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Synthesis of 3,3-disubstituted-2,3-dihydro-azanaphthoquinones *via* simultaneous alkyne oxidation and nitrile hydration of *ortho*-alkynylarenenitriles†

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o-Alkynylarenenitriles when heated with $Pd(OAc)_2/H_2O/(\pm)$-CSA in DMSO undergo simultaneous alkyne oxidation and nitrile hydration to give 3-aryl-3-hydroxy-2,3-dihydroazanaphthoquinones. Upon treatment with (±)-CSA, these compounds form 3-arylazanaphthoquinones *in situ*, which add to electron-rich aromatics and terminal alkene/alkyne to afford 3,3-disubstituted-2,3-dihydroazanaphthoquinones.

Introduction

Azanaphthoquinone (**A**) is a structurally appealing compound as it contains multiple functional groups: amide, imine and ketone (Fig. 1). Given the popularity of naphthoquinones in organic chemistry, it is surprising that only little is known about azanaphthoquinone and its derivatives.[1] This may be correlated with the lack of a generalized method for the synthesis of this type of compound. Somewhat familiar azanaphthoquinones are 3-aryl derivatives **B**, which were usually synthesized by a thermal rearrangement of 3-azido-3-aryl-1,3-indanediones, which in turn were prepared by a multistep procedure.[1d,e] Despite the limited synthetic routes, certain nucleophilic addition, cycloaddition and photochemical insertion reactions of **B** have been studied.[1e,f] It is also worth noting that these compounds may be related to 3-aryltetrahydroisoquinolines (**C**), the subunits of tetrahydroisoquinoline alkaloids.[2]

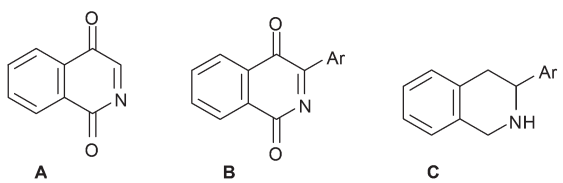

Fig. 1 Structures of azanaphthoquinone (**A**), 3-arylazanaphthoquinones (**B**) and 3-aryltetrahydroisoquinolines (**C**).

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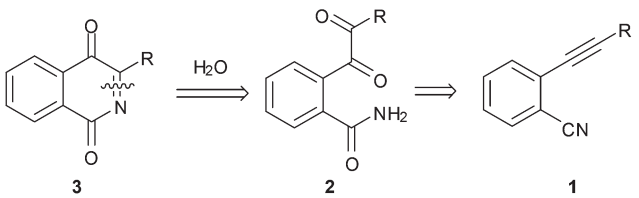
†Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all products, including copies of ^1H and ^{13}C NMR spectra and X-ray structural information of **5e** (CIF). CCDC 959881. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00852a



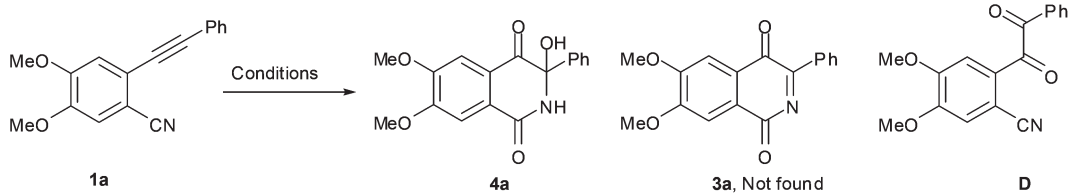
Scheme 1 Proposed route to azanaphthoquinones.

In continuation of our interest in the synthetic applications of *o*-functionalized alkynylarenes,[3] it occurred to us that in the case of *o*-alkynylarenenitriles (**1**), if the triple bond is oxidized to the α-diketo unit and simultaneously, the nitrile is selectively hydrated to the amide group, the resulting diketoarylamides **2** would undergo cyclodehydration to produce 3-substituted azanaphthoquinones **3** (Scheme 1). A variety of reagents, including $KMnO_4$,[4] I_2/DMSO,[5] Fe(III) or Pd(II) compounds/DMSO,[6–9] MsOH/HCO_2H/DMSO-HBr/H_2O,[10] oxone/TFA,[11] and $[Ru(cymene)Cl_2]_2/I_2/H_2O_2$ [12] are known for the oxidation of alkynes to α-diketones. Likewise, numerous reagents such as $Ru(OH)_x/Al_2O_3$,[13] TFA/H_2SO_4,[14] $Pd(OAc)_2$/MeCH=NOH,[15] Ag nanoparticles,[16] complexes of Fe, Ru, Rh, Pd, Os, Pt and Au[17] and CeO_2 [18] are available for the selective hydration of nitriles to amides. But, no method exists for carrying out both the transformations simultaneously in compounds such as *o*-alkynylarenenitriles. Hence the dual transformation would be quite useful in synthetic chemistry.

