Facile synthesis of 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one derivatives catalysed by ceric ammonium nitrate

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Ceric ammonium nitrate efficiently catalyses the reaction of acenaphthenequinone with indoles afforded symmetrical 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one in excellent yields within 2h under ethanol refluxing, as well as 2-hydroxy-2-indolylacenaphthen-1(2*H*)-one with indoles afforded the corresponding unsymmetrical 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one. This provides an efficient route to the synthesis of symmetrical and unsymmetrical 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one derivatives.

Keywords: acenaphthenequinone, indole, ceric ammonium nitrate, 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one

Indole framework is present in many substances commonly found in nature,[1,2] as well as in many compounds that show pharmacological and biological activities.[3–5] Among them, bisindolylalkanes(BIAs) are an important class of bioactive metabolite.[6,7] With more versatile bisindolylalkanes,[8] the demand for an efficient synthesis of bisindolylalkanes becomes of interest in organic synthesis.[9,10] The bis(indolyl)alkane moiety is also present in various natural products possessing important biological activity.[11,12] Therefore, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives have been reported in the literature by reaction of indole with various aldehydes and ketones in the presence of either a Lewis acid or a protic acid.[13–16] The acenaphthenequinone is one of the most significant intermediates for the synthesis of many natural products and biologically active compounds.

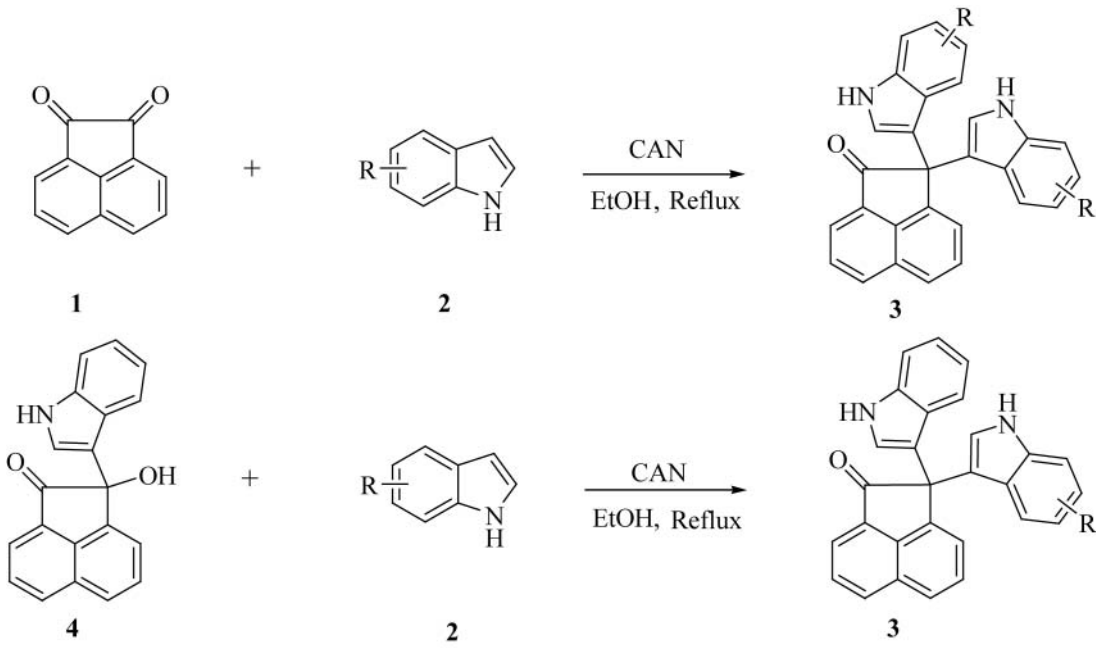
In recent years, ceric ammonium nitrate (CAN) has attracted much attention as an inexpensive and easily available catalyst for various organic reactions.[17–20] The reaction of indoles with carbonyl catalysed by CAN afford the symmetrical bisindolymethane derivatives, which has been reported recently.[21,22]

I now describe a reaction of acenaphthenequinone **1** with indoles **2** or 2-hydroxy(2-indo-3-lyl)acenaphthylen-1(2*H*)-one **4** with indoles **2** using a catalytic amount of CAN, which provide an efficient route to the synthesis of symmetrical and unsymmetrical 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one derivatives, respectively (Scheme 1).

