Pergamon

Tetrahedron Letters 41 (2000) 2381–2384

TETRAHEDRON LETTERS

Synthesis of 1-amino- and 1-hydroxy-9,10-anthraquinone derivatives based on reaction sequences between 2-acetyl-1,4-naphthoquinone and enamines

Kazuhiro Kobayashi,* Masaharu Uchida, Shinya Watanabe, Atsushi Takanohashi, Miyuki Tanmatsu, Osamu Morikawa and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552, Japan

Received 8 December 1999; revised 20 January 2000; accepted 21 January 2000

Abstract

2-Acetyl-1,4-naphthoquinone was treated with pyrrolidine (or morpholine) enamines, derived from cyclic and acyclic ketones, in DMF at room temperature for 24–72 h to afford 3,4-disubstituted 1-pyrrolidino(or morpholino)-9,10-anthraquinones. On the other hand, when the treatment of 2-acetyl-1,4-naphthoquinone with enamines for 2 min was followed by addition of water and heating at 100°C for 2 h, the corresponding 1-hydroxy-9,10-naphthoquinone derivatives were obtained.

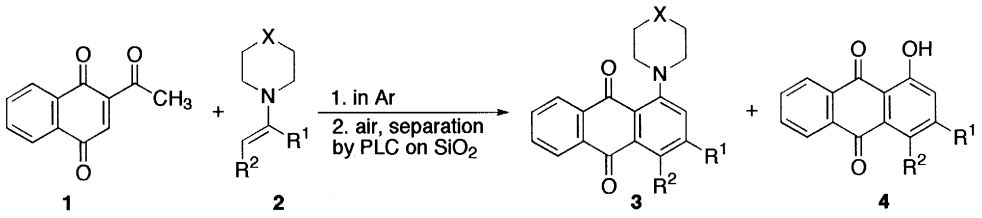
Keywords: anthraquinones; cyclization; enamines; Michael additions; quinones.

We previously demonstrated that enamines underwent conjugate addition to 2-hydroxy- or 2-(1-hydroxyalkyl)-1,4-naphthoquinones, followed by intramolecular cyclization, to give naphtho[2,3-*b*]furan-4,9-diones[1] or 1*H*-naphtho[2,3-*c*]pyran-5,10-diones.[2] Herein, we wish to report that reactions of 2-acetyl-1,4-naphthoquinone (**1**)[3,4] with enamines **2** gave 1-amino-9,10-anthraquinone derivatives **3**, along with small quantities of the corresponding 1-hydroxy-9,10-anthraquinones **4** in some cases. 1-Amino-9,10-anthraquinone derivatives have been of interest due to their use as dyes and pigment intermediates[5] and as precursors in the synthesis of other useful organic materials.[6] Some preparations of this class of molecules have been achieved by the halogenation of 9,10-anthraquinone followed by substitution with amines[5c,7] or a related reaction sequence.[8] The nitration of 9,10-anthraquinone, followed by reduction, has also been reported to give 1-amino-9,10-anthraquinones.[9] However, each of these methods suffered from low regioselectivity in the first step. In this letter, we also describe that a brief reaction of **1** with enamines and subsequent hydrolytic treatment led to almost exclusive formation of **4**. Not only the high efficiency of this class of compounds in organic synthesis[10] but also the discovery that a number of natural products having the 1-hydroxy-9,10-anthraquinone skeleton exhibit useful pharmacological properties[11] has aroused interest in their synthesis.[12]

* Corresponding author. Tel: +81 857 31 5263; fax: +81 857 31 5263; e-mail: kkoba@chem.tottori-u.ac.jp (K. Kobayashi)

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00168-4

The preparation of 1-amino-9,10-anthraquinone derivatives **3** is outlined in Scheme 1, and the yields and reaction conditions are summarized in Table 1. We first conducted the reaction of 2-acetyl-1,4-naphthoquinone (**1**)[3] with 1-pyrrolidinocyclohexene (**2a**) in toluene under argon. This solvent was used for the preparation of naphtho[2,3-*b*]furan-4,9-diones[1] and 1*H*-naphtho[2,3-*c*]pyran-5,10-diones.[2] The reaction proceeded to an appreciable extent at reflux temperature. After usual aqueous workup and subsequent purification by preparative TLC on silica gel, the 1-pyrrolidino-9,10-anthraquinone **3a** was isolated in low yield from the rather complicated mixture of products (entry 1). The sequence was found to proceed smoothly in DMF at room temperature to afford **3a** in good yield, along with a small quantity of the corresponding 1-hydroxy derivative **4a** (entry 2). Similar results were obtained by using other pyrrolidine enamines **2c**, **d**, and **f** (entries 4, 5, and 8). Morpholine enamines (**2b**, **e**, and **g**) were also allowed to react with **1** under the same conditions. Whereas these reactions proceeded more slowly than those using the pyrrolidine enamines, 1-morpholino-9,10-anthraquinones (**3b**, **e**, and **g**) were obtained in fair yields along with only trace amounts of the corresponding 1-hydroxy-9,10-anthraquinones (entries 3, 6, and 9). As shown in entry 7, higher reaction temperature led to a considerable reduction in reaction time. However, the yield of the 1-morpholino-9,10-anthraquinone **3e** decreased, and 1-hydroxy-9,10-anthraquinone **4d** was obtained as the major product.



