# ONE-POT SYNTHESIS OF INDOLEQUINONE DERIVATIVES FROM 2-ACYLAMINO-1,4-NAPHTHO(OR BENZO)QUINONES AND ENAMINES

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*Abstract-* 1*H*-Benz[*f*]indole-4,9-diones (**3**) were prepared in a one-pot reaction in moderate to good yields by treating 2-acylamino-1,4-naphthoquinones (**1**) with enamines (**2**). The similar pyrrole ring formation reaction also took place on treatment of a 2-trifluoroacetylamino-1,4-benzoquinone (**7**) with enamines (**2**), giving 1*H*-indole-4,7-diones (**8**) in moderate yields. 4,9-Diacetoxy-1-acetyl-2-ethyl-3-methylbenz[*f*]indole (**6**) was isolated after treatment of the crude mixture obtained from the reaction of 2-acetylamino-1,4-naphthoquinone (**1b**) with 3-morpholino-2-pentene (**2c**) with acetic anhydride and pyridine under argon. This indicates that the initial products in these reactions proved to be the respective hydroquinone derivatives, the air oxidation of which yielded the indolequinones.

In a previous paper,[1] we reported on a one-pot synthesis of naphtho[2,3-*b*]furan-4,9-diones in good yields by treating 2-hydroxy-1,4-naphthoquinones with enamines in refluxing toluene, as a modification of the Kakisawa's method.[2] In this paper, we wish to describe an extension of this reaction to the one-pot formation of 1*H*-benz[*f*]indole-4,9-dione (**3**) and 1*H*-indole-4,7-dione derivatives (**8**) from 2-acylamino-1,4-naphthoquinones (**1**) and a 1-trifluoroacetylamino-1,4-benzoquinone (**7**). The key to the success of the present reactions was the choice of *N*-trifluoroacetyl substituent of 2-aminoquinones. This causes the operationally simple reaction procedure which is carried out at room temperature. Recently, indolequinone derivatives have attracted much interest for synthesis[3] due to their clinically useful biological activities.[4] Although a number of methods for preparing indolequinone derivatives have been reported,[5] most of them are not simple and involve multi-step conversion.

2-Amino-1,4-naphthoquinone was first used as a starting material in this study. However, for example,
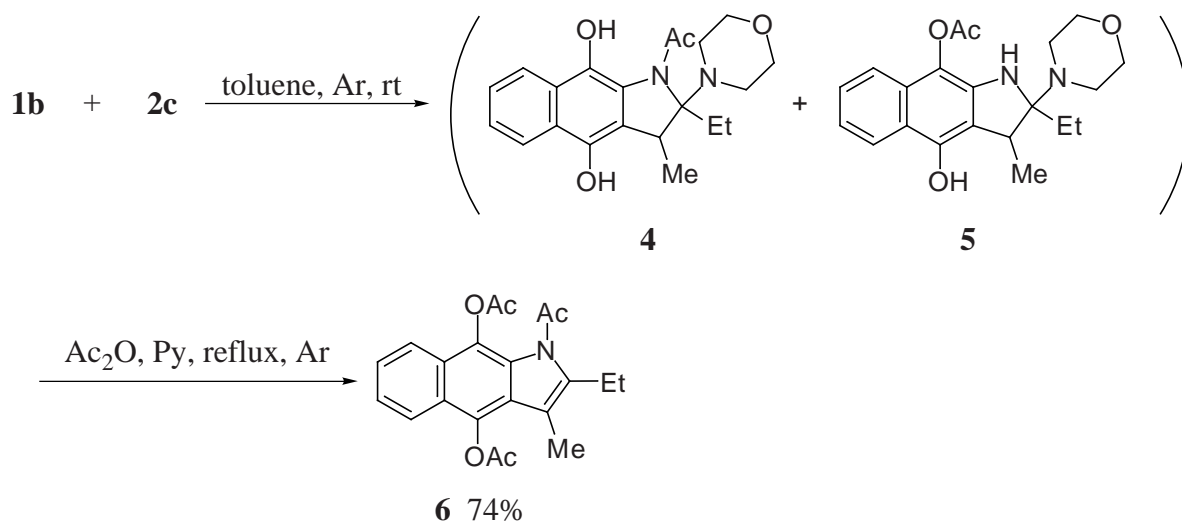
**Scheme 1**

