Unexpected Spiro-benzoquinolines in the Reaction of *N*-(Arylidene)naphthalen-2-amine, Arylaldehyde, and 1,3-Dimethylbarbituric Acid in Water

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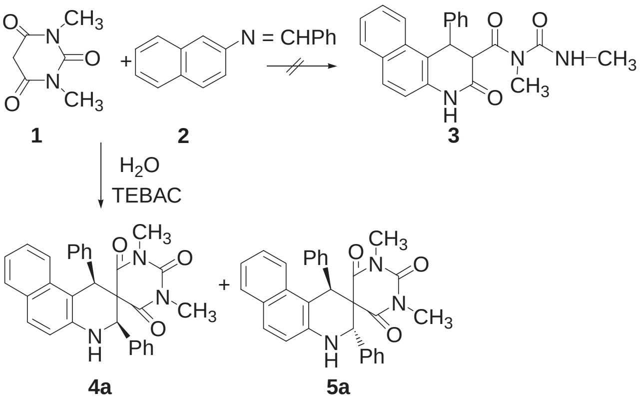
A series of unexpected pyrimidine spiro-benzoquinolines were developed based on the reaction of *N*-(arylidene)naphthalen-2-amine, arylaldehyde, 1,3-dimethylbarbituric acid in aqueous media catalyzed by triethylbenzylammonium chloride (TEBAC). The structure of the product **4a** was confirmed by X-ray diffraction studies. In addition, the water was chosen as green solvent.

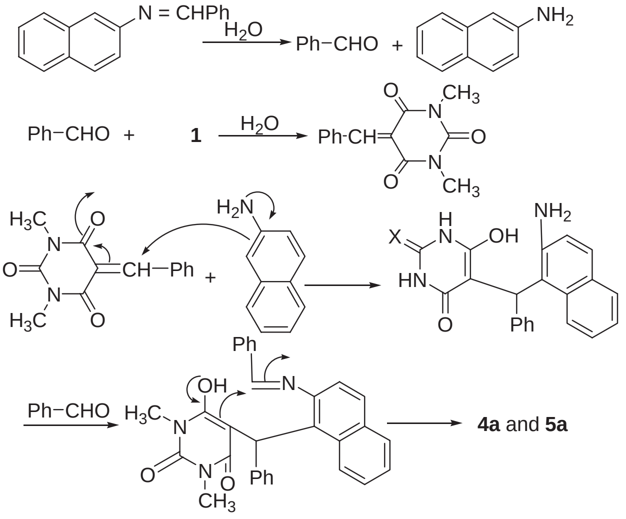
The pyrimidine spiro-quinoline and its derivatives are well-known compounds using as antibacterial agents.[1] Only a few studies concerning the synthesis of these active compounds were reported in the literature.[2] However, they are either tedious or have low yields, besides that organic solvents were used during all of the reactions. In order to avoid the disadvantages such as toxicity and instability that many organic solvents inherently have, we have working to find a new procedure that will be environmentally friendly, and easy to operate for the synthesis of those above-mentioned compounds. Specifically, 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 demonstrated that hydrophobic effects could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic chemistry in 1980s,[3] there has been a growing recognition that water becomes an attractive medium for many organic reactions.[4] On the other hand, organic reactions in water without using harmful organic solvents is one of the current focuses especially in the environmentally conscious society today.

As part of our current studies on the development of new routes to synthesize heterocyclic compounds in water, we have reported the reactions of Schiff base with different 1,3-dicarbonyl compound using water as a medium.[5] Recently, we selected the barbituric acid or thiobarbituric acid as 1,3-dicarbonyl compounds because of their low pK_a, with an unexpected ring-opening of a barbituric acid or thiobarbituric acid in the synthesis of which benzo[*f*]quinolin-3-carbonyl urea and thiourea derivatives were obtained.[6]

This unexpected ring-opening of a barbituric acid or thiobarbituric acid reaction stimulated us to find some other N-substituted barbituric acid as substrates to obtain the N-substituted benzo[*f*]quinolin-3-carbonyl urea and thiourea derivatives. As a representative, we selected 1,3-dimethylbarbituric acid **1** to prove our assumption (Scheme 1). To our delighted, the reaction of **1** and *N*-(benzylidene)naphthalen-2-amine (**2**) proceeded smoothly. However, the desired ring-opening N-substituted benzo[*f*]quinolin-3-carbonyl urea **3** were not detected after all, but the *cis*- and *trans*-pyrimidine spiro-quinolines **4a** and **5a** were obtained in 62% yield (Scheme 1).



