A one-pot conversion of artemisinin to arteether

Guo-Feng Wei¹*, Zu-Liang Huang¹, Guang-Yu Pan², Xian-Jiu Liao², Li Qian²
¹School of Basic Medical Science, Youjiang Medical University for Nationalities, Baise 533000, (PR CHINA)
²Department of Chemistry, Youjiang Medical University for Nationalities, Baise 533000, (PR CHINA)

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INTRODUCTION

Morbidity and mortality due to malaria are increasing in the developing world[1]. An estimated 300 to 500 million clinical cases and 1.5 to 2.7 million deaths occur each year due to malaria[2]. Artemisinin, an unusual sesquiterpene lactone bearing endoperoxide linkage, is isolated from the Chinese medicinal herb artemisia annua[3-5], is widely used to treat malaria in various countries. However, for its high recent recrudescence rate and its low solubility in both oil and water, the utility of artemisinin as an antimalarial medicine are limited to great extent[6-8]. As a semi-synthetic derivative of artemisinin, arteether possess more lipid soluble and effective antimalarial than artemisinin[7,9], is consider as one of the most rapidly act-

ABSTRACT

A one-pot preparation of anti-malaria arteether was developed. The influences of the trifluoroactic acid amount, reaction temperature, pH value as well as reaction time were studied in this paper.

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KEYWORDS

One-pot synthesis; Artemisinin; Arteether.

Scheme 1

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RESULTS AND DISCUSSION

Arteether could be given readily by a trifluoroactic acid induced one-pot synthesis process. Experiment results show that the trifluoroactic acid amount, reaction temperature, pH value as well as reaction time could influence the reaction (TABLE 1).

TABLE 1 showed that addition of trifluoroactic acid was favorable to the yield increase obviously. In the absence of trifluoroactic acid, 52.0% yield of arteether was obtained (entry 2, TABLE 1), while the yield increased rapidly to 84.9% in the presence of 10 mmol of trifluoroactic acid (entry 1, TABLE 1). The amount of trifluoroactic acid could influence the yield, experiments shows that 10 mmol of trifluoroactic acid was the optimum amount (entries 1-5, TABLE 1).

Reaction temperature plays a important role in this reaction, controlled the temperature in a range of 0 ~5°C, the optimum yield was obtained (84.9%, entry 1, TABLE 1), higher temperature lead to yield decrease sharply (entries 6-7, TABLE 1), this might be explained by high temperature lead to further dehydration of intermediate dihydroartemisinin in the process.

The pH value was also observed influencing the reaction to some extent. When pH value was controlled at 2, the reaction proceeded readily with optimum yield (84.9%, entry 1, TABLE 1), higher or lower pH value lead to yield decrease directly: e. g. when the pH value was controlled at 1, a lower yield was obtained (72.7%, TABLE 1), meanwhile, higher pH value also lead to yield decrease obviously (entries 8-11, TABLE 1).

In summary, we have developed a convenient trifluoroactic acid induced one-pot synthesis of arteether.

EXPERIMENTAL

Analysis and instruments

$^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ on a Bruker Avance 600 DRX spectrometer using TMS as an internal standard. IR spectra were obtained in KBr disks flake on RFX-65 FTIR spectrometer. GC-MS were recorded on a HP 6890-5937 mass spectrometer. Elemental Analyses were performed on a Heraeus CHN-O Rapid elemental analyzer instrument. HF$_{254}$ plates were used for analytical TLC chromatography.

General procedure for the preparation of arteether

A ethanol solution (800 ml) of artemisinin (22.85 g, 0.081 mol) was stirred at 0 ~5°C, KBH$_4$ (0.018 mol) was added in batches (within 30 minutes). After stirring for 3 hrs, trifluoroactic acid was added (pH was controlled for 2), the mixture was stirred for subsequent 3 h. Yields determined by GC analysis. In the absence of trifluoroactic acid

Heraeus CHN-O Rapid elemental analyzer instrument.

Arteether

White cream crystalline powder, m. p. 79 ~ 81°C.

$^1$HNMR(600MHz, DMSO-d$_6$): 0.84(3H, d, J = 7.2 Hz, CH$_3$), 0.89(3H, d, J = 5.9 Hz, CH$_3$), 1.26(3H, s,
CH₃), 0.96(3H, t, J = 6.5 Hz, CH₃), 1.10 ~ 1.15(1H, m, H-1), 3.17 ~ 4.02(m, 2H, OCH₂CH₃), 4.26 (1H, d, J = 10.0 Hz, H-12), 2.29 ~ 2.34(1H, m, H-11), 5.09 (1H, s, H-5), 1.30 ~ 1.34 (1H, m, H-7); ¹³CNMR (150MHz, DMSO-d₆): 51.8(C-1), 25.1(C-2), 35.4(C-3), 102.1(C-4), 86.7(C-5), 81.8(C-6), 44.3(C-7), 23.4(C-8), 34.6(C-9), 35.7(C-10), 32.0(C-11), 93.6(C-12), 14.7(C-13), 19.4(C-14), 29.1(C-15), 62.8 (-OCH₂-), 15.6(CH₂CH₃); IR (KBr) ν (cm⁻¹): 2980, 1491, 1385, 1143, 1026, 885, 841; FABMS: m/z 313 (M⁺+H), 267[M-OCH₂CH₃]⁺.

β-Arteether
¹H NMR(600MHz, DMSO-d₆): 0.84(3H, d, J = 7.1 Hz, CH₃), 0.90(3H, d, J = 5.9 Hz, CH₃), 1.27(3H, s, CH₃), 0.96(3H, t, J = 6.5 Hz, CH₃), 1.10 ~ 1.15(1H, m, H-1), 3.23 ~ 4.02(m, 2H, OCH₂CH₃), 4.67(1H, d, J = 4.0 Hz, H-12), 2.29 ~ 2.34(1H, m, H-11), 5.20 (1H, s, H-5), 1.28 ~ 1.33(1H, m, H-7); ¹³CNMR (150MHz, DMSO-d₆): 51.8(C-1), 25.5(C-2), 35.5(C-3), 103.1(C-4), 88.0(C-5), 81.4(C-6), 44.3(C-7), 23.7(C-8), 35.1(C-9), 35.6(C-10), 32.0(C-11), 93.8(C-12), 14.7(C-13), 19.6(C-14), 29.0(C-15), 62.9 (-OCH₂-), 15.6(CH₂CH₃); IR (KBr) ν (cm⁻¹): 2980, 1491, 1385, 1143, 1026, 885, 841; FABMS: m/z 313 [M + H]⁺, 267[M-OCH₂CH₃]⁺.

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