



One-Pot Synthesis of Hydroxy Substituted 1,4-Naphthoquinone with 2-Pyrones

LIXIA JIA^{1,2,*}, HUIMIN WANG², HUI ZHAO², XINYUAN SONG¹, JUNQIONG HU² and GUOHUA SHAN²

¹College of Chemistry, Chemical Engineering & Biotechnology, Donghua University, Shanghai 201620, P.R. China

²College of Textile Engineering, Xinjiang University, Urumqi 830046, P.R. China

*Corresponding author: Fax: +86 991 8582412; Tel: +86 991 8583362; Email: lixiajia868@126.com; sgh_119@126.com

(Received: 5 April 2011;

Accepted: 19 October 2011)

AJC-10536

In the presence of base-catalyzed, Diels-Alder reaction, involving one-pot decarboxylation-oxidation reaction of 4-hydroxy-6-methyl-2-pyrone with 1,4-benzoquinone, gave 7-hydroxyl-5-methyl-1,4-naphthoquinone. In a similar way, 6-chloro-5-hydroxyl-1,4-naphthoquinone was also obtained with a reasonable yield by using environment-friendly catalyst and solvent.

Key Words: 2-Pyrone, Naphthoquinone, Diels-Alder reaction, Decarboxylation, One-pot.

INTRODUCTION

The 1,4-naphthoquinone moiety, which demonstrates a wide range of biological activities, is an important component of a large number of natural products¹. As a result, novel 1,4-naphthoquinone derivatives have drawn much attention for their extraction and synthesis. According to our early research^{2,3}, hydroxy substituted 1,4-naphthoquinones have significant UV protection for dyed wool fibre. Meanwhile, they are very attractive pigments with antifungal activities for carpet fabrics. Until now, a number of synthetic methods about 1,4-naphthoquinone derivatives have been reported⁴⁻⁸, but only limited simple and effective methods deal with hydroxy substituted 1,4-naphthoquinones⁹.

Diels-Alder reaction is one of the most efficient methods to synthesize 1,4-naphthoquinones. To our best of knowledge, 1,3-butadiene, as a common diene component of Diels-Alder reaction, has disadvantages of gas-state, inflammability and by-effect. On the other hand, the 2-pyrone moiety is not only an important component of many natural products, but also a significant intermediate compound^{10,11}. In this paper, we provided a synthetic method of using hydroxy substituted 2-pyrone as diene component to enable Diels-Alder reaction easily and the yield of target compounds efficiently under mild conditions. Based on Diels-Alder reaction and decarboxylation-oxidation in one pot, 7-hydroxy-5-methyl-1,4-naphthoquinone (**4a**) and 6-chloro-5-hydroxyl-1,4-naphthoquinone (**4b**) were prepared from 1,4-benzoquinone and corresponding hydroxy substituted 2-pyrone.

EXPERIMENTAL

All of reagents in this work were purchased from Xiyu Chemical Ltd., in chemical pure grade. Melting points were

measured in open capillary tubes using a melting point B-545. TLC was performed on pre-coated 60G 254 silica gel using CHCl₃-EtOH 1:2 as a solvent. The compounds were detected with Perkin-Elmer Lambda 17 UV/VIS spectrophotometer. Column chromatography was performed on silica gel G60 (70-230 mesh). IR spectra were taken with a Bruker Equinox 55 Infrared spectrometer using KBr pellets. NMR spectra were recorded on a Varian Inova-400 MHz NMRA spectrometer using DMSO-*d*₆ as a solvent. Elemental analyses were performed on Perkin-Elmer 2400 series II CHNS/O analyzer. The concentration of target compound was expressed by Lambert-Bill Law in EtOH.

