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An Efficient Approach For Dihydroartemisinine In The Presence Of Phase Transfer Catalyst

Guo-Feng Wei, Jin-Sheng Cheng*, Zu-Liang Huang, You-Cheng He

School of Basic Medical Science, Youjiang Medical College for Nationalities, Baise 533000, (P.R.CHINA)

E-mail: chengjins@hotmail.com

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ABSTRACT

An efficient reductive preparation of dihydroartemisinine from artemisinine with KBH_4 in the presence of phase transfer catalyst was reported in this paper. The influences of the amount of reductant, catalysts, reaction temperature as well as reaction time were investigated in this paper.

KEYWORDS

Artemisinine;
Dihydroartemisinine;
HDTMAB;
Phase transfer catalyst.

INTRODUCTION

Malaria still claims many victims in the developing world. An additional problem is that the parasite that causes the disease has become resistant to many of the commonly used anti-malarial medicines[1]. Artemisinine is a natural substance and an excellent alternative to existing malaria medicines. It is extracted from the artemisia annua L plant (Chinese herb, also called qinghaosu, (Klayman,1985),) and works fast with few side-effects[2]. As a response to increasing levels of resistance to antimalarial medicines, WHO recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or Nivaquine etc., should use combination therapies, preferably those containing artemisinine derivatives for falciparum malaria[3], this so-called ACT-therapy (artemisinine-based combination therapy) is currently the best treatment against malaria.

We now know that the unusual structural feature of artemisinine, the 1,2,4-trioxane ring, is the basis for the unique antimalarial action of the drug. It is the endoperoxide linkage in the ring which 'triggers' artemisinine to 'explode' - but only in the vicinity of the Plasmodium parasite. The endoperoxide bond is cleaved when it comes into contact with iron (II), releasing reactive radicals which ultimately destroy the parasite[4]. On the other hand, there are other authors, Eckstein-Ludwig etal[4], proposed PfATP6, a sarco/endoplasmic reticulum Ca^{2+}-ATPase, as artemisinine's target and inferred that artemisinine might act by mobilizing intracellular Ca^{2+} stores[5].

The most accessible functionality in artemisinine is the lactone group, so it was here that chemists made the first chemical modifications to the natural product. Reduction of artemisinine produced dihydroartemisinine ((3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12aR) -decahydro-3, 6, 9-trimethyl-3, 12-epoxy-12H pyrano [4, 3-j]-1, 2-benzodioxepin-10-ol, DHA), in which the lactone group had been converted to a lactol (hemiacetal) group. The intact 1, 2, 4-trioxane

ring in dihydroartemisinine retained a potency greater than that of artemisinine itself, though dihydroartemisinine lacked stability *in vivo*. However, this problem could be solved by attaching a substituent to the free hydroxyl group. In addition, by making a careful selection of this substituent, it was also possible to control the solubility of the resultant drug. Dihydroartemisinine represent the more successful semi-synthetic first generation drugs for the treatment of malaria[6].

In general, dihydroartemisinine is a potent antimalarial drug that reduces parasitaemia by 90% within 24 hours after starting treatment. Dihydroartemisinine has been used in the treatment of multi-drug resistant falciparum malaria in China, it was also shown to act against Schistosoma Japonicum, Leishmania major etc[6c].

Dihydroartemisinine was normally produced by reduction of artemisinine with sodium borