. Atomic scattering factors were incorporated in the computer programs. Details of crystal data and refinement are gathered in Table 1.

Results and discussion

In our previous and present studies, the synthesis of some hydroxyquinolines and their carboxylic acid derivatives have been reported and characterized by using IR, MS, UV–Vis, multinuclear NMR spectroscopic techniques, and single crystal X-ray diffraction method (Scheme 1) [6,7]. X-ray crystal structure analysis showed the presence of hydrogen-bond donating and accepting sites between the pyridine and hydroxyl functional groups. It has been demonstrated by solution and solid state NMR studies that there was a tautomeric equilibrium among the neutral, cationic and anionic species of hydroxyquinoline carboxylic acids obtained by protonation or deprotonation, through the evaluation of ^{13}C and ^{15}N chemical shifts [10]. The largest effect is visible in the ^{15}N NMR spectra which allow to distinguish the species between protonated and unprotonated pyridine rings. These measurements are best applicable in the solid state.

Synthetic remarks

The compounds of hydroxymethylquinolines **2a**, **2b** and **2c** have been synthesized by adopting Skraup–Doebner–Von Miller