Scheme 1.

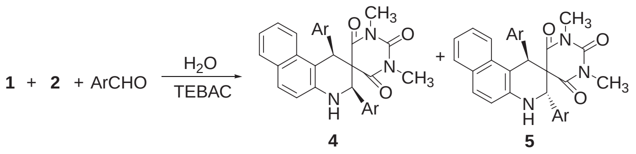


Scheme 2.

Although the detailed mechanism of above reaction has not been clarified yet, the formation of *cis*- and *trans*-spiroquinolines **4a** and **5a** can be explained by a possible mechanism presented in Scheme 2.

From the Scheme 2, we could see that two molecules of benzaldehydes attend the reaction. In order to prove our assumption, one-pot three-component reaction of arylaldehyde, *N*-(arylidene)naphthalen-2-amine, and 1,3-dimethylbarbituric acid was carried out in aqueous media catalyzed by TEBAC at 100 °C (Scheme 3), with **4a** and **5a** (Ar = Ph) being obtained in slightly high yield (76%).

In order to apply this reaction to a library synthesis, various kinds of *N*-(arylidene)naphthalen-2-amine and arylaldehyde



Scheme 3.

Table 1. TEBAC-catalyzed reaction of *N*-(arylidene)naphthalen-2-amine, arylaldehyde, and 1,3-dimethylbarbituric acid[a,7]

Entry	Ar	Time/h	Cis:trans[b]	Yields/%[c]
1	C_6H_5	12	70:30	76
2	4-FC_6H_4	10	52:48	81
3	4-BrC_6H_4	14	42:58	75
4	3-ClC_6H_4	14	40:60	84
5	4-ClC_6H_4	12	44:56	82
6	4-$CH_3OC_6H_4$	14	62:38	82
7	3-$NO_2C_6H_4$	10	72:28	78
8	4-$NO_2C_6H_4$	10	31:69	73
9	2-$NO_2C_6H_4$	10	5:95	74
10	2,4-$Cl_2C_6H_3$	10	5:95	72
11	3,4-$Cl_2C_6H_3$	12	33:67	78

[a]Reaction condition: 10-mL water, 2 mmol **1**, 2 mmol **2**, 2 mmol arylaldehyde, and 20 mol % TEBAC, 100 °C. [b]Determined by ^{1}H NMR spectroscopy. [c]Isolated yield by silica-gel column chromatography.

were subjected to react with **1** to give the corresponding **4** and **5**, and representative examples are shown in Table 1. All of the **2** and arylaldehyde gave expected products with good yields, either bearing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkoxyl group) under the same reaction conditions.

In the further study, we find that the products **4a** and **5a** can be obtained in 60% yield by three-component reaction of benzaldehyde, 2-aminonaphthalene, and **1** in water at 100 °C in the presence of TEBAC. This result possibly indicates that the cleavage of the C=N bond may take place in the mechanism mentioned above.

The products **4** and **5** were characterized by ^{1}H NMR, IR spectra, and elemental analyses. The structure of **4a** was further confirmed by X-ray diffraction analysis.[8] The molecular structure of **4a** was shown in Figure 1.

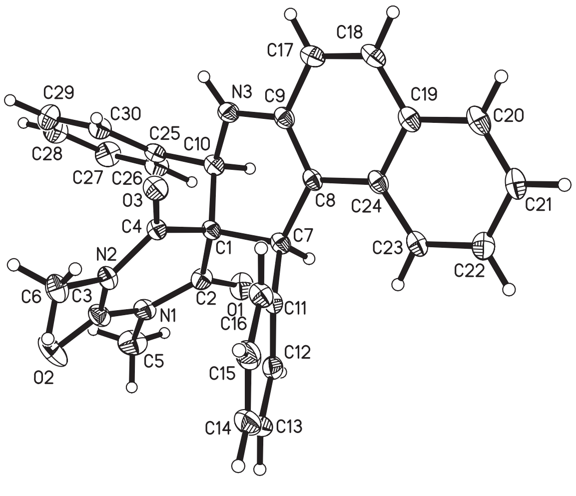


Figure 1. The crystal structure of the product **4a**.

