Synthesis of 4,8-dimethoxy-1-naphthol *via* an acetyl migration

Qijing Zhang[1], Jinyun Dong[1], Qing Cui[1], Shaoshun Li[1,], Jiahua Cui[1]

[1]School of Pharmacy, Shanghai Jiao Tong University, Shanghai, China

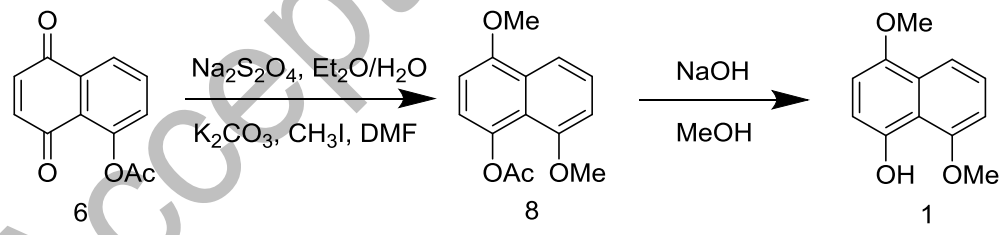
Corresponding author E-mail: Shaoshun Li ssli@sjtu.edu.cn; Jiahua Cui cpucjh@sjtu.edu.cn.

[1]Both authors contributed equally to this work.

Abstract

Rested on an acetyl migration, an efficient synthesis of 4,8-dimethoxy-1-naphthol **(1)** has been achieved with high overall yield. Compared with the reported method, there were several advantages. Firstly, the reaction conditions were mild. Secondly, the work-up of each step was much simpler. Thirdly, juglone as the starting material in the synthesis was readily available. The solvent and reaction temperature greatly influenced the migration process.

Graphical Abstract



KEYWORDS: 4,8-dimethoxy-1-naphthol, acetyl migration, juglone derivatives

INTRODUCTION

4,8-dimethoxy-1-naphthol **(1) (**Scheme 1**)**, a juglone derivative, is of great importance in organic synthesis. It served as a building block in the total synthesis of naturally occurring naphthoquinones[1–4] and their bioactive synthetic analogous,[5–8] which were prepared by aryl-aryl coupling reactions. Its bromo, acetyl and formal group-contained derivatives **(2-4)** were also extremely important fine chemicals in both industry and academic chemistry.[9–13]

Preparation of **(1)** rested on the Baeyer-Villager (B-V) oxidation-rearrangement of 1,5-dimethoxy-4-naphthaldehyde and further hydrolysis of the formate ester moiety.[14–16] The work-up of the oxidation was somewhat tedious because of the excessive use of *m*-chloroperbenzoic acid in the reaction. If the work-up was not properly handled, the yield would be much lower than the reported value.

The synthesis could also be achieved through the Diels-Alder reaction between 1-methoxycyclohexa-1,3-diene and 1,4-benzoquinone and further elimination of the ethylene bridge in the methylated adduct.[17] This method has not been used extensively since the thermal elimination should be carried out under stringent conditions with the temperature of 220 °C. In addition, the reductive methylation of juglone methyl ether was also reported.[18] However, this method also has not been widely used since the starting material was not easy to obtain.

Herein, we reported an efficient synthesis of **(1)** with high overall yield via an acetyl migration under mild conditions.

RESULTS AND DISCUSSION

Our study starts from the juglone **(5)** that was prepared by our reported method.[19] The acelytion of juglone according to Fisher's method[20] gave acetyljuglone **(6)** with high yield. Then this acelyted naphthoquinone **(6)** was reduced to corresponding hydroquinone **(7)** stoichiometrically by using sodium dithionite.[21] The acetyl migration in basic condition and further methylation to afford 1-acetoxy-4,8-dimethoxynaphthalene **(8)** as a key intermediate. The hydrolysis of the acetate and further acidic work-up obtained the title compound with high yield. Its spectroscopic characteristic was in consistence with the reported value of the naphthol **(1)** obtained by the B-V reaction. The bromination, Fries-rearrangement and hexamine aromatic formylation of **(1)** afforded its 2-bromo **(2)**, 2-acetyl **(3)** and 2-formyl **(4)** derivatives, respectively.

Great efforts have been made to investigate the effects of solvent and reaction temperature toward the proceeding of migration. The first part of our study, different kinds of solvents including DMSO, CH_3CN, acetone and DMF were chosen as reaction medium to prepare **(8)**. As shown in Table 1, target compound was obtained with different yields varying from 18% to 84%, and DMF was regarded as the best solvent among these selected organic solvents. Further, in an effort to find the most suitable temperature for the migration, the reaction was studied with DMF as a solvent under various temperatures from -10 °C to 60 °C. The results were presented in Table 2. Interestingly, elevation of the reaction temperature from 0 °C to 60 °C and i of **(8)** was dramatically from 92% to 35%, sequentially. Of note, the yield of **(8)** was

decreased to 65% when the reaction mixture temperature was cooled to -10 °C. It was considered that 0 °C was the most suitable temperature for the migration. Generally speaking, solvent and reaction temperature greatly influenced the proceeding of migration and finding the best solvent and temperature to improve yield was of great importance.

