Synthesis of 2-acetylbenzo[*h*]- and 3-acetylbenzo[*f*]quinolines by the reaction of benzo[*h*]- and benzo[*f*]quinolines with C_2H_5OH and CCl_4 catalyzed by Cu-containing catalysts

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Abstract

2-Acetylbenzo[*h*]quinoline and 3-acetylbenzo[*f*]quinolines have been selectively synthesized in yields of 58% and 60%, respectively, by the reaction of benzo[*h*]quinoline and benzo[*f*]quinoline with ethanol and carbon tetrachloride catalyzed by Cu-containing catalysts. The molecular structure of 3-acetylbenzo[*f*]quinoline was confirmed by X-ray diffraction method.

Keywords: 2-Acetylbenzo[*h*]quinoline, 3-acetylbenzo[*f*]quinoline, benzo[*h*]quinoline, benzo[*f*]-quinoline, copper compounds

Introduction

Acyl derivatives of benzoquinolines are an important class of organic compounds. They are used in the synthesis of antimalarial agents, azahelicenes having unique optical and spectral properties, sensitizers, and ligands for coordination chemistry.[1-8]

The known methods for the synthesis of acetylbenzoquinolines are complicated and comprise several steps. For example, 2-acetylbenzo[*h*]quinoline **1** was synthesized in a 77% yield in two steps from 2-bromobenzo[*h*]quinoline by metallation with n-butyllithium followed by acylation of 2-lithiobenzo[h]quinoline with *N,N*-dimethylacetamide at -78 ºC.[7]

2-Acetylbenzo[*h*]quinoline **1** can be prepared by reduction of methyl 2-benzo[*h*]-quinolinecarboxylate, which is difficult to obtain, with trimethylaluminum.[9]

To our knowledge, no mention of the synthesis of 3-acetylbenzo[*f*]quinoline **2** is present in the literature. A method for the preparation of its regioisomer, 2-acetylbenzo[*f*]quinoline, by cyclization of 2-napthylamine with acetoacetaldehyde dimethyl acetal was reported.[10]

In this paper we wish to report the results of our investigations into the Cu-catalyzed acylation reaction of benzo[*h*]quinoline **3** and benzo[*f*]quinoline **4** with the CCl_4–C_2H_5OH–metal complex catalyst system, which generates *in situ* acetaldehyde, in order to develop a one-step method for the synthesis of 2-acetylbenzo[*h*]- **1** and 3-acetylbenzo[*f*]quinolines **2**.

In our previous work, this system with $Fe[C_5H_5]_2$ as the catalyst was successfully used for the synthesis of 1-acetylisoquinoline from isoquinoline.[11]

According to the literature data, in recent years, for the functionalization of quinoline and its derivatives, metal complex catalysts have been successfully used.[12,13]

Results and Discussion

Our ongoing studies have shown that the acetylation of benzo[*h*]- and benzo[*f*]quinolines with C_2H_5OH and CCl_4 can be also catalyzed by copper compounds. Among copper salts and complexes ($Cu(acac)_2$, $CuOAc$, $Cu(OAc)_2$, $Cu(C_6H_5CO_2)_2 \cdot 2H_2O$, $Cu(C_6H_4(OH)CO_2)_2$, $CuBr$, $CuBr_2$, $CuCl_2 \cdot 2H_2O$ and CuI) selected as catalysts, CuI was found to be the most effective and selective. Thus, the interaction between benzo[*h*]quinoline **3**, C_2H_5OH and CCl_4 in the presence of CuI as the catalyst under optimized reaction conditions (150 ºC, 6 h, [CuI]: [benzo[*h*]quinoline **3**]:[ethanol]:[CCl_4] molar ratio = 1:100:1000:1000) led to the formation of 2-acetylbenzo[*h*]quinoline **1** in 58% yield (Scheme 1, Table 1).
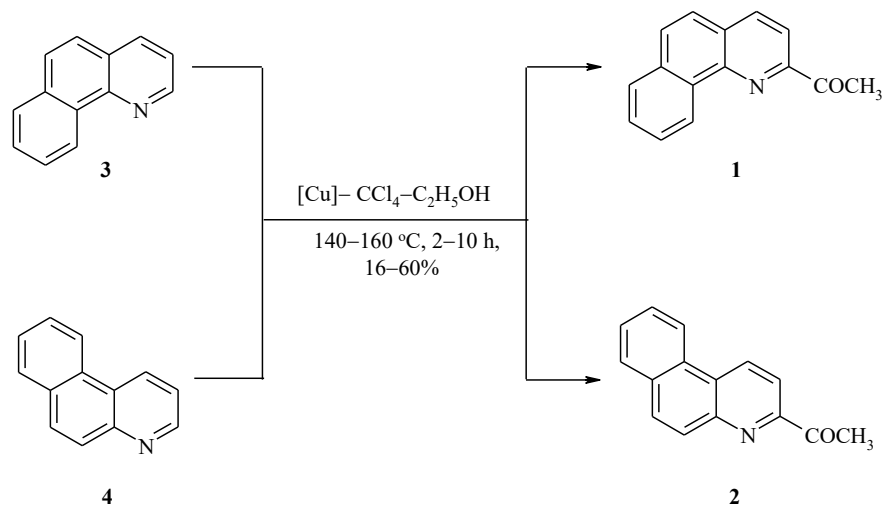
Scheme 1. The reaction of benzo[*h*]quinoline **3** with ethyl alcohol.

