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Synthesis of 3, 3-Disubstituted-2,3-Dihydroazanaphthoquinones via Simultaneous Alkyne Oxidation and Nitrile Hydration of *ortho*-Alkynylarenenitriles

Karuppusamy Sakthivel^a and Kannupal Srinivasan^{*a}

^aSchool of Chemistry, Bharathidasan University, Tiruchirappalli-620 024, Tamil Nadu, India

Email: srinivasank@bdu.ac.in; Tel: +91-431-2407053-538

Abstract: *o*-Alkynylarenenitriles when heated with Pd(OAc)₂/H₂O/(±)-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-arylanaphthoquinones *in situ*, which add with 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 (Figure 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 to the lack of a generalized method for the synthesis of this type of compounds. 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 to note that these compounds may be related to 3-aryltetrahydroisoquinolines (**C**), the subunits of tetrahydroisoquinoline alkaloids.²

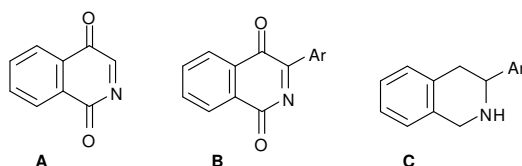
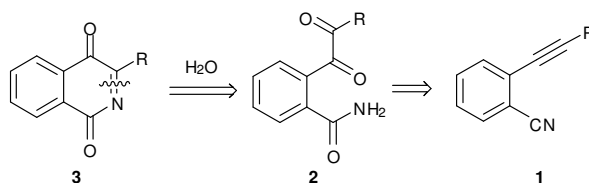


Figure 1. Structures of azanaphthoquinone (**A**), 3-arylanaphthoquinones (**B**) and 3-aryltetrahydroisoquinolines (**C**)

In continuation of our interest in the synthetic applications of *o*-functionalized alkynylarenes,³ it occurred to us that in case of *o*-alkynylarenenitriles (**1**), if the triple bond is oxidized to α -diketo unit and simultaneously, the nitrile is selectively hydrated to amide group, the resulting diketoarylamides **2** would undergo cyclodehydration to produce 3-substituted azanaphthoquinones **3** (Scheme 1). A variety of reagents, including KMnO₄,⁴ I₂/DMSO,⁵ Fe(III) or Pd(II) compounds/ DMSO,⁶⁻⁹ MsOH/HCO₂H/DMSO-HBr/H₂O,¹⁰

oxone/TFA,¹¹ and $[\text{Ru}(\text{cymene})\text{Cl}_2]_2/\text{I}_2/\text{H}_2\text{O}_2$ ¹² are known for the oxidation of alkynes into α -diketones. Likewise, numerous reagents such as $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$,¹³ $\text{TFA}/\text{H}_2\text{SO}_4$,¹⁴ $\text{Pd}(\text{OAc})_2/\text{MeCH}=\text{NOH}$,¹⁵ Ag nanoparticles,¹⁶ complexes of Fe, Ru, Rh, Pd, Os, Pt and Au¹⁷ and CeO_2 ¹⁸ are available for the selective hydration of nitriles into 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.



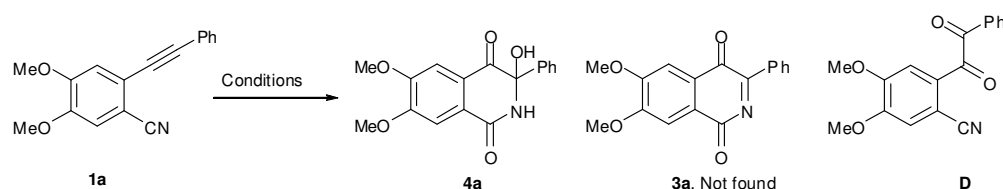
Scheme 1. Proposed route to azanaphthoquinones

Results and discussion

We chose *o*-alkynylbenzonitrile **1a** as a model substrate for identifying optimal reagents and conditions for the simultaneous oxidation/hydration reactions and subsequent cyclodehydration to form the azanaphthoquinone **3a**. Since $\text{Pd}(\text{OAc})_2/\text{CuBr}_2/\text{DMSO}$ ⁹ system has been previously used for the oxidation of alkynes and $\text{Pd}(\text{OAc})_2/\text{MeCH}=\text{NOH}$ ¹⁵ (H_2O source) system for the hydration of nitriles, we envisaged that $\text{Pd}(\text{OAc})_2(1\text{equiv.})/\text{DMSO}/\text{H}_2\text{O}$ 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 into imines (subsequently, to ketones) by $\text{Pd}(\text{OAc})_2/\text{DMSO}$ in the presence of TFA.¹⁹ Hence, we expected that the addition of TFA to $\text{Pd}(\text{OAc})_2/\text{DMSO}/\text{H}_2\text{O}$ 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 (\pm)-CSA for the reaction (entries 5-7) and found that (\pm)-CSA afforded **4a** in a high yield of 87% (entry 7). With a view to reduce the amount of $\text{Pd}(\text{OAc})_2$ employed, we conducted the reaction with 50 and 30 mol% of $\text{Pd}(\text{OAc})_2$. 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 (\pm)-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 $\text{Pd}(\text{OAc})_2$ by other catalysts such as $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{dba})_3$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and $\text{Pd}(\text{dppf})\text{Cl}_2$ and $\text{Ni}(\text{dppf})\text{Cl}_2$.