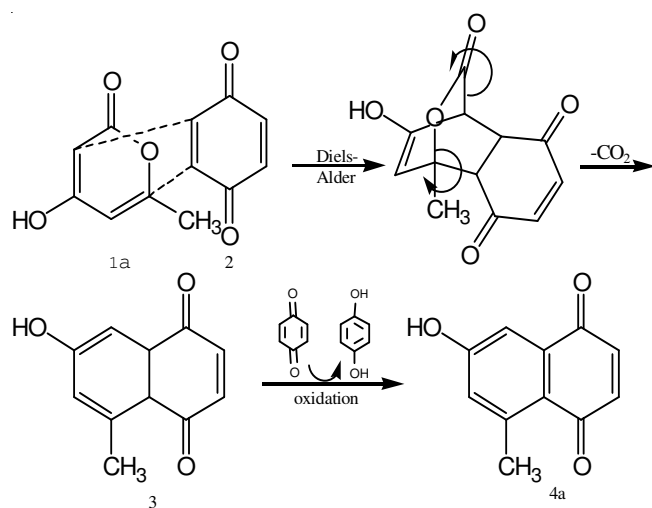
7-Hydroxy-5-methyl-1,4-naphthoquinone 4a: 1,4-Benzoquinone (**2**) (0.8639 g, 7.992 mmol), triethanolamine (0.053 mL, 0.3996 mmol) and 4-hydroxy-6-methyl-2-pyrone **1a** (0.504 g, 3.996 mmol) were added in blended solvent (EtOH: Et₂O, 1:4, 50 mL), then the mixture was stirred at 35 °C for 3.5 h. During this period, the yellow brown crystal was deposited in blended solvents continuously. Then the filtration was evaporated with a rotary evaporator. The crude product, collected from crystallization and evaporation, was washed with Et₂O, then recrystallized in EtOH-EtOAc and purified by column chromatography on silica gel (eluent: hexane-EtOAc, 50:1) to give **4a**; Yield: 0.7080 g (94.2 %); m.p. 119-120 °C. IR (neat): 3393, 2981, 1798, 1666, 1575, 1509, 1448, 1202 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 1-1.6 (s, 2H), 1.8-2.4 (d, 3H), 2.4-3.2 (s, 1H), 5-6 (m, 1H), 6.4-7 (m, 1H); ¹³C NMR (100 MHz): δ 19.5, 103.4, 115.0, 115.8, 137.0, 137.1, 140.6, 141.9, 160.0, 185.1, 185.7. Anal. calcd. for C₁₁H₈O₃: C, 70.21; H, 4.28. Found: C, 70.04; H, 4.45.

6-Chloro-5-hydroxy-1,4-naphthoquinone 4b: Typical procedure of synthesis is similar to compound **4a**. Added 1,4-

benzoquinone **2** (0.8639 g, 7.992 mmol), triethanolamine (0.053 mL, 0.3996 mmol) and 4-chloro-3-hydroxy-2-pyrone **1b** (0.5854 g, 3.996 mmol) in blended solvent (EtOH-Et₂O, 1:4, 45 mL); yield: 1.5380 g (92.3 %); m.p. 145-146 °C. IR (neat): 3376, 3038, 1657, 1592, 1467, 13667, 1240, 1211 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): 6.89(s, 2H), 7.50 (d, 1H), 7.68 (d, 1H), 12.37 (m, 1H); ¹³C NMR (100 MHz): δ 115.3, 119.1, 129.4, 130.3, 136.5, 138.7, 139.8, 157.1, 183.8, 190.2; Anal. calcd. for C₁₀H₅ClO₃: C, 57.58; H, 2.41. Found: C, 57.42; H, 2.59.

RESULTS AND DISCUSSION

In our research, 4-hydroxy-6-methyl-2-pyrone (**1a**), one of the simplest natural product, is *s-cis* diene with electron-donating group and 1,4-benzoquinone (**2**) is dienophile with electron-drawing group. Both reagents are favourable for Diels-Alder reaction. A possible reaction mechanism is shown in **Scheme-I**. First, base-catalyzed Diels-Alder reaction of **1a** and **2** gives intermediate compound with the structure of endo-configuration. Then dihydro-naphthoquinone (**3**) is produced by decarboxylation. Finally, an oxidation of **3** by another unreacted **2** furnishes **4a**. Target compound **4b** has been synthesized in the same approach.



Scheme-I Possible reaction mechanism of **4a**

Because Diels-Alder reaction can be affected by polarity of organic solvents under certain conditions, we investigated the influence of solvent on reaction in certain ratio of reagents and catalysts. The solubilities of the reactants were listed in Table-1. It is difficult for **1a** and **2** to dissolve in CHCl₃, which is contrary to the literature that used CHCl₃ as solvent⁹. On the other hand, EtOH or H₂O can also be served as favourable solvent. The solubility of **1a** or **2** in the blended solvent follows the ratio of EtOH-Et₂O and it is better than that in individual. For example, although **1a** or **2** was dissolved in Et₂O with 0.00 % or 1.43 %, respectively, the solubility of **1a** or **2** increased to 0.78 % or 5.32 % in EtOH-Et₂O of 1:10, as well as 4.81 % or 6.26 % in ratio of 1:4.