Table 1. Dependence of 2-acetylbenzo[*h*]quinoline **1** on the catalyst nature and reaction conditions

Entry	Molar ratio [cat] : [**3**] : [CCl$_4$] : [EtOH]	Catalyst	Temperature, h°C	t, h	Yield of **1**, %
1	1 : 100 : 1000 : 1000	CuI	140	6	34
2	1 : 100 : 1000 : 1000	Cu(acac)$_2$	150	6	33
3	-«-	Cu(OAc)$_2$	-«-	-«-	43
4	-«-	Cu(OAc)	-«-	-«-	46
5	-«-	C$_{14}$H$_{10}$O$_4$Cu · 2H$_2$O	-«-	-«-	40
6	-«-	C$_{14}$H$_{10}$O$_6$Cu	-«-	-«-	45
7	-«-	CuBr	-«-	-«-	43
8	-«-	CuBr$_2$	-«-	-«-	40
9	-«-	CuI	-«-	-«-	58
10	1 : 100 : 1000 : 1500	-«-	-«-	-«-	45
11	1 : 100 : 1000 : 500	-«-	-«-	-«-	37
12	1 : 100 : 1500 : 1000	-«-	-«-	-«-	47
13	1 : 100 : 500 : 1000	-«-	-«-	-«-	20
14	1 : 100 : 500 : 1500	-«-	-«-	-«-	34
15	1 : 100 : 1500 : 500	-«-	-«-	-«-	40
16	1 : 100 : 1500 : 1500	-«-	-«-	-«-	50
17	1 : 100 : 1000 : 1000	-«-	-«-	2	20
18	-«-	-«-	-«-	10	40
19	-«-	-«-	160	6	40

In the presence of other copper-containing catalysts such as Cu(acac)$_2$, CuOAc, Cu(OAc)$_2$, C$_{14}$H$_{10}$O$_4$Cu · 2H$_2$O, C$_{14}$H$_{10}$O$_6$Cu, CuBr, CuBr$_2$, or CuCl$_2$ · 2H$_2$O , the yield of 2-acetylbenzo[*h*]quinoline **1** was lower, being 30–50%. It should be noted that at temperatures below 140 °C the yield of **1** did not exceed 15%.

It is noteworthy that increase in the reaction time to more than 10 h is undesirable, as the yield of 2-acetylbenzo[*h*]quinoline **1** decreases to 40% due to resinification of the products.

Benzo[*f*]quinoline **4** reacts with C$_2$H$_5$OH and CCl$_4$ in a similar way to afford 3-acetylbenzo[*f*]quinoline **2**, its yield in the presence of Cu(OAc)$_2$ being 60%. When the reaction was catalyzed by CuI, CuBr$_2$, Cu(acac)$_2$, Cu(C$_6$H$_5$CO$_2$)$_2$·2H$_2$O, Cu(C$_6$H$_4$(OH)CO$_2$)$_2$, or CuCl$_2$·2H$_2$O, the yield of 3-acetylbenzo[*f*]quinoline **2** was 20-50% (Scheme 1, Table 2).

