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One-Pot Three-Step Synthesis of Naphtho[2,3-*a*]carbazole-5,13-diones using a Tandem Radical Alkylation–Cyclization–Aromatization Reaction Sequence

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Abstract: A three-step, one-pot tandem reaction including radical nucleophilic alkylation/cyclization/aromatization was developed using 0.3 equivalents of silver(I) acetate (AgOAc) as the catalyst and 2 equivalents of ammonium persulfate [$(NH_4)_2S_2O_8$] as the oxidant. This strategy is highly efficient for the assembly of pentacyclic complex carbazoles from aryl-fused bromobenzoquinones and indol-3-ylpropanoic acid acids in 52–72% overall yields (three steps). This new approach provides a significant improvement over the previously reported methods and would greatly facilitate analog library construction of pentacyclic complex carbazoles and benefit further biological evaluation of these compounds.

Keywords: cyclization; naphtho[2,3-*a*]carbazole-5,13-diones; radical nucleophilic alkylation; silver catalysts; tandem reactions

The tricyclic carbazole nucleus is an important structural scaffold frequently found in numerous natural alkaloids and synthetic derivatives.[1,2] Most of these compounds, including simply substituted carbazoles, as well as annellated polycyclic complex molecules, possess various pharmacological properties, such as anti-HIV, anticancer, antibacterial and antifungal activities.[3,4]

Among these compounds, heterocycle-fused carbazoles have received much attention due to their significant anticancer activity. Representative compounds include the indole-fused cabazoles rebeccamycin (topoisomerase I inhibitor),[5–11] and staurosporine (kinase inhibitor)[12–16], and the pyrrole-fused carbazole granulatimide (checkpoint kinase 1 inhibitor)[17–22] (Figure 1). Such diversified pharmacological profiles

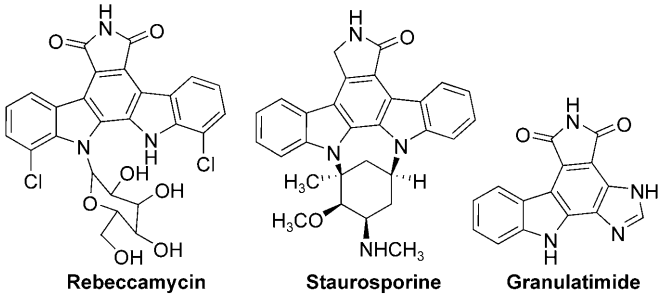


Figure 1. Representative complex carbazoles.

of these complex carbazoles have also spurred great efforts by the synthetic chemists since only a very limited range of synthetic methods have been reported.[23–32]

Naphthalene-1,4-dione-fused carbazoles (naphtho[2,3-*a*]carbazole-5,13-diones) represent a unique class of pentacyclic complex carbazoles possessing significant cell growth inhibition against several tumour cell lines.[33,34] However, few syntheses have been reported so far to access this class of electron-deficient com-

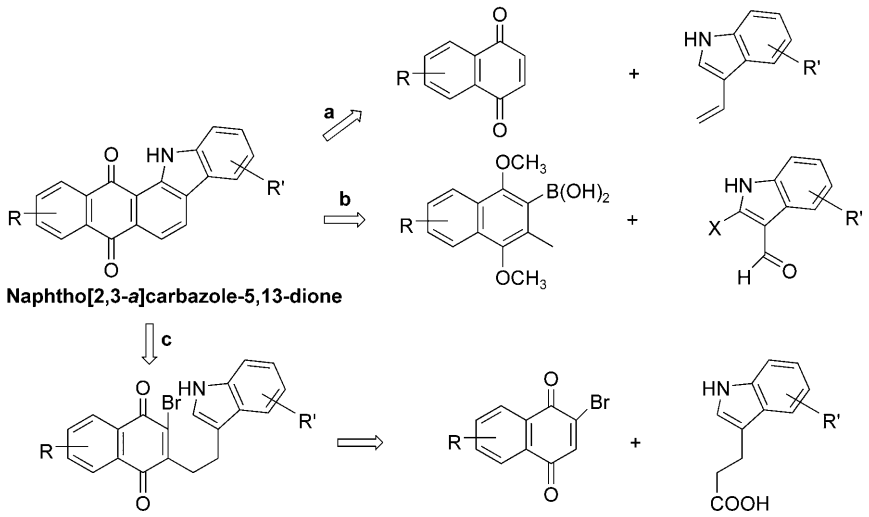
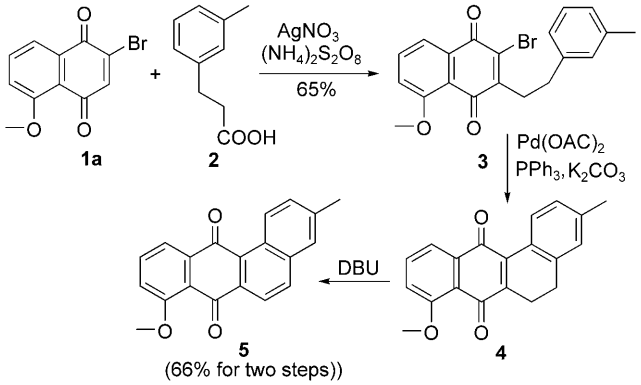