As shown in Table 1, this method worked with a wide variety of substrates. In most cases, the reaction proceeded smoothly to produce the corresponding 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one **3** in good yield. We found that the conversion rate of the indoles bearing electron-withdrawing group (5-nitro-1*H*-indole **2h**) had a lower conversion rate than the indoles bearing electron donating groups (5-methoxyl-1*H*-indole **2e**, 7-methyl-1*H*-indole **2g**), this indicated that

Table 1 The reaction of acenaphthenequinone with indoles catalysed by CAN

Entry	Indoles	Products	Isolated yield/%	M. p. /°C
1	**2a** (R = H)	**3a**	93	289–290°C
2	**2b** (R = 1-Me)	**3b**	92	>300°C
3	**2c** (R = 2-Me)	**3c**	87	291–292°C
4	**2d** (R = 2-Ph)	**3d**	83	>300°C
5	**2e** (R = 5-OMe)	**3e**	93	>300°C
6	**2f** (R = 5-Br)	**3f**	89	>300°C
7	**2g** (R = 7-Me)	**3g**	92	258–259°C
8	**2h** (R = 5-NO_2)	**3h**	80	212–213°C



Scheme 1

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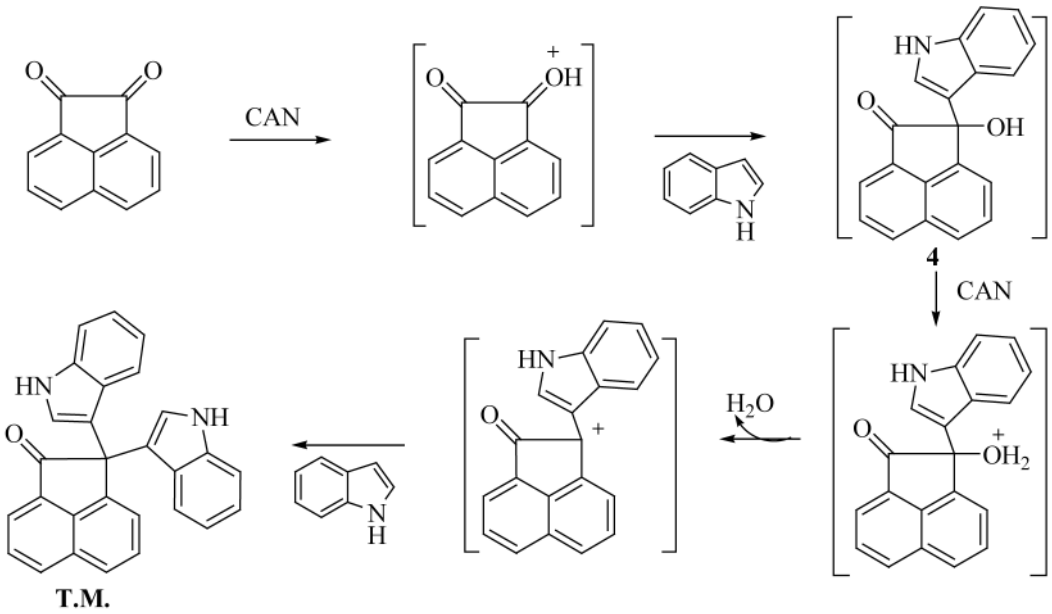

Scheme 2

electron-donating groups had increased reaction yields. On the other hand, electron-withdrawing groups, which deactivated the indole ring, had decreased yields.

The reaction was probably preceded as shown in Scheme 2. The 2-hydroxy(2-indo-3-lyl)acenaphthylen-1(2*H*)-one **4** may be formed *in situ* as a key intermediate, which cannot be obtained in this system.

