ISSN 0974 – 5211

Journal of Natural Products

Volume 3 (2010)

www.JournalofNaturalProducts.com

Research Paper

Facile One-pot Conversion and Characterization of Dihydroartemisinin and Artemether

Guo-Feng Wei*, Xian-Jiu Liao, Guang-Yu Pan, Zu-Liang Huang, Jin-Sheng Cheng, You-Cheng He

School of Basic Medical Science, Youjiang Medical University for Nationalities, Baise 533000, PR China

* Corresponding Author

(Received 20 July 2010; Revised 27 July-10 August 2010; Accepted 15 August 2010)

ABSTRACT

A phase transfer catalyst one-pot reduction preparation of dihydroartemisinin and trifluoroacetic acid induced one-pot synthesis of artemether were developed. The influences of the catalysis, reaction temperature as well as reaction time were discussed. We chose HDTMAB as phase transfer catalyst, conducted the reaction at room temperature for 5 hr, 91.4% yield of dihydroartemisinin was obtained. In the presence of 10 mmol of trifluoroacetic acid, controlled the temperature in the range of 0 ~ 5^{o}C for 6.5 hr and controlled the pH value at 2, 83.6% yield of artemisinin was obtained, The proposed method were convenient and economic,with satisfactory results.

Keywords: One-pot synthesis; Dihydroartemisinin; Artemether.

INTRODUCTION

Artemisinin is extracted from the *artemisia annua* L plant (a Chinese herb, also called qinghaosu) is a sesquiterpene lactones that widely used to treat malaria (Hassan, et al., 1992; Kiaymau, 1985; Hsu, 2006), a disease that annually claims many victims in the developing world. However, its low solubility in both oil and water has limited the utility of artemisinin as an antimalarial medicine. As a semi-synthetic derivatives, dihydroartemisinin and artemether possesses superior lipid solubility and antimalarial activities to artemisinin (Lin, et al., 1989). Currently, dihydroartemisinin was normally produced by reduction of artemisinin with sodium borohydride (Li, et al., 1981; Lin, et al., 1987). And this has suffered from some drawbacks, for example, lower temperature (which was needed for the process), and high expense (the reductant $NaBH_4$ are quite expensive), inflammable and explosive characteristics restricted

heavily the application of this approach. Artemether was normally produced by reduction of artemisinin with sodium borohydride with a successive methylation for the second process. However, long process lead to low yield of artemether. In recently years, we developed an efficient phase transfer catalyst induced one-pot reduction preparation for dihydroartemisinin and facile one-pot preparation process for artemether.