1 + 2 → 3

i) toluene, Ar, rt
ii) aq. NaOH, air
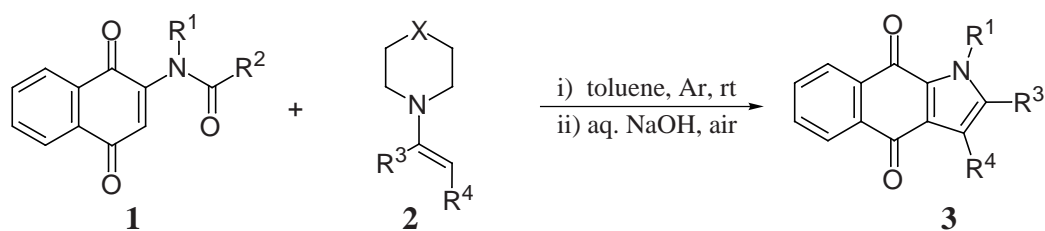
**Table.** Preparation of $1H$-Benz[$f$]indole-4,9-diones (**3**)

| Entry | Aminoquinone **1** | Enamine **2** | Product **3** (Yield/%)[a] |
|-------|--------------------|---------------|----------------------------|
| 1 | **1a** (R$^1$=H, R$^2$=CF$_3$) | **2a** [R$^3$R$^4$=(CH$_2$)$_4$, X=nil] | **3a** (87) |
| 2 | **1b** (R$^1$=H, R$^2$=Me) | **2a** | **3a** (44)[b] |
| 3 | **1c** (R$^1$=H, R$^2$=Ph) | **2a** | **3a** (44) |
| 4 | **1a** | **2b** [R$^3$R$^4$=(CH$_2$)$_5$, X=nil] | **3b** (65) |
| 5 | **1a** | **2c** (R$^3$=Et, R$^4$=Me, X=O)[c] | **3c** (68) |
| 6 | **1a** | **2d** (R$^3$=$n$-Pr, R$^4$=Et, X=O)[c] | **3d** (57) |
| 7 | **1a** | **2e** (R$^3$=H, R$^4$=Me, X=O)[c] | **3e** (76) |
| 8 | **1d** (R$^1$=Ph, R$^2$=CF$_3$) | **2a** | **3f** (16) |

[a]Isolated yields. [b]Along with the corresponding $N$-acetyl derivative (**3a'**) (13%). [c]A mixture of stereoisomers was used.

heating of this quinone and 1-pyrrolidinocyclohexene at reflux temperature in toluene resulted in the formation an intractable mixtures of products. We then decided to react 2-acylamino-1,4-naphthoquinones (**1**) with enamines (**2**). Acylaminoquinones (**1**) were readily available from the respective 2-amino-1,4-naphthoquinones using the methods reported by Kuo *et al*.[6] The preparation of benz[$f$]indole-4,9-diones (**3**) from 2-acylamino-1,4-naphthoquinones (**1**) and enamines (**2**) is outlined in Scheme 1. Thus, acylaminoquinones (**1**) were allowed to react with enamines (**2**) in toluene at room temperature under argon. After consumption of the starting material, treatment of the reaction mixture with 10% aqueous sodium hydroxide in the air gave, after separation by preparative TLC on silica gel, benzindolequinone derivatives (**3**) in the yields listed in the Table. It indicates that substitution of trifluoroacetyl group on 2-amino group was more efficient than in the case of the other two acyl substituents (Entries 1–3). Similarly, the reaction of enamines derived from acyclic ketones or aldehyde with 2-trifluoroacetylamino-1,4-naphthoquinone (**1a**) proceeded smoothly to give the corresponding benzindolequinones (**3**) in good yields (Entries 5–7). Although no indolequinone formation occurred using 2-[methyl(trifluoroacetyl)]amino-1,4-naphthoquinone, 2-[phenyl(trifluoroacetyl)]amino-1,4-naphthoquinone (**1d**) proved to be usable in the