Figure 2. Retro-synthetic approaches to the synthesis of naphtho[2,3-*a*]carbazole-5,13-diones.

plex carbazoles which restricted further structure-activity relationship studies on them.

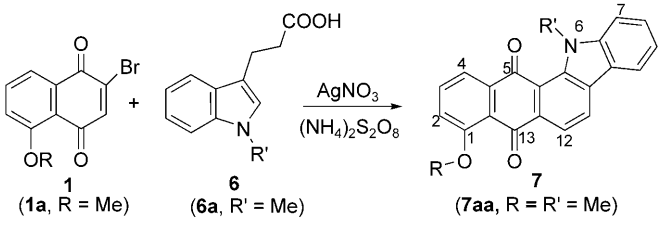
The first structural example of the naphtho[2,3-*a*]carbazole-5,13-diones was reported by Pindur et al.[35a] in 1990 who used a Diels–Alder reaction of naphthalene-1,4-dione and 3-vinylindole to access the prototypical pentacyclic carbazole complex in only 10% yield (*path a*, Figure 2, R = R′ = H). The second strategy to access this chemotype was reported by Koning et al. in 2003[36] and 2006[37] who used a Suzuki–Miyaura coupling between substituted naphthalenylboronic acids and 3-formylindoles followed by a light-assisted cyclization (*path b,* Figure 2). Apparently, these two methods are far below the optimum since the former approach led to extremely poor yield of the proposed product along with large amount of polymerized side products,[35] whereas the latter method used unusually substituted substrates and a high pressure mercury lamp irradiation to initiate the condensation/cyclization reaction. Therefore, a more efficient new methodology is highly needed to conveniently prepare naphtho[2,3-*a*]carbazole-5,13-diones for compound library construction and for drug screening.

We recently reported a strategy to synthesize anthraquinone **5** from bromoquinone **1a** and arylpropanoic acid **2**, a key intermediate to the natural product marmycin A, through a tandem three-step reaction approach.[38] This includes silver-catalyzed decarboxylic radical alkylation[39–41] yielding bromide **3**, palladium-catalyzed cyclization to offer tetracyclic product **4**, and DBU-assisted aromatization (Scheme 1). This strategy is very efficient yielding the target compound **5** in a 40% three-step overall yield. To explore further the utility of this approach, we envisioned that replacement of *m*-tolylpropanoic acid **2** with indol-3-ylpropanoic acid and submission to the same reaction



Scheme 1. Previous synthesis of benzo[*a*]anthraquinone **5** *via* a tandem multistep reaction.

sequence as outlined in Scheme 1 would produce our targetted pentacyclic carbazole complex – the naphtho[2,3-*a*]carbazole-5,13-diones (*path c*, Figure 2). Quite surprisingly, we found that the reaction of bromide **1a** and indol-3-ylpropanoic acid **6a** under the same conditions did not proceed in a step-by-step manner as proposed, instead all three steps occurred in one pot consequently leading to the final compound **7aa** directly (Scheme 2). To explore the generality and application of this reaction, we herein



Scheme 2. Synthesis of 1-methoxy-6-methylnaphtho[2,3-*a*]carbazole-5,13-dione (**7aa**).

report our studies on the synthesis of a small library of naphtho[2,3-*a*]carbazole-5,13-diones as well as a study of the reaction mechanism.

