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A one-pot conversion of artemisinin to arteether

Guo-Feng Wei[1]*, Zu-Liang Huang[1], Guang-Yu Pan[2], Xian-Jiu Liao[2], Li Qian[2]

[1]School of Basic Medical Science, Youjiang Medical University for Nationalities, Baise 533000, (PR CHINA)

[2]Department of Chemistry, Youjiang Medical University for Nationalities, Baise 533000, (PR CHINA)

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ABSTRACT

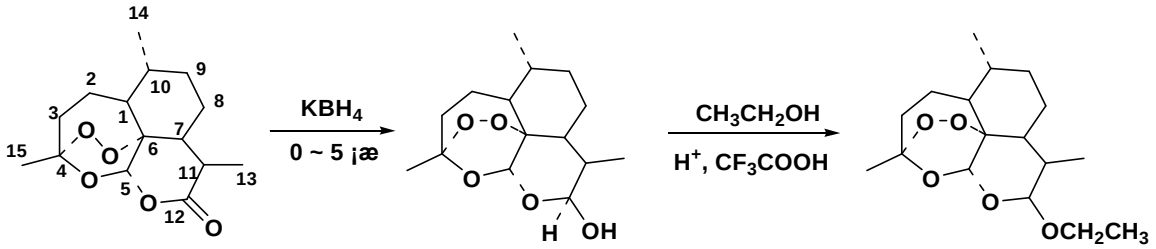
A one-pot preparation of anti-malaria arteether was developed. The influences of the trifluoroactic acid amount, reaction temperature, pH value as well as reaction time were studied in this paper.

KEYWORDS

One-pot synthesis;
Artemisinin;
Arteether.

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 medicines 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 acting antimalarial today and has been used as a very effective medicine to treat malaria, especially for the high-risk malaria patients and for the multi-drug resistant malaria parasite in the world with high cure rate ranged from 93 to 100% and low recrudescence rate[1,10-13]. Currently, arteether was normally prepared in two steps. In the first step, artemisinin is reduced with $NaBH_4$ in CH_3CH_2OH to prepared dihydroartemisinin, in the second step, dihydroarte- misinin was conversion to arteether by ethylation. And this would suffered from some drawbacks, for example, high expense, inflammable and explosive, and long process lead to low yield of arteether. In recently years, we developed an efficient and facile one-pot preparation process for arteether. Herein, we are glad to report our results.



Artemisinin Dihydroartemisinin 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 dihydroartemisin 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.

TABLE 1 : Trifluoroactic acid induced one-pot synthesis of arteether[a]

Entry	T/°C	t/h	pH	trifluoroactic acid amount/mmol	Yield [b] /%
1	<5	6.5	2	10.0	84.9
2	<5	6.5	2	_c	52.0
3	<5	6.5	2	5.0	68.2
4	<5	6.5	2	15.0	83.5
5	<5	6.5	2	20.0	82.9
6	10	6.5	2	10.0	41.2
7	25	6.5	2	10.0	23.4
8	<5	6.5	3	10.0	76.3
9	<5	6.5	4	10.0	55.4
10	<5	6.5	6	10.0	38.5
11	<5	6.5	1	10.0	72.7

[a]Reaction conditions: *artemisinin* (20 g, 0.081 mol) was dissolved in ethanol (800 ml), with the mixture 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. [b]Yields determined by GC analysis. [c] In the absence of trifluoroactic acid

EXPERIMENTAL

Analysis and instruments

^1H 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 the mixture within 30 minutes.

The homogeneous solution was stirred at 0~5°C for 3 h before trifluoroactic acid (15 mmol) was added, the pH value of this mixture was steadily controlled at 2. The mixture was allowed to stir at 0~5°C for another 3 h (Scheme 1). Filtration, and washed the residue with saturated NaCl solution, crude product was given. The product was purified via flash column chromatography using hexane as eluent and the product was a mixture of α- and β-isomers, which was isolated in the ratio of 30 : 70 and calculated on the basis of ^1H NMR.

Arteether

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

α-Arteether

^{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,

CH_3), 0.96(3H, t, J = 6.5 Hz, CH_3), 1.10 ~ 1.15(1H, m, H-1), 3.17 ~ 4.02(m, 2H, OCH_2CH_3), 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); ^{13}CNMR (150MHz, DMSO-d_6): 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 (-OCH_2-), 15.6(CH_2CH_3); IR (KBr) ν (cm^{-1}): 2980, 1491, 1385, 1143, 1026, 885, 841; FABMS: m/z 313 (M^++H), 267[M- OCH_2CH_3]$^+$.

β-Arteether

^{1}HNMR(600MHz, DMSO-d_6): 0.84(3H, d, J = 7.1 Hz, CH_3), 0.90(3H, d, J = 5.9 Hz, CH_3), 1.27(3H, s, CH_3), 0.96(3H, t, J = 6.5 Hz, CH_3), 1.10 ~ 1.15(1H, m, H-1), 3.23 ~ 4.02(m, 2H, OCH_2CH_3), 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); ^{13}CNMR (150MHz, DMSO-d_6): 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 (-OCH_2-), 15.6 (CH_2CH_3); IR (KBr) ν (cm^{-1}): 2980, 1491, 1385, 1143, 1026, 885, 841; FABMS: m/z 313 [M + H]$^+$, 267[M-OCH_2CH_3]$^+$.

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