**Scheme 2**



**8a** $R^1R^2 = (CH_2)_4$   55%
**8b** $R^1 = Et$, $R^2 = Me$  50%
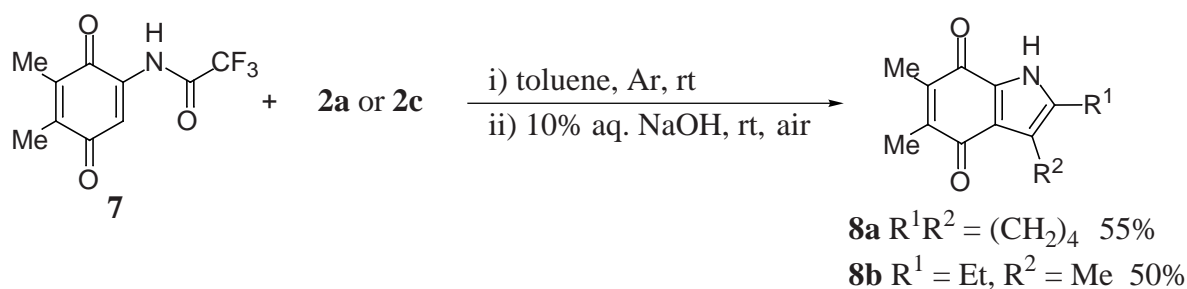
**Scheme 3**

present reaction to afford the desired indolequinone (**3f**) in low yield (Entry 8). We observed that yields were significantly lower if the alkaline treatment was omitted in each case.

The initial products in the present reaction appeared to be the hydroquinone derivatives, such as **4** and **5** (the formation of these adducts is analogous to the one proposed for the reaction of 2-hydroxy-1,4-naphthoquinones with enamines leading to naphtho[2,3-*b*]furan-4,9-diones[1]). Thus, 4,9-diacetoxy-1-acetyl-2-ethyl-3-methylbenz[*f*]indole (**6**) could be isolated in good yield when the crude reaction mixture from **1b** and **2c** was treated with acetic anhydride and pyridine as shown in Scheme 2. Probably, these initial adducts were hydrolyzed, lost an amine, and were oxidized to give the indolequinones.

Similarly, reaction of 5,6-dimethyl-2-trifluoroacetylamino-1,4-benzoquinone (**7**) with enamines, followed by alkali hydrolysis, afforded indole-4,7-dione derivatives (**8**) in moderate yields (Scheme 3).

In conclusion, we have shown that a range of indolequinone derivatives could be prepared from 2-trifluoroacetylamino-1,4-quinones and enamines. Since the method employs readily available starting materials and is experimentally simple, it may be of value in heterocyclic quinone synthesis.

# EXPERIMENTAL

The mps were determined on a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The IR spectra were determined with a Perkin-Elmer 1600 Series FT IR spectrophotometer as KBr disks unless otherwise stated. The $^1$H NMR spectra were determined in CDCl$_3$ (unless otherwise stated) using SiMe$_4$ as an internal reference with either a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz or a JNX-PMX 60 NMR spectrometer operating at 60 MHz. $J$ Values are given in Hz. Low-resolution MS spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). TLC was carried out on a Merck Kieselgel 60 PF$_{254}$. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

**Starting Materials.** 2-Acylaminoquinones (**1**) and (**7**) were prepared following the methods reported by Kuo *et al.*[6] Physical, spectral, and analytical data for new compounds are as follows. **1a:** mp 129–130 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3316, 1741, 1672, 1657, 1624, 1525; $\delta_H$ (60 MHz) 7.20 (1H, s), 7.6–7.9 (2H, m), 8.0–8.3 (2H, m), 9.10 (1H, br s); MS *m/z* 269 (M$^+$, 100). Anal. Calcd for C$_{12}$H$_6$NO$_3$F$_3$: C, 53.54; H, 2.25; N, 5.20. Found: C, 53.70; H, 2.22; N, 5.10. **1d:** mp 141–142 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 1716, 1681, 1665, 1626, 1594; $\delta_H$ (60 MHz) 6.60 (1H, s), 7.35 (5H, s), 7.6–8.2 (4H, m); MS *m/z* 345 (M$^+$, 53), 276 (35), 248 (59), 77 (00). Anal. Calcd for C$_{18}$H$_{10}$NO$_3$F$_3$: C, 62.62; H, 2.92; N, 4.06. Found: C, 62.61; H, 2.92; N, 4.02. **7:** mp 78–79 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3257, 1740, 1662, 1654, 1633; $\delta_H$ (60 MHz) 3.10 (6H, s), 7.40 (1H, s), 8.70 (1H, br s); MS *m/z* 247 (M$^+$). Anal. Calcd for C$_{10}$H$_8$NO$_3$F$_3$: C, 48.59; H, 3.26; N, 5.67. Found: C, 48.55; H, 3.31; N, 5.58. Enamines (**2a–d**)[7] and (**2e**)[8] were prepared according to appropriate reported procedures.