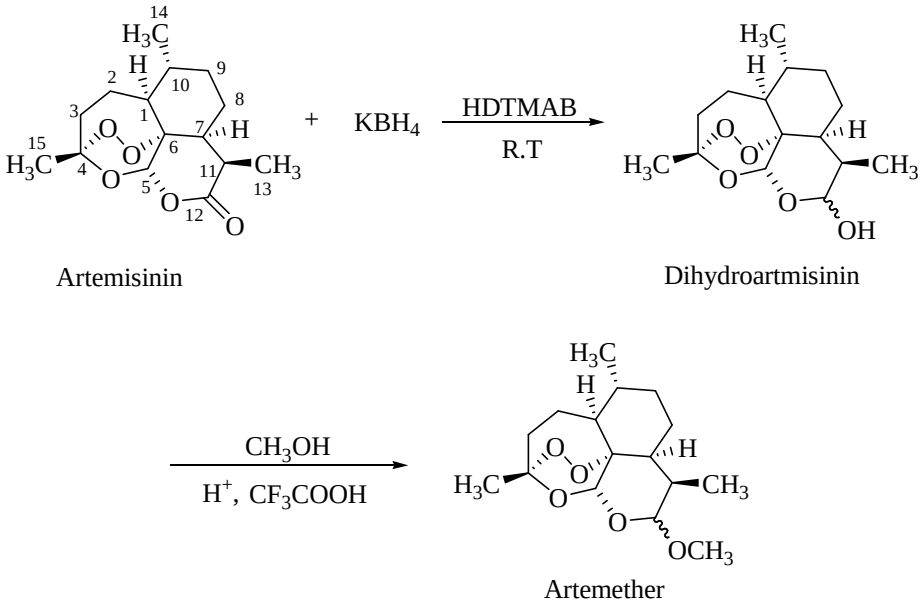
MATERIALS AND METHODS

***Chemicals*:** All the chemicals used were of analytical grade.

General procedure for the preparation of dihydroartemisinin*:** The mixture of *artemisinin* (0.81 mol), KBH_4, PTA (0.05 mol) in ethyl alcohol (200 ml) was stirred at 20^oC for desired reaction time, after complete conversion of acetylene as monitored by GC analyses, the mixture was filtered, and the solvents was removed by rotary evaporation to give crude product. The product was then purified by flash column chromatography to afford the product as a mixture of ***α **–** and ***β*** – isomers isolated in the ratio of 40 : 60 which was calculated on the basis of ^1H NMR.

***General procedure for the preparation of artemether*:** As depicted in Scheme 1, *artemisinin* (22.85 gm, 0.081 mol) was dissolved in methanol (800 ml), with the mixture stirred at 0 ~ 5^oC, KBH_4 (0.018 mol) was added in batches (within 30 min.).

Reactive temperature was steadily controlled in the range of 0 ~ 5^oC. After stirring for 3 hr, trifluoroacetic acid (15 mmol) was added (pH for this mixture was controlled at 2), the mixture was stirred for another 3 hr (reaction temperature was controlled in the range of 0 ~ 5^oC), after washing (with saturated NaCl solution) and filtrating, crude product was given. The product was then purified by flash column chromatography to afford the product as a mixture of ***α*** **–** and ***β*** – isomers isolated in the ratio of 30 : 70 which was calculated on the basis of ^1H NMR.



Scheme 1

RESULTS

Reductant, catalyst, reaction temperature and reaction time could influence the

yields of dihydroartemisinin. The influences of reaction temperature and reaction time and pH value as well as the addition amount of trifluoroacetic acid to the yields of artemether. Spectral data of dihydroartemisinin and artemether were showed below.

Dihydroartemisinin: White cream crystalline powder, m. p. 148 ~ 150^{o}C.

***α*–Dihydroartemisinin** ^{1}HNMR(600MHz, DMSO-d_6): 0.82(3H, d, J = 7.3 Hz, CH_3), 0.87(3H, d, J = 6.0 Hz, CH_3), 1.24(3H, s, CH_3), 1.11 ~ 1.15(1H ,m, H-1), 4.73(1H, d, J = 9.8 Hz, H-12), 6.20(1H ,d ,J = 3.8 Hz, OH), 2.29 ~ 2.32(1H ,m, H-11), 5.60 (1H ,s, H-5), 1.31 ~ 1.34 (1H ,m, H-7), 1.66 ~ 1.80(2H, m, H-8), 2.03 ~ 2.15(2H, m, H-3); ^{13}CNMR(150MHz, DMSO-d_6): 52.0(C-1), 86.5(C-5), 80.6(C-6), 43.9(C-7), 24.3(C-8), 34.5(C-9), 36.6(C-10), 31.0(C-11), 94.6(C-12), 13.7(C-13), 19.8(C-14), 26.3(C-15).

