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CHEMISTRY

A New General Method for the Synthesis of 2,6'-Diquinoline Derivatives

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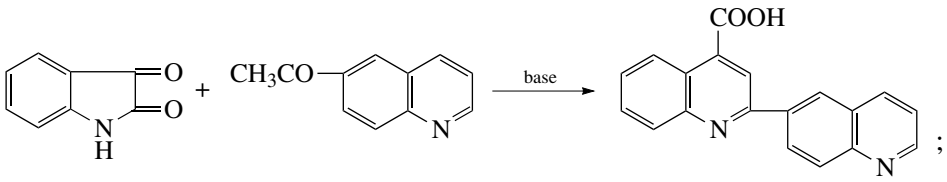
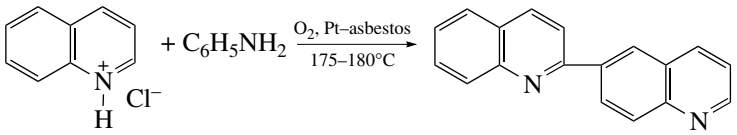
The best-known methods for the synthesis of 2,6'-diquinolines are as follows:

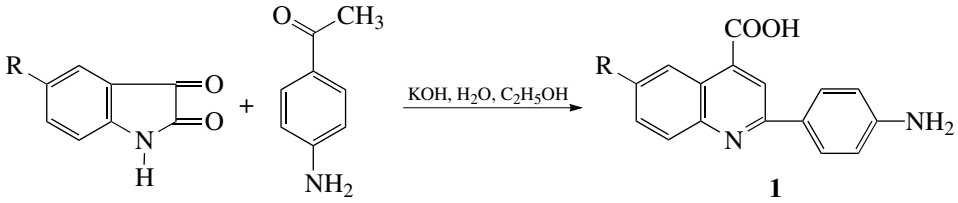
(1) the Pfitzinger reaction of isatins and acetylquinolines, for example [1],



(2) the heating of anilines with quinoline hydrochloride in the presence of a platinum catalyst, for example [2],



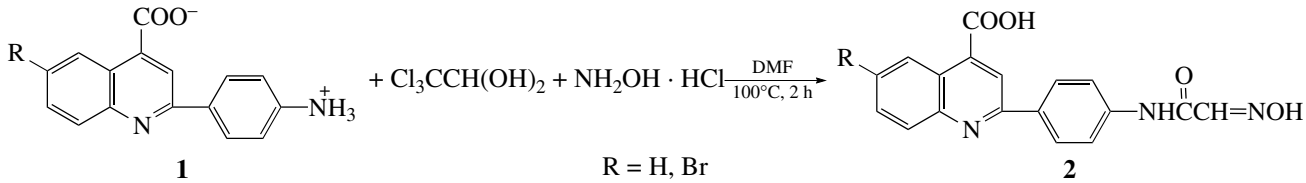
We suggest a new and more general method for the synthesis of 2,6'-diquinoline derivatives on the basis of 6-R-2-(4-aminophenyl)quinoline-4-carboxylic acids (**1**); previously [3, 4], we reported on a convenient and simple method of synthesis of **1**:



1

R = H, Br, NO_2

Using the known two-step Sandmeyer method of synthesis of isatins [5], we obtained the corresponding isonitrosoacetanilides (**2**) in 76–87% yields by the reaction of amines **1** with chloral hydrate and hydroxylamine hydrochloride in a DMF medium:



1 R = H, Br **2**

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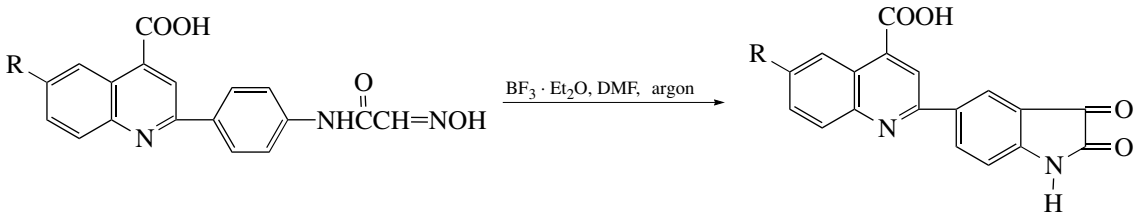
In [6], the preparation of compound **2** (R = H) in 38% yield was reported, but the compound was not characterized.