Initially, we explored the feasibility of the synthetic strategy by reacting 2-bromo-5-methoxy-1,4-naphthoquinone (**1a**) with *N*-methyl-indol-3-ylpropanoic acid (**6a**) to give the decarboxylic radical alkylation product, similar to the preparation of compound **3** using 2 equivalents of $(NH_4)_2S_2O_8$ as the oxidant and 0.3 equivalents of $AgNO_3$ as the catalyst (Scheme 2). However, we found that this reaction did not stop at the radical alkylation step, subsequent cyclization and aromatization occurred simultaneously under the same reaction system without addition of $Pd(OAc)_2$ and DBU to facilitate the cyclization and aromatization steps, therefore carbazole **7aa** was isolated as the sole product in 26% yield (entry 1, Table 1).

Table 1. Effects of catalysts and solvents.[a]

Entry	Catalyst	Solvent	Yield[b]
1	$AgNO_3$ (0.3 equiv.)	CH_3CN/H_2O	26%
2	AgOTf (0.3 equiv.)	CH_3CN/H_2O	20%
3	Ag_3PO_4 (0.3 equiv.)	CH_3CN/H_2O	34%
4	Ag_2SO_4 (0.3 equiv.)	CH_3CN/H_2O	35%
5	Ag_2CO_3 (0.3 equiv.)	CH_3CN/H_2O	68%
6	AgOAc (0.3 equiv.)	CH_3CN/H_2O	70%
7	$AgNO_3$ (0.3 equiv.) + $CuSO_4$ (0.3 equiv.)	CH_3CN/H_2O	19%
8	$Mn(OAc)_3$ (0.3 equiv.)	CH_3CN/H_2O	trace
9	AgOAc (0.1 equiv.)	CH_3CN/H_2O	58%
10	AgOAc (1.0 equiv.)	CH_3CN/H_2O	66%
11	AgOAc (0.3 equiv.)	dioxane/H_2O	44%
12	AgOAc (0.3 equiv.)	DMF/H_2O	41%

[a] To a mixture of 2-bromo-1,4-naphthoquinone (**1a**, 0.16 mmol), 3-(1-methyl-1*H*-indol-3-yl)propanoic acid (**6a**, 0.246 mmol) and an appropriate silver salt in CH_3CN (5 mL) at 80 °C, was added dropwise over period of 5 min a solution of $(NH_4)_2SO_8$ (0.32 mmol, 72.6 mg) in water (2 mL). The reaction mixture was stirred at the same temperature for 12 h, and then worked up.

[b] Isolated yields.

To validate the practicality of this process and to optimize the reaction conditions, we screened various metal catalysts and solvent systems. The results are summarized in Table 1.

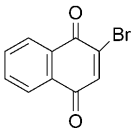
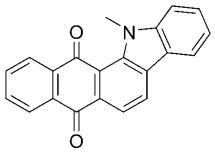
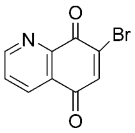
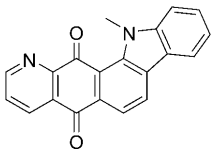
From the results above (entries 1–7, Table 1), all the silver catalysts can initiate the reaction, but the yields varied significantly. AgOAc and Ag_2CO_3 appeared to be the best of choices giving compound **7aa** in 70% and 68% isolated yield, respectively (entries 6 and 5). Other radical initiators, such as $Mn(OAc)_3$[42] did not promote this reaction (entry 8) at all. The amount of silver catalyst is also an important impact factor for the yield of the product. Neither lower (0.1 equiv., entry 9) nor stoichiometric amounts (1.0 equiv., entry 10) of AgOAc gave better yields. Other solvents, such as dioxane and DMF also did not offer any improvement to this reaction. It is of note that two equivalents of oxidant $(NH_4)_2S_2O_8$ were generally necessary to achieve a good conversion of the indol-3-ylpropanoic acid. Therefore, 0.3 equiv. of AgOAc in CH_3CN/H_2O was proven as the best catalyst/solvent combination among the conditions we screened.