In fact, EtOH has been taken as both solvent and catalyst for such reaction. It is hard to control the rate of reaction and separate products after synthesis. Meanwhile, both target compounds of **4a** and **4b** have perfect crystal ability in Et₂O with lower boiling point. As a result, we use blended solvent EtOH-

Reactant	CHCl ₃	EtOH	H ₂ O	Et ₂ O
1a (%)	0.06	6.98	0.63	—
2 (%)	1.64	4.82	1.08	1.43

Reactant	EtOH-Et ₂ O			
	1:4	1:6	1:8	1:10
1a (%)	4.81	—	0.97	0.78
2 (%)	6.264	3.66	4.60	5.32

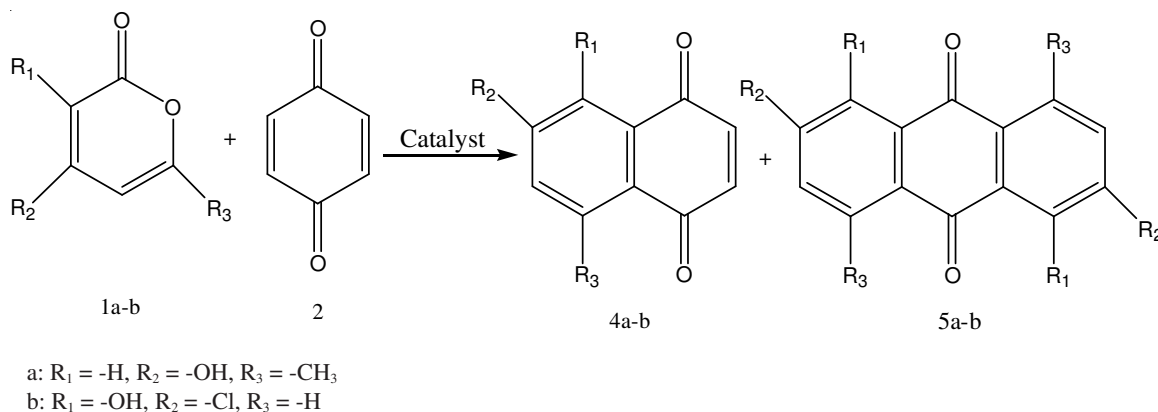
Et₂O to reduce rate of reaction and simplify the separation or purification of target compounds. Under the certain condition, with the ratio increase of Et₂O in EtOH-Et₂O, the yields of compound **4a** decreased (Table-2). Finally, the ratio of EtOH-Et₂O was chosen as 1:4-1:8.

Entry	n _{EtOH} : n _{Et2O} : n _{Et3N}	n _{1a} : n ₂	Temp (°C)	Yield (%)
1	1:4: 0.1	1:1.4	35	80.28
2	1:4: 0.1	1:1.6	35	82.38
3	1:4: 0.1	1:2.0	35	94.18
4	1:6: 0.1	1:2.0	35	52.95
5	1:8: 0.1	1:2.0	35	50.52
6	1:10: 0.1	1:2.0	35	48.12
7	1:4: 0.1	1:3.0	35	90.65
8	1:4: 0.1	1:2.0	25	74.95
9	1:4: 0.1	1:2.0	30	81.02
10	1:4: 0.1	1:2.0	40	81.13

The influence of the triethylamine (Et₃N) can be seen from Table-3. Without Et₃N under 35 °C even refluxing condition, the reaction did not proceed. On the other hand, with the addition of Et₃N, the reaction proceeded smoothly and the target compound **4a** was obtained in a reasonable yield after purification. Furthermore, it was shown in Figs.1 and 2 that the effect of triethanolamine (TEOA) on the yield was better than that of Et₃N under certain condition. In our research, Et₃N or triethanolamine was not only the catalyst of Diels-Alder reaction, but also the decarboxylation agent of intermediate compound, which was favourable for target compounds. So we chose environment-friendly triethanolamine as the catalyst with the amount of 0.1 equivalents.

Entry	n _{Et3N}	Temp (°C)	Time (h)	Yield (%)
1	—	reflux	7.0	—
2	—	35	7.0	—
3	0.01	35	3.5	44.32
4	0.05	35	3.5	46.66
5	0.10	35	3.5	94.42
6	0.30	35	3.5	98.42

The Diels-Alder reaction was reported to depend on both reagent concentration and reaction temperature⁴. In present case, over a range of reaction temperature from 30 to 80 °C, the yield of target compound **4a** changed rapidly with the rise of temperature as shown in Figs.1 and 2. Also a by-product (**5a**), which seems to be produced by the addition of **1a** to **4a**, was obtained (**Scheme-II**). In order to obtain the desired



Scheme-II: Synthesis of hydroxy substituted 1,4-naphthoquinone in one-pot

compound **4a** and reasonable yield, it is a feasible way to control the temperature below 35 °C and treatment **1a** with excess of reagent **2**.