Scheme 1. Reactions of 2-acetyl-1,4-naphthoquinone (**1**) with enamines **2**

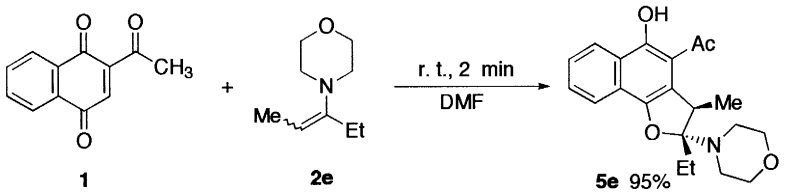
Table 1
Preparation of 1-amino-9,10-anthraquinone derivatives **3** according to Scheme 1

Entry	**2**	Solv	Temp	Time/h	**3** (Yield/%)[a]	**4** (Yield/%)[a]
1	**2a** [$R^2R^3 = (CH_2)_4$, X = nil]	PhMe	reflux	6	**3a** (24)	—
2	**2a**	DMF	r. t.	24	**3a** (82)	**4a** (15)
3	**2b** [$R^2R^3 = (CH_2)_4$, X = O]	DMF	r. t.	72	**3b** (65)	—
4	**2c** [$R^2R^3 = (CH_2)_5$, X = nil]	DMF	r. t.	24	**3c** (72)	**4c** (12)
5	**2d** [R^2 = Et, R^3 = Me, X = nil][b]	DMF	r. t.	24	**3d** (78)	**4d** (10)
6	**2e** [R^2 = Et, R^3 = Me, X = O][b]	DMF	r. t.	72	**3e** (67)	—
7	**2e**	DMF	130 °C	4	**3e** (21)	**4d** (35)
8	**2f** [R^2 = *n*-Pr, R^3 = Et, X = nil][b]	DMF	r. t.	24	**3f** (70)	**4f** (10)
9	**2g** [R^2 = *n*-Pr, R^3 = Et, X = O][b]	DMF	r. t.	72	**3g** (61)	—

[a]Isolated yields after purification by preparative TLC.
[b]Mixtures of stereoisomers were used. For preparations, see ref. 14.

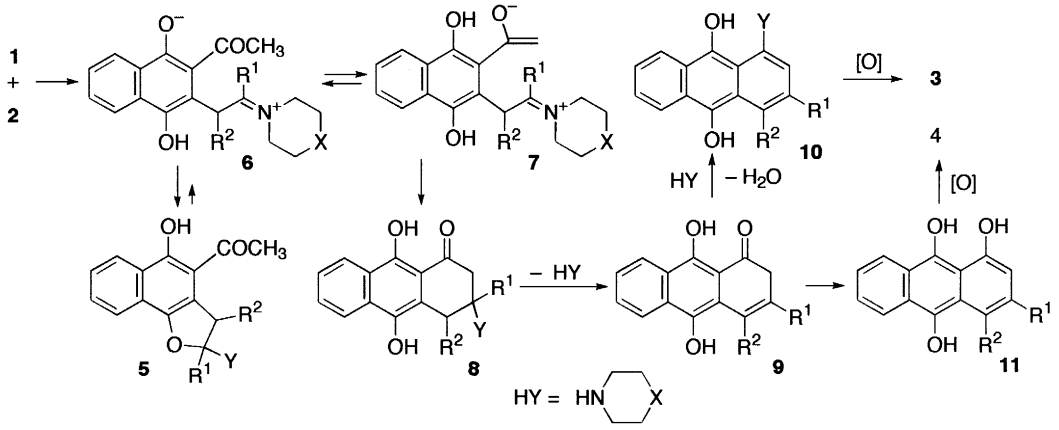
The progress of the reactions could easily be monitored by TLC analysis. In each case, just after the addition of an enamine to a solution of **1** in DMF, most of the starting material disappeared, and a large yellow spot appeared. After 5 to 10 min, a small red (for pyrrolidine enamines) or orange (for

morpholine enamines) spot (attributable to the aminoanthraquinone **3**) appeared. The red or orange spot gradually became larger along with a reduction of the yellow one. When pyrrolidine enamines were used, a lemon-yellow spot (attributable to the hydroxyanthraquinone **4**) appeared within 20 min after the beginning of each of the reactions. We attempted to isolate the initially formed intermediate. Thus, the reaction of **1** with **2e** was quenched immediately after mixing the two starting materials. We obtained the naphthofuran derivative **5e** in high yield, as shown in Scheme 2. The *cis*-configuration of the 2-ethyl group relative to the 3-methyl group of this product was established by NOE analysis; irradiation of the signal at δ 1.30 due to the 3-methyl resulted in enhancement (7.2%) of the signal at δ 2.03 due to one of methylenes of the 4-ethyl.