The second step of the isatin synthesis by the Sandmeyer method consists in the cyclization of isonitrosoacetanilides **2** under the action of strong acids. However, the author of [6] failed to convert the resulting isonitrosoacetanilide into isatin using sulfuric acid as a cyclization agent.

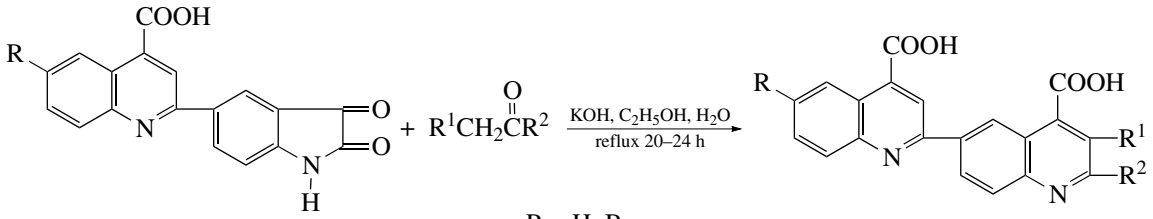
We also failed to convert compounds **2** (R = H, Br) into corresponding isatins in a sulfuric acid medium.

We managed to convert compounds **2** (R = H, Br) into corresponding isatins **3** (R = H, Br) in 78–93% yields using boron trifluoride etherate in DMF under an argon atmosphere as the cyclization reagent.



2 **3** (R = H, Br)

We conducted the Pfitzinger reaction of isatins **3** (R = H, Br) with certain ketones in an aqueous alcohol medium in the presence of KOH, which gave the corresponding derivatives of 2,6'-diquinoline (**4**) in 38–82% yields:



3 R = H, Br **4**

R, R^1, R^2 = H, CH^3, CH^3; H, H, C_6H_5; H, H, ferrocenyl; Br, H, $C_6H_4NH_2$-4

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrophotometer (as KBr pellets). UV spectra were obtained on a Uvidek-610 spectrophotometer in a 1% aqueous sodium hydroxide solution. ^{1}H NMR spectra were recorded on a Bruker AC-300 or WM-250 spectrometer in DMSO-d_6–CCl_4 solutions. The reaction course and purity of resulting compounds were monitored by paper chromatography and thin-layer chromatography (TLC) on Silufol UV-254 plates with development in iodine vapors. The synthesis of 6-R-2-(4-aminophenyl)quinoline-4-carboxylic acids **1** was described in [3, 4].

