HETEROCYCLES, Vol. 96, No. 2, 2018, pp. 334 - 338. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 19th December, 2017, Accepted, 30th December, 2017, Published online, 23rd January, 2018
DOI: 10.3987/COM-17-13859

AN EFFICIENT SYNTHESIS OF 1-HYDROXY-5,8-DIMETHOXY-2-NAPHTHALDEHYDE

Qijing Zhang, Jinyun Dong, Guang Huang, and Shaoshun Li*

School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai, 200240, China. E-mail: ssli@sjtu.edu.cn

Abstract – An efficient method for the preparation of 1-hydroxy-5, 8-dimethoxy-2-naphthaldehyde (**1**) was developed with a high overall yield (73.8%). Compared with the previously reported method, the reaction conditions are milder and the work-up of each step is much simpler. Moreover, the starting material considerably reduces the cost and is suitable for large-scale preparations.

Naphthoquinone derivatives have attracted considerable interests by scientists due to its beneficial biological activities, such as antitumor,[1,2] antiviral,[3] antibacterial[4] and antifungal[5] properties. The entitled 1-hydroxy-5, 8-dimethoxy-2-naphthaldehyde (**1**), served as a key intermediate, was widely used in the synthesis of some important naphthoquinone derivatives. In Zhang's[6] work, a novel shikonin derivative DMAKO-05 (Figure 1) was obtained from **1** and proved to have a potent inhibitory effect on cellular proliferation.

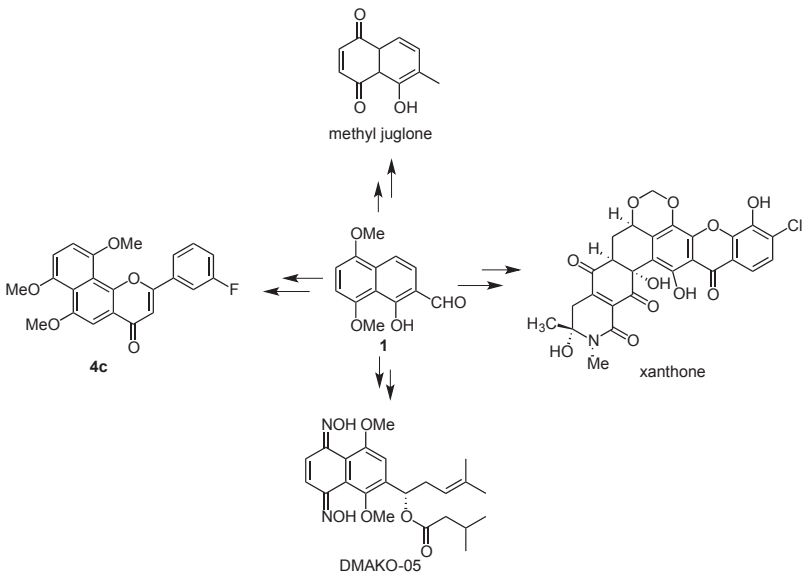
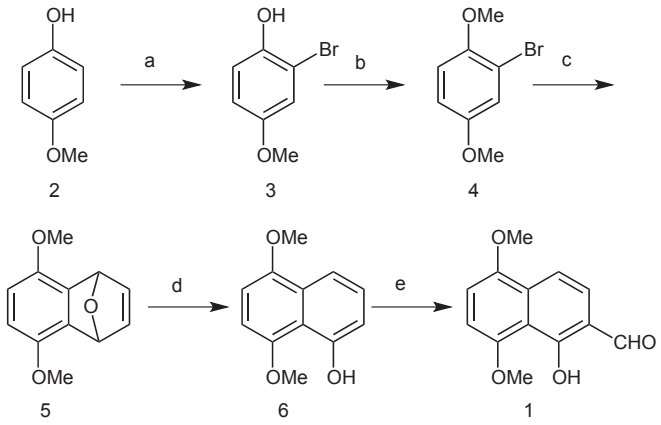


Figure 1. The key intermediate of **1** in organic synthesis

A series of natural xanthone products, generated by the fungal phytopathogen *Cercospora beticola*,[7,8] were prepared by Kramer and co-workers[9] via cycloaddition of substituted naphthoquinone monoketal and shown antimicrobial and anticoccidial activities; methyl juglone, possessing antitubercular activity,[10] was synthesized from **1** by Gotthard and Bernd.[11]

