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An Efficient Strategy for the Synthesis of Naphtho[2,3-*b*][1,6]naphthyridines Promoted by Acetic Acid

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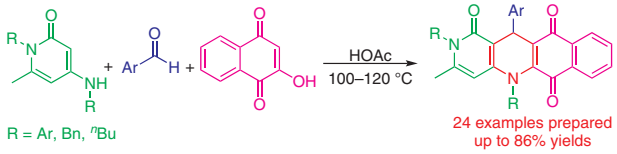

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Abstract A three-component domino reaction for the synthesis of naphtho[2,3-*b*][1,6]naphthyridine derivatives has been established. Such strategy exhibited excellent substrate scope including various enaminones and aldehydes that afforded a series of multifunctionalized naphtho[2,3-*b*][1,6]naphthyridine derivatives with 70–86% yields. The advantages of bond-forming efficiency, accessibility of starting materials, and water as sole byproducts provide invaluable access to biological 1,6-naphthyridines.

Key words aminopyridinone, 2-hydroxynaphthalene-1,4-dione, naphtho[2,3-*b*][1,6]naphthyridines, acetic acid, synthesis

In recent years, naphthyridine derivatives are widely studied and have a wide range of applications in various areas, including pharmaceutical agents of treatment of various human diseases and animal husbandry parasite control, industrial lubricating coolants for metal processing, and ligands of analytical chemistry.[1] Consequently, naphthyridines, as bipyridine scaffold compounds, have been found in various natural alkaloids, which have appreciable chemical and biological importance.[2] Among them, 1,6-naphthyridines play an important role in organic and biological chemistry due to their unique therapeutic and pharmacological properties.[3] Furthermore, the introduction of an aromatic ring onto them could greatly improve biological properties of 1,6-naphthyridine derivatives.[4] For example, the compounds **I** are efficient 2-adrenoreceptor antagonists for the treatment of hypertonia, depression, diabetes, and inhibition of thrombocyte aggregation (Figure 1).[5] Benzo[*b*][1,6]naphthyridine **II** can be used as a potent phosphodiesterase 5 inhibitor for the treatment of Alzheimer's disease.[6] Compounds **III** exhibit antibacterial and anti-HSV-1 activities.[7] Benzo[*h*]naphtho[1,2-*b*][1,6]naphthyridines **IV** can be against four cancer cell lines, such as K562 (human leukaemia cancer cell line), MCF7 (human breast cancer cell line), Hep-G2 (human liver cancer cell line), and HeLa (human cervical cancer cell line) by SRB method.[8] Dibenzo[*b*,*h*][1,6]naphthyridines **V**, as the conjugated π-bridge, are designed and synthesized for dye-sensitized solar cells (DSSCs).[9] Thus, the development of simple and efficient protocols toward synthesizing new functionalized 1,6-naphthyridine derivatives, especially for the benzo[1,6]naphthyridines or naphtho[1,6]naphthyridines using readily available starting materials, is highly desirable.

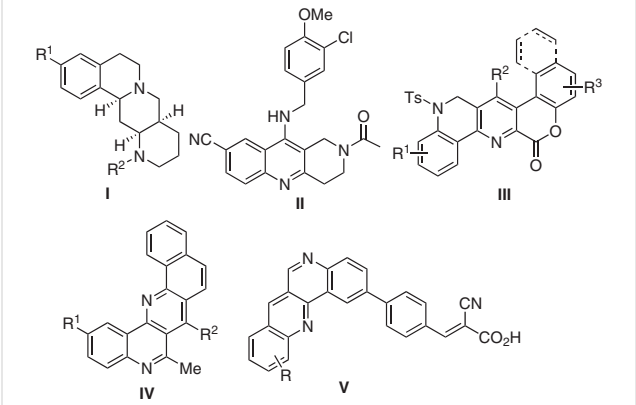

Figure 1 Several representative active molecules with the benzo[l,6]naphthyridine scaffold