Results and discussion

We chose *o*-alkynylbenzonitrile **1a** as a model substrate for identifying optimal reagents and conditions for the simul-

Table 1 Optimisation of reaction conditions for the simultaneous alkyne oxidation and nitrile hydration process[a]



S. No.	Reaction conditions	Yield of **4a**[b] (%)
1	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, 120 °C, 24 h	NR
2	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, TFA (20 mol%), 120 °C, 12 h	65
3	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, AcOH (20 mol%), 120 °C, 12 h	NR
4	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, TfOH (20 mol%), 120 °C, 12 h	76
5	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, MsOH (20 mol%), 120 °C, 12 h	53
6	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, PTSA (20 mol%), 120 °C, 12 h	68
7	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, CSA (20 mol%), 120 °C, 12 h	87
8	$Pd(OAc)_2$ (50 mol%), DMSO, H_2O, CSA (20 mol%), 120 °C, 12 h	72[c]
9	$Pd(OAc)_2$ (30 mol%), DMSO, H_2O, CSA (20 mol%), 120 °C, 12 h	49[d]
10	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, CSA (10 mol%), 120 °C, 12 h	60
11	$Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, CSA (30 mol%), 120 °C, 12 h	84
12	I_2 (2 equiv.), DMSO, H_2O, 120 °C, 24 h	55[e]
13	I_2 (2 equiv.), DMSO, H_2O, CSA (20 mol%), 120 °C, 24 h	42[f]
14	I_2 (4 equiv.), DMSO, H_2O, 150 °C, 24 h	70[g]

[a] No reaction occurs at rt. [b] Isolated yield. [c,d,e,f,g] The corresponding alkyne oxidation product (diketobenzonitrile **D**) was produced as a by-product in 7, 30, 35, 50 and 25% yields, respectively.

taneous oxidation/hydration reactions and subsequent cyclodehydration to form the azanaphthoquinone **3a**. Since the $Pd(OAc)_2/CuBr_2/DMSO$[9] system has been previously used for the oxidation of alkynes and the $Pd(OAc)_2$/MeCH=NOH[15] (H_2O source) system for the hydration of nitriles, we envisaged that the $Pd(OAc)_2$(1 equiv.)/DMSO/H_2O system would be a right choice to begin with. However, with this system, **1a** remained inert at room temperature as well as at 120 °C even after 24 h (Table 1, entry 1). Larock *et al*. have reported the conversion of nitriles to imines (subsequently, to ketones) by $Pd(OAc)_2$/DMSO in the presence of TFA.[19] Hence, we expected that the addition of TFA to $Pd(OAc)_2$/DMSO/H_2O would promote the dual transformation. Pleasingly, when 20 mol% of TFA was added to the reaction, it afforded the aminol **4a** in 65% yield as the only isolable product, without undergoing further dehydration (entry 2). Our attempts to dehydrate/oxidize **4a** to **3a** by heating with acidic Al_2O_3 or DDQ (including microwave irradiation) did not work. Nevertheless, we thought this aminol would be as good as the respective azanaphthoquinone **3a** with respect to its chemical reactions (see later), because the dehydration could be effected *in situ* during the course of a reaction. Hence, we proceeded with tuning the reaction conditions further. The reaction did not occur when AcOH was used instead of TFA (entry 3). However, the yield rose to 76% when TfOH was used (entry 4). We tested the suitability of other sulphonic acids such as MsOH, PTSA and (±)-CSA for the reaction (entries 5–7) and found that (±)-CSA afforded **4a** in a high yield of 87% (entry 7). With a view to reduce the amount of $Pd(OAc)_2$ employed, we conducted the reaction with 50 and 30 mol% of $Pd(OAc)_2$. We found that the yields are also correspondingly decreased and also **4a** was accompanied by the corresponding diketobenzonitrile **D** (entries 8 and 9). Reducing the amount of (±)-CSA to 10 mol% lowered the yield (entry 10) while increasing its amount to 30 mol% did not alter the yield much (entry 11). No reaction occurred when DMSO was replaced by 1,4-dioxane and when $Pd(OAc)_2$ was replaced by other catalysts such as $Pd(PPh_3)_4$, $Pd(dba)_3$, $Pd(PPh_3)_2Cl_2$ and $Pd(dppf)Cl_2$ and $Ni(dppf)Cl_2$. Since iodine is known to promote many of the transformations that palladium do,[20] we tested the utility of I_2 for the dual transformation. Interestingly, when the reaction was conducted with 2 equiv. of iodine in DMSO/H_2O, **4a** was produced in 55% yield along with **D** (entry 12). The inclusion of (±)-CSA reduced the yield to 42% (entry 13). When the reaction was conducted with 4 equiv. of iodine at 150 °C, the yield rose to 70% (entry 14). Based on the high yield, we selected $Pd(OAc)_2$ (1 equiv.), H_2O (1 equiv.), and CSA (20 mol%) in DMSO at 120 °C as apt reagents and conditions for the dual transformation. If the requirement of a sub-stoichiometric amount (1 equiv. for activating two functional groups) of expensive $Pd(OAc)_2$ is a matter of concern, inexpensive iodine may be opted with some compromise in the yield (which gave 70% yield of **4a**).