In order to prove the mechanism, intermediates 2-hydroxy (2-indo-3-lyl)acenaphthylen-1(2*H*)-one were synthesised according to the reported methods.[23] We found that the reaction of 2-hydroxy(2-indo-3-lyl)acenaphthylen-1(2*H*)-one **4** with indole **2a** in the presence of CAN (10 mol%) and anhydrous C_2H_5OH (10 mL) proceeded smoothly giving the 2,2-bis(1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one **3a**. (Table 2)

Encouraged by this result, a number of other indoles were applied to this reaction. Compound **4** smoothly reacted with substituted indole **2** in the presence of CAN under refluxing to afford the unsymmetrical 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one **3** in high yields as expected. (Table 2)

In conclusion, we have developed a simple, convenient and efficient method for synthesis of symmetrical and unsymmetrical 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-one derivatives using catalytic amount of CAN under ethanol refluxing. At the same time, we proposed a plausible mechanism.

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were determined on a Varian VXP-500s spectrometer using DMSO as solvent and tetramethylsilane (TMS) as internal reference. IR spectra was obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elementary analyses were performed by a Carlo-Erba EA1110 CNNO-S analyzer.

Table 2 The reaction of 2-hydroxy(2-indo-3-lyl)acenaphthylen-1(2*H*)-one(**4**) with indoles catalysed by CAN

Entry	Indoles	Products	Isolated yield/%	M. p./°C
1	**2a** (R = H)	**3a**	92	289–290°C
2	**2b** (R = 1-Me)	**3i**	92	252–253°C
3	**2e** (R = 5-OMe)	**3j**	93	291°C
4	**2g** (R = 7-Me)	**3k**	90	196–197°C

General procedure

The mixture of **1** (0.18 g, 1 mmol), **2** (2 mmol), CAN (0.06 g, 0.1 mmol) and anhydrous C_2H_5OH (10 mL) was refluxed for 2 hours. After complete conversion as indicated by TLC, the reaction mixture was washed by cool water (3×5 mL) and cool ethanol (3×5 mL). The crude mixture was purified by flash chromatography to afford the pure product (**3a–h**):

3a: 2,2-Bis(1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3419 (NH), 3359, 3122, 3056, 1684, 1621, 1600, 1493, 1457, 1430, 1414, 1340, 1102, 781, 752, 739 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 10.99 (s, 2H, NH), 8.36 (d, 1H, *J* = 8.0 Hz), 8.01–7.99 (m, 2H), 7.91–7.88 (m, 1H), 7.70–7.67 (m, 1H), 7.55 (d, 1H, *J* = 7.0 Hz), 7.35 (d, 2H, *J* = 8.5 Hz), 7.02–6.98 (m, 4H), 6.84 (d, 2H, *J* = 2.5 Hz), 6.76–6.72 (m, 2H). Anal. Calcd for $C_{28}H_{18}N_2O$: C, 84.40; H, 4.55; N, 7.03. Found: C, 84.36; H, 4.69; N, 6.91%.

3b: 2,2-Bis(1-methyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3418, 3054, 2932, 2880, 2821, 1718, 1621, 1600, 1545, 1533, 1466, 1330, 1250, 1208, 977, 786, 740 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.36 (d, 1H, *J* = 8.0 Hz), 8.00 (t, 2H, *J* = 7.5 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.02–7.08 (m, 4H), 6.87 (s, 2H), 6.78 (t, 2H, *J* = 7.5 Hz), 3.68 (s, 6H). Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.40; H, 5.22; N, 6.70%.

3c: 2,2-Bis(2-methyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3385 (NH), 3343, 3048, 1713, 1619, 1601, 1491, 1460, 1428, 1022, 782, 752, 742 cm^{-1}. ^{1}H NMR(500 MHz, DMSO-d_6): δ (ppm) 10.90 (s, 2H, NH). 8.33 (d, 1H, *J* = 8.0 Hz), 8.03–8.01 (m, 2H), 7.88–7.85 (m, 1H), 7.66–7.63 (m, 1H), 7.42 (d, 1H, *J* = 7.0 Hz), 7.20 (t, 2H, *J* = 7.0 Hz), 6.89–6.84 (m, 2H), 6.59 (t, 1H, *J* = 7.5 Hz), 6.55–6.51 (m, 2H), 6.32 (d, 1H, *J* = 8.5 Hz), 1.80 (s, 6H). Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.37; H, 5.32; N, 6.66%.