In the past several decades, the multicomponent domino reactions (MDRs), which can offer easy access to functionalized heterocyclic structures with chemical and pharmaceutical interest, have been developed in the organic and medical chemical laboratory.[10] These reactions have attracted special attention because of their simplicity, efficiency, convenience, and atom economy.[11] Thus, the development of a domino strategy for the synthesis of 1,6-naphthyridine derivatives is still an important and promising

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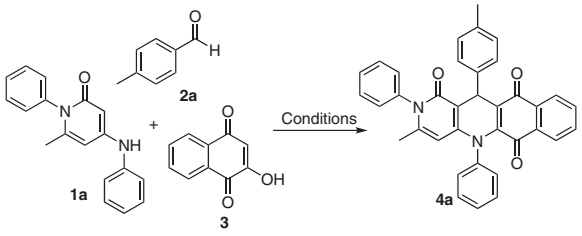
subject. In the recent years, our group has established several multicomponent domino reactions for the synthesis of heterocycles.[12] More recently, we reported a series of 1,6-naphthyridine derivatives with potential pharmaceutical value via a three-component domino reaction using 4-(arylamino)pyridin-2(1*H*)-ones as substrates.[13] In continuation of our efforts to construct these useful heterocyclic blocks, we here report another domino strategy for the synthesis of naphtho[2,3-*b*][1,6]naphthyridine derivatives using 4-(arylamino)pyridin-2(1*H*)-ones, aldehydes, and 2-hydroxynaphthalene-1,4-dione as starting materials. The present approach represents a special example for the construction of naphtho[1,6]naphthyridine derivatives with 70–86% yields.

In the beginning, the three-component domino reaction of 6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1*H*)-one (**1a**), 4-methylbenzaldehyde (**2a**), and 2-hydroxynaphthalene-1,4-dione (**3**) was employed as a model reaction to optimize the experimental conditions. Initially, no desired product **4a** was obtained when the model reaction was carried out without any catalyst, even after longer reaction times (Table 1, entry 1). Then, the model reaction was repeated many times in the presence of different acidic catalysts, such as inorganic acids including sulfuric acid (H_2SO_4) and hydrochloric acid (HCl), organic acids including trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (TsOH) and acetic acid (HOAc), and Lewis acids including $Sc(OTf)_3$ and $Y(OTf)_3$. The results were summarized in Table 1 (entries 2–8). It was noted that all the acidic catalysts could promote the model reaction. For further details, the acetic acid exhibited the best activities and gave the desired product **4a** with 67% yield. We also noted that the yields of product **4a** were increased from 42% to 73% when the catalyst loading was increased from 5 mol% to 40 mol%. Subsequently, various reaction media, including water (H_2O), ethanol (EtOH), tetrahydrofuran (THF), acetonitrile (MeCN), and *N*,*N*-dimethylformamide (DMF), were explored for this transformation (entries 12–16). We found that the protic solvents, such as water, ethanol, and glycol showed good adaptability for the domino reaction. However, none of them proved better than glycol. Thus, the three-component reaction was carried out many times in glycol with different temperatures. The yields of product **4a** were increased from 0% to 73% as the temperature varied from room temperature to 100 °C (Table 1, entries 5 and 17–20). Further increasing the temperature to 120 °C failed to improve the yield of the desired product **4a** obviously (Table 1, entry 21). To our delight, up to 84% yield of product **4a** was obtained when the model reaction was carried out using acetic acid as reaction media and catalyst under the above optimized conditions (Table 1, entry 22). Therefore, the optimal experimental conditions for the domino reaction were heating the reaction mixture at 100 °C for 4 h using acetic acid as reaction media and catalyst.