With the optimized reaction conditions in hand, we next set out to explore the substrate scope and limitations of this approach. Therefore, a series of *N*-substituted indol-3-ylpropanoic acids (**6a–f**, entries 1–6, Table 2) and various bromoquinones (**1a–e**, entries 7–10, Table 2) were used, and their cyclization was conducted under the optimized conditions (0.3 equiv. of AgOAc in CH_3CN/H_2O). All these reactions proceeded smoothly and provided the corresponding pentacyclic carbazoles in good isolated yields (52–72%). In the case of the hydroxy-substituted bromobenzoquinoline **1b** (entry 7), the corresponding product **7ba** was obtained in 67% isolated yield indicating that no protection of the free hydroxy group is needed. A similar result was obtained with *N*-non-protected indol-3-ylpropanoic acid **6b** (entry 2) which led to cabazole **7ab** in 52% yield. In addition, non-substituted naphthalenedione **1f** and bromoquinonedione **1g** also participated in this reaction very well and provided carbazoles **7fa**[37] and **7ga** in 55% and 65% yields, respectively (entries 11 and 12, Table 2). Therefore, electronic or steric differences of the substituents in both substrates did not exert significant effects on the yields confirming the generality of this reaction protocol.

The high regioselectivity of this reaction can be ascribed to the directing effect of the Br functionality which makes the radical attack occur on the *ortho*-vinyl carbon. To further evaluate the importance of the Br substituent in the substrate **1**, a small series of naphthalenediones **1h–k** with varying substituents in the starting quinones as Br-replacement were employed and their reactions with indol-3-ylpropanoic acid **6a** were conducted. From the results summarized in Table 3, the Br-substituent remains the most active (entry 11 in Table 2, entry 1 in Table 3) affording the product **7fa** in 55% isolated yield. The Cl- or H-substituted substrates also participated in this reaction but gave much lower yields (entries 2 and 3, Table 3). Reactions with substrates containing OH (**1j**) or OAc (**1k**) functions did not occur (entries 4 and 5, Table 3), likely due to the breakdown potentials of these functions to the radical species.

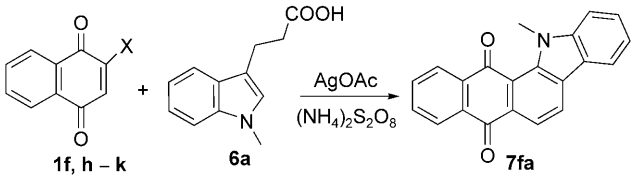
It is our speculation that lack of the Br-function in substrates **1** would lead to products with different regiochemistry largely depending on the electronic properties of the substituents on the benzenoid ring of **1**.[43–46] Therefore, substrates **1l–o** were reacted with

Table 2. Reactions of bromoquinones **1a–g** and indol-3-ylpropanoic acids **6a–f**.[a]

Entry	1	R	6	R′	Product	Yield[b]
1	**1a**	Me	**6a**	Me	**7aa**	70%
2	**1a**	Me	**6b**	H	**7ab**	52%
3	**1a**	Me	**6c**	Bn	**7ac**	64%
4	**1a**	Me	**6d**	allyl	**7ad**	63%
5	**1a**	Me	**6e**	3-methyl-2-butenyl	**7ae**	52%
6	**1a**	Me	**6f**	*n*-Pr	**7af**	59%
7	**1b**	H	**6a**	Me	**7ba**	67%
8	**1c**	Ac	**6a**	Me	**7ca**	72%
9	**1d**	allyl	**6a**	Me	**7da**	69%
10	**1e**	Bn	**6a**	Me	**7ea**	67%
11	**1f**		**6a**	Me	**7fa**[37]	 55%
12	**1g**		**6a**	Me	**7ga**	 65%

[a] The reaction was conducted same as described in Table 1 under optimized conditions (0.3 equiv of AgOAc in CH_3CN/H_2O).[b] Isolated yields.

Table 3. Reactions of naphthalene-diones **1f**, **h–k** and acids **6a**.



Entry	X	Product	Yield[b]
1	Br (**1f**)	**7fa**	55%
2	Cl (**1h**)	**7fa**	18%
3	H (**1i**)	**7fa**	29%
4	OH (**1j**)	**7fa**	none
5	OAc (**1k**)	**7fa**	trace

[a] The reaction was conducted same as described in Table 1 under optimized conditions.
[b] Isolated yields.

acid **6a** and the regioselectivity of the products was evaluated.