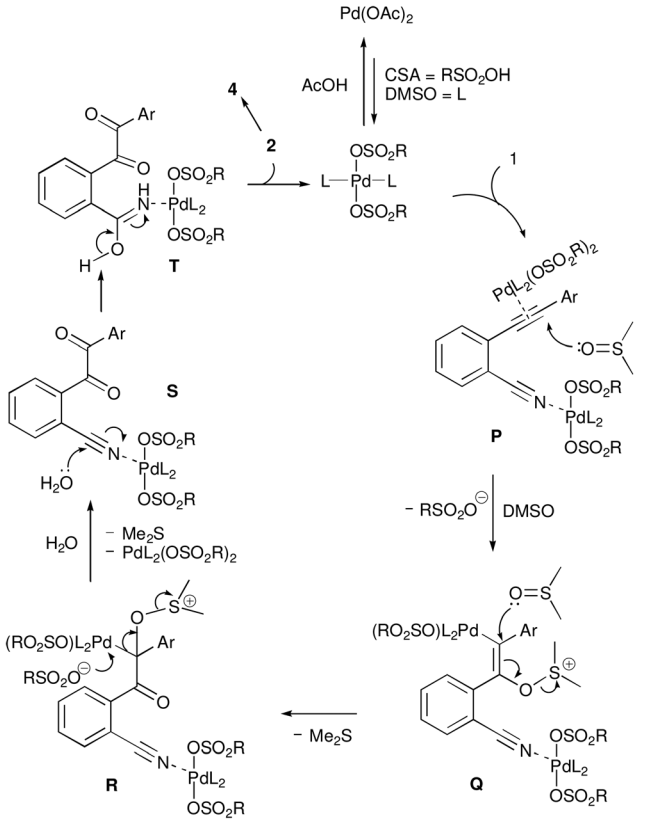
Using the optimized reaction conditions, the scope of the reaction was investigated for various *o*-alkynylarenenitriles (Table 2). The substrates **1a–e** having different aryl groups attached to the alkyne unit furnished the corresponding aminols **4a–e** in 51–87% yields (entries 1–5). The yield was low and the reaction time was 36 h for **1d** which possesses an *o*-anisyl group (entry 4), which may be attributed to the steric hindrance posed by the methoxy group. The reaction failed for the substrate **1f** which bears an electron-deficient *p*-nitrophenyl ring (entry 6) and also for **1g** which bears an aliphatic

Table 2 The scope of the dual transformation[a]

Entry	Nitrile	Product	Yield[b] (%)
1	Ar = Ph, **1a**	**4a**	87 (70)[c]
2	Ar = 4-MeC_6H_4, **1b**	**4b**	73 (48)[c]
3	Ar = 4-$OMeC_6H_4$, **1c**	**4c**	78 (43)[c]
4	Ar = 2-$OMeC_6H_4$, **1d**	**4d**	51[d]
5	Ar = 4-ClC_6H_4, **1e**	**4e**	69 (52)[c]
6	Ar = 4-$NO_2C_6H_4$, **1f**	—	NR[e]
7	**1g**	—	NR[e]
8	**1h**	**4f**	58[f]
9	**1i**	**4g**	55[f]
10	**1j**	**4h**	78
11	**1k**	**4i**	59
12	**1l**	**4j**	81

