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One-pot synthesis of isoquinoline-5,8-dione derivatives from acylquinones and enamines

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Abstract

A new and facile method for the preparation of isoquinolinequinone derivatives has been developed. Treatment of 2-acyl-1,4-naphthoquinones or 2-acyl-5,6-dimethyl-1,4-benzoquinones with enamines (or imines), followed by addition of aqueous NH_3 in MeOH afforded benz[*g*]isoquinoline-5,10-dione or isoquinoline-5,8-dione derivatives, respectively, in moderate to good yields.

Keywords: enamines; imines; isoquinolines; Michael reactions; quinones.

In recent years, increasing recognition of the biological activities of natural[1] and synthetic[2] isoquinolinequinone derivatives has stimulated renewed synthetic interest[3] in this class of molecules. For example, the efficient synthesis of naturally occurring dioxygenated and trioxygenated 3-methylbenz[*g*]isoquinoline-5,10-diones has recently been accomplished by Krapcho and Waterhouse.[3e] Most recently, Kesteleyn and De Kimpe have elegantly synthesized two benzisoquinolinequinone antibiotics.[3f] It has been noted, however, that most of these methods require several steps and/or involve tedious reaction conditions. On the other hand, we have recently reported that reactions of 2-acetyl-1,4-naphthoquinone with enamines gave 1-amino-9,10-anthraquinone derivatives.[4] As an extension of this work, we herein report that 2-acylquinones **1** were treated successively with enamines **2** (or imines **3**) and then ammonia in one-pot to give isoquinolinequinone derivatives **4**.

The 2-acylquinones **1** and **5**, employed for the present study, were prepared by oxidation of the respective acylhydroquinones, which were readily prepared by the reported methods.[5–8] The procedure we have developed for the synthesis of isoquinolinequinones **4** is outlined in Scheme 1. Reactions of 2-acyl-1,4-naphthoquinones **1** with enamines **2** or imines **3** in THF for 2–5 min,

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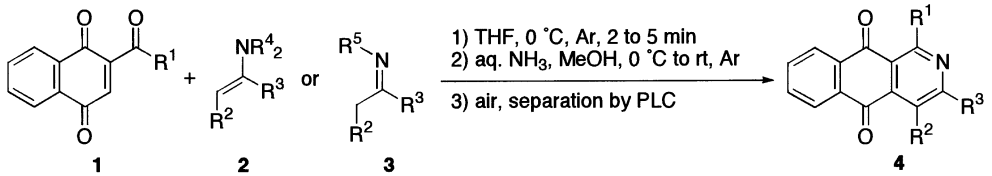
followed by addition of aqueous ammonia in MeOH, led to the formation of benz[*g*]isoquinoline-5,10-diones **4a** and **4c**–**k**, after usual workup and subsequent isolation by preparative TLC on silica gel. The yields of the products are listed in Table 1. When pyrrolidino enamines were used, good yields of the expected products were generally realized (entries, 1, 3, 5, and 8). Morpholino enamines, on the other hand, appeared to afford somewhat poorer results (entries 4 and 6). The lower basicity of morpholine compared with that of pyrrolidine may explain these results. Imines, such as (cyclohexylidene)cyclohexylamine (**3a**) and (isopropylidene)isopropylamine (**3b**) proved to be usable in the present transformation, and led to the formation of the corresponding isoquinolinequinones in good yields (entries 2, 7 and 9–11). The latter worked as an enamine derived from acetone, which is troublesome to prepare.



1 **2** **3** **4**

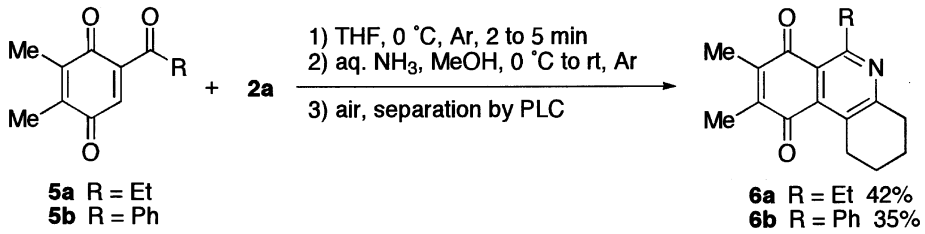
Scheme 1.