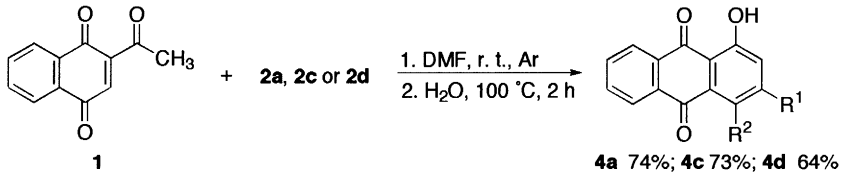
Scheme 2. Isolation of the initial product **5e** from the reaction of **1a** with **2e**

The foregoing results indicated that a possible reaction mechanism for the formation of 1-amino- and 1-hydroxy-9,10-anthraquinone derivatives (**3** and **4**) involves the rearrangement of the initially formed furan intermediate **5**, as illustrated in Scheme 3. This intermediate was produced by the conjugate addition of enamines to the acetylquinone **1**, forming **6**, followed by furan ring formation, and slowly rearranges to the tricyclic ketone intermediate **8**, through the enolate intermediate **7**. After elimination of the amine from **8**, the resulting intermediate **9** gives the aminohydroanthraquinone **10** or the hydroxyhydroanthraquinone **11**. These hydroquinones are oxidized during the workup and/or purification procedures to give the aminoanthraquinone **3** and hydroxyanthraquinone **4**. The lower basicity of morpholine compared to that of pyrrolidine may explain the observation that the reactions using morpholine enamines at room temperature gave the 1-morpholinoanthraquinones almost exclusively.



Scheme 3. Probable mechanism for the formation of 1-amino and 1-hydroxy-9,10-anthraquinone derivatives **3** and **4**

Subsequently, we reasoned that the initial adducts **5** would be converted into 1-hydroxy-9,10-anthraquinones **4** predominantly by treating with water in basic media. Thus, after confirmation of the formation of the initial adducts, water was added, and the resulting mixtures were heated at 100°C. As shown in Scheme 4, the desired products **4a**, **c** and **d** were obtained in good yields, along with only trace amounts of the corresponding 1-pyrrolidino derivatives.



Scheme 4. Selective preparation of 1-hydroxy-9,10-anthraquinones **4**

In conclusion, the present reactions provide convenient preparative methods of 1-amino- and 1-hydroxy-9,10-anthraquinone derivatives bearing alkyl substituents at the 3- and 4-positions. The methods compare favorably in terms of regioselectivity and simplicity of operation with the previously reported methods. We are continuing to investigate the possibility of applying the present sequences to the synthesis of related polycyclic quinone derivatives.[13]