Furthermore, Cui and co-workers[12] used **1** derivative (1,4,5,8-tetramethoxy-2-naphthaldehyde) to synthesize a series of new α-naphthoflavones as CYP1 inhibitors. Of the note, the fluorine-containing naphthoflavone **4c** exhibited a high selectivity for CYP1B1 over CYP1A1 and CYP1A2 and was identified as the most potent CYP1B1 inhibitor ever reported. Heretofore, there is only one reported method[11] for synthesis of **1** via electrophilic substitution reaction of paraformaldehyde in the presence of $SnCl_4$ with a low yield of 50%. Additionally, stannic chloride is hazardous to the environment and the work-up is also tedious. Therefore, it's necessary to develop a new method for the synthesis of **1** with the inexpensive *p*-methoxyphenol (**2**) as starting material (Scheme 1).



Scheme 1. Reagents and conditions: a) Br_2, CH_2Cl_2; b) MeI, K_2CO_3, acetone; c) $NaNH_2$, furan, THF, reflux; d) HCl, MeOH; e) $TsOH{\cdot}H_2O$, hexamethylenetetramine, AcOH, reflux

A convenient and efficient method to synthesize **1** was established. Unlike the reported method, we used the cheap and available material **2** to prepare **3** in the presence of Br_2 in dichloromethane and this conversion was complete. After methylation of **3**, the resultant compound **4** generates a benzyne intermediate in the presence of sodium amide, which is followed by a Diels-Alder cycloaddition reaction with furan to afford **5**. Hydrolysis of **5** by treatment with HCl in MeOH gave **6** in good yield. Finally, we obtained **1** via the Duff formylation[13] of **6**.

An improved synthesis of 1-hydroxy-5,8-dimethoxy-2-naphthaldehyde with a high overall yield of 73.8% was described. This method is also available for other similar preparations. Compared with the reported method, our method has several advantages. Firstly, the starting material is cheaper and the yield is higher.

Secondly, the reaction conditions are milder and the work-up of each step is simpler. Thirdly, the reactions in this paper are suitable for large-scale preparations.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers and purified using standard techniques.[14] Column chromatography was conducted on silica gel (100–200 mesh) from the Qingdao Ocean Chemical Factory. Melting points were determined on a SGW X-4 micromelting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were measured on an Agilent 400 spectrometer (400 MHz) and chemical shifts were recorded with tetramethylsilane as the internal standard.

2-Bromo-4-methoxyphenol (3). Br_2 (64.7 g, 403 mmol) dissolved in CH_2Cl_2 (30 mL) was slowly added dropwise to a solution of *p*-methoxyphenol (**2**) (50 g, 403 mmol) in CH_2Cl_2 (200 mL) under the ice bath. The reaction mixture was stirred for 2 h then poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with a solution of saturated aqueous $NaHCO_3$ and NaCl in sequence and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (petroleum ether: EtOAc, 20:1, V/V) to give **3** (80.0 g, 98.7%) as colourless solid, mp 43-44 °C (lit.[15] 42-43 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 2.9 Hz, 1H), 6.92 (d, J = 8.9 Hz, 1H), 6.78 (dd, J = 8.9, 2.9 Hz, 1H), 4.70 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 146.4, 116.8, 116.3, 115.3, 109.9, 55.9.

2-Bromo-1, 4-dimethoxybenzene (4). To a suspension solution of **3** (13.3 g, 65 mmol) and K_2CO_3 (35.9 g, 260 mmol) in dried acetone (100 mL) under nitrogen atomosphere, MeI (11.1 g, 3.1 mmol) was slowly added under ice bath. After the addition, the mixture was allowed to warm to room temperature and was stirred overnight. After completion of the reaction, the K_2CO_3 was filtered out, then the filtrate evaporated under reduced pressure and the residue was subjected to flash column chromatography (petroleum ether: EtOAc, 30:1, V/V) to give **4** (13.9 g, 97.9%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.73 (m, 2H), 3.76 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 150.1, 118.9, 113.5, 112.7, 111.8, 56.7, 55.8.