***β*–Dihydroartemisinin** ^{1}HNMR(600MHz, DMSO-d_6): 0.82(3H, d, J = 7.3 Hz, CH_3), 0.87(3H, d, J = 6.0 Hz, CH_3), 1.23(3H, s, CH_3), 1.10 ~ 1.14(1H ,m, H-1), 4.96 (1H, d, J = 3.5 Hz, H-12), 6.21(1H ,d ,J = 3.8 Hz, OH), 2.30 ~ 2.33(1H ,m, H-11), 5.43 (1H ,s, H-5), 1.30 ~ 1.34 (1H ,m, H-7), 1.67 ~ 1.80(2H, m, H-8), 2.01 ~ 2.14(2H, m, H-3); ^{13}CNMR(150MHz, DMSO-d_6): 52.0(C-1), 24.4(C-2), 35.9(C-3), 103.2(C-4), 86.8(C-5), 80.7(C-6), 43.9(C-7), 24.2(C-8), 34.5(C-9), 36.8(C-10), 31.0(C-11), 95.4(C-12), 13.5(C-13), 19.7(C-14), 26.2(C-15); IR (KBr) v (cm^{-1}): 3383, 2990, 1448, 1139, 871, 831; FABMS: m/z 285 $[M+H]^+$, 267$[M-OH]^+$.

Artemether: White cream crystalline powder, m. p. 86 ~ 88^{o}C.

***α*–Artemether** ^{1}HNMR(600MHz, DMSO-d_6): 0.83(3H, d, J = 7.1 Hz, CH_3), 0.89(3H, d, J = 5.8 Hz, CH_3), 1.28(3H, s, CH_3), 1.10 ~ 1.15(1H ,m, H-1), 3.36(s, 3H, OCH_3), 4.15(1H, d, J = 10.0 Hz, H-12), 2.28 ~ 2.32(1H ,m, H-11), 5.10(1H ,s, H-5), 1.30 ~ 1.33 (1H ,m, H-7); ^{13}CNMR(150MHz, DMSO-d_6): 51.7(C-1), 25.2(C-2), 35.5(C-3), 102.0(C-4), 86.9(C-5), 81.6(C-6), 44.3(C-7), 23.6(C-8), 34.8(C-9), 35.6(C-10), 32.0(C-11), 93.8(C-12), 14.5(C-13), 19.6(C-14), 29.1(C-15), 61.8(-O**C**H_3); IR (KBr) v (cm^{-1}): 2972, 1491, 1378, 1143, 1028, 880, 836; FABMS: m/z 299 (M^++H), 267(M^+−OH)].

***β*–Artemether** ^{1}HNMR(600MHz, DMSO-d_6): 0.83(3H, d, J = 7.1 Hz, CH_3), 0.90(3H, d, J = 5.8 Hz, CH_3), 1.27(3H, s, CH_3), 1.10 ~ 1.16(1H ,m, H-1), 3.39(s, 3H, OCH_3), 4.52(1H, d, J = 4.0 Hz, H-12), 2.30 ~ 2.35(1H ,m, H-11), 5.21 (1H ,s, H-5), 1.29 ~ 1.32 (1H ,m, H-7); ^{13}CNMR(150MHz, DMSO-d_6): 51.9(C-1), 25.4(C-2), 35.5(C-3), 103.0(C-4), 87.9(C-5), 81.5(C-6), 44.3(C-7), 23.5(C-8), 35.0(C-9), 35.7(C-10), 32.2(C-11), 93.7(C-12), 14.7(C-13), 19.5(C-14), 29.0(C-15), 61.9(-O**C**H_3); IR (KBr) v (cm^{-1}): 2977, 1485, 1382, 1141, 1028, 883, 838; FABMS: m/z 299 $[M + H]^+$, 267$[M - OCH_3]^+$.

DISCUSSION

The previous prepared of dihydroartemisinin is by reduction of artemisinin with $NaBH_4$ in MeOH (Brossi, et al, 1988), this would suffers from two major drawbacks: (1) highly basic and low temperature (0 ~ 5^{o}C) reaction conditions. If low temperature condition are not maintained, it will lead to rapid degradation of artemisinin and dihydroartemisinin. (2) During the addition of $NaBH_4$, great care has to be excised because $NaBH_4$ reacts exothermically with MeOH, and this has potentially flammable and explosive. Our facile One-pot conversion of dihydroartemisinin does not suffer from the above drawbacks. Dihydroartemisinin was given readily by reduction of artemisinin with KBH_4 in the presence of phase transfer catalyst HDTMAB (Hexa-Dexyl-Tri-Methyl-Ammonium Bromide). Our experiment results show that artemisinin underwent the reduction reaction smoothly, conducted the reaction at room