Table 2 Dependence of the yield of 3-acetylbenzo[*f*]quinoline **2** on the catalyst nature and reaction conditions

Entry	Molar ratio [cat] : [**4**] : [CCl$_4$] : [EtOH]	Catalyst	Temperature, h°C	t, h	Yield of **2**, %
1	1 : 100 : 750 : 6500	CuI	150	6	50
2	-«-	CuBr$_2$	-«-	-«-	55
3	-«-	Cu(acac)$_2$	-«-	-«-	50
4	-«-	Cu(OAc)$_2$	-«-	-«-	60
5	-«-	Cu(C$_6$H$_5$CO$_2$)$_2$·2H$_2$O	-«-	-«-	17
6	-«-	Cu(C$_6$H$_4$(OH)CO$_2$)$_2$	-«-	-«-	28
7	-«-	CuCl$_2$·2H$_2$O	-«-	-«-	34
8	1 : 100 : 400 : 6500	Cu(OAc)$_2$	-«-	-«-	21
9	1 : 100 : 1500 : 6500	-«-	-«-	-«-	47
10	1 : 100 : 750 : 3000	-«-	-«-	-«-	60
11	1 : 100 : 1500 : 3000	-«-	-«-	-«-	57
12	1 : 100 : 400 : 3000	-«-	-«-	-«-	46
13	1 : 100 : 750 : 3000	-«-	160	-«-	30
14	-«-	-«-	150	3	16
15	-«-	-«-	-«-	9	60
16	-«-	-«-	140	6	26

The structures of compounds **1** and **2** were proved by the data of 1D (^{1}H, ^{13}C) and 2D (COSY, HSQC, HMBC) NMR spectroscopy and by comparison with the spectra of the starting benzo[*h*]-**3** and benzo[*f*]quinolines **4**.

Indeed, the ^{13}C NMR signal for the C-2 atom of 2-acetylbenzo[*h*]quinoline **1** is shifted downfield (δ 151.60 ppm) with respect to the C-2 signal of the protonated carbon atom (δ 148.81 ppm) of benzo[*h*]quinoline **3**.

Our attempts to grow a single crystal for 2-acetylbenzo[*h*]quinoline **1** were unsuccessful. Therefore, we did not give the X-ray diffraction data. As product **1** is a known compound, we have given only one-dimensional NMR spectrum. Taking into account the referee's advises, we have recorded new one-dimensional (^{1}H, ^{13}C) and two-dimensional (COSY, HSQC, HMBC)

spectra for this compound. These data have been included in the Supplementary Material. The appropriate changes have been also made in the text by inserting the following lines:

In the COSY spectrum of compound **1** one could observe the four-spin system (d, δ = 7.93; t, δ =7.77; t, δ = 7.80; d, δ = 9.35 ppm) associated with proton interactions in the ring C and assigned to four protons H (7,8,9,10). The spectrum also demonstrates the two-spin system associated with proton interactions in the ring B and assigned to H(5) and H(6). Two-proton singlet at δ = 8.24 ppm was assigned to degenerate protons H(3) and H(4) in the ring A, which is consistent with the published data.[8,9] The HSQC and HMBC experimental data fully confirmed the structure **1**. Thus, the H(4) signal (δ = 8.24) has a cross peaks with C(2) and C(10″) signals at δ = 151.60 and δ = 145.38 ppm respectively. The low-field H-10 signal at δ = 9.35 correlated to quaternary carbon peaks at 133.71 ppm for C(10′) and 145.38 ppm for C(10″).

3-Acetylbenzo[*f*]quinoline **2** was characterized by 2D (COSY, HSQC, HMBC) NMR data. The low-field doublet for the H-1 proton (δ 8.98 ppm; $^3J_{HH}$ 8 Hz) coupled with the H-2 proton (δ 8.25 ppm) is correlated in the HMBC experiment with two signals for the C-3 (δ 152.63 ppm) and C-4a (δ 147.22 ppm) carbon atoms bearing no hydrogens owing to the ^3J three-bond spin-spin coupling, ^{1}H-1 – ^{13}C-3 (^{13}C-4a).