Table 1 Optimization for the Synthesis of Compound **4a**[a]



Entry	Catalyst (mg)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	–	glycol	100	12	0
2	H_2SO_4 (10)	glycol	100	4	33
3	HCl (10)	glycol	100	4	12
4	TFA (10)	glycol	100	4	41
5	HOAc (10)	glycol	100	4	67
6	TsOH (10)	glycol	100	4	45
7	$Sc(OTf)_3$ (10)	glycol	100	4	17
8	$Y(OTf)_3$ (10)	glycol	100	4	25
9	HOAc (5)	glycol	100	4	42
10	HOAc (20)	glycol	100	4	70
11	HOAc (40)	glycol	100	4	73
12	HOAc (10)	EtOH	reflux	4	51
13	HOAc (10)	H_2O	100	4	45
14	HOAc (10)	THF	reflux	4	35
15	HOAc (10)	MeCN	reflux	4	43
16	HOAc (10)	DMF	100	4	37
17	HOAc (10)	glycol	rt	12	0
18	HOAc (10)	glycol	40	4	21
19	HOAc (10)	glycol	60	4	39
20	HOAc (10)	glycol	100	4	73
21	HOAc (10)	glycol	120	4	74
22	–	HOAc	100	4	84

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3** (0.5 mmol), and solvent (3.0 mL) at given temperature and reaction time.
[b] Isolated yields.

With the optimized reaction conditions in hand, we then explored the generality of the domino reaction for the synthesis of different naphtho[2,3-*b*][1,6]naphthyridine derivatives by alternating the substituted aminopyridinones **1** and aldehydes **2** (Table 2).[14] At first, different aromatic aldehydes were investigated using 6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1*H*)-one (**1a**) and 2-hydroxynaphthalene-1,4-dione (**3**) as model substrates. To our delight, a wide range of substituted groups bearing aromatic aldehydes, including methyl, methoxy, fluoro, chloro, bromo, nitro, and cyano groups all tolerated the reaction and gave the products with good to excellent yields (Table 2, 4a–n). At the same time, we also noted steric effects, that is, the

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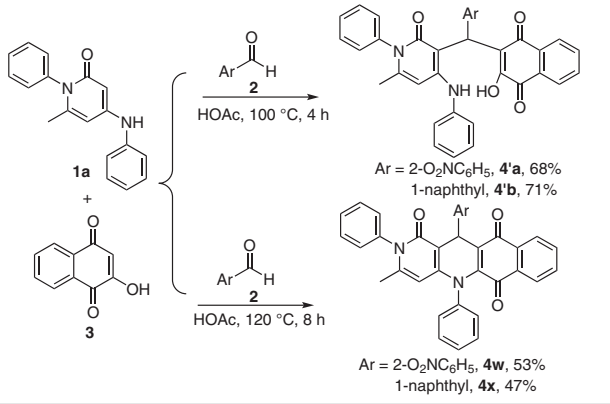
benzaldehydes with the substituent at *para* position exhibited higher reaction activities than those bearing groups at *meta*/*ortho* positions and afforded the corresponding products with higher yields. Among them, the 2,6-dichlorobenzaldehyde (**2n**) with high steric hindrance only gave the product **4n** with 70% yield. Thus, the steric effect of aromatic aldehydes influenced the transformation of the reaction obviously. In addition, the aliphatic aldehydes including *n*-heptanal and 3-methyl butanal have been used to replace benzaldehyde for the model reaction, respectively. Unluckily, no corresponding product was obtained, which may be attributed to the low stability of the condensed intermediate between aliphatic aldehyde and 2-hydroxynaphthalene-1,4-dione (**3**).