3d: 2,2-Bis(2-phenyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3410 (NH), 3337, 3051, 1710, 1599, 1488, 1456, 1224, 993, 786, 768, 742, 700 cm^{-1}. ^{1}H NMR(500 MHz, DMSO-d_6): δ (ppm) 11.02 (s, 1H), 10.85 (s, 1H), 8.30 (d,1H, *J* = 8.0 Hz), 7.83 (t, 1H, *J* = 7.5 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 1H, *J* = 7.0 Hz), 7.25 (d, 1H, *J* = 7.0 Hz), 7.21(t, 1H, *J* = 7.5 Hz), 7.15 (d, 1H, *J* = 8.5 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 7.07–7.05 (m, 2H), 7.03 (d, 1H, *J* = 8.0 Hz), 6.94–6.83 (m, 8H), 6.66 (t, 1H, *J* = 7.0 Hz), 6.61 (d, 2H, *J* = 7.5 Hz), 6.56 (t, 1H, *J* = 7.5 Hz), 6.43 (s, 1H). Anal. Calcd for $C_{40}H_{26}N_2O$: C, 87.25; H, 4.76; N, 5.09. Found: C, 87.35; H, 4.82; N, 4.96%.

3e: 2,2-Bis(5-methoxy-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3399 (NH), 3370, 3138, 2933, 2825, 1700, 1622, 1582, 1484, 1456, 1437, 1259, 1217, 1029, 799, 780 cm^{-1}. ^{1}H NMR(500 MHz, DMSO-d_6): δ (ppm) 10.82 (s, 2H), 8.37 (d, 1H, *J* = 8.0 Hz), 8.01 (t, 2H, *J* = 7.0 Hz), 7.92–7.89 (m, 1H), 7.72–7.69 (m, 1H), 7.54 (d, 1H, *J* = 7.0 Hz), 7.24 (d, 2H, *J* = 9.0 Hz), 6.85 (d, 2H, *J* = 3.0 Hz),

6.68–6.66 (m, 2H), 6.41 (d, 2H, *J* = 2.5 Hz), 3.40 (s, 6H). Anal. Calcd for $C_{30}H_{22}N_2O_3$: C, 78.59; H, 4.84; N, 6.11. Found: C, 78.45; H, 4.82; N, 6.26%.

3f: 2,2-Bis(5-bromo-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3431 (NH), 3340, 3121, 3051, 1709, 1683, 1600, 1564, 1493, 1457, 1417, 1334, 1283, 1096, 884, 794, 783 cm^{-1}. ^1H NMR(500 MHz, DMSO-d_6): δ (ppm) 11.25 (s, 2H), 8.40 (d, 1H, *J* = 8.0 Hz), 8.06–8.04 (m, 2H), 7.94–7.91 (m, 1H), 7.75–7.72 (m, 1H), 7.53 (d, 1H, *J* = 7.0 Hz), 7.35 (d, 2H, *J* = 9.0 Hz), 7.15–7.13 (m, 4H), 6.93 (d, 2H, *J* = 2.5 Hz). Anal. Calcd for $C_{28}H_{16}Br_2N_2O$: C, 60.46; H, 2.90; N, 5.04. Found: C, 60.37; H, 3.01; N, 5.11%.

3g: 2,2-Bis(7-methyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3425(NH), 3126, 3049, 2967, 2851, 1711, 1598, 1493, 1458, 1430, 1101, 789, 779, 745 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 10.93 (s, 2H, NH), 8.35 (d, 1H, *J* = 8.0 Hz), 7.99 (t, 2H, *J* = 6.5 Hz), 7.89 (t, 1H, *J* = 8.0 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 7.0 Hz), 6.85–6.79 (m, 6H), 6.65 (t, 2H, *J* = 7.5 Hz), 2.42 (s, 6H). Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.56; H, 5.13; N, 6.64%.

3h: 2,2-Bis(5-nitro-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3365 (NH), 1706, 1623, 1518, 1470, 1429, 1333, 1256, 1110, 783, 739 cm^{-1}. ^1H NMR(500 MHz, DMSO-d_6): δ (ppm) 11.83 (s, 2H), 8.45 (d, 1H, *J* = 8.0 Hz), 8.10 (t, 2H, *J* = 7.0 Hz), 7.98–7.92 (m, 5H), 7.78–7.75 (m, 1H), 7.61 (d, 1H, *J* = 6.5 Hz), 7.56 (d, 2H, *J* = 9.0 Hz), 7.24 (d, 2H, *J* = 2.5 Hz). Anal. Calcd for $C_{28}H_{16}N_4O_5$: C, 68.85; H, 3.30; N, 11.47. Found: C, 68.94; H, 3.22; N, 11.34%.

