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SYNTHESIS OF 6,7-DIHYDRODIBENZO[*b,j*]PHENANTHROLINE DERIVATIVES BY PFITZINGER CONDENSATION OF ISATIN AND CYCLIC DIKETONES

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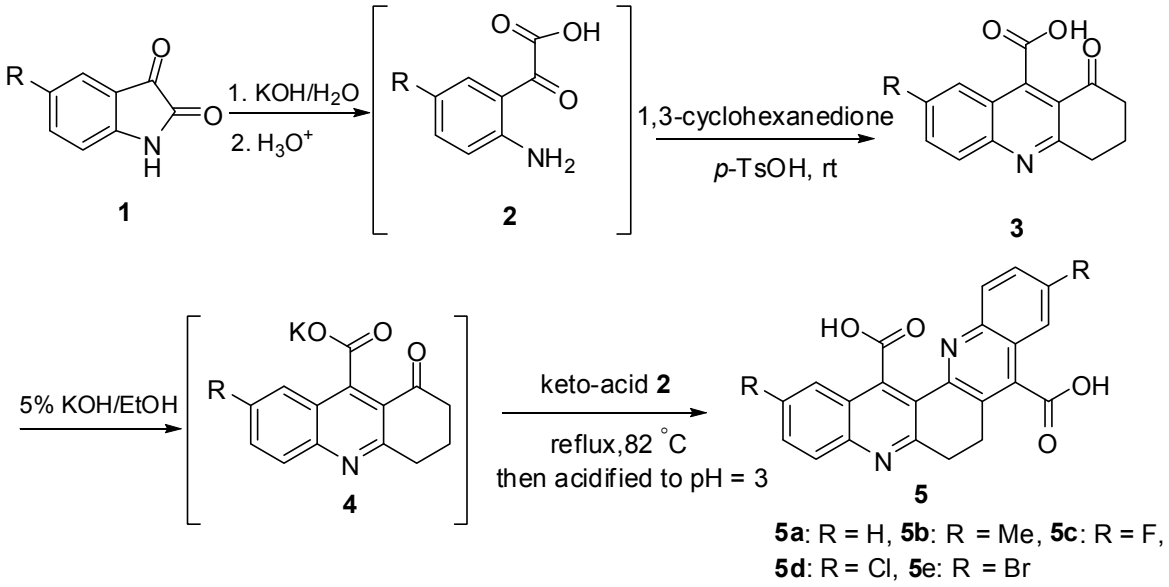
Abstract – All two kinds of 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives were synthesized by Pfitzinger condensation of isatins with 1,3-cyclohexanedione and 1,4-cyclohexanedione respectively. Structures of the derivatives were confirmed by NMR and other spectra data.

The family of acridine derivatives includes many pharmacologically significant compounds such as actinomycin-D, daunomycin, and adriamycin, and some of which show the significant bioactivity of inhibiting topoisomerase emzyme.[1-3] As one type of acridine compounds, the 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives may be of new use and interesting. The Pfitzinger reaction[4] is probably a shortcut to obtain these derivatives, yet there are few successful examples synthesized by 1,3-diketones and isatins via this reaction up to date. During our investigation of synthetic methodologies,[5,6] we had established a simple method for synthesis of quinoline-4-carboxylic acid derivatives by an improved Pfitzinger protocol, then we further explored synthesis of 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives by Pfitzinger condensation. Herein, we will report successful synthesis of several 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives by double condensations of isatins with 1,3-cyclohexanedione and 1,4-cyclohexanedione in aqueous media.