[a] Reaction conditions: $Pd(OAc)_2$ (1 equiv.), DMSO, H_2O, CSA (20 mol %), 120 °C, 12 h. [b] Isolated yield. [c] The number in parenthesis is the yield obtained when the I_2/H_2O/DMSO system was employed. [d] The reaction time was 36 h. [e] No reaction. [f] The reaction required 2 equiv. of $Pd(OAc)_2$ and 50 mol% of CSA and 24 h for completion.

chain instead of an aryl group (entry 7), probably due to a significant change in the electronic nature of the alkyne unit. We also changed the substituents on the main aryl ring. When no or single methoxy group was present on the ring, the yields of the aminols (**4f** and **4g**) were low (entries 8 and 9). However,



Scheme 2 Mechanism for the formation of aminol **4**.

the methylenedioxy unit in the place gave a good yield of the respective aminol **4h** (entry 10).

Further, we investigated the scope of the reaction for heterocyclic *o*-alkynylarenenitriles (entries 11 and 12). For the quinoline-based nitrile **1k**, only the nitrile group underwent hydration while the triple bond did not get oxidized. The resulting benzamide upon intramolecular hydroamination afforded the lactam **4i** (entry 11). For the tetrahydrobenzothiophene-based nitrile **1l**, only the triple bond was oxidized while the nitrile group remained inert to give the diketo product **4j** (entry 12).

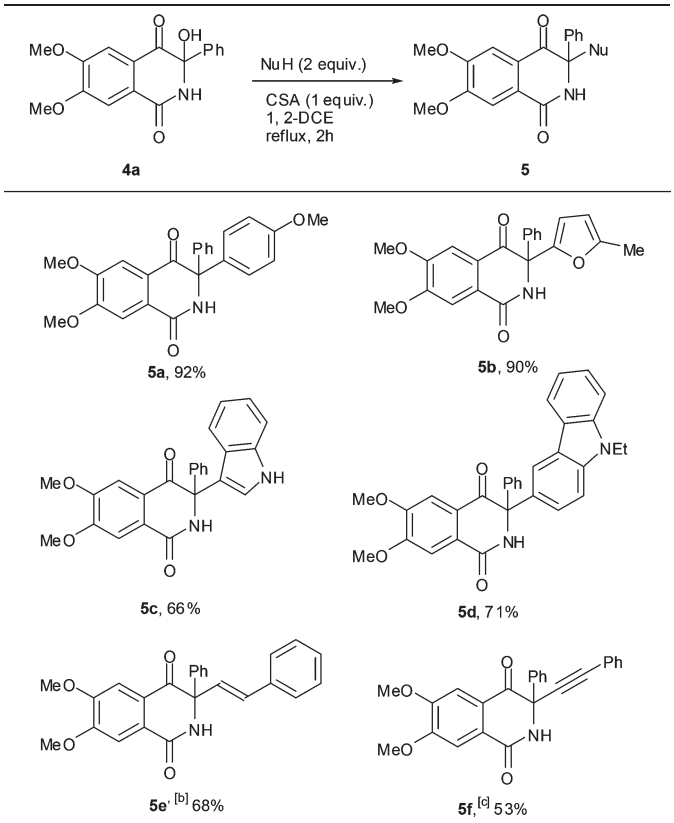
The mechanism for the oxidation of the triple bond by $Pd(OAc)_2$/DMSO in the presence of an additive is known.[9] Similarly, the mechanism for hydration of nitrile to amide by Pd-catalysts has been well-documented.[21] By combining the two mechanisms, a plausible mechanism for the formation of aminols **4** from the alkynylbenzonitriles **1** is derived as shown in Scheme 2. A catalytically active Pd complex is generated *in situ* by the replacement of acetate ligands of $Pd(OAc)_2$ by camphorsulphonate (RSO_2O^-).[19,22] The complex coordinates simultaneously to both the triple bond and the nitrile group of **1** to give **P**. The triple bond of **P** is attacked by a molecule of DMSO to give **Q** *via* displacement of the RSO_2O^- ligand.[9] Again, another molecule of DMSO attacks **Q** making a molecule of Me_2S to leave, forming **R**. The attack of RSO_2O^- on **R** regenerates a part of the catalyst and eliminates another molecule of Me_2S, giving **S**. Simultaneously, the nitrile group of **S** is

attacked by a water molecule.[15,19,21] The attack leads to iminol **T**, which undergoes tautomerization to amide and regenerates the catalyst. The resulting diketobenzamide **2** undergoes cyclization to afford **4**. Careful monitoring of the reactions indicates that the alkyne oxidation precedes nitrile hydration and thus, the process is, even though simultaneous, not synchronous.