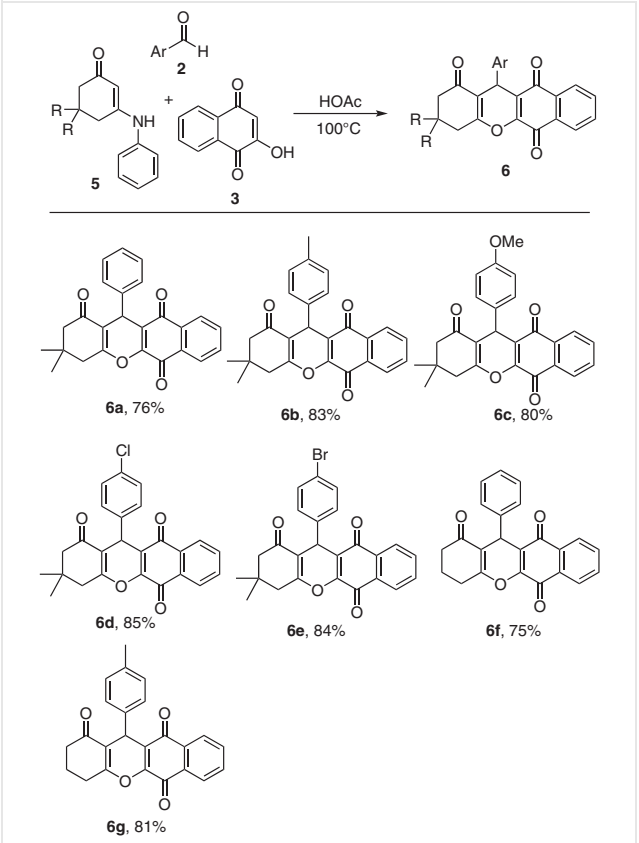
To further expand the scope of the reaction, various 4-(arylamino)pyridin-2(1*H*)-ones (**1**) were prepared and subjected to the domino cyclization reaction (Table 2, 4o–v). A wide range of functional groups on the phenyl substituent of the substrates **1**, such as methyl, methoxyl, fluoro, chloro, and trifluoromethyl, were investigated. Fortunately, all the 4-(arylamino)pyridin-2(1*H*)-one substrates were well tolerated in the domino reaction with different aromatic aldehydes (**2**) and 2-hydroxynaphthalene-1,4-dione (**3**) and gave the corresponding products **4** with 75–84% yields. The electron effect of the aryl ring of 4-(arylamino)pyridin-2(1*H*)-ones is not obvious in the reaction. It was worth mentioning that the substrate 4-(arylamino)pyridin-2(1*H*)-one bearing aliphatic substituents including benzyl and *n*-butyl also exhibited good reaction activities and gave the corresponding products with 75% and 78% yields, respectively. Additionally, when the aromatic aldehydes, such as 2-nitrobenzaldehyde (**2o**) and fused aldehyde 1-naphthaldehyde (**2p**) were used, the ring-opening compounds (**4'a** and **4'b**) were obtained with 68% and 71% yields at the same conditions, respectively (Scheme 1).



Scheme 1 Substrate scope for synthesis of **4**

To our delight, the desired products **4w** and **4x** were given with 47–53% yields when the reaction temperature was increased to 120 °C for 8 h, respectively. We attributed it to the steric hindrance of substrate aldehydes which influenced the formation of a new pyridine ring.

To further expand the scope of substrates, we were eager to see the result of the reactions when 3-(arylamino)cyclohex-2-en-1-ones **5** were employed as three-component partners with benzaldehydes **2** and 2-hydroxynaphthalene-1,4-dione (**3**) (Scheme 2).[15] Unfortunately, the desired products were not obtained. Instead, the products **6**[16] were formed with good to excellent yields. The probable reason for these results was the poor stability of enaminone **3** in acetic acid at 100 °C, which hampered the formation of the desired product. The electronic effect of the aldehydes had little influence on the efficiency of the reaction. Other enaminones, that is, 5,5-dimethyl-3-(*p*-tolylamino)cyclohex-2-en-1-one and 3-[(4-chlorophenyl)amino]-5,5-dimethylcyclohex-2-en-1-one, were selected for our study. Again, we obtained the product **6a** with similar yield for the same reason.



Scheme 2 Synthesis of 2-aryl-2,3,4,12-tetrahydro-1*H*-benzo[*b*]xanthene-1,6,11-triones. *Reagents and conditions*: **5** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol), and acetic acid (3.0 mL) at 100 °C for about 4 h. Isolated yields are given.