The 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives seem to be readily synthesized by Pfitzinger condensation of isatin and1,4-cyclohexanedione or 1,3-cyclohexanedione in a 2:1 molar ratio. However, the cyclic diketones generally react with one molecule of istain to give the quinoline, few of them react with two molecules of isatins and it usually requires higher reaction temperature (>160 °C) for the formation of the biquinoline. On the other hand, it showed impossible to obtain the corresponding pure quinolines[7] by reaction of isatins with such cyclic diketones as 1,3-cyclohexanedione or

1,4-cyclohexanedione under the usual Pfitzinger conditions, although many other synthetic methods for synthesis had been developed due to their importance for drug researches in recent years.[8]

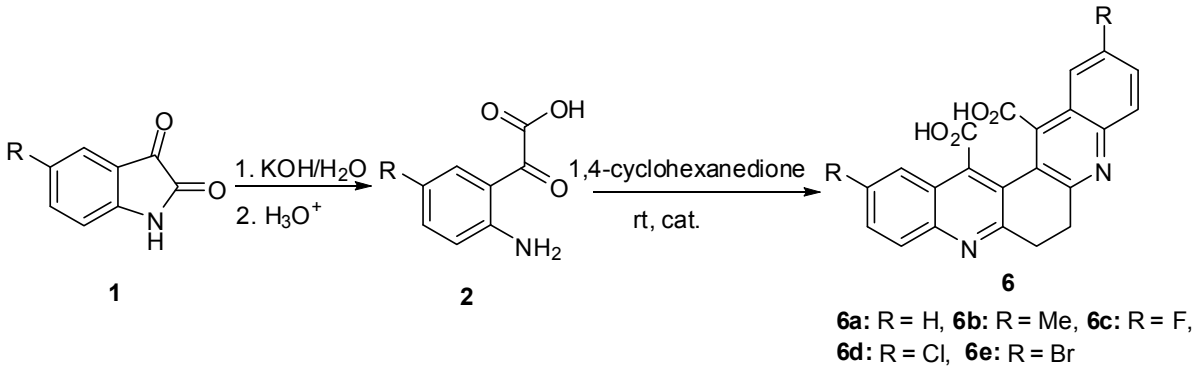
In our improved protocol as shown in Scheme 1, the 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives could be achieved from isatins **1** and 1,3-cyclohexanedione by two steps. In the first step, ring-opening reaction of **1** occurred under alkaline condition and then transferred to the intermediate keto-acid **2** by acidification, which consequently condensated with 1,3-cyclohexanedione to give the monocondensed product **3**. In the second step, the corresponding quinoline-4-carboxylic acid **3** was isolated and condensed again with one molecule of isatin at about 82 °C to give the 6,7-dihydrodibenzo[*b,j*]-phenanthroline derivative **5**. It should be noted that the two steps of condensations using different keto-acid substrates should be separately performed, the final productions would be very complex if they were successively performed in one pot. Unsimilar with the common Pfitzinger in the first step, the keto-acid **2** was necessary for the condensation, but the keto-acid salt **4** should be still used in the second step. In addition, in the first step, the copper sulphate appeared to be the best catalyst and the pH should be always kept at 2-3 with hydrochloric acid till the quinoline **3** precipitated from water completely according to our previous work.[6]



Scheme 1. The 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives prepared from isatins and 1,3-cyclohexanedione in two steps

The generality of this procedure was also explored. The same protocol could also be applied to other similar diquinolines from the corresponding alkyl or halogen-substituted acid salts and 1,3-cyclohexanedione. The highest yield was achieved with 5-methylindoline-2,3-dione in 85%, and the lowest, with 5-bromoindoline-2,3-dione in 57%.

Surprisingly, the 1,4-cyclohexanedione was showed to react readily with two molecules of the alkyl or halogen-substituted isatin **1** to form biquinoline **6** as Scheme 2. Consendation of 1,4-cyclohexanedione with isatin under acid condition would give the biquinoline **6** in one step regardless of the ratio of 1,4-cyclohexanedione to **1** in the reaction was 1:2 or not. The double condensations could go on successfully in one step and gave the biquinolines **6** .The reason why this reaction happened was probably due to 1,4-cyclohexanedione with two keto groups separated by more than one carbon atom and the steric hindrance became smaller for condensation.[9] The lowest yield for **6e** was 35%, although the yields were not very high, the corresponding biquinolines can be conveniently prepared by this method with isatins. Other diketones such as 5,5-dimethyl-1,3-cyclohexanedione, 1,3-indanedione were also tried to be used to prepare the biquinolines but failed.