Isonitrosoacetanilide 2 (R = H). Chloral hydrate (0.92 g, 0.006 mol) was dissolved in 2.5 mL of H_2O, and 7.9 g (0.56 mol) of Na_2SO_4 was added. The mixture was heated to 60°C. A solution of 1.1 g (0.016 mol) of $NH_2OH \cdot HCl$ in 2 mL of H_2O was prepared separately under heating. The heated mixture was combined with the solution. A mixture of 1.32 g (0.005 mol) of 2-(4-aminophenyl)quinoline-4-carboxylic acid in 14 mL of DMF and 0.4 mL of concentrated HCl was prepared simultaneously and heated to 80°C, and then the first combined mixture was added. The resulting mixture was heated to 95°C and kept at this temperature for 2 h. The reaction mixture was cooled in an ice bath, and H_2O cooled to 0°C was added until the formation of a precipitate was observed. The precipitate was washed with water on a filter and dried in air. Yield, 1.27 g (76%), mp 263–265°C (DMF–H_2O). IR (KBr, ν, cm^{-1}): 764 (1,2-disubstituted benzene ring), 840 (1,4-disubstituted benzene ring), (3430 (OH), 930 (OH), 1740 (C=O) (in COOH)), (3452 (OH), 1650 (C=N), 980 (N–O) in (CH=NOH)), (3420 (NH), 1640 (C=O) (in CONH)). UV (λ_{max}, nm ($\log\varepsilon$)): 232.5 (2.87), 290.53 (2.89), 339.44 (2.84). ^{1}H NMR (250 kHz, δ, ppm): 7.68 (m, 1H, 7-H), 7.71 (s, 1H, 14-H), 7.83 (m, 1H, 6-H), 7.92 (d, 2H, 10,12-H), 8.13 (d, 1H, 5-H), 8.28 (d, 2H, 9,11-H), 8.44 (s, 1H, 3-H), 8.63 (d, 1H, 8-H), 10.29 (s, 1H, NOH), 12.15 (s, 1H, COOH).

For $C_{18}H_{13}N_3O_4$ anal. calcd. (wt %): C, 64.47; H, 3.90; N, 12.53.

Found (wt %): C, 64.09; H, 3.72; N, 12.21.

Isonitrosoacetanilide 2 (R = Br). Yield, 1.8 g (87%); **2** does not melt up to 300°C (DMF–H_2O). IR (KBr, ν, cm^{-1}): 828 (1,4-disubstituted benzene ring), 868 (1,2,4-trisubstituted benzene ring), (3762 (OH), 980 (OH), 1720 (C=O) (in COOH)), (3340 (OH), 1681 (C=N), 1016 (N–O) (in CH=NOH)), (3430 (NH), 1664 (C=O) (in CONH)), 652 (C–Br). UV (λ_{max}, nm ($\log\varepsilon$)): 296.21 (2.74), 299.33 (2.74), 347.22 (2.64).

For $C_{18}H_{12}BrN_3O_4$ anal. calcd. (wt %): C, 52.19; H, 2.92; N, 10.14.

Found (wt %): C, 52.38; H, 3.18; N, 9.79.

5-(4-Hydroxycarbonylquinolyl-2)isatin 3 (R = H). An argon flow was passed through a solution of 0.84 g (0.0025 mol) of isonitrosoacetanilide **2** (R = H) in 3 mL of DMF, and 1.3 mL of freshly distilled $BF_3 \cdot Et_2O$ was added. The mixture was heated for 2 h at 90°C and another 3 h at 120°C. After cooling, the reaction mixture was poured into a water–ice mixture. The resulting precipitate was filtered off, washed with water, and dried in air. Yield, 0.68 g (78%); mp 223–225°C (decomp.) (from DMF–H_2O). IR (KBr, ν, cm^{-1}): 764 (1,2-disubstituted benzene ring); 808, 864 (1,2,4-trisubstituted benzene ring); 3372 (NH); 1664 (C^{14}=O); (3490 (OH), 860 (OH), 1704 (C=O) (in COOH)). UV (λ_{max}, nm ($\log\varepsilon$)): 283.93 (2.82), 285.88 (2.82), 287.85 (2.82), 289.85 (2.82). ^{1}H NMR (250 MHz, δ, ppm): 7.72 (m, 1H, 7-H), 7.83 (m, 1H, 6-H), 7.94 (s, 1H, 10-H), 8.14 (d, 1H, 5-H), 8.28 (d, 2H, 11,12-H), 8.43 (s, 1H, 3-H), 8.65 (d, 1H, 8-H), 9.14 (s, 1H, NH), 11.06 (s, 1H, COOH).

For $C_{18}H_{10}N_2O_4$ anal. calcd. (wt %): C, 67.89; H, 3.46; N, 8.79.

Found (wt %): C, 67.47; H, 3.37; N, 8.37.