Table 1
Preparation of benz[*g*]isoquinoline-5,10-diones **4** from 2-acyl-1,4-naphthoquinones **1** with enamines **2** (or imines **3**)

Entry	**1**	**2** or **3**	**4** (Yield/%)[a]
1	**1a** (R^1 = Me)	**2a** [R^2R^3 = $(CH_2)_4$, $NR^4{}_2$ = pyrrolidino]	**4a** (66)
2	**1a**	**3a** [R^2R^3 = $(CH_2)_4$, R^5 = cyclohexyl] [b]	**4a** (56)
3	**1a**	**2c** [R^2R^3 = $(CH_2)_3$, $NR^4{}_2$ = pyrrolidino]	**4c** (72)
4	**1a**	**2d** [R^2R^3 = $(CH_2)_5$, $NR^4{}_2$ = morpholino]	**4d** (48)
5	**1a**	**2e** (R^2 = Me, R^3 = Et, $NR^4{}_2$ = pyrrolidino)[c,d]	**4e** (64)
6	**1a**	**2f** (R^2 = Me, R^3 = H, $NR^4{}_2$ = morpholino)[c,d]	**4f** (45)
7	**1a**	**3b** (R^2 = H, R^3 = Me, R^5 = isopropyl)[b]	**4g** (66)
8	**1b** (R^1 = Et)	**2a**	**4h** (64)
9	**1b**	**3b**	**4i** (61)
10	**1c** (R^1 = *n*-Pr)	**3b**	**4j** (64)
11	**1d** (R^1 = Ph)	**3b**	**4k** (48)

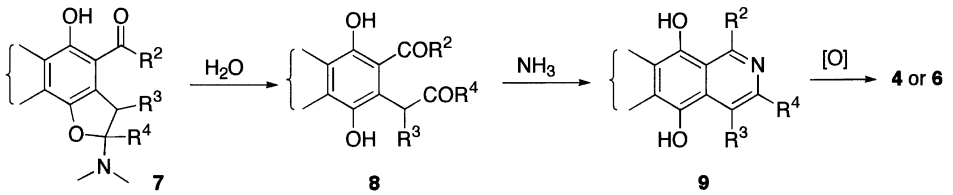
[a] Isolated yields after preparative TLC on silica gel.
[b] Ref. 10.
[c] A mixture of stereoisomers was used.
[d] Ref. 11.

Isoquinoline-5,8-diones **6a** and **6b** were also produced from 2-acyl-5,6-dimethyl-1,4-benzoquinones **5a** and **5b** in a manner similar to that for the preparation of benz[*g*]isoquinoline-5,10-diones, though the yields of the products were somewhat lower than those of benzisoquinolinequinones. These results are illustrated in Scheme 2. In order to investigate the limitations of the present transformation, 2-acyl-1,4-benzoquinones, such as 2-acetyl- and 2-propionyl-1,4-benzoquinones, were subjected to the reaction conditions described above. Each of the reactions gave a very complex mixture of products, from which no more than a trace amount of the expected isoquinolinequinone derivatives could be isolated. It can be assumed that addition of enamines at the 5- and/or 6-positions as well as the 3-position occurs simultaneously.



Scheme 2.

A plausible pathway leading to the formation of the isoquinolinequinones **4** or **6** is outlined in Scheme 3. Brief treatment of the acylquinones **1** with enamines **2** or imines **3** afforded the intermediate hydroxybenzofuran derivatives **7**.[4] Addition of aqueous ammonia hydrolyzed **5** to give the diketo intermediates **8**, which were condensed with ammonia to give rise to the dihydroxyisoquinoline derivatives **9**. These hydroquinones were oxidized during workup and/or separation procedures to give **4** or **6**. To substantiate this pathway, we isolated one of the intermediates **7** and allowed it to react with aqueous ammonia under conditions similar to those described above for the preparation of isoquinolinequinones. Thus, addition of aqueous ammonia in MeOH to a THF solution of **7e**[4] gave **4e** in 60% yield. This result confirms the intermediacy of **5** in the present formation of isoquinolinequinones.



Scheme 3.

A typical experimental procedure is given for the preparation of **4a** from **1a** and **2a**. To a stirred solution of 2-acetyl-1,4-naphthoquinone (**1a**) (0.10 g, 0.51 mmol) in THF (5 ml) at 0°C under argon was added 1-pyrrolidinocyclohexene (**2a**) (84 mg, 0.50 mmol) dropwise. After 2 min at the same temperature, aqueous NH_3 (29%, 2.0 ml) in MeOH (1.0 ml) was added, and stirring was continued for an additional 2 h at room temperature. The resulting mixture was diluted with water and extracted with Et_2O three times. The combined extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was separated by preparative TLC on SiO_2 to give **4a** (92 mg, 66%).[9]

The results mentioned in the previous section demonstrate that isoquinolinequinone derivatives can be easily prepared from readily available starting materials, acylquinones and enamines (or imines). Studies on the synthesis of natural products having the isoquinolinequinone skeleton are now underway in our laboratory and will be reported elsewhere.