These data unambiguously indicate that the acetyl group is located at the C-3 atom of the pyridine moiety of **2**.

The structure of 3-acetylbenzo[*f*]quinoline **2** was confirmed unambiguously by X-ray diffraction. As can be seen from Fig. 1, the atoms of the benzoquinoline moiety are coplanar to an accuracy of 0.01 Å. The peripheral benzene and pyridine rings form dihedral angles of 0.429° and 1.038°, respectively, with the central benzene ring, while the angle between the peripheral rings is 1.125°. The torsion angles N4 – C3 – C11 – O13 and N4 – C3 – C11 – C12 are 174.57° and 6.15°, respectively, which attests to slight deviation of the acetyl group from the benzoquinoline plane. In the crystal, the molecules of compound **2** form stacks along the b axis, the intermolecular distance between the centers of the benzene ring being 5.588 Å. Note that the shortest distance between the proton of the central benzene ring of a molecule in one stack and nitrogen of the neighboring molecule is 3.572Å, which is much longer than the sum of the van der Waals radii (2.7Å); hence, no intermolecular hydrogen bonds are formed.
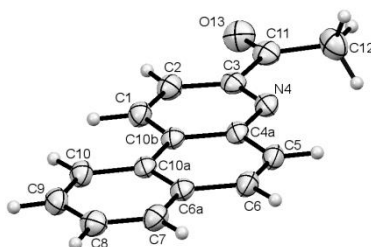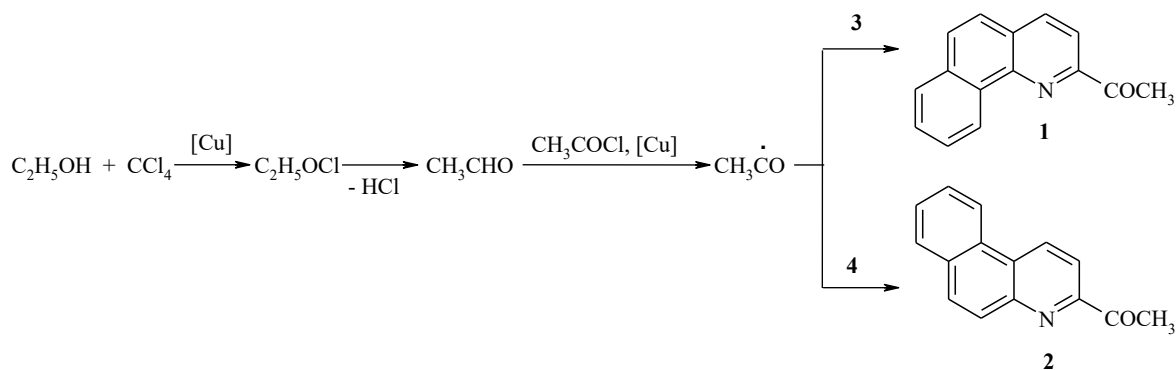

Figure 1. Geometry of the molecule of compound **2**. The atoms are shown by thermal ellipsoids (p = 50%).

In view of the data obtained in the previous study,[11] the possible reaction mechanism may include the oxidation of ethanol to acetaldehyde by CCl_4 under the action of the metal complex catalyst. Subsequently, acetaldehyde generates the acetyl radical, which reacts with benzo[*h*]quinoline **3** or benzo[*f*]quinoline **4** to yield 2-acetylbenzo[*h*]- **1** and 3-acetylbenzo[*f*]quinolines **2** similarly to the Minisci reaction (Scheme 2).[14]

$$C_2H_5OH + CCl_4 \xrightarrow[\text{[Cu]}]{} C_2H_5OCl \xrightarrow[- HCl]{} CH_3CHO \xrightarrow[\text{CH}_3\text{COCl, [Cu]}]{} CH_3\overset{\bullet}{C}O$$