From the results in Table 4, without the Br function, naphthalenedione **1i** showed a much lower reactivity yielding product **7fa** in 29% yield (entry 3 in Table 3, entry 1 in Table 4). Substrates **1l** and **1m** with an electron-withdrawing substituent showed a much higher reactivity offering products **7ga** and **7ma** in 65% and 62% isolated yields but with the opposite regiochemistry (entries 2 and 3, Table 4). The high regioselectivity in the case of **1l** can be rationalized by the electron-withdrawing property of the pyridyl function making the C-8 carbonyl more electron deficient than the C-5 carbonyl due to electron delocalization. The electron deficiency of C-8 is transferred to C-6, leading to preferential nucleophilic attack at this position. Therefore, compound **7ga** was formed as the sole product. In the case of nitro-substituted substrate **1m**, although a similar regiochemistry was expected, however, compound **7ma** with the opposite regiochemistry was obtained, likely due to the steric effects between the NO_2, carbonyl and the *N*-Me groups. The absolute configurations of compounds **7ga** and **7ma** were confirmed by all the spectroscopic data, especially the one- and two-dimensional NMR data. Notably, in the $^3J_{CH}$-optimized HMBC experiment of **7ga**, the carbonyl C-5 correlates with both H-4 and H-6, and no proton correlations exist for the carbonyl C-13, while in compounds **7aa** and **7ma** with the opposite regiochemistry to that of **7ga**, the carbonyl C-5 and C-13 each correlates to one proton (C-5 to H-4, C-13 to H-12) as shown in Figure 3.

Similarly, an electron-donating substituent (OMe) at C-1 in substrate **1n** (entry 4, Table 4) makes the C-8 carbonyl more electron rich than the C-5 carbonyl leading to slightly more electron deficiency at C-7 than C-6, therefore radical attack preferentially occurred at this carbon and subsequently formed compound **7aa** as the major product, along with a substantial amount of compound **7na** formed from a nucleophilic attack at C-6. The regioselectivity was determined to be 1.2:1 by ^{1}H NMR, and 1.33:1 by LC-MS.

Table 4. Reactions of substituted naphthalenediones (**1l–o**) or quinolinedione (**1i**) and indolic acids **6a**.[a]

Entry	Substrate **1**	Product	Yield[b]
1	**1i**	**7fa**	29%
2	**1l**	**7ga**	65%
3	**1m**	**7ma**	62%
4	**1n**	**7aa** + **7na**	14%[c] (1.2:1)[d]; (1.33:1)[e]
5	**1o**	**7ba** + **7oa**	52%[c](1:9)[d]; (1:6.7)[e]

[a] The reaction was conducted same as described in Table 1 under optimized conditions.
[b] Isolated yields.
[c] Isolated yield of the inseparable mixture.
[d] Determined by ^{1}H NMR.
[e] Determined by LC-MS.

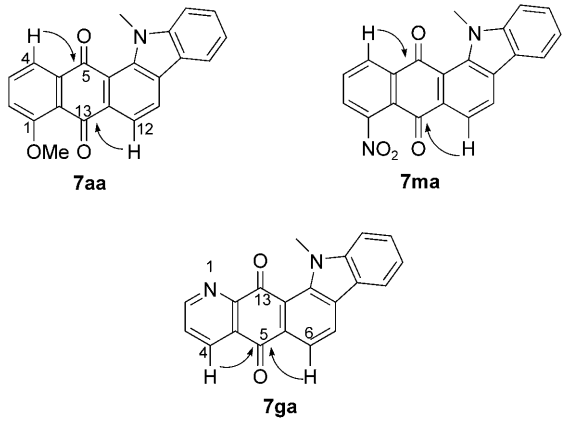


Figure 3. HMBC correlations for compounds **7aa**, **7ma** and **7ga**.

The low regioselectivity may be due to the poor directing effect of the MeO-substituent in this case. Interestingly, the regioselectivity was reversed in the case of C-1 OH-substituted substrate **1o** (entry 5, Table 4) which led to product **7oa** (C-6 nucleophilic attack) formed dominantly over C-7 nucleophilic attack product **7ba** (1:9 by ^{1}H NMR, and 1:6.7 by LC-MS). This can be rationalized by the internal OH-chelating effect to the C-8 carbonyl, which is in agreement to the observation of Csaky et al. who recently reported a dicationic Pd-catalyzed addition of arylboronic acids to benzo-fused 1,4-quinones.[45] To further confirm compound **7ba** obtained as the minor product in this reaction, a certain amount of the sample **7ba** prepared previously in prepared as in Table 2 (entry 7) was added to the NMR sample of **7ba** and **7oa**, the ratio of the two regioisomers was increased from 1:9 to 1:4, on the basis of the ^{1}H NMR signals.