5, 8-Dimethoxy-1-naphthol (6). To a suspension of sodium amide (8.5 g, 218 mmol) in anhydrous THF (100 mL) was added furan (59.3 g, 872 mmol) and the mixture warmed to 50 °C under nitrogen. **4** (11 g, 50.7 mmol) dissolved in anhydrous THF (20 mL) was added to the reaction mixture which was then stirred at 50 °C for 24 h. After cooled to room temperature, EtOAc (80 mL) and water (80 mL) were added to the solution. The organic layer was separated and washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil **5** without further purification which was dissolved in MeOH (100 mL) containing conc. hydrochloric acid (5 mL) and the mixture heated at reflux for 3 h. MeOH was removed under reduced pressure and the residue

partitioned between EtOAc and water. The organic layer was washed with a solution of saturated aqueous $NaHCO_3$ and saturated aqueous NaCl in sequence and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (petroleum ether: EtOAc, 10:1, V/V) to give **6** (9.5 g, 91.3%) as white solid, mp 102–103 °C (lit.[16] 103–104 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.69 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.91 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 4.00 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 150.2, 149.9, 128.3, 127.3, 115.5, 113.0, 111.3, 103.2, 102.9, 56.3, 55.7.

1-Hydroxy-5, 8-dimethoxy-2-naphthaldehyde (1). *p*-Toluenesulfonic acid monohydrate (5.59 g, 29.4 mmol), hexamethylenetetramine (4.12 g, 29.4 mmol) and **6** (2 g, 9.8 mmol) were dissolved in acetic acid (30 mL), and the mixture was heated at reflux for 5 h under nitrogen atmosphere. After the completion of the reaction, the solution was cooled to room temperature and poured into ice water, extracted with EtOAc. The organic layer was washed with a solution of saturated aqueous $NaHCO_3$ and saturated aqueous NaCl in sequence and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (petroleum ether: EtOAc, 10:1, V/V) to give **1** (1.9 g, 83.7%) as yellow solid, mp 118-119 °C (lit.[11] 120 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 10.49 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 4.01 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 161.2, 151.4, 149.9, 130.9, 124.2, 115.5, 113.3, 109.0, 107.3, 105.1, 56.5, 55.9.

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 and ^{13}C NMR spectra.

REFERENCES

1. R. C. Montenegro, A. J. Araújo, M. T. Molina, J. D. B. M. Filho, D. D. Rocha, E. Lopéz-Montero, M. O. F. Goulart, E. S. Bento, A. P. N. N. Alves, C. Pessoa, M. O. de Moraes, and L. V. Costa-Lotufo, *Chem. Biol. Interact.*, 2010, **184**, 439.
2. W. Zhou, Y. Peng, and S.-S. Li, *Eur. J. Med. Chem*, 2010, **45**, 6005.
3. R.-B. Wang, W. Zhou, Q.-Q. Meng, X. Zhang, J. Ding, Y. Xu, H.-L. Song, K. Yang, J.-H. Cui, and S.-S. Li, *ChemMedChem*, 2014, **9**, 2798.
4. V. K. Tandon, D. B. Yadav, R. V. Singh, M. Vaish, A. K. Chaturvedi, and P. K. Shukla, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3463.

5. K. Sasaki, H. Abe, and F. Yoshizaki, *Biol. Pharm. Bull.*, 2002, **25**, 669.
6. X. Zhang, R.-B. Wang, W. Zhou, S. Xiao, Q.-Q. Meng, and S.-S. Li, *AAPS PharmSciTech*, 2015, **16**, 259.
7. D. K. Winter, D. L. Sloman, and J. A. Porco Jr., *Nat. Prod. Rep*., 2013, **30**, 382.
8. P.-H. Ducrot, J. Einhorn, L. Kerhoas, J.-Y. Lallemand, M.-L. Milat, J.-P. Blein, A. Neuman, and T. Prangé, *Tetrahedron Lett.*, 1996, **37**, 3121.
9. C. S. Kramer, M. Nieger, and S. Bräse, *Eur. J. Org. Chem.*, 2014, 2150.
10. R. Sharma, D. Panigrahi, and G. P. Mishra, *Med. Chem. Res.*, 2012, **21**, 2006.
11. G. Wurm and B. Goeßler, *Arch. Pharm.*, 1989, **322**, 569.
12. J. Cui, Q. Meng, X. Zhang, Q. Cui, W. Zhou, and S. Li, *J. Med. Chem.*, 2015, **58**, 3534.
13. T. Tanoue, A. Terada, and Y Matsumoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2736.
14. W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann, Amsterdam, 2009.
15. S. Kajigaeshi, T. Kakinami, T. Okamoto, H. Nakamura, and M. Fujikawa, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4187.
16. R. G. F. Giles, A. B. Hughes, and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1581.