5-(6-Bromo-4-hydroxycarbonylquinolyl-2)isatin 3. Yield, 0.93 g (93%); **3** does not melt up to 300°C (from DMF–H_2O). IR (KBr, ν, cm^{-1}): 760 (1,2-disubstituted benzene ring); 828, 869 (1,2,4-trisubstituted benzene ring); 3364 (NH); 1664 (C^{14}=O); (3486 (OH), 870 (OH), 1724 (C=O) (in COOH)); 644 (R = Br). UV (λ_{max}, nm ($\log\varepsilon$)): 259.87 (2.71), 293.43 (2.78), 348.19 (2.70). ^{1}H NMR (250 MHz, δ, ppm): 7.72 (s, 1H, 10-H), 7.96 (d, 1H, 7-H), 8.06 (s, 1H, 5-H), 8.31 (d, 2H, 11,12-H), 8.38 (s, 1H, 3-H), 8.51 (d, 1H, 8-H), 8.92 (s, 1H, NH), 9.44 (s, 1H, COOH).

For $C_{18}H_9BrN_2O_4$ anal. calcd. (wt %): C, 54.43; H, 2.28; N, 7.05.

Found (wt %): C, 54.74; H, 2.47; N, 6.74.

2,6'-Diquinoline 4 (R = H, R^1 = R^2 = CH_3). A solution of 1.6 g (0.005 mol) of isatin **3** (R = H), 2.25 mL (0.01 mol) of methyl ethyl ketone, and 1.62 g of KOH in 13 mL of alcohol and 0.3 mL of H_2O was heated under reflux for 24 h (TLC monitoring). The reaction mixture was cooled, diluted with ice water, and acidified with diluted hydrochloric acid to pH 6. The precipitate was filtered off, washed, and dried in air. Yield, 1.03 g (55%); mp 280–283°C (from DMF–H_2O). IR (KBr, ν, cm^{-1}): 756 (1,2-disubstituted benzene ring); 816, 880 (1,2,4-trisubstituted benzene ring); (3356 (OH); 3200 (OH); 976 (OH); 960 (OH); 1644, 1608 (C=O) (two COOH)). UV (λ_{max}, nm ($\log\varepsilon$)): 282.80 (2.83), 346.26 (2.69), 473.48 (1.41), 482.62 (1.40). ^{1}H NMR (250 MHz, δ, ppm): 2.39 (s, 6H, 2 CH_3), 6.73 (d, 2H, 10,11-H), 7.56 (m, 1H, 7-H), 7.75 (m, 1H, 6-H), 8.03 (d, 1H, 5-H), 8.28 (s, 1H, 3-H), 8.43 (s, 1H, 9-H), 8.57 (d, 1H, 8-H), 9.16 (s, 1H, COOH).

For $C_{22}H_{16}N_2O_4$ anal. calcd. (wt %): C, 70.96; H, 4.33; N, 7.52.

Found (wt %): C, 71.28; H, 4.48; N, 7.17.

2,6'-Diquinoline 4 (R = H, R^1 = H, R^2 = C_6H_5). Yield, 0.8 g (38%); mp 263–265°C (from DMF–H_2O). IR (KBr, ν, cm^{-1}): 756 (1,2-disubstituted benzene ring); 668, 737 (monosubstituted benzene ring); 816, 828 (1,2,4-trisubstituted benzene ring); (3360 (OH); 3198 (OH); 910 (OH); 880 (OH); 1685, 1640 (C=O) (two COOH)). UV (λ_{max}, nm ($\log\varepsilon$)): 282.68 (2.79), 345.11 (2.65). ^{1}H NMR (250 MHz, δ, ppm): 6.74 (d, 2H, 10,11-H), 7.57 (m, 1H, 7-H), 7.75 (m, 1H, 6-H), 7.64–7.94 (m, 5H, C_6H_5), 8.02 (s, 1H, 9-H), 8.04 (d, 1H, 5-H), 8.31 (s, 1H, 3-H), 8.44 (d, 1H, 14-H), 8.57 (d, 1H, 8-H), 9.14 (s, 1H, COOH).