Since iodine is known to promote many of the transformations that palladium do,²⁰ we tested the utility of I₂ for the dual transformation. Interestingly, when the reaction was conducted with 2 equiv. of iodine in DMSO/H₂O, **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.), H₂O (1 equiv.), CSA (20 mol%) in DMSO at 120°C as apt reagents and conditions for the dual transformation. If the requirement of 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 yield (which gave 70% yield of **4a**).

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 ₂ O, 120 °C, 24 h	NR
2	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, TFA (20 mol%), 120 °C, 12 h	65
3	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, AcOH (20 mol%), 120 °C, 12 h	NR
4	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, TfOH (20 mol%), 120 °C, 12 h	76
5	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, MsOH (20 mol%), 120 °C, 12 h	53
6	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, PTSA (20 mol%), 120 °C, 12 h	68
7	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, CSA (20 mol%), 120 °C, 12 h	87
8	Pd(OAc) ₂ (50 mol%), DMSO, H ₂ O, CSA (20 mol%), 120 °C, 12 h	72 ^c
9	Pd(OAc) ₂ (30 mol%), DMSO, H ₂ O, CSA (20 mol%), 120 °C, 12 h	49 ^d
10	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, CSA (10 mol%), 120 °C, 12 h	60
11	Pd(OAc) ₂ (1 equiv.), DMSO, H ₂ O, CSA (30 mol%), 120 °C, 12 h	84
12	I ₂ (2 equiv.), DMSO, H ₂ O, 120 °C, 24 h	55 ^e
13	I ₂ (2 equiv.), DMSO, H ₂ O, CSA (20 mol%), 120 °C, 24 h	42 ^f
14	I ₂ (4 equiv.), DMSO, H ₂ O, 150 °C, 24 h	70 ^g

^aNo reaction occurs at rt. ^bIsolated yield. ^{c, d, e, f, g}The corresponding alkyne oxidation product (diketobenzonitrile **D**) was produced as a byproduct in 7, 30, 35, 50 and 25 % yields, respectively.

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 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 *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 electron-deficient *p*-nitrophenyl ring (entry 6) and also for **1g** which bears an aliphatic chain instead of aryl group (entry 7), probably due to 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, methylenedioxy unit in the place gave a good yield of the respective aminol **4h** (entry 10).

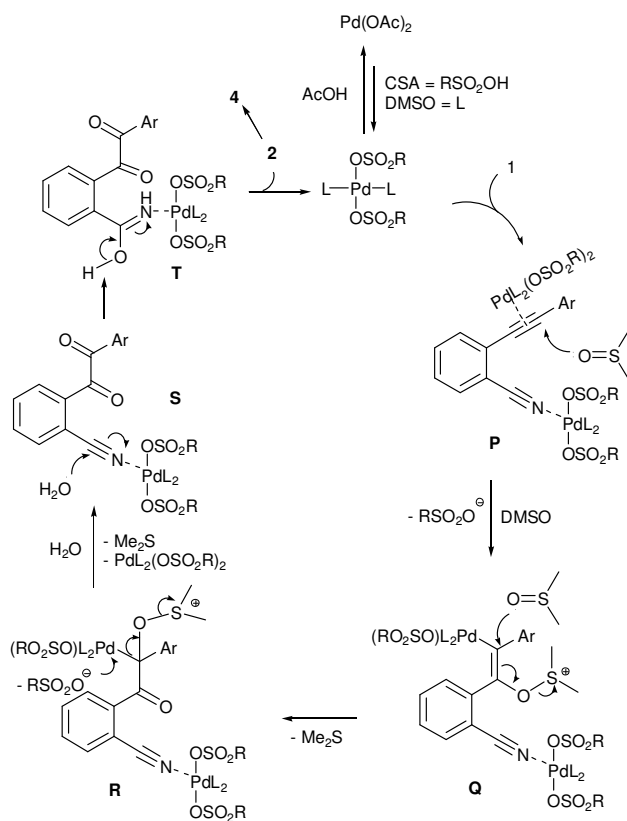
Table 2. The scope of the dual transformation.^a

Entry	Nitrile	Product	Yield (%) ^b
1	Ar = Ph, 1a	4a	87 (70) ^c
2	Ar = 4-MeC ₆ H ₄ , 1b	4b	73 (48) ^c
3	Ar = 4-OMeC ₆ H ₄ , 1c	4c	78 (43) ^c
4	Ar = 2-OMeC ₆ H ₄ , 1d	4d	51 ^d
5	Ar = 4-ClC ₆ H ₄ , 1e	4e	69 (52) ^c
6	Ar = 4-NO ₂ C ₆ H ₄ , 1f	-	NR ^e
7		-	NR ^e
8			58 ^f
9			55 ^f
10			78
11			59
12			81

^a Reactions conditions: Pd(OAc)₂ (1 equiv.), DMSO, H₂O, CSA (20 mol%), 120 °C, 12 h. ^b Isolated yield. ^c The number in parenthesis is the yield obtained when I₂/H₂O/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.