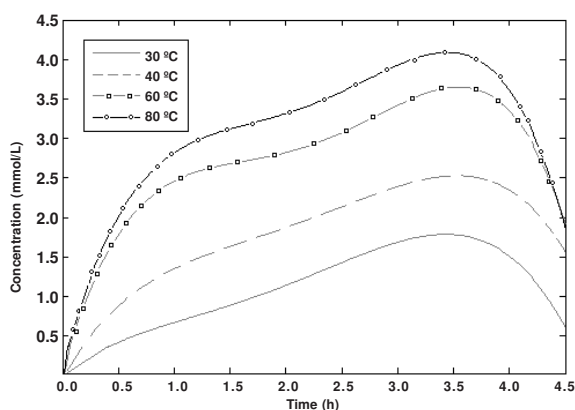


Fig. 1. Effect of triethylamine on yield of **4a**

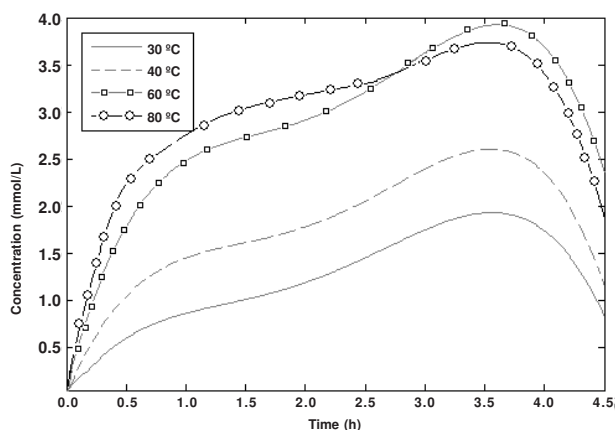


Fig. 2. Effect of triethanolamine on yield of **4a**

Finally, based on the synthesis of compound **4a**, we also tried to apply 3-hydroxy-2-pyrone derivatives for the synthesis of another hydroxy substituted 1,4-naphthoquinones. In the presence of 0.1 equivalents of TEOA, 4-chloro-3-hydroxy-2-pyrone (**1b**) was also converted to the corresponding **4b** in excellent yield (92.3 %). The ultraviolet spectrum of **4a** and **4b** have the strong absorbing band in 240-260 nm and the

middle absorbing band in 280-300 nm, which is the characteristic absorbance of 1,4-naphthoquinones. Especially, another absorbing band in 416-420 nm is an existing evidence of α -OH at benzene ring of 1,4-naphthoquinones, which means that **4b** is a 5 or 8-hydroxy substituted 1,4-naphthoquinone. Moreover, **4a** and **4b** have the absorbance of IR spectrum in $\nu(C=O)$ (1675-1653 cm^{-1}), $\nu(OH)$ (3600-3130 cm^{-1}) and naryl (1600-1480 cm^{-1}). Compared with **4a**, the absorbance of **4b** in $\nu(C=O)$ shifts from 1666 to 1657.38 cm^{-1} by the association of α -OH with $\nu(C=O)$.

Conclusion

Through the base-catalyzed Diels-Alder reaction, we have improved an effective one-pot synthesis of 7-hydroxy-5-methyl-1,4-naphthoquinone **4a** and 6-chloro-5-hydroxy-1,4-naphthoquinone **4b** with hydroxy substituted 2-pyrone **1a** or **1b** and 1,4-benzoquinone **2**. This reaction proceeds very smoothly under mild condition. It is possible to prepare various hydroxy substituted 1,4-naphthoquinone derivatives from different hydroxy substituted 2-pyrone by this reaction. Further exploitation of this strategy towards the synthesis of more naphthoquinone dyes for wool is in progress and will be reported in future.

ACKNOWLEDGEMENTS

This work was supported by National Natural Science Foundation of China (No. 20962019). The authors wish to express their gratitude toward Prof. Pengfen Xu of Lanzhou University for the paper revision.

REFERENCES

1. J.Q. Gu, *J. Nat. Prod.*, **67**, 1156 (2004).
2. L.N. Pan, M.S. Thesis, Xinjiang University, China (2008).
3. L.Y. Wang, M.S. Thesis, Xinjiang University, China (2008).
4. A. George, *J. Org. Chem.*, **67**, 2358 (2002).
5. J.Z. Svete, C. Adez, B. Stanovnik and M. Tisler, *Synthesis*, **70** (1990).
6. V. Kepe, S. Polanc and M. Kocovar, *Heterocycles*, **48**, 671 (1998).
7. F. Bellina, M. Biagetti, A. Carpita and R. Rossi, *Tetrahedron Lett.*, **42**, 2859 (2001).
8. B. Stanovnik and J. Svete, *Chem. Rev.*, **104**, 2433 (2004).
9. T. Komiyama, Y. Takaguchi and S. Tsuboi, *Synthesis*, 1405 (2006).
10. T. Komiyama, Y. Takaguchi, A.T. Gubaidullin, V.A. Mamedov, I.A. Litvinov and S. Tsuboi, *Tetrahedron Lett.*, **61**, 2541 (2005).
11. T. Komiyama, Y. Takaguchi and S. Tsuboi, *Tetrahedron Lett.*, **45**, 6299 (2004).