**1*H*-2,3,4,5-Tetrahydrobenzo[*b*]carbazole-6,11-dione (3a). General Procedure.** To a stirred solution of 2-trifluoroacetylamino-1,4-naphthoquinone (**1a**) (0.27 g, 1.0 mmol) in toluene (10 mL) under argon at rt was added 1-pyrrolidinocyclohexene (**2a**) (0.15 g, 1.0 mmol). After stirring for 5 h, 10% aqueous NaOH (10 mL) was added, and the resulting mixture was stirred for an additional 15 min. Saturated aqueous ammonium chloride (30 mL) was added, and the organic layer was separated. The aqueous layer was extracted with Et$_2$O twice (20 mL each). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. After evaporation of the solvent the residue was purified by preparative TLC on silica gel (hexane–AcOEt 2:1) to give **3a** (0.22 g, 87%): yellow needles; mp 290–291 ˚C (decomp) (CHCl$_3$) [lit.,[9] mp 290 ˚C (decomp)].

Compound (**3a**) was also prepared by using either 2-acetylamino-1,4-naphthoquinone (**1b**) or 2-benzoylamino-1,4-naphthoquinone (**1c**) in place of **1a** according to the above–mentioned procedure. Compound (**3a'**) was obtained along with **3a** from the reaction of **1b** and **2a**.

**1-Acetyl-1*H*-2,3,4,5-tetrahydrobenzo[*b*]carbazole-6,11-dione (3a'):** yellow needles; mp 180–182 ˚C (hexane); $\nu_{max}$/cm$^{-1}$ 1737, 1665, 1654 cm$^{-1}$; $\delta_H$ (270 MHz) 1.75–1.9 (4H, m), 2.73 (3H,

s),2.73 (2H, t, $J$ = 5.7), 2.89 (2H, t, $J$ = 5.7), 7.65–7.75 (2H, m), 8.05–8.15 (2H, m); MS $m/z$ 251 (100). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.00; H, 5.32; N,4.48.

**2,3,4,5-Tetrahydro-1$H$,6$H$-benzo[$f$]cyclohepta[$b$]indole-7,12-dione (3b):** as described for **3a**, with **1a** and **2b** (5h)**;** yellow needles; mp 216–217 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3204, 1641; $\delta_H$ (270 MHz) 1.7–1.8 (2H, m), 1.85–1.9 (2H, m), 2.0–2.15 (2H, m), 2.8–2.9 (2H, m), 3.1–3.2 (2H, m), 7.55–7.7 (2H, m), 8.0–8.2 (2H, m), 9.80 (1H, br s); MS $m/z$ 265 (M$^+$, 73),250 (100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.00; H, 5.82;  N, 5.30.

**2-Ethyl-3-methyl-1$H$-benz[$f$]indole-4,9-dione (3c):** as described for **3a**, with **1a** and **2c** (30 h)**;** yellow needles; mp 239–240 ˚C (decomp) (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3217, 1668, 1644; $\delta_H$ (270 MHz) 1.32 (3H, t, $J$ = 7.4), 2.38 (3H, s), 2.76 (2H, q, $J$ = 7.4), 7.6–7.7 (2H, m), 8.05–8.2 (2H, m), 10.20 (1H, s); MS $m/z$ 239 (M$^+$, 46), 224 (100). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.36; H, 5.34; N, 5.87.

**3-Ethyl-2-propyl-1$H$-benz[$f$]indole-4,9-dione (3d):** as described for **3a**, with **1a** and **2d** (72 h)**;** yellow needless; mp 203–205 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3226, 1662, 1637; $\delta_H$ (270 MHz, DMSO–$d_6$) 1.02 (3H, t, $J$ = 7.3), 1.22 (3H, t, $J$ = 7.3), 1.74 (2H, sextet $J$ = 7.3), 2.70 (2H, t, $J$ = 7.3), 2.82 (2H, q, $J$ = 7.3), 7.6–7.7 (2H, m), 8.0–8.2 (2H, m), 10.06 (1H, br s); MS $m/z$ 267 (M$^+$, 58), 252 (45), 238 (100). Anal. Calcd For $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.46; H, 6.49; N, 5.09.