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 diketone product **4j** (entry 12).

The mechanism for the oxidation of triple bond by $\text{Pd}(\text{OAc})_2/\text{DMSO}$ in the presence of 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 $\text{Pd}(\text{OAc})_2$ by camphorsulphonate (RSO_2O^-).^{19,22} The complex coordinates simultaneously to both triple bond and 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 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.



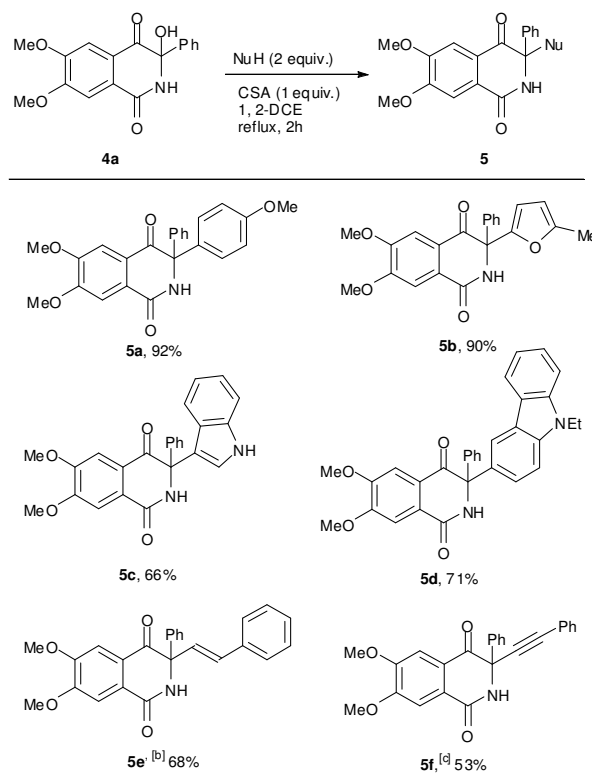
Scheme 2. Mechanism for the formation of aminol **4**.

It is interesting 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, chilenine²³ 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 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 azanaphthoquinone **3a** would have formed *in situ* and then undergone nucleophilic addition (however, isolation of **3a** did not materialise). To our delight, 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).

Table 3. Nucleophilic addition reactions of **4a**.^a



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

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 (Figure 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 C-H bond of terminal alkene/alkyne to a ketimine moiety.

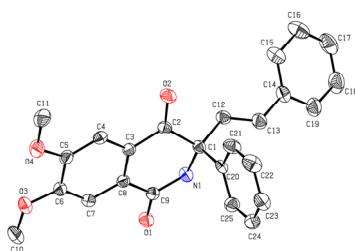


Figure 2: ORTEP plot of the crystal structure of **5e** (at 30% probability level)

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 ¹H and ¹³C 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

Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂; EtOAc/hexane, 8:2 v/v) to afford the compounds **4a-j**. **Using I₂/H₂O/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. Na₂S₂O₃ 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 I₂/H₂O/DMSO]. M.p. 202-204 °C. ¹H 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). ¹³C 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 C₁₇H₁₅NO₅: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₁₃NO₄: 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 I₂/H₂O/DMSO]. M.p.: 199-201 °C. ¹H 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). ¹³C 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 C₁₈H₁₇NO₅: 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 I₂/H₂O/DMSO]. M.p.: 183-185 °C. ¹H 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). ¹³C 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 C₁₈H₁₇NO₆: 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. ¹H 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). ¹³C 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 C₁₈H₁₇NO₆: 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 I₂/H₂O/DMSO]. M.p.: 196-198 °C. ¹H 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). ¹³C 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 C₁₇H₁₄ClNO₅: 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). ¹H 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). ¹³C 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 C₁₅H₁₁NO₃: 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. ¹H 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). ¹³C 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 C₁₆H₁₃NO₄: 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. ¹H 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). ¹³C 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 C₁₆H₁₁NO₅: 298.0715 [M + H]⁺, found: 298.0712.

3-Phenylbenzo[*b*][1,6]naphthyridin-1(2H)-one (4i): Yellow solid. Yield: 24 mg (59%). M.p.: 260-262 °C. ¹H 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). ¹³C 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 C₁₈H₁₂N₂O: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₁₃NO₂S: 318.0565 [M + Na]⁺, found: 318.0565.

General procedure for the synthesis of dihydroazanaphthaquinones 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 Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂; 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₄H₂₁NO₅: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₁₉NO₅: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₆H₂₂N₂O₄: 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. ¹H NMR (400 MHz, CDCl₃): 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, 8 H), 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₃₁H₂₆N₂O₄: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₅H₂₁NO₄: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₅H₁₉NO₄: 398.1392 [M + H]⁺, found: 398.1393.

[†]Electronic supplementary information (ESI) available (see footnote on the first page of this article): Experimental procedures and characterisation data for all products, including copies of ¹H and ¹³C NMR spectra and X-ray structural information (CCDC 959881) of **5e** (CIF) are available in the Supporting Information.

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