A Clean Procedure for the Synthesis of Chromeno[4,3-*b*]benzo[*f*]quinoline and Quinolino[4,3-*b*]benzo[*f*]quinoline Derivatives in Aqueous Media

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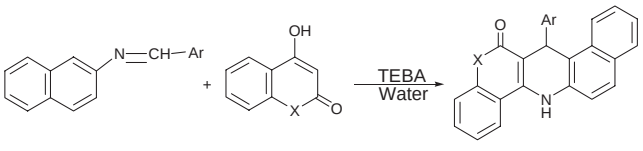
A short and simple synthesis of chromeno[4,3-*b*]benzo[*f*]-quinoline and quinolino[4,3-*b*]benzo[*f*]quinoline derivatives were accomplished in high yields via the reaction of *N*-benzilidenenaphthalen-2-amine and 4-hydroxycoumarin or 4-hydroxyquinolin-2-one in aqueous media catalyzed by TEBAC. The structures were established by spectroscopic data and further confirmed by X-ray diffraction analysis.

It is known that many quinoline[1] or chromene[2] containing compounds exhibit a wide spectrum of pharmacological activities. To the best of our knowledge, only a few examples[3] of heteroaromatic rings containing quinoline and chromene in a molecule have been mentioned in the literature, furthermore their syntheses are all performed in the ordinary organic solvent. It was reported that chromenoquinolines and their derivatives were possessing biological and pharmacological activities,[4] such as bacteriostatic activity,[5] glucocorticoid modulators,[6] anti-inflammatory effects,[7] and selective progesterone receptor modulators.[8] Because of the toxic and volatile nature of many organic solvents, we investigated the synthesis of these potential active compounds under environmentally friendly conditions. Particularly, we focused our attention on the use of water as reaction medium. They were considered very promising and attractive substitutes for volatile organic solvents and were widely used in the green chemistry area, since Breslow,[9] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in 1980s. There has been growing recognition that water is an attractive medium for many organic reactions[10] because it is less expensive, less dangerous and environment-friendly. As part of our current studies on the development of new routes to heterocyclic systems,[11] we now report an efficient and clean synthetic route to chromeno[4,3-*b*]benzo[*f*]quinoline and quinolino[4,3-*b*]benzo[*f*]quinoline derivatives in aqueous media catalyzed by TEBAC (triethylbenzyl ammonium chloride).

When the reaction of *N*-benzilidenenaphthalen-2-amine **1** and 4-hydroxycoumarin or 4-hydroxyquinolin-2-one **2** was performed in water in the presence of TEBAC at 100 °C, high yields of chromeno[4,3-*b*]benzo[*f*]quinoline or quinolino[4,3-*b*]-benzo[*f*]quinoline derivatives were obtained (Scheme 1).



1 **2** **3**

Scheme 1.

In order to apply this reaction to a laboratory synthesis, various kinds of *N*-benzilidenenaphthalen-2-amine and **2** were subjected to form the corresponding chromeno[4,3-*b*]benzo[*f*] quinoline or quinolino[4,3-*b*]benzo[*f*]quinoline derivatives **3**, and representative examples are shown in Table 1. All of the *N*-ben-

Table 1. The results on the reaction of **1** and **2** in water at 100 °C[12]

Entry	Ar	X	Time/h	Yields/%
3a	4-BrC_6H_4	O	8	93.3
3b	2-ClC_6H_4	O	12	94.0
3c	3-ClC_6H_4	O	12	90.2
3d	4-ClC_6H_4	O	12	87.8
3e	2,4-$Cl_2C_6H_3$	O	10	90.9
3f	3,4-$Cl_2C_6H_3$	O	10	95.0
3g	4-HOC_6H_4	O	12	92.3
3h	4-$(CH_3)_2NC_6H_4$	O	12	95.2
3i	2-$NO_2C_6H_4$	O	8	90.5
3j	4-$CH_3OC_6H_4$	O	10	92.7
3k	2-ClC_6H_4	NH	8	94.2
3l	4-ClC_6H_4	NH	8	90.2
3m	3,4-$Cl_2C_6H_3$	NH	8	93.2
3n	2,4-$Cl_2C_6H_3$	NH	8	97.0
3o	4-FC_6H_4	NH	8	92.5
3p	4-BrC_6H_4	NH	10	93.5
3q	4-$CH_3OC_6H_4$	NH	12	91.6
3r	3-ClC_6H_4	NH	10	87.8

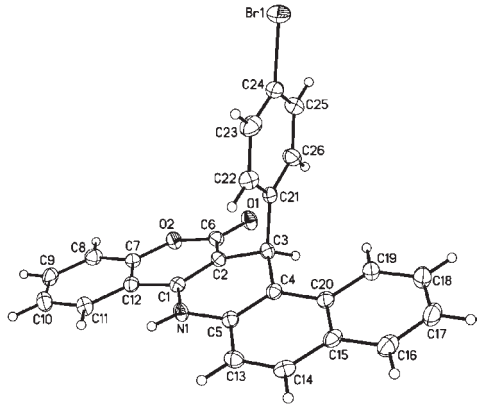
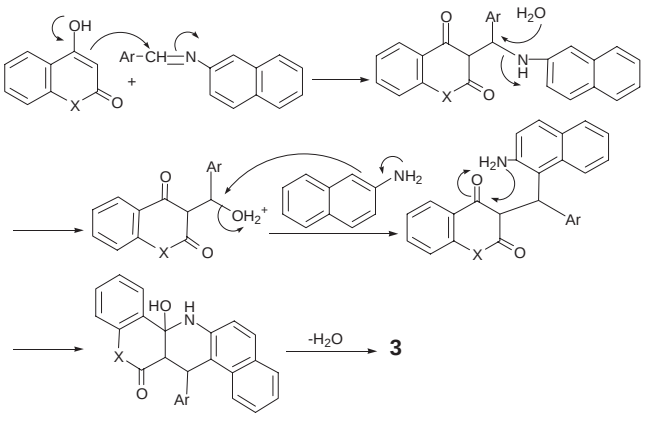


Figure 1. The crystal structure of the product **3a**.



Scheme 2.

zilidenenaphthalen-2-amine gave expected products in high yields and purity. The products **3** were completely characterized by IR, ^{1}H NMR, and elemental analyses. The analyses were in agreement with their structures. The IR spectra for **3a** exhibited sharp bands at 3310 cm^{-1} (NH) and 1657 cm^{-1} (C=O). The ^{1}H NMR spectrum of **3a** exhibited a singlet identified methine (5.91) along with multiplets (7.28–8.40) for aromatic protons. The NH proton resonance at 10.18 disappeared after addition of D_2O to the DMSO-d_6 solution of **3a**. In order to further confirm the structure of the product, the X-ray diffraction analysis[13] of **3a** was carried out.

Though the detailed mechanism of the above reaction has not been clarified yet, the formation of **3** can be explained by the possible mechanism presented in Scheme 2.

In the further study, we find the product **3a** can be obtained in 82% yield by three-component reaction of 4-bromobenzaldehyde, 2-aminonaphthalene, and **2** in water at 100 °C in the presence of TEBAC.[14] This result possibly indicates that the cleavage of the C=N bond maybe take place in the mechanism mentioned above. But it should be noted that in this three-component reaction the starting material of solid 4-bromobenzaldehyde always stays in the bottom of the condenser when the reaction temperature is controlled above 80 °C, which reduces the reaction yield badly, meanwhile the reaction time is long.

In addition, in order to show the general scope of this reaction, we also tried the reaction of **2** with other Schiff base containing substituented aniline, such as *p*-toluidine. But we could not get the expected pyrido[3,2-*c*]chromene derivative, we think a possible reason is that the activity of *p*-toluidine is less than that of 2-aminonaphthalene.