It is interesting to note that the functional group pattern (ketone, 3° alcohol and amide functional groups in a six-membered ring) found in the aminols **4** is present in the precursor used in the total synthesis of the alkaloid, chilenine[23] and also in the tricyclic core of secondary metabolites ugibohlin, isophakellin and styloguanidine.[24]

To prove the point that the aminols **4** would behave like respective azanaphthoquinones in their reactions, the nucleophilic addition reactions of **4a** were investigated. We reasoned that the dehydration and the nucleophilic addition would be assisted by acid catalysts, because Nicolaou *et al.* have used triflic acid in the case of 3-aryl-3-hydroxyoxindoles for generating an *all*-carbon quaternary center at C-3 by Friedel–Crafts alkylation with aromatics.[25] Thus we employed triflic acid (1 equiv.) for the addition of anisole to **4a** and found that the expected nucleophilic addition product **5a** was produced in 92% yield when the reaction was carried out in 1,2-DCE at reflux for 2 h (Table 3). This suggests that the corresponding

Table 3 Nucleophilic addition reactions of **4a**[a]



[a] Isolated yield. [b] Reaction time was 6 h. [c] Reaction time was 12 h.

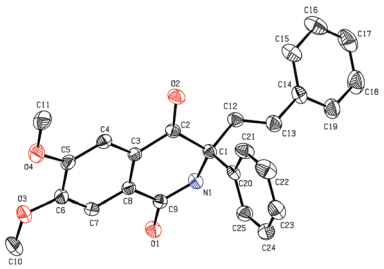


Fig. 2 ORTEP plot of the crystal structure of **5e** (at 30% probability level).

azanaphthoquinone **3a** would have formed *in situ* and then undergone nucleophilic addition (however, isolation of **3a** did not materialise). To our delight, an identical yield was obtained when (±)-CSA was used in the place of triflic acid in the reaction. Hence we switched to (±)-CSA for subsequent reactions due to its less corrosiveness. The scope of the reaction was investigated using various nucleophilic substrates such as 2-methylfuran, indole, 9-ethylcarbazole, styrene and phenylacetylene (Table 3).

In all cases, the respective nucleophilic addition products were produced in good to reasonable yields. Among the products **5a–f**, the structure of **5e** was confirmed by X-ray analysis (Fig. 2). The addition of styrene and phenylacetylene to **4a** (*via* **3a**) deserves a comment, because the addition of terminal alkenes/alkynes to imines, which is an effective protocol for accessing synthetically important allylamines/propargylamines, is invariably accomplished using transition metal compounds in the literature.[26] The two examples given here, therefore, represent intriguing metal-free direct addition of the C–H bond of terminal alkene/alkyne to a ketimine moiety.

Conclusions

In summary, we have developed an efficient palladium (or iodine)-mediated procedure for the simultaneous alkyne oxidation and nitrile hydration of *o*-alkynylarenenitriles for accessing 3-aryl-3-hydroxy-2,3-dihydroazanaphthoquinones. These compounds might behave like respective azanaphthoquinones in their chemical reactions as evidenced by their nucleophilic addition reactions. With the availability of a general route to (dihydro)azanaphthoquinones, the arena is now open for scouting their synthetic potentials and other applications.

Experimental

General remarks

Melting points were determined using an apparatus by the open capillary tube method and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer. HRMS (ESI) were recorded on Q-Tof mass spectrometers. X-ray crystallographic data were collected on a CCD diffractometer using graphite-monochromated Mo-Kα

radiation. Thin layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (100–200 mesh) was used for column chromatography.