temperature for 5 h, 91.4% yield of dihydroartemisinin was obtained. Meanwhile, in the conversion of dihydroartemisinin to atemether, optimum yield was obtained by the addition of trifluoroacetic acid in the presence of MeOH. Our Experiment results show that, the optimum reaction condition might be: in the presence of 10 mmol of trifluoroacetic acid, controlled the temperature in the range of 0 ~ 5^{o}C for 6.5 h and controlled the pH value at 2, 83.6% yield of atemether was obtained. Compared to the previous prepared of atemether in two steps which reqires two independent aqueous work-up steps (Lin, et al., 1987; El-Feraly, et al., 1992; Bhakuni, et al., 1995), our facile One-pot conversion of artemisinin to atemether does not require any aqueous work-up. The special features of the process are simple operations and absence aqueous work-up. As the process is conducted in a single pot, it is well suited for industrial synthesis of atemether.

CONCLUSION

To prepare dihydroartemisinin, the optimum reaction condition might be: artemisinin (0.81 mol), KBH_4 (0.18 mol) and PTC (0.05 mol) was stirred in ethyl alcohol (200 ml) at 20^{o}C for 5 h. Meanwhile, to prepare artemether, the optimum reaction condition might be: In the presence of 10 mmol of trifluoroacetic acid, controlled the temperature in the range of 0 ~ 5^{o}C for 6.5 hr and controlled the pH value at 2. The proposed method were convenient and economic,with satisfactory results.

Acknowledgements: We are grateful to Guangxi Zhuang Autonomous Region Department of Science (NO. 200610), Youjiang Medical Univ. for Nationalities (Grant 2005) for financial support.

REFERENCES

Bhakuni, R.S., Jain, D.C., Sharma, R.P., (1995): An improved procedure for the synthesis of ethers of dihydroartemisinin. *Ind. J. Chem.,* 34B(6): 529-530.

Brossi, A., Venugopalan, B., Gerpe, L.G.,Yeh, H.J.C., Flippen-Anderson, J.L., Buchs, P., Luo, X.D., Milhous, W., (1988): a new antimalarial drug: Synthesis and antimalarial properties. *J. Med. Chem.*, 31(3): 645- 650.

El-Feraly, F.S., Al-Yahya, M.A., Orabi, K.Y., McPhail, D.R., McPhail, A.T., (1992): A new method for the preparation of arteether and its C-9 epimer. *J. Nat. Prod.*, 55(7):878-883.

Hassan, A.M., Bjorkman, A., Landberg, L.A., Ashton, M., (1992): The effect of arteisinin, its derivatives and mefloquine against chloroquine-resistant strains of Plasmodium falciparum in vitro.*Trans R Soc Trop Med Hyg.*, 86(4): 365-367.

Hsu, E., (2006): The history of qing hao in the Chinese materia medica. *Trans R Soc Trop Med Hyg.*, 100(6): 505-508.

Kiaymau, D.L., (1985): Qinghaosu (artemisinin): an antimalarial drug from China. *Science*, 228: 1049-1055.

Li, Y., Yu, P.L., Chen, Y.X., Li, L.Q., Gai, Y.Z., Wang, D.S., Zheng, Y.P., (1981): Studies on analogs of artemisinin I. the synthesis of ethers, carboxylic esters and carbonates of dihydroartemisinin. *Yaoxue Xuebao.*, 6: 429-439.

Lin, A.J., Klayman D.L., Milhous W.K., (1987): Antimalarial activity of new water-soluble dihydroartemisinin derivatives. *J. Med. Chem.,* 30: 2147-2150.

Lin, A.J., Lee, M. Klayman, D.L., (1989): Antimalarial activity of new water-soluble dihydroartemisinin derivatives. 2. Stereospecificity of the ether side chain *J. Med .Chem.,* 32: 1249-1252.