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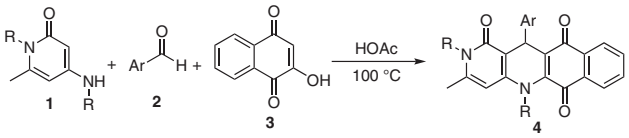
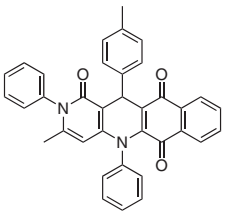
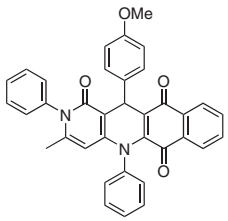
Table 2 Synthesis of Naphtho[2,3-*b*][1,6]naphthyridine-2,5-dione Derivatives **4**[a,b]

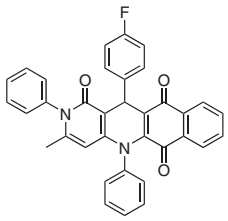




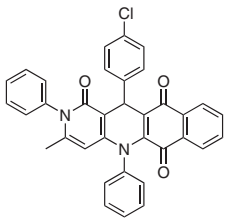
4a, 84%



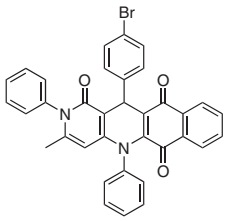
4b, 78%



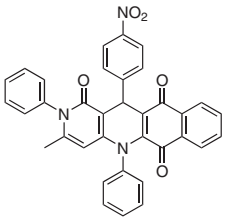
4c, 82%



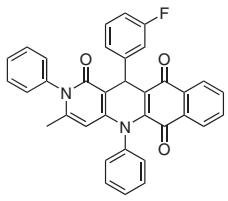
4d, 86%



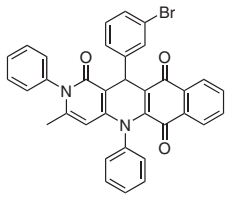
4e, 85%



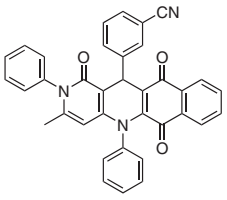
4f, 86%



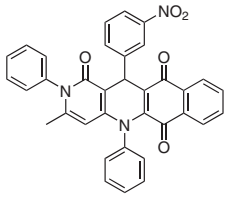
4g, 78%



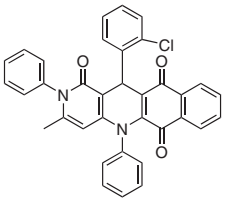
4h, 83%



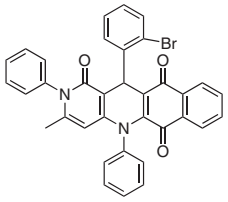
4i, 81%



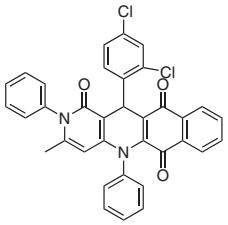
4j, 80%



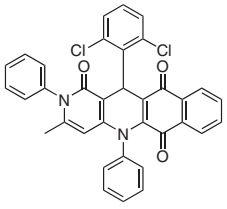
4k, 74%



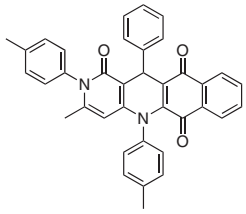
4l, 75%



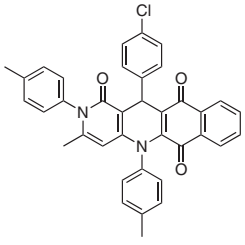
4m, 73%



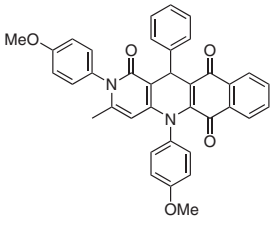
4n, 70%



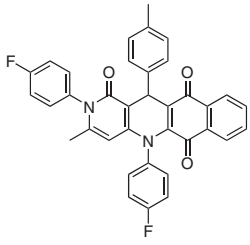
4o, 78%



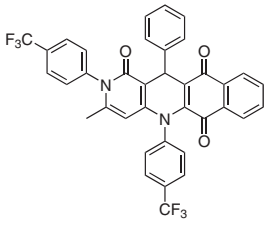
4p, 84%



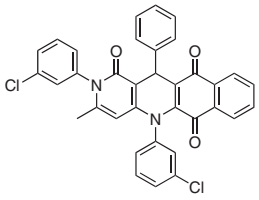
4q, 80%



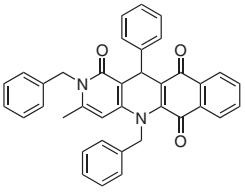
4r, 81%



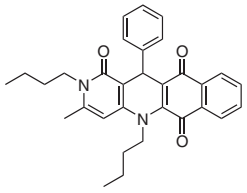
4s, 76%



4t, 79%



4u, 75%



4v, 77%

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol), and acetic acid (3.0 mL) at 100 °C for about 4 h.
[b] Isolated yields.

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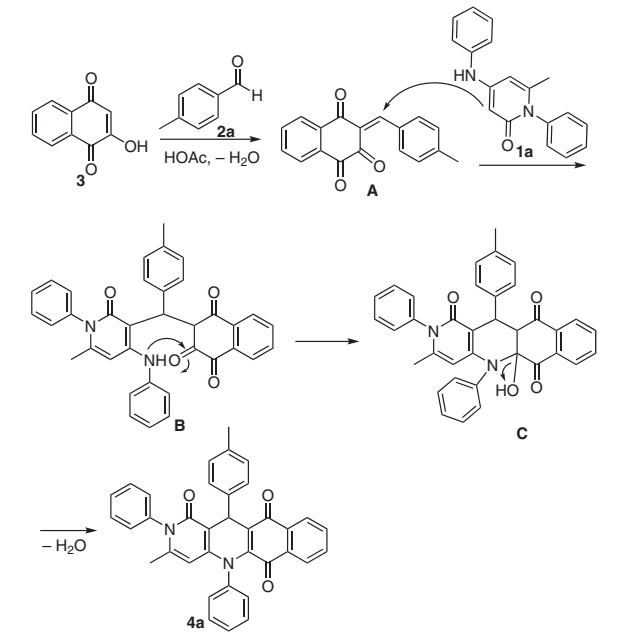