Scheme 2. The possible reaction mechanism

Conclusions

2-Acetylbenzo[*h*]quinoline **1** and 3-acetylbenzo[*f*]quinoline **2** were synthesized by acetylation of benzo[*h*]quinoline **3** and benzo[*f*]quinoline **4** by means of C_2H_5OH and CCl_4 in the presence of copper-containing catalysts.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-400 spectrometer (400.13 and 100.62 MHz, respectively) in $CDCl_3$, the chemical shifts are referred to TMS. Mass spectra were run on a Shimadzu GCMS-QP2010Plus GC/MS spectrometer (an SPB-5 capillary column, 30 m × 0.25 mm, helium as a carrier gas, temperature programming from 40 to 300ºC at 8 °C/min, evaporation temperature 280 ºC, temperature of the ion source 200 ºC, ionization energy 70 eV). Chromatographic analysis was carried out on a Shimadzu GC-9A, GC-2014 instrument [2 m × 3 mm column, silicone SE-30 (5%) on Chromaton N-AW-HMDS as the stationary phase, temperature programming from 50 to 270 ºC at 8 °C/min, helium as the carrier gas (47 mL/min)]. The single crystal of **2** was prepared by slow evaporation of it $CHCl_3$ solution. Intensities of 4060 reflections (2557 independent reflections, R_{int} = 0.0178) were measure on a XCalibur Eos diffractometer with graphite monochromated Mo-Kα radiation (graphite monochromated Mo kα radiation, λ = 0.71073 Å, w-scan technique, $2\theta_{max}$ = 62.25°, T = 200.2K). Collection and processing of data performed with using the program CrysAlis[Pro] Oxford Diffraction Ltd., Version

1.171.36.20. The structure was solved by direct methods as implemented in the program SHELXS-97.[13] The refinement was carried out using SHELXL-97.[15] The structure was refined by a full-matrix least-square technique using anisotropic thermal parameters for non-hydrogen atoms.

Crystal data of **2**: $C_{15}H_{11}NO$, $M = 221.25$, monoclinic, $P2_1/n$(no. 14), $a = 9.6319(11)$ Å, $b = 5.5882(5)$ Å, $c = 20.3798(15)$ Å, $\beta = 101.533(10)$, $V = 1074.79(18)$ Å^3, $T = 200.(2)$, $D_{calc} = 1.367$ mg/mm^3, $Z = 4$, reflections collected = 4060, independent reflections = 2557 ($R_{int} = 0.0178$), final R indexes [$I > 2\sigma(I)$]: $R_1 = 0.0631$, $wR_2 = 0.1700$; R indexes (all data): $R_1 = 0.0884$, $wR_2 = 0.1935$. Crystallographic data for the structure of **1** have been deposited in the Cambridge Crystallographic Data Centre as a CIF deposition with file number CCDC 1033630. Copies of these data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk) or from http://www.ccdc.cam.ac.uk/data_request/cif.

The reactions were carried out in a 10 mL glass ampoule placed in a 17 mL stainless-steel microautoclave with continuous stirring and controlled heating.

Synthesis of 2-acetylbenzo[*h*]quinoline (1). An ampoule was charged in an argon flow with CuI (0.0021 g, 0.01 mmol), benzo[*h*]quinoline **3** (0.2 g, 1 mmol), CCl$_4$ (1.1 mL, 10 mmol), and C_2H_5OH (0.65 mL, 10 mmol). The sealed ampoule was placed in an autoclave, and the autoclave was tightly closed and heated for 6 h at 150 ºC with continuous stirring. After completion of the reaction, the autoclave was cooled down to room temperature, and the ampoule was opened. The reaction mixture was passed through an Al_2O_3 layer and neutralized with an aqueous solution of Na_2CO_3. The product was extracted with CHCl$_3$. The organic phase was filtered through a silica gel layer using chloroform as the eluent. The reaction product was eluted with the first portion of the solvent and the starting benzo[*h*]quinoline **3** was eluted with the subsequent portion. The isolated **1** can be recycled to the reaction after evaporation of the solvent. From the first portion, the solvent was distilled off, and 2-acetylbenzo[*h*]quinoline **1** was recrystallized from ethanol. The total yield of 2-acetylbenzo[*h*]quinoline **1** was 58%.