Scheme 2. The 6,7-dihydrodibenzo[*b,j*]phenanthroline derivatives prepared from isatins and 1,4-cyclohexanedione in one-step

Constructions of all the compounds **5** and **6** were confirmed by NMR and other spectra data. The symmetrical configuration of the compounds **6a-e** was proved by NMR, Specifically, the resonance signals of the ^{13}C-NMR and DEPT were clearly half of the total number of carbons in biquinolines **6** for each corresponding compound. Because of their poor solubility in DMSO-d_6 and other common deuterated reagents, the compounds **6d** and **6e** were elucidated by the solid state NMR Spectroscopy, MS and element analysis.

The detailed mechanism of the Pfitzinger reaction we preferred to think was probably the Claisen condensation path as shown in our previous work.[6]

EXPERIMENTAL

The melting points were measured on WRS-1B digital melting points apparatus and are uncorrected. The progress of the reaction was monitored by TLC. ^{1}H NMR spectra were determined on a Brucker AVANCE 400 NMR spectrometer at 400 MHz in DMSO-d_6 using TMS as internal standard. ^{1}H MAS

and ^{13}C CP/MAS NMR experiments were performed on Bruker AVANCE III 600 spectrometer at a resonance frequency of 600.1 MHz and 150.9 MHz, respectively. The chemical shifts of ^{1}H and ^{13}C NMR were externally referenced to TMS. Elemental analysis was estimated on an Elementar Vario EL-III element analyzer. Mass spectra were determined using a MSD VL ESI1 spectrometer.

General procedure for the synthesis of 6,7-dihydrodibenzo[*b,j*][1,7]phenanthroline-8,14-dicarboxylic acid (5a).

The mixture of keto-acid salt **2** (203 mg, 1 mmol) and compound **4** (279 mg, 1 mmol) in 5% ethanolic KOH solution (5 mL) was heated to reflux for 5 h. After cooling, the solvent was evaporated. Water was added and the mixture was acidified with concentrated hydrochloric acid to pH 2-3 and the precipitate appeared. After filtration, the yellow solid **5a** was purified by chromatography on silica gel eluting with $CHCl_3$/MeOH (3:1).

6,7-Dihydrodibenzo[*b,j*][1,7]phenanthroline-8,14-dicarboxylic acid (5a): A yellow powder; 288.9 mg yield 78%; mp 273–274 °C; R_f 0.49 (2:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.23 (dd, J = 4.0, 7.2 Hz, 2H), 3.34 (dd, J = 4.0, 7.2 Hz, 2H), 7.63–7.67 (m, 1H), 7.68–7.72 (m, 1H), 7.78–7.82 (m, 1H), 7.83–7.89 (m, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.05 (t, J = 8.0 Hz, 2H), 13.78 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.9, 31.8, 122.3, 123.0, 123.6, 125.2, 125.7, 127.2, 127.6, 128.7, 129.0, 129.5, 130.8, 139.2, 146.0, 147.3, 150.2, 159.9, 168.8, 169.1. Anal. Calcd for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.33; H, 3.80; N, 7.58.

2,10-Dimethyl-6,7-dihydrodibenzo[*b,j*][1,7]phenanthroline-8,14-dicarboxylic acid (5b): A brown powder; 338.7 mg, yield 85%, mp 291–293 °C; R_f 0.51(2:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (s, 3H), 2.56 (s, 3H), 3.25 (dd, J = 4.0, 7.2 Hz, 2H), 3.34 (dd, J = 4.0, 7.2 Hz, 2H), 7.65–7.71 (m, 4H), 7.96–8.00 (m, 2H), 13.67 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.4, 21.6, 25.1, 31.6, 122.2, 122.7, 123.3, 123.5, 124.1, 126.5, 128.5, 128.9, 132.0, 133.0, 136.8, 138.0, 138.4, 144.6, 145.9, 149.5, 158.7, 168.3, 169.1. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.34; H, 4.56; N, 7.01.