General procedure for simultaneous alkyne oxidation and nitrile hydration

To a solution of *o*-alkynylarenenitriles **1** (0.15 mmol) in DMSO (5 mL) were added palladium(II) acetate (34 mg, 0.15 mmol) (67 mg, 0.30 mmol for **4f** and **4g**) and (±)-camphorsulphonic acid (46 mg, 20 mol%) (116 mg, 50 mol% for **4f** and **4g**) and water (3 μL, 0.15 mmol) and stirred at 120 °C for 12 h (36 h for **4d** and 24 h for **4f** and **4g**). The reaction mixture was then diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexane, 8 : 2 v/v) to afford the compounds **4a–j**. **Using I_2/H_2O/DMSO:** To a solution of *o*-alkynylarenenitriles **1** (0.15 mmol) in DMSO (5 mL) were added iodine (152 mg, 0.6 mmol) and water (3 μL, 0.15 mmol) and stirred at 150 °C for 24 h. The reaction mixture was then quenched with aq. $Na_2S_2O_3$ solution and worked up as described above.

3-Hydroxy-6,7-dimethoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (4a). Pale yellow solid. Yield: 41 mg (87%) [33 mg (70%) using I_2/H_2O/DMSO]. M.p. 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H), 7.59 (s, 1H), 7.46–7.44 (m, 2H), 7.35–7.29 (m, 5H), 3.96 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.3, 161.1, 154.3, 152.3, 140.6, 128.2, 128.0, 126.4, 126.2, 123.4, 109.1, 107.4, 85.5, 56.1, 55.9 ppm. HRMS (ESI) calcd for $C_{17}H_{15}NO_5$: 314.1028 $[M + H]^+$, found: 314.1027.

4,5-Dimethoxy-2-(2-oxo-2-phenyl-acetyl)-benzonitrile (D). Pale yellow solid. M.p.: 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.44 (s, 1H), 7.26 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 190.4, 153.4, 152.1, 135.1, 132.8, 130.2, 129.2, 129.1, 117.3, 116.6, 113.6, 105.6, 56.7, 56.4. HRMS (ESI) calcd for $C_{17}H_{13}NO_4$: 296.0917 $[M + H]^+$, found: 296.0923.

3-Hydroxy-6,7-dimethoxy-3-(4-methylphenyl)-2,3-dihydroisoquinoline-1,4-dione(4b). Off-white solid. Yield: 36 mg (73%) [23 mg (48%) using I_2/H_2O/DMSO]. M.p.:199–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H), 7.59 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.28 (s, 1H), 7.26 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.9, 161.6, 154.8, 152.7, 138.2, 138.1, 129.1, 126.9, 126.6, 124.0, 109.5, 107.9, 86.0, 56.6, 56.4, 21.1 ppm. HRMS (ESI) calcd for $C_{18}H_{17}NO_5$: 328.1185 $[M + H]^+$, found: 328.1185.

3-Hydroxy-6,7-dimethoxy-3-(4-methoxyphenyl)-2,3-dihydroisoquinoline-1,4-dione (4c). Pale yellow solid. Yield: 40 mg (78%) [22 mg (43%) using I_2/H_2O/DMSO]. M.p.: 183–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 1H), 7.58 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.28 (s, 1H), 7.24 (s, 1H), 6.88 (d, J = 8.8 Hz, 2H), 3.96 (s, 3H), 3.85 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.4, 161.2, 159.3, 154.2, 152.2, 132.5, 127.5, 126.3, 123.5, 113.4, 109.0, 107.5, 85.4, 56.1, 55.9, 55.1 ppm. HRMS (ESI) calcd for $C_{18}H_{17}NO_6$: 366.0954 $[M + Na]^+$, found: 366.0958.

3-Hydroxy-6,7-dimethoxy-3-(2-methoxyphenyl)-2,3-dihydroisoquinoline-1,4-dione (4d). Pale yellow solid. Yield: 26 mg (51%). M.p.: 180–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.58 (s, 1H), 7.40 (s, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.11 (s, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.5, 160.5, 155.7, 153.6, 151.9, 130.7, 129.4, 126.9, 126.4, 124.2, 119.9, 111.5, 109.0, 107.0, 82.0, 56.0, 55.9, 55.5 ppm. HRMS (ESI) calcd for $C_{18}H_{17}NO_6$: 344.1134 $[M + H]^+$, found: 344.1132.