In conclusion, the interesting and unexpected spiroquinolines were synthesized based on the reaction between *N*-(arylidene)naphthalen-2-amine, arylaldehyde, and 1,3-dimethylbarbituric acid in aqueous media catalyzed by TEBAC. The notable features of this procedure are good yields, mild reaction conditions, easy work-up, inexpensive reagents, and environmentally friendly procedure. In addition, the water was chosen as green solvent.

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7 General procedure for **4** and **5**: A suspension of the mixture of 1,3-dimethylbarbituric acid **1** (2 mmol), *N*-(arylidene)naphthalen-2-amine **2** (2 mmol), arylaldehyde (2 mmol), and TEBAC (0.111 g) was stirred in water (10 mL) at 100 °C for 10–14 h. The powder formed was collected by filtration, and washed with water. The pure compounds were obtained by silica-gel column chromatography with petroleum ether–acetone (3:1). For the representative compounds **4a** and **5a**: mp 198–200 °C. IR (KBr, ν, cm^{-1}): 3390, 3041, 2958, 1743, 1676, 1622, 1558, 1541, 1516, 1478, 1451, 1407, 1377, 1337, 1248, 1149, 1121, 1075, 1020, 810, 756, 703. MS: $m/z = 476$ ($M^+ + 1$, 100), 419 (4), 384 (5), 320 (15), 232 (36), 215 (10), 154 (10). Anal. calcd for $C_{30}H_{25}N_3O_3$: C, 75.77; H, 5.30; N, 8.84%. Found: C, 75.81; H, 5.38; N, 8.72%. Cis isomer **4a**: ^{1}H NMR (DMSO-d_6, δ, ppm): 2.63 (s, 3H, CH_3), 2.94 (s, 3H, CH_3), 4.72 (s, 1H, CH), 5.55 (s, 1H, CH), 6.33 (d, $J = 8.0$ Hz, 1H, NH), 6.86–6.98 (m, 3H, ArH), 7.19–7.22 (m, 5H, ArH), 7.28–7.29 (m, 3H, ArH), 7.37–7.38 (m, 3H, ArH), 7.67–7.73 (m, 2H, ArH). Trans isomer **5a**: ^{1}H NMR (DMSO-d_6, δ, ppm): 2.95 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 5.23 (s, 1H, CH), 5.31 (s, 1H, CH), 6.99–7.17 (m, 8H, ArH), 7.24–7.26 (m, 3H, ArH), 7.33–7.34 (m, 3H, ArH), 7.54 (d, $J = 7.6$ Hz, 1H, NH), 7.57–7.63 (m, 2H, ArH). The data of cis isomer was obtained by determining the ^{1}H NMR of a single crystal after X-ray diffraction analysis. The data of trans isomer was assigned by eliminating the data of cis isomer in the ^{1}H NMR of the product obtained by silica-gel column chromatography.

8 X-ray diffraction analysis for **4a**: $C_{30}H_{25}N_3O_3$; $M_r = 475.53$, light-yellow block crystals, $0.45 \times 0.43 \times 0.17$ mm^3, Orthorhombic, space group $Pca2_1$, $a = 15.8386(16)$, $b = 8.5314(8)$, $c = 17.3856(18)$ Å, $V = 2349.2(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.344$ g cm^{-3}. $F(000) = 1000$, $\mu(\text{Mo K}\alpha) = 0.088$ mm^{-1}. Intensity data were collected on Rigaku Mercury diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) using omega scan mode with $3.35° < \theta < 25.35°$. 2224 unique reflections were measured and 2152 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least-squares technique to $R = 0.0374$ and $wR = 0.0888$.

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