The plausible interpretation of the migration was that the anion (11) (Scheme 2) was more stable than anion (9). The hydroxy group on C(1) as an electron donating group greatly increased the electron density of A-ring especially in alkali condition and the increase in the electron density could possibly enhance the nucleophilicity of the 4-oxygen anion. During the migration, the oxygen anion on C(4) of **(9)** first attacked the carbonyl carbon in the acetyl group, leading to the formation of a hexatomic ring-contained intermediate **(10)**. Cleavage of the initial C-O bond provided the more stable negative ion **(11)**. Thus the presence of C-1 hydroxyl group and the involvement of the favored 6-membered intermediate should be the reasons for the high-yielding migration.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers and purified using standard techniques.[22] Column chromatography was conducted on silica gel (100-200 mesh) from Qingdao Ocean Chemical Factory. Juglone was prepared by the oxidation of 1,5-naphthelendiol using Fremy's radical.[19] Melting points were determined on a SGW X-4 micromelting point apparatus. ^{1}H NMR Spectra were measured on a Bruker Avance

400 spectrometer (400 MHz) and chemical shifts were recorded with tetramethylsilane as the internal standard.

General Proceduce For The Synthesis Of (8)

Dry solvent (6 mL) was added to hydroquinone **(7)** (109 mg, 0.5 mmol) and K_2CO_3 (414 mg, 3 mmol) under nitrogen atmosphere. The mixture was stirred for 20 min at 0 °C and then methyl iodide (1.2 mmol) was dropwise added. After the addition, the reaction was continued for 3 h and the color of the suspension gradually turned from dark purple to brown. After completion of the reaction, ethyl acetate (15 mL) was added and the mixture was filtered. The filtrate was sequentially washed with cold water (10 mL×2) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography to give compound **(8),** 113 mg (92%).

4,8-dimethoxy-1-naphthol (1): Under nitrogen atmosphere, a NaOH aqueous solution (20%) was added dropwise to an ice cooled suspension of **(8)** (1 g, 4 mmol) in methanol (30 mL). After the addition, the solid was dissolved and a white solid gradually precipitated from the solution. When all the starting materials were consumed, the mixture was concentrated to one-half volume under reduced pressure and the residue was diluted with cold water, acidified with HCl solution (5.0 M). Usual extraction with ethyl acetate (15 mL×3) afforded the title compound as an off-white solid. Recrystallization from *n*-hexane gave the product **(1)** as a white plate, 0.81 g (98%).

ACKNOWLEDGEMENTS

The research is supported by China Postdoctoral Science Foundation (Grant No. 2014M561479) and Hong Kong Scholar program (XJ2015032). We are grateful to the Instrumental Analysis Center of Shanghai Jiao Tong University for recording the ^{1}H NMR spectra.

REFERENCES

[1] Giles, R. G.; Green, I. R.; Hugo, V. I.; Mitchell, P. R.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2383-2388.

[2] Tanoue, Y.; Sakata, K.; Hashimoto, M.; Morishita, S. I.; Hamada, M.; Kai, N.; Nagai, T. *Tetrahedron*, **2002**, 58, 99-104.

[3] Uno, H. *J. Org. Chem.*, **1986**, 51, 350-358.

[4] Okamoto, I.; Doi, H.; Kotani, E.; Takeya, T. *Tetrahedron Lett.* **2001**, 42, 2987-2989.

[5] Brimble, M. A.; Nairn, M. R.; Park, J. *Org. Lett.*, **1999**, 1, 1459-1462.

[6] Zhang, H.; Zembower, D. E.; Chen, Z. *Bioorg. Med. Chem. Lett.*, **1997**, 7, 2687-2690.

[7] Otsuka, T.; Okamoto, I.; Kotani, E.; Takeya, T. *Tetrahedron Lett.*, **2004**, 45, 2643-2647.

[8] Takeya, T.; Doi, H.; Ogata, T.; Otsuka, T.; Okamoto, I.; Kotani, E. *Tetrahedron*, **2004**, 60, 6295-6310.

[9] Williams, W.; Sun, X.; Jebaratnam, D. *J. Org. Chem.*, **1997**, 62, 4364-4369.

[10] Maruyama, K.; Uno, H.; Naruta, Y. *Chemistry Lett.*, **1983**, 12, 1767-1770.

[11] Naruta, Y.; Uno, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.*, **1981**, 1277-1278.