Similar to our previous domino reaction processes, the present reactions showed the following attractive characteristics: (1) easily available starting materials, (2) simple and efficient one-pot procedure, (3) water as the sole by-product. In addition, the structures of synthetic new compounds were all confirmed by their ^{1}H NMR, ^{13}C NMR, and HRMS spectra.

On the basis of the experimental results, a reasonable mechanism for this three-component domino reaction is represented in Scheme 3. Firstly, the intermediate **A** was generated from the Knoevenagel reaction between 2-hydroxynaphthalene-1,4-dione **3** and aldehyde **2a** and further underwent the Michael addition with aminopyridinones **1a** to afford intermediate **B**. After an intramolecular cyclization of intermediate **B** in the presence of acetic acid, the intermediate **C** was formed, which was further converted into the expected product **4a** after elimination of H_2O.



Scheme 3 The plausible mechanism for the formation of **4a**

In conclusion, a simple and efficient strategy for the preparation of polysubstituted naphtho[2,3-*b*][1,6]naphthyridine derivatives via domino reaction processes has been developed, which could provide a series of potential biological molecules. Undoubtedly, the operational simplicity and environmentally friendly nature make the strategy highly attractive. Other features of this method include bond-forming efficiency, inexpensive and easily available starting materials (6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1*H*)-ones, aldehydes, and 2-hydroxynaphthalene-1,4-dione), and the acquisition of activating products with good to excellent yields.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1479-4420.