3-(4-Chlorophenyl)-3-hydroxy-6,7-dimethoxy-2,3-dihydroisoquinoline-1,4-dione (4e). Off-white solid. Yield: 36 mg (69%) [27 mg (52%) using I_2/H_2O/DMSO]. M.p.:196–198 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.60 (s, 1H), 7.46–7.41 (m, 5H), 7.30 (s, 1H), 3.97 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.8, 161.1, 154.4, 152.3, 139.7, 133.0, 128.3, 128.0, 126.4, 123.3, 109.1, 107.5, 84.9, 56.1, 55.9 ppm. HRMS (ESI) calcd for $C_{17}H_{14}ClNO_5$: 370.0458 $[M + Na]^+$, found: 370.0463.

3-Hydroxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (4f). Pale yellow solid. Yield: 22 mg (58%). M.p.: 179–181 °C (lit.[1a] 181–183 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (s, 1H), 8.16 (dd, J = 7.6, 0.8 Hz, 1H), 7.94–7.87 (m, 2H), 7.83–7.77 (m, 1H), 7.50–7.46 (m, 2H), 7.45 (s, 1H), 7.37–7.30 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.2, 161.3, 140.1, 135.2, 133.2, 131.6, 129.7, 128.4, 128.1, 127.7, 126.4, 126.3, 85.4 ppm. HRMS (ESI) calcd for $C_{15}H_{11}NO_3$: 276.0637 $[M + Na]^+$, found: 276.0643.

3-Hydroxy-7-methoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (4g). Pale yellow solid. Yield: 23 mg (55%). M.p.:164–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 2.8 Hz, 1H), 7.46–7.44 (m, 2H), 7.37 (s, 1H), 7.34–7.29 (m, 4H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.8, 164.7, 160.9, 140.5, 134.1, 129.2, 128.2, 128.0, 126.2, 122.8, 119.7, 111.2, 85.3, 56.0 ppm. HRMS (ESI) calcd for $C_{16}H_{13}NO_4$: 284.0923 $[M + H]^+$, found: 284.0922.

7-Hydroxy-7-phenyl-6,7-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline-5,8-dione (4h). Pale yellow solid. Yield: 35 mg (78%). M.p.:176–178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.29 (s, 1H), 7.61 (s, 1H), 7.54–7.52 (m, 2H), 7.45–7.39 (m, 4H), 7.34 (s, 1H), 6.33 (d, J = 11.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.1, 166.0, 158.5, 156.7, 145.7, 134.2, 133.5, 133.3, 131.5, 131.0, 111.8, 110.0, 108.4, 90.5. HRMS (ESI) calcd for $C_{16}H_{11}NO_5$: 298.0715 $[M + H]^+$, found: 298.0712.

3-Phenylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (4i). Yellow solid. Yield: 24 mg (59%). M.p.: 260–262 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H), 9.34 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.01–7.93 (m, 3H), 7.72–7.68 (m, 1H), 7.64–7.58 (m, 3H), 7.08 (d, J = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 153.0, 150.6, 144.4, 137.5, 133.5, 132.6, 129.9, 129.7, 128.9, 128.0, 126.9, 126.1, 126.0, 119.6, 104.4. HRMS (ESI) calcd for $C_{18}H_{12}N_2O$: 273.1028 $[M + H]^+$, found: 273.1026.

2-(2-Oxo-2-phenylacetyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (4j). Red solid. Yield: 36 mg (81%). M.p.: 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 2.86–2.77 (m, 4H), 1.90–1.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 181.7, 149.9, 140.9, 138.6, 135.2, 132.2, 130.6, 129.0, 115.9, 113.5, 25.6, 24.3, 22.6, 21.6. HRMS (ESI) calcd for $C_{17}H_{13}NO_2S$: 318.0565 $[M + Na]^+$, found: 318.0565.

General procedure for the synthesis of dihydroazanaphthoquinones 5

To a solution of **4a** (31 mg, 0.1 mmol) in 1,2-dichloroethane (5 mL) were added (±)-camphor sulphonic acid (23 mg, 0.1 mmol) and arene, alkene or alkyne (0.2 mmol) and heated under reflux for 2 h (6 h for **5e** and 12 h for **5f**). The reaction mixture was then diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc–hexane, 7 : 1 v/v) to afford the compounds **5a–f**.

6,7-Dimethoxy-3-(4-methoxyphenyl)-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (5a). Pale orange solid. Yield: 37 mg (92%). M.p. 199–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.46 (s, 1H), 7.32 (s, 5H), 7.24 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 162.2, 159.6, 154.7, 153.0, 141.3, 133.0, 129.3, 128.6, 128.4, 128.0, 125.9, 125.5, 114.0, 109.4, 108.2, 74.1, 56.6, 56.4, 55.3 ppm. HRMS (ESI) calcd for $C_{24}H_{21}NO_5$: 404.1498 $[M + H]^+$, found: 404.1483.