2,10-Difluoro-6,7-dihydrodibenzo[*b,j*][1,7]phenanthroline-8,14-dicarboxylic acid (5c): A brown powder; 329.1 mg, yield 81%, mp 304–305 °C; R_f 0.43 (2:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.28–3.30 (m, 2H), 3.32–3.34 (m, 2H), 7.58–7.65(m, 2H), 7.77–7.83 (m, 2H), 8.09–8.17 (m, 2H), 13.62 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.0, 31.4, 108.6, 108.8, 120.0, 121.0, 122.9, 124.0, 124.2, 127.7, 131.8, 132.1, 138.6, 143.2, 144.6, 149.7, 158.9, 159.4, 161.3, 161.9, 168.0, 168.7. Anal. Calcd for $C_{22}H_{14}F_2N_2O_4$: C, 65.03; H, 2.98; F, 9.35; N, 6.89. Found: C, 65.03; H, 2.97; F, 9.36; N, 6.88.

2,10-Dichloro-6,7-dihydrodibenzo[*b,j*][1,7]phenanthroline-8,14-dicarboxylic acid (5d): A yellow powder; 276.7 mg, yield 63%, mp 301–302 °C; R_f 0.46 (2:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz,

DMSO-d_6) δ 3.32 (dd, J = 3.8, 7.2 Hz, 2H), 3.38 (dd, J = 3.8, 7.2 Hz, 2H), 7.89–7.94 (m, 4H), 8.07–8.12 (m, 2H), 13.88 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.0, 31.4, 122.9, 123.4, 123.6, 124.0, 124.2, 128.4, 130.6, 131.0, 131.2, 131.5, 131.9, 132.9, 137.6, 138.4, 144.3, 145.8, 150.5, 160.5, 167.5, 168.5. Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_4$: C, 60.16; H, 2.75; Cl, 16.14; N, 6.38. Found: C, 60.14; H, 2.76; Cl, 16.16; N, 6.36.

2,10-Dibromo-6,7-dihydrodibenzo[*b,j*][1,7]phenanthroline-8,14-dicarboxylic acid (5e): A yellow powder; 301.0 mg, yield 57%, mp 303–305 °C; R_f 0.48 (2:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.17–3.24 (m, 4H), 7.77–7.97 (m, 4H), 8.12–8.14 (m, 2H), 12.95 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.8, 31.1, 122.7, 123.2, 123.4, 123.8, 124.0, 128.2, 130.4, 130.8, 131.0, 131.3, 131.7, 132.7, 137.4, 138.2, 144.1, 145.6, 150.3, 160.3, 167.2, 168.3. Anal. Calcd for $C_{22}H_{14}Br_2N_2O_4$: C, 50.03; H, 2.29; Br, 30.26; N, 5.30. Found: C, 50.03; H, 2.27; Br, 30.26; N, 5.31.

General procedure for the synthesis of 6,7-dihydrodibenzo[*b,j*][4,7]phenanthroline-13,14-dicarboxylic acid (6a). The mixture of isatin (294 mg, 2 mmol) and potassium hydroxide (250 mg) in water (5 mL) was stirred at room temperature for 30 min. Then the mixture was acidified with concentrated hydrochloric acid to pH 2-3 and added 1,4-cyclohexanedione (112 mg, 1 mmol), *p*-TsOH·H_2O (17 mg, 0.1 mmol). The resulting mixture was stirred and the precipitate appeared. The reaction progress was monitored by TLC (silica gel; $CHCl_3$/MeOH, 3:1, v/v). After the starting material had vanished, the precipitate was filtered out, washed with water, and recrystalized to afford the compound **6a**.