In summary, we have developed a three-step, one-pot tandem radical nucleophilic alkylation/cyclization/aromatization reaction approach to assemble pentacyclic complex carbazoles. Using 0.3 equiv. of AgOAc as the catalyst and 2 equiv. of $(NH_4)_2SO_8$ as the oxidant, a series of naphtho[2,3-*a*]carbazole-5,13-diones were synthesized in 52–72% overall yields from aryl-fused bromobenzoquinones and indol-3-ylpropanoic acids. The bromo-function in the benzoquinone substrates is

a determinant for the regioselectivity of the products. However, both the electronic and steric properties of the C-1 substituents in the benzoquinones will play crucial roles in the cases of non-bromobenzoquinone substrates. The current approach offers a significant improvement over the previously reported synthetic methods and would facilitate further biological evaluation on this category of compounds.

Experimental Section

Typical Procedure for the Silver-Catalyzed Three-Step, One-Pot Tandem Reaction

A mixture of the appropriately substituted 2-bromo-1,4-naphthoquinone 1 (0.16 mmol), indol-3-ylpropanoic acid 6 (0.246 mmol) and AgOAc (0.048 mmol) in acetonitrile (5 mL) was heated at 80 °C under N_2. To this mixture was added dropwise over period of 5 min a solution of $(NH_4)_2SO_8$ (0.32 mmol, 72.6 mg) in distilled H_2O (2 mL). The reaction mixture was stirred at the same temperature for 12 h. Ice/water was added to quench the reaction and the mixture was extracted with EtOAc. The extracts were combined and washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:4) to afford corresponding naphtho[2,3-a]carbazole-5,13-diones **7** as solids.

1-Methoxy-6-methylnaphtho[2,3-*a*]carbazole-5,13-dione (7aa): Yield: 70%; yellow solid; mp 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (d, 1H, J = 8.1 Hz), 8.19 (d, 1H, J = 7.8 Hz), 8.09 (d, 1H, J = 7.8 Hz), 7.84 (dd, 1H, J = 0.9 Hz, 7.8 Hz), 7.69 (t, 1H, J = 7.8 Hz), 7.53 (m, 2H), 7.30 (m, 2H), 4.05 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.1, 182.8, 159.7, 144.9, 139.1, 137.7, 134.7, 133.9, 129.9, 127.9, 125.2, 121.8, 121.3, 120.7, 120.6, 119.1, 119.0, 118.7, 116.9, 110.2, 56.5, 35.4; MS (EI-LR): m/z = 341 (M^+); HR-MS (EI): m/z = 341.1047, calcd. for $C_{22}H_{15}NO_3$ (M^+): 341.1052.

12-Methylquinolino[*a*]carbazole-5,13-dione (7ga): Yield: 65%; red solid; mp 258–260 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (d, 1H, J = 4.2 Hz), 8.56 (d, 1H, J = 7.8 Hz), 8.38 (d, 1H, J = 7.5 Hz), 8.20 (d, 1H, J = 7.8 Hz), 8.09 (d, 1H, J = 7.2 Hz), 7.68 (m, 1H), 7.56 (m, 2H), 7.31 (t, 1H, J = 7.5 Hz), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 182.9, 182.1, 154.5, 150.2, 145.3, 139.9, 135.1, 131.5, 131.3, 129.7, 128.6, 127.4, 125.6, 121.5, 120.9, 120.8, 119.3, 118.7, 110.4, 35.8; MS (EI-LR): m/z = 312 (M^+); HR-MS (EI): m/z = 312.0901, calcd. for $C_{20}H_{12}N_2O_2$ (M^+): 312.0899.

6-Methyl-1-nitronaphtho[2,3-*a*]carbazole-5,13-dione (7ma): Yield: 62%; red solid; mp 267–269 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (m, 2H), 8.13 (m, 2H), 7.88 (t, 1H, J = 7.8 Hz), 7.73 (d, 1H, J = 7.5 Hz), 7.58 (m, 2H), 7.34 (m, 1H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 181.3, 180.2, 148.6, 145.3, 139.5, 135.9, 134.2, 131.6, 131.5, 129.1, 128.6, 126.8, 125.7, 124.5, 121.5, 121.1, 120.8, 118.9, 118.2, 110.3, 35.6; MS (EI-LR): m/z = 356 (M^+); HR-MS (EI): m/z = 356.0799, calcd. for $C_{21}H_{12}N_2O_4$ (M^+): 356.0797.

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