Synthesis of 3-acetylbenzo[*f*]quinoline (2). An ampoule was charged in an argon flow with Cu(OAc)$_2$ (0.5 mg, 0.0027 mmol), benzo[*f*]quinoline **4** (50 mg, 0.27 mmol), CCl$_4$ (0.19 ml, 1.96 mmol), and C_2H_5OH (0.49 ml, 8.29 mmol). The sealed ampoule was placed in an autoclave and the autoclave was tightly closed and heated for 6 h at 150 ºC with continuous stirring. After completion of the reaction, the autoclave was cooled down to room temperature, and the ampoule was opened. The reaction mixture was passed through an Al_2O_3 layer and neutralized with an aqueous solution of Na_2CO_3. The product was extracted with chloroform. The solvent was distilled off. The resulting 3-acetylbenzo[*f*]quinoline **2** was passed through a silica gel column using chloroform as the eluent. A 3-acetylbenzo[*f*]quinoline **2** sample of 98% purity was prepared by recrystallization from a 1 : 1 ethyl acetate : hexane mixture. The total yield of 3-acetylbenzo[*f*]quinoline **2** was 60%.

2-Acetylbenzo[*h*]quinoline (1).[8-9] Yield 58%; mp 115-116 °C. ^{1}H NMR (400.13 MHz, CDCl$_3$): 3.00 s (3H, COCH$_3$), 7.69 d (1H, *J* 9 Hz; C^{5}H), 7.80 t (1H, 8 Hz; C^{9}H), 7.77 t (1H, *J* 8 Hz; C^{8}H), 7.88 d (1H, *J* 9 Hz; C^{6}H), 7.93 д (1H, *J* 8 Hz; C^{7}H), 8.24 s (2H, C^{3,4}H), 9.35 d (1H, *J* 8 Hz; C^{10}H). ^{13}C NMR (100.62 MHz, CDCl$_3$): 25.77 (C^{12}), 118.87 (C^3), 124.48 (C^{10}), 124.92 (C^5), 127.50 (C^9), 127.97 (C^7), 128.35 (C$^{4'}$), 128.63 (C^8), 133.71 (C$^{10'}$), 130.00 (C^6), 131.63 (C$^{6'}$), 136.49 (C^4), 145.38 (C$^{10''}$), 151.60 (C^2), 200.68 (C^{11}). MS: *m/z* (%)=221.10 (M$^+$, 100), 194.10 (11.06), 193.10 (74.59), 180.10 (11.90), 179.10 (87.51), 178.10 (83.11), 177.10 (20.89), 176.10 (4.25), 153.15 (3.87), 152.15 (10.38), 151.15 (33.51), 150.15 (15.77), 125.15 (3.98), 89.10 (4.17), 75.15 (7.71), 43.05 (10.91).

3-Acetylbenzo[*f*]quinoline (2). Yield 60%; mp 146 °C. ^{1}H NMR (400.13 MHz, CDCl$_3$): 2.91 s (3H, COCH$_3$), 7.71-8.61 m (4H), 8.01 s (2H), 8.25 d (1H, *J* 8.6 Hz), 8.98 d (1H, *J* 8.6 Hz). ^{13}C NMR (100.62 MHz, CDCl$_3$): 25.66 (C^{12}), 118.49 (C^2), 123.24 (C^{10}), 127.39 (C^9), 127.43 (C$^{10''}$), 128.24 (C^8), 128.48 (C^6), 128.78 (C^7), 129.17 (C$^{10'}$), 131.36 (C^1), 131.44 (C^5), 132.47 (C$^{6'}$), 147.22 (C$^{4'}$), 152.63 (C^3), 200.49 (C^{11}). MS: *m/z* (%)=221.05 (M$^+$, 97.33), 194.05 (12.92), 193.05 (81.33), 180.05 (13.11), 179.05 (100.00), 178.05 (83.16), 177.05 (27.48), 176.05 (5.51), 152.10 (19.21), 151.10 (49.87), 150.10 (22.01), 126.05 (4.48), 89.00 (4.65), 76.05 (4.60), 75.05 (10.89), 63.00 (4.07), 51.00 (3.52).

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