6,7-Dihydrodibenzo[*b,j*][4,7]phenanthroline-13,14-dicarboxylic acid (6a): A yellow powder, 281.5 mg, yield 76%, mp 264–265 °C (MeOH); R_f 0.49 (4:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19 (d, J = 10.7 Hz, 2H), 3.30 (d, J = 10.5 Hz, 2H), 7.68 (t, J = 7.4 Hz, 2H), 7.85 (t, J = 7.5 Hz, 2H), 8.09 (d, J = 8.0 Hz, 2H), 8.37 (d, J = 8.4 Hz, 2H), 13.90 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.6, 121.9, 123.3, 124.1, 125.7, 127.2, 129.0, 137.0, 145.2, 159.4, 165.6. Anal. Calcd for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56; O, 17.28. Found: C, 71.33; H, 3.81; N, 7.57; O, 17.29.

2,11-Dimethyl-6,7-dihydrodibenzo[*b,j*][4,7]phenanthroline-13,14-dicarboxylic acid (6b): A yellow powder, 235.7 mg, yield 79%, mp 349–350 °C (MeOH). R_f 0.48 (4:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 2H), 2.53 (s, 2H), 3.13–3.27 (m, 4H), 6.81 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 13.69 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.1, 33.0, 109.3, 109.5, 120.6, 131.8, 131.9, 144.3, 159.1, 160.6, 161.6, 167.0. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.34; H, 4.56; N, 7.02.

2,11-Difluoro-6,7-dihydrodibenzo[*b,j*][4,7]phenanthroline-13,14-dicarboxylic acid (6c): A yellow powder; 264.0 mg, yield 65%, mp 293–294 °C (MeOH); R_f 0.40 (4:1 $CHCl_3$–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.18–3.31 (m, 4H), 7.81 (td, J = 2.8, 8.4 Hz, 2H), 8.05 (dd, J = 2.2, 10.8 Hz, 2H), 8.17

(dd, J = 5.6, 9.2 Hz, 2H), 14.11 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 32.8, 109.2, 120.4, 120.6, 124.0, 124.1, 131.7, 144.1, 158.9, 160.4, 161.4, 166.9. Anal. Calcd for $C_{22}H_{14}F_2N_2O_4$: C, 65.03; H, 2.98; F, 9.35; N, 6.89. Found: C, 65.04; H, 2.96; F, 9.35; N, 6.88.

2,11-Dichloro-6,7-dihydrodibenzo[*b,j*][4,7]phenanthroline-13,14-dicarboxylic acid (6d): A brown powder; 224.0 mg, yield 51%, mp 296–297 °C; R_f 0.39 (4:1 $CHCl_3$–MeOH); ^{13}C CP/MAS NMR δ 33.1, 122.3, 124.7, 130.1, 144.3, 160.3, 177.4. Anal. Calcd for $C_{22}H_{12}Cl_2N_2O_4$: C, 60.16; H, 2.75; Cl, 16.14; N, 6.38. Found: C, 60.16; H, 2.76; Cl, 16.15; N, 6.38. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{12}Cl_2N_2O_4$, 438.1921; found, 438.1915.

2,11-Dibromo-6,7-dihydrodibenzo[*b,j*][4,7]phenanthroline-13,14-dicarboxylic acid (6e): A brown powder; 184.9 mg, yield 35%, mp 289–290 °C; R_f 0.43 (4:1 $CHCl_3$–MeOH); ^{13}C CP/MAS NMR δ 32.4, 121.3, 124.4, 129.9, 144.2, 160.2, 177.7. Anal.Calcd for $C_{22}H_{12}Br_2N_2O_4$: C, 50.03; H, 2.29; Br, 30.26; N, 5.30. Found: C, 50.02; H, 2.26; Br, 30.25; N, 5.32. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{12}Br_2N_2O_4$, 525.9196; found, 525.9193.

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