**3-Methyl-1$H$-benz[$f$]indole-4,9-dione (3e):** as described for **3a**, with **1a** and **2e** (6 h); yellow needles; mp 249–250 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3206, 1649; $\delta_H$ (270MHz, DMSO-$d_6$) 2.34 (3H, d, $J$ = 0.4), 7.13 (1H, br. s), 7.75–7.8 (2H, m), 8.0–8.05 (3H, m); MS $m/z$ 211 (M$^+$, 100). Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.88; H, 4.28; N, 6.65.

**5-Phenyl-1,2,34-tetrahydro-5$H$-benzo[$b$]carbazole-6,11-dione (3f):** as described for **3a**, with **1d** and **2a** (3 h); yellow needles; mp 208–210 ˚C (hexane–CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ 3236 and 1654; $\delta_H$ (270 MHz) 1.7–1.9 (4H, m), 2.36 (2H, t, $J$ = 5.1), 2.99 (2H, t, $J$ = 5.1), 7.25–7.35 (2H, m), 7.5–7.65 (5H, m), 7.95–8.05 (1H, m), 8.1–8.2 (1H, m); MS $m/z$ 327 (M$^+$, 100). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 81.00; H, 5.21; N, 4.24.

**4,9-Diacetoxy-1-acetyl-2-ethyl-3-methyl-1$H$-benz[$f$]indole (6).** After treatment of 2-acetylamino-1,4-naphthoquinone (**1b**) (0.22 g, 1.0 mmol) with **2c** (0.16 g, 1.0 mmol) under similar conditions as described for the preparation of **3a** for 24 h, the resulting precipitate was filtered off (0.33 g) and dissolved in pyridine and acetic anhydride (5 mL each). The solution was heated at 100 ˚C for 14 h and the solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel (hexane–AcOEt 1:2) to give **6** (0.27 g, 74%): a yellow viscous oil; $Rf$ 0.72; $\nu_{max}$/cm$^{-1}$ (neat) 1770, 1716; $\delta_H$ (270 MHz) 1.18 (3H, t, $J$ = 7.3), 2.31 (3H, s), 2.45 (3H, s), 2.53 (3H, s), 2.61 (3H, s),

2.88 (2H, q, $J = 7.3$), 7.35–7.55 (2H, m), 7.75–7.95 (2H, m); MS $m/z$ 367 (M$^+$, 7), 325 (35), 283 (45), 241 (100). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.78; H, 5.76; N, 3.81.

**2,3-Dimethyl-5,6,7,8-tetrahydro-9$H$-carbazole-1,4-dione (8a).** The reaction of 2-trifluoroacetylamino-1,4-benzoquinone (**7**) (0.16 g, 0.73 mmol) with **2a** (0.16 g, 1.0 mmol) under similar conditions as described for the preparation of **3a** for 1.5 h gave a precipitate, which was filtered off (0.16 g) and treated with aqueous 10% NaOH (10 mL) for 15 min. The reaction mixture was worked up and purified in a manner similar to that described for the preparation of **3a** to give **8a** (92 mg, 55%): orange needles; mp 229–231 °C (hexane–CH$_2$Cl$_2$) (lit.,[9] 229-230 °C).

**5,6-Dimethyl-2-ethyl-3-methyl-1$H$-indole-4,7-dione (8b):** as described for **8a**, with **7** and **2c** (2 h); orange needles; mp 218–219 °C (hexane–CH$_2$Cl$_2$); $\nu_{max}/cm^{-1}$ 3240, 1649 (sh), 1630, 1607; $\delta_H$ (270 MHz) 1.24 (3H, t, $J = 7.3$), 2.03 (6H, s), 2.25 (3H, s), 2.64 (2H, q, $J = 7.3$), 9.40 (1H, s); MS $m/z$ 217 (M$^+$, 100). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.72; H, 6.95; N, 6.39.

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