[12] Brimble, M. A.; Burgess, C.; Halim, R.; Petersson, M.; Ray, J. *Tetrahedron*, **2004**, 60, 5751-5758.

[13] Tanoue, Y.; Terada, A.; Matsumoto, Y. *Bull. Chem. Soc. Jpn*, **1989**, 62, 2736-2738.

[14] Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.*, **1979**, 44, 2153-2158.

[15] Syper, L. *Synthesis*, **1989**, 3, 167-172.

[16] Syper, L.; Młochowski, J.; Kloc, K. *Tetrahedron*, **1983**, 39, 781-792.

[17] Hugo, V. I.; Snijman, P. W.; Green, I. R. *Synth. Commun.*, **1993**, 23, 577-584.

[18] Chorn, T. A.; Giles, R. G.; Green, I. R.; Hugo, V. I.; Mitchell, P. R.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1339-1343.

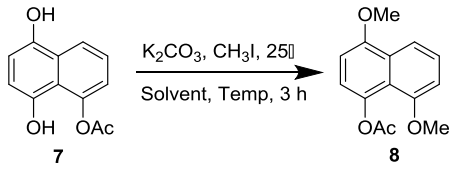
[19] Cui, J. H.; Li, S. S. *J. Chin. Chem. Soc.*, **2013**, 60, 1163.

[20] Fieser, L. F.; Dunn, J. T. *J. Org. Chem.*, **1937**, 59, 1016-1021.

[21] Qabaja, G.; Jones, G. B. *J. Org. Chem.*, **2000**, 65, 7187-7194.

[22] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Burlington, USA, 2009.

Table 1. Synthesis of 1-acetoxy-4,8-dimethoxynaphthalene at 25 °C in different solvent.[a]



Entry	Solvent	Temperature (℃)	Yield(%)
1	Acetone	25	65
2	CH_3CN	25	37
3	DMSO	25	18
4	DMF	25	84

Yields were reported as a mean of three experiments.

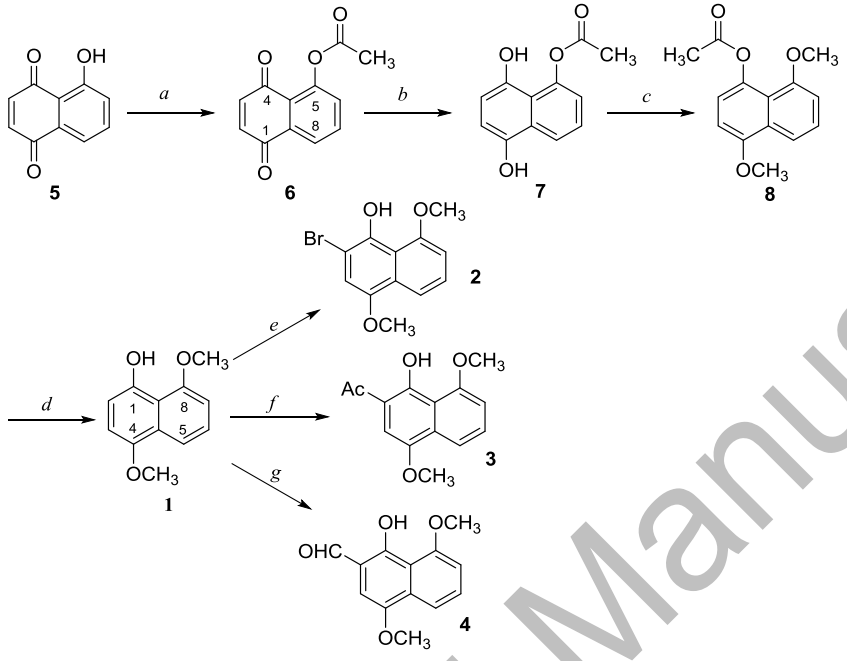
[a]Conditions: 7 (0.5 mmol), K_2CO_3 (3 mmol), CH_3I (1.2 mmol), and dry solvent (6 mL) at 25℃.

Table 2. Synthesis of **(8)** in DMF at various temperatures.

Entry	Solvent	Temperature (℃)	Yield(%)
1	DMF	-10	65
2	DMF	0	92
3	DMF	25	84
4	DMF	40	68
5	DMF	60	35

Yields were reported as a mean of three experiments.

Scheme 1. *a*) $(CH_3CO)_2O$, cat Conc. H_2SO_4. *b*) $Na_2S_2O_4$, Et_2O/H_2O. *c*) CH_3I, K_2CO_3, DMF. *d*) NaOH, MeOH, ice-bath. *e*) Br_2, CH_2Cl_2, -78 ℃. *f*) $(CH_3CO)_2O$, Py, BF_3-Et_2O. *g*) *p*-toluenesulfonic acid, hexamethylenetetramine, AcOH, 85 ℃.



Scheme 2. The plausible mechanism for the acetyl migration.