6,7-Dimethoxy-3-(5-methylfuran-2-yl)-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (5b). Orange solid. Yield: 34 mg (90%). M.p.: 190–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.47–7.44 (m, 3H), 7.37–7.32 (m, 3H), 6.76 (s, 1H), 6.23 (d, J = 3.2 Hz, 1H), 5.95–5.94 (m, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6, 162.0, 154.9, 153.5, 153.1, 150.1, 138.8, 128.73, 128.70, 126.9, 126.0, 124.7, 110.9, 109.5, 108.3, 106.3, 70.1, 56.7, 56.4, 13.7 ppm. HRMS (ESI) calcd for $C_{22}H_{19}NO_5$: 378.1341 $[M + H]^+$, found: 378.1346.

6,7-Dimethoxy-3-(1-methyl-1*H*-indol-3-yl)-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (5c). Pale orange solid. Yield: 28 mg (66%). M.p.:158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71(s, 1H), 7.54–7.52 (m, 2H), 7.47 (s, 1H), 7.36–7.30 (m, 4H), 7.24–7.20 (m, 2H), 7.02 (t, J = 7.2 Hz, 1H), 6.85 (s, 1H), 6.62 (s, 1H), 4.04 (s, 3H), 3.95 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 162.4, 154.6, 153.0, 140.2, 137.8, 129.4, 128.7, 128.5, 127.3, 125.8, 125.5, 125.3, 122.4, 120.6, 120.0, 115.4, 109.7, 109.4, 108.5, 70.7, 56.6, 56.4, 33.0 ppm. HRMS (ESI) calcd for $C_{26}H_{22}N_2O_4$: 427.1658 $[M + H]^+$, found: 427.1658.

3-(9-Ethyl-9*H*-carbazol-3-yl)-6,7-dimethoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (5d). Pale orange solid. Yield: 35 mg (71%). M.p.: 236–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 1.6 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.49 (s, 1H), 7.47–7.34 (m, 8H), 7.26 (s, 1H), 7.20 (t, J = 7.4 Hz, 1H), 6.83 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 162.3, 154.6, 153.0, 142.0, 140.4, 139.7, 131.1, 128.6, 128.4, 128.3, 126.0, 125.9, 125.7, 125.6, 122.8, 122.7, 120.6, 120.0, 119.2, 109.4, 108.60, 108.58, 108.2, 74.9, 56.6, 56.4, 37.6, 13.8 ppm. HRMS (ESI) calcd for $C_{31}H_{26}N_2O_4$: 491.1971 $[M + H]^+$, found: 491.1972.

(*E*)-6,7-Dimethoxy-3-phenyl-3-styryl-2,3-dihydroisoquinoline-1,4-dione (5e). Pale yellow solid. Yield: 27 mg (68%). M.p.: 224–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.51–7.47 (m, 3H), 7.42–7.26 (m, 8H), 6.85 (d, J = 16.0 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 6.60 (s, 1H), 4.04 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 162.3, 154.9, 153.1, 140.9, 135.6, 131.8, 130.0, 129.0, 128.7, 128.6, 128.5, 126.94, 126.85, 126.0, 124.7, 109.5, 108.2, 71.8, 56.7, 56.4 ppm. HRMS (ESI) calcd for $C_{25}H_{21}NO_4$: 400.1549 $[M + H]^+$, found: 400.1549.

6,7-Dimethoxy-3-phenyl-3-(phenylethynyl)-2,3-dihydroisoquinoline-1,4-dione (5f). Pale orange solid. Yield: 21 mg (53%). M.p.:196–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.72–7.70 (m, 2H), 7.51–7.49 (m, 2H), 7.46 (s, 1H), 7.40–7.32 (m, 6H), 6.62 (brs, 1H), 4.07 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 161.6, 155.1, 153.2, 138.9, 132.0, 129.1, 129.0, 128.9, 128.4, 126.6, 126.0, 124.0, 121.6, 109.8, 108.7, 86.8, 86.3, 66.7, 56.7, 56.5 ppm. HRMS calcd for $C_{25}H_{19}NO_4$: 398.1392 $[M + H]^+$, found: 398.1393.

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