References

1. Kobayashi, K.; Tanaka, K.; Uneda, T.; Maeda, K.; Morikawa, O.; Konishi, H. *Synthesis* **1998**, 1243–1245.
2. Kobayashi, K.; Uchida, M.; Uneda, T.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **1998**, *39*, 7725–7728.
3. Read, G.; Ruiz, V. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 235–243.
4. Utilization of 2-acyl-1,4-naphthoquinones as synthetic precursors for polycyclic quinone derivatives: Kraus, G. A.; Shi, J.; Reynolds, D. *J. Org. Chem.* **1990**, *55*, 1105–1106. De Koning, C. B.; Giles, R. G. F.; Green, I. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2743–2748. Brimble, M. A.; Phythian, S. J.; Prabaharan, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2855–2860. Brimble, M. A.; Duncalf, L. J.; Phythian, S. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1399–1403.
5. For earlier examples, see: (a) *Kirk-Othmer Encyclopedia of Chemical Technology*; 3rd ed.; John Wiley & Sons: New York, 1978; Vol. 2, pp. 719–728. For recent patents: (b) Hagen, H.; Dupuis, J. German Patent 1993, 4131874; *Chem. Abstr.* **1993**, *119*, 97979n. (c) Matsuzaki, Y.; Shimamura, T.; Takuma, H. Japanese Patent 1994, 247912; *Chem. Abstr.* **1995**, *122*, 80909d.
6. For recent reports: Furlong, M. T.; Abramson, H. N.; Akamike, N. A.; Wormser, H. C. *Synth. Commun.* **1990**, *20*, 2691–2697. Dikalov, S. I.; Rumyantseva, G. V.; Piskunov, A. V.; Weiner, L. M. *Biochemistry* **1992**, *31*, 8947–8953. Shvartsberg, M. S.; Ivanchikova, I. D.; Fedenok, L. G. *Tetrahedron Lett.* **1994**, *35*, 6749–6752.
7. Wormser, H. C.; Sardessai, M. S.; Abramson, H. N. *Synth. Commun.* **1993**, *23*, 3211–3222.
8. Suzuki, H.; Kawakami, T. *Tetrahedron Lett.* **1994**, *35*, 9217–9220.
9. Zielske, A. G. *J. Org. Chem.* **1987**, *52*, 1305–1309.
10. Cambie, R. C.; Milbank, J. B. J.; Rutledge, P. S. *Aust. J. Chem.* **1996**, *49*, 1203–1215. Krohn, K.; Boeker, N.; Floerke, U.; Freund, C. *J. Org. Chem.* **1997**, *62*, 2350–2356. Ge, P.; Russell, R. A. *Tetrahedron* **1997**, *53*, 17469–17476.
11. Chang, P.; Lee, K. H. *J. Nat. Prod.* **1985**, *48*, 948–951. Zembower, D. E.; Kam, C. M.; Power, J. C.; Zalkow, L. H. *J. Med. Chem.* **1992**, *35*, 1597–1605. Kelly, T. R.; Ma, Z.; Xu, W. *Tetrahedron Lett.* **1992**, *33*, 7713–7714.
12. Smith, C. W.; Ambler, S. J.; Steggles, D. J. *Tetrahedron Lett.* **1993**, *34*, 7447–7450. Zhao, H.; Biehl, E. *J. Nat. Prod.* **1995**, *58*, 1970–1974. Zhang, X.; Fox, B. W.; Hadfield, J. A. *Synth. Commun.* **1996**, *26*, 49–62. Danielson, K. *Acta Chem. Scand.* **1996**, *50*, 954–957. Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 4387–4410.
13. All new compounds have been fully characterized by a combination of spectral [^{1}H (270 MHz, $CDCl_3$) and/or ^{13}C NMR (67.8 MHz, $CDCl_3$, *J* values are given in hertz), IR (KBr disk), and mass] and combustion analysis. Spectral data for selected compounds follow. **3a**: ν/cm^{-1} 1651, 1630; δ_H 1.8–1.85 (4H, m), 1.95–2.05 (4H, m), 2.85–2.9 (2H, m), 3.2–3.3 (6H, m), 6.95 (1H, s), 7.6–7.7 (2H, m), 8.1–8.2 (2H, m); δ_{13C} 22.50, 25.99, 28.75, 31.98, 52.32, 68.18, 120.01, 125.74, 126.20, 128.70, 130.71, 132.06, 132.95, 133.28, 133.90, 135.05, 144.70, 147.99, 181.00, 186.95; *m/z* 331 (M^+, 26), 314 (100). **4a**: ν/cm^{-1} 3480, 1662, 1635; δ_H 1.75–1.85 (4H, m), 2.85–2.9 (2H, m), 2.25–2.3 (2H, m), 7.04 (1H, s), 7.7–7.8 (2H, m), 8.2–8.3 (2H, m), 13.08 (1H, s); *m/z* 278 (M^+, 68), 263 (100). **3b**: ν/cm^{-1} 1668, 1652; δ_H 1.8–1.85 (4H, m), 2.85–2.9 (2H, m), 3.1–3.2 (6H, m), 3.95–4.05 (4H, m), 7.08 (1H, s), 7.65–7.7 (2H, m), 8.05–8.2 (2H, m); *m/z* 347 (M^+, 13), 330 (100). **3d:** ν/cm^{-1} 1659, 1631; δ_H 1.26 (3H, t, *J* 7.8), 1.95–2.05 (4H, m), 2.62 (3H, s), 2.77 (2H, q, *J* 7.8), 3.25–3.35 (4H, m), 7.03 (1H, s), 7.6–7.75 (2H, m), 8.1–8.2 (2H, m); *m/z* 319 (M^+, 89), 262 (100). **5e**: ν/cm^{-1} 3440, 1610; δ_H 1.07 (3H, t, *J* 7.3), 1.30 (3H, d, *J* 6.9), 2.03 (1H, dq, *J* 15.2, 7.3), 2.21 (1H, dq, *J* 15.2, 7.3), 2.6–2.75 (8H, m including s at 2.71), 3.6–3.75 (4H, m), 7.49 (1H, t, *J* 8.2), 7.61 (1H, t, *J* 8.2), 7.92 (1H, d, *J* 8.2), 8.41 (1H, d, *J* 8.2), 14.02 (1H, s); *m/z* 355 (M^+, 0.05), 268 (100).
14. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.