In conclusion, an efficient green chemistry method for the synthesis of chromeno[4,3-*b*]benzo[*f*]quinoline and quinolino [4,3-*b*]benzo[*f*]quinoline derivatives. Compared to other methods,[3] this new method has the advantages of high yields, mild reaction conditions, easy work-up, inexpensive reagents and environmentally friendly procedure.

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12 The general procedure is represented as follow: A suspension of a mixture of *N*-benzilidenenaphthalen-2-amine **1** (2 mmol), 4-hydroxycoumarins or 4-hydroxyquinolin-2-one **2** (2 mmol) and TEBAC (0.1 g) was stirred in water (10 mL) at 100 °C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline power formed recrystallized from DMF and water to give pure **3**. **3a**: mp >300 °C (Lit.[3a], 378–380 °C). IR (KBr, ν, cm^{-1}): 3310, 3056, 1657, 1621, 1588, 1570, 1527, 1511, 1478, 1430, 1404; ^{1}H NMR (DMSO-d_6, δ): 5.91 (s, 1H, CH), 7.30 (d, J = 8.8 Hz, 2H, ArH), 7.37–7.40 (m, 4H, ArH), 7.46–7.50 (m, 2H, ArH), 7.64–7.68 (m, 1H, ArH), 7.73 (d, J = 8.8 Hz, 2H, ArH), 7.88 (d, J = 7.6 Hz, 1H, ArH), 7.91–7.98 (m, 2H, ArH), 8.39 (d, J = 7.2 Hz, 1H, ArH), 10.18 (s, 1H, NH); Anal. Calcd for $C_{26}H_{16}BrNO_2$: C, 68.74; H, 3.55; N, 3.08%; Found: C, 68.92; H, 3.54; N, 3.13%. **3k**: mp >300 °C; IR (KBr, ν, cm^{-1}): 3648, 3329, 3064, 1667, 1639, 1621, 1590, 1570, 1531, 1460, 1406; ^{1}H NMR (DMSO-d_6, δ): 6.32 (s, 1H, CH), 7.03–7.08 (m, 2H, ArH), 7.26–7.35 (m, 4H, ArH), 7.44–7.51 (m, 3H, ArH), 7.71 (d, J = 8.8 Hz, 1H, ArH), 7.82 (d, J = 8.0 Hz, 1H, ArH), 7.83 (d, J = 8.8 Hz, 1H, ArH), 8.26 (d, J = 8.4 Hz, 1H, ArH), 8.35 (d, J = 8.0 Hz, 1H, ArH), 9.65 (s, 1H, NH), 11.15 (s, 1H, NH); Anal. Calcd for $C_{26}H_{17}ClN_2O$: C, 76.37; H, 4.19; N, 6.85%. Found: C, 76.22; H, 4.18; N, 6.90%.

13 Crystal data for **3a**: $C_{26}H_{16}BrNO_2$; M_r = 454.31, orange-yellow block crystals, 0.59 × 0.34 × 0.15 mm^3, monoclinic, space group $P2_1/c$, a = 7.3681(8), b = 13.5483(14), c = 19.662(3) Å, β = 100.372(4)°, V = 1930.7(4) Å^3, Z = 4, D_{calcd} = 1.563 g·cm^{-3}. $F(000)$ = 920, μ(Mo Kα) = 2.153 mm^{-1}. Intensity data were collected on Rigaku Mercury diffractometer using ω scan mode with 3.01° < θ < 27.48°. 4412 unique reflections were measured and 3827 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. R = 0.0446, wR = 0.0968.

14 The general three-component reaction procedure for **3a** is described as follows: A suspension of a mixture of 4-bromobenzaldehyde (2 mmol), 2-aminonaphthalene (2 mmol), 4-hydroxycoumarin **2** (2 mmol), and TEBAC (0.1 g) was stirred in water (10 mL) at 100 °C for 24 h. The reaction mixture was allowed to cool to room temperature. The solid was purified by column chromatogaraphy on silica gel (200–300 mesh) using petroleum ether (bp 60–90 °C)–acetone (1:1) as eluent to give **3a** in 82% yield.

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