For $C_{26}H_{16}N_2O_4$ anal. calcd. (wt %): C, 74.27; H, 3.83; N, 6.66.

Found (wt %): C, 74.58; H, 3.54; N, 6.31.

2,6'-Diquinoline 4 (R = H, R^1 = H, R^2 = ferrocenyl). Yield, 2.16 g (82%); mp 163–165°C (from DMF–H_2O). IR (KBr, ν, cm^{-1}): 764 (1,2-disubstituted benzene ring); 828, 880 (1,2,4-trisubstituted benzene ring); 1004, 1116, 1280 (ferrocenyl); (3356 (OH); 3204 (OH); 848 (OH); 860 (OH); 1652, 1592 (C=O) (two COOH)). UV (λ_{max}, nm ($\log\varepsilon$)): 281.01 (2.74), 343.57 (2.58), 445.12 (1.28), 451.55 (1.27), 470.23 (1.24). ^{1}H NMR (250 MHz, δ, ppm): 4.24–4.81 (m, 9H, ferrocenyl), 6.72 (d, 2H, 10,11-H), 7.69 (m, 1H, 7-H), 7.76 (m, 1H, 6-H), 8.05 (d, 1H, 5-H), 8.32 (s, 1H, 3-H), 8.58 (d, 1H, 8-H).

For $C_{30}H_{20}N_2O_4Fe$ anal. calcd. (wt %): C, 68.19; H, 3.81; N, 5.30.

Found (wt %): C, 67.87; H, 3.98; N, 5.21.

2,6'-Diquinoline 4 (R = Br, R^1 = H, R^2 = 4-$H_2NC_6H_4$). Yield, 1.62 g (63%); mp 298–300°C (from DMF–H_2O). IR (KBr, ν, cm^{-1}): 824 (1,4-disubstituted benzene ring); 815, 872 (1,2,4-trisubstituted benzene ring); (3348 (OH), 962 (OH), 1644 (C=O) (in COOH)); 3348, 1212 (NH_2). UV (λ_{max}, nm ($\log\varepsilon$)): 268.70 (2.71), 271.03 (2.71), 274.60 (2.71), 291.92 (2.73), 294.67 (2.73), 354.91 (2.61). ^{1}H NMR

(250 MHz, δ, ppm): 6.72 (d, 2H, 10,11-H), 7.85 (d, 1H, 7-H), 7.88 (d, 1H, 6-H), 7.91–8.06 (m, 4H, C_6H_4), 7.97 (s, 1H, 9-H), 8.02 (s, 1H, 5-H), 8.06 (s, 1H, 3-H), 8.39 (s, 1H, 12-H), 8.85 (d, 1H, 8-H), 10.48 (s, 1H, COOH).

For $C_{26}H_{16}BrN_3O_4$ anal. calcd. (wt %): C, 70.71; H, 3.70; N, 9.65.

Found (wt %): C, 70.98; H, 3.65; N, 9.48.

REFERENCES

1. Waley, S.G., *J. Chem. Soc.*, 1948, p. 2008.
2. Weidel, H., *Monatsh. Chem.*, 1887, vol. 8, p. 120.
3. Shvekhgeimer, M.-G.A. and Kondrashova, N.N., *Khim. Geterotsikl. Soedin.,* 2002, no. 2, p. 275.
4. Shvekhgeimer, M.-G.A. and Kondrashova, N.N., *Dokl. Akad. Nauk*, 2002, vol. 383, no. 2, pp. 221–225 [*Dokl. Chem.* (Engl. Transl.), vol. 383, nos. 1–3, pp. 72–74].
5. Sandmeyer, T., *Helv. Chim. Acta,* 1919, vol. 2, p. 230.