The mixture of **4** (0.30 g, 1 mmol), **2** (1 mmol), CAN (0.06 g, 0.1 mmol) and anhydrous C_2H_5OH (10 mL) was refluxed for 1 hour. After complete conversion as indicated by TLC, the reaction mixture was washed by cool water (3×5 mL) and cool ethanol (3×5 mL). The crude mixture was purified by flash chromatography to afford the pure product **3i–k.**

3i: 2-(1*H*-indol-3-yl)-2-(1-methyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3350 (NH), 3115, 3049, 2931, 2827, 1702, 1599, 1488, 1457, 1422, 1336, 1250, 1222, 1099, 788, 739 cm^{-1}. ^1H NMR(500 MHz, DMSO-d_6): δ (ppm) 10.98 (s, 1H), 8.36 (d, 1H, *J* = 8.0 Hz), 8.00 (t, 2H, *J* = 8.0 Hz), 7.90 (t, 1H, *J* = 7.5 Hz), 7.70 (t, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 6.5 Hz), 7.38–7.34 (m, 2H), 7.07 (t, 2H, *J* = 7.5 Hz), 7.00 (t, 1H, *J* = 7.5 Hz), 6.96 (d, 1H, *J* = 8.5 Hz), 6.86 (d, 1H, *J* = 2.5 Hz), 6.84 (s, 1H), 6.79 (t, 1H, *J* = 7.5 Hz), 6.73 (t, 1H, *J* = 7.5 Hz), 3.67 (s, 3H). Anal. Calcd for $C_{29}H_{20}N_2O$: C, 84.44; H, 4.89; N, 6.79. Found: C, 84.57; H, 4.82; N, 6.68%.

3j: 2-(1*H*-indol-3-yl)-2-(5-methoxy-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3406 (NH), 3126, 3056, 2938, 2831, 1701, 1621, 1578, 1482, 1459, 1341, 1255, 1213, 1099, 782, 743 cm^{-1}. ^1H NMR(500 MHz, DMSO-d_6): δ (ppm) 10.97 (s, 1H), 10.82 (s, 1H), 8.37 (d, 1H, *J* = 8.0 Hz), 8.01 (t, 2H, *J* = 7.5 Hz), 7.91–7.88 (m, 1H), 7.71–7.68 (m, 1H), 7.54 (d, 1H, *J* = 6.5 Hz), 7.34 (d, 1H, *J* = 8.5 Hz), 7.23 (d, 1H, *J* = 8.5 Hz), 6.99 (t, 1H, *J* = 7.5 Hz), 6.94 (d, 1H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 2.5 Hz), 6.79 (d, 1H, *J* = 2.5 Hz), 6.73 (d, 1H, *J* = 7.5 Hz), 6.68–6.66 (m, 1H), 6.44 (d, 1H, *J* = 2.0 Hz), 3.41 (s, 3H). Anal. Calcd for $C_{29}H_{20}N_2O_2$: C, 81.29; H, 4.70; N, 6.54. Found: C, 81.34; H, 4.76; N, 6.46%.

3k 2-(1*H*-indol-3-yl)-2-(7-methyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one. IR (KBr) ν 3410 (NH), 3051, 2954, 2922, 2857, 1713, 1620, 1600, 1494, 1457, 1431, 1342, 1099, 785, 745 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 10.97 (s, 1H), 10.93 (s, 1H), 8.35 (d, 1H, *J* = 8.0 Hz), 8.01–7.94 (m, 2H), 7.89 (t, 1H, *J* = 7.5 Hz), 7.70–7.67 (m, 1H), 7.55–7.52 (m, 1H), 7.34 (d, 1H, *J* = 8.0 Hz), 7.07 (d, 1H, *J* = 8.0 Hz), 7.01–6.98 (m, 1H), 6.83–6.72 (m, 5H), 6.66–6.61 (m, 1H), 2.41 (s, 3H). Anal. Calcd for $C_{29}H_{20}N_2O$: C, 84.44; H, 4.89; N, 6.79. Found: C, 84.54; H, 4.76; N, 6.83%.

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