References and Notes

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(14) **General Procedure for the Synthesis of 5,12-Dihydronaphtho[2,3-*b*][1,6]naphthyridine-1,6,11(2*H*)-triones 4a–v**

A mixture of aminopyridinone **1** (0.5 mmol), aldehyde **2** (0.5 mmol), 2-hydroxynaphthalene-1,4-dione **3** (0.5 mmol), and HOAc (3.0 mL) was stirred and heated at 100 °C for about 4 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with cold water (10 mL). The crude products were filtered by Büchner funnel and further purified by recrystallization from hot 95% ethanol to afford the desired pure products **4** as red to red brown solid.

3-Methyl-2,5-diphenyl-12-(*p*-tolyl)-5,12-dihydronaphtho[2,3-*b*][1,6]naphthyridine-1,6,11(2*H*)-trione (4a)

Red brown solid; mp 290–292 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.03 (d, *J* = 8.0, 1.2 Hz, 1 H, ArH), 7.82 (d, *J* = 7.6, 0.8 Hz, 1 H, ArH), 7.63–7.66 (m, 5 H, ArH), 7.42–7.49 (m, 4 H, ArH), 7.51–7.53 (m, 3 H, ArH), 7.19 (d, *J* = 7.2 Hz, 1 H, ArH), 7.12 (d, *J* = 8.0 Hz, 2 H, ArH), 7.04–7.08 (m, 1 H, ArH), 5.77 (s, 1 H, CH), 5.58 (s, 1 H, CH), 2.30 (s, 3 H, CH_3), 1.82 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 187.8, 182.1, 165.0, 161.6, 153.6, 145.5, 139.7, 138.1, 135.3, 134.2, 133.9, 133.1, 132.6, 131.2, 129.7, 129.6, 129.5, 129.1, 128.9, 128.3, 127.8, 126.6, 126.4, 124.6, 123.1, 99.5, 35.5, 21.6, 21.0. HRMS (ESI): *m/z* calcd for $C_{36}H_{27}N_2O_3$ [M + H]$^+$: 535.2022; found: 535.2021

(15) **General Procedure for the Synthesis of 12-Aryl-2,3,4,12-tetrahydro-1*H*-benzo[*b*]xanthene-1,6,11-triones 6**

Similarly, the mixture of 3-(arylamino)cyclohex-2-en-1-one **1** (0.5 mmol), aldehyde **2** (0.5 mmol), 2-hydroxynaphthalene-1,4-dione (**3**, 0.5 mmol), and HOAc (3.0 mL) was stirred and heated at 100 °C for about 4 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with cold water (10 mL). The crude products were filtered by Büchner funnel and further purified by recrystallization from hot 95% ethanol to afford the desired pure products **6** as red to red-brown solid.

3,3-Dimethyl-12-phenyl-2,3,4,12-tetrahydro-1*H*-benzo[*b*]xanthene-1,6,11-trione (6a)

Red solid; mp 232–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.14 (t, *J* = 5.6 Hz, 1 H, ArH), 8.00–8.02 (m, 1 H, ArH), 7.71–7.73 (m, 2 H, ArH), 7.41 (d, *J* = 7.6 Hz, 2 H, ArH), 7.28 (t, *J* = 7.6 Hz, 2 H, ArH), 7.18 (t, *J* = 7.2 Hz, 1 H, ArH), 5.16 (s, 1 H, CH), 2.65–2.78 (m, 2 H, CH_2), 2.25–2.35 (m, 2 H, CH_2), 1.17 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 196.2, 182.9, 178.0, 162.8, 149.0, 142.5, 134.5, 133.7, 131.6, 130.6, 128.7, 128.5, 127.2, 126.6, 126.5, 125.3, 114.3, 50.7, 40.7, 32.8, 32.4, 29.1, 27.4. HRMS (ESI): *m/z* calcd for $C_{25}H_{21}O_4$ [M + H]$^+$: 385.1440; found: 385.1449

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