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9. All new compounds gave satisfactory spectral [^{1}H NMR ($CDCl_3$, *J* values are given in hertz), IR (KBr disk), and mass] and analytical data. **4a**: mp 151–152°C; ν/cm^{-1} 1672; δ_H (270 MHz) 1.85–1.95 (4H, m), 3.01 (3H, s), 3.05 (2H, t, *J* 6.2 Hz), 3.33 (2H, t, *J* 6.2), 7.75–7.8 (2H, m), 8.13 (1H, d, *J* 8.1), 8.18 (1H, d, *J* 8.1); *m*/*z* 277 (M^+, 100). **4c**: mp 165°C; ν/cm^{-1} 1671; δ_H (270 MHz) 2.2–2.3 (2H, m), 3.05–3.15 (5H, m), 3.52 (2H, t, *J* 7.6), 7.75–7.85 (2H, m), 8.15–8.3 (2H, m); *m*/*z* 263 (M^+, 100). **4d**: mp 146–147°C; ν/cm^{-1} 1669; δ_H (270 MHz) 1.75–1.95 (6H, m), 3.00 (3H, s), 3.20–3.25 (2H, m), 3.3–3.4 (2H, m), 7.7–7.85 (2H, m), 8.05–8.20 (2H, m); *m*/*z* 291 (M^+, 100). **4e**: mp 137–138°C; ν/cm^{-1} 1676; δ_H (500 MHz) 1.33 (3H, t, *J* 7.6), 2.73 (3H, s), 3.0–3.05 (5H, m), 7.7–7.8 (2H, m), 8.1–8.2 (2H, m); *m*/*z* 265 (M^+, 100). **4f**: mp 149–151°C; ν/cm^{-1} 1675; δ_H (270 MHz) 2.78 (3H, s), 3.05 (3H, s), 7.7–7.9 (2H, m), 8.15–8.25 (2H, m), 8.72 (1H, s); *m*/*z* 237 (M^+, 100) **4g**: mp 190°C; ν/cm^{-1} 1679, 1668; δ_H (270 MHz) 2.72 (3H, s), 3.08 (3H, s), 7.75–7.85 (2H, m), 7.86 (1H, s), 8.20–8.35 (2H, m); *m*/*z* 237 (M^+, 100). **4h**: mp 144–145°C; ν/cm^{-1} 1674, 1655; δ_H (270 MHz) 1.35 (3H, t, *J* 7.3), 1.85–1.95 (4H, m), 3.06 (2H, t, *J* 6.2), 3.3–3.45 (4H, m), 7.75–7.8 (2H, m), 8.1–8.25 (2H, m); *m*/*z* 291 (M^+, 100). **4i**: mp 165–167°C; ν/cm^{-1} 1677; δ_H (270 MHz) 1.37 (3H, t, *J* 7.6), 2.72 (3H, s), 3.47 (2H, q, *J* 7.6), 7.75–7.9 (3H, m), 8.2–8.35 (2H, m); *m*/*z* 251 (M^+, 100). **4j**: mp 127–128°C; ν/cm^{-1} 1667; δ_H (270 MHz) 1.10 (3H, t, *J* 7.3), 1.78 (2H, sextet, *J* 7.6), 2.71 (3H, s), 3.35–3.45 (2H, m), 7.7–7.9 (3H, m), 8.2–8.35 (2H, m); *m*/*z* 265 (M^+, 44), 250 (88), 237 (100). **4k**: mp 215–217°C; ν/cm^{-1} 1677; δ_H (270 MHz) 2.79 (3H, s), 7.48 (5H, s), 7.75–7.85 (2H, m), 7.99 (1H, s), 8.15–8.3 (2H, m); *m*/*z* 299 (M^+, 76), 298 (100). **6a**: mp 92–93°C; ν/cm^{-1} 1647; δ_H (270 MHz) 1.29 (3H, t, *J* 7.4), 1.8–1.95 (4H, m), 2.11 (3H, s), 2.13 (3H, s), 3.01 (2H, t, *J* 6.3), 3.15–3.3 (4H, m); *m*/*z* 269 (M^+, 100). **6b**: mp 171–172°C; ν/cm^{-1} 1658; δ_H (270 MHz) 1.88 (4H, br s), 2.04 (3H, s), 2.12 (3H, s), 3.0–3.1 (2H, m), 3.25–3.35 (2H, m), 7.3–7.45 (5H, m); *m*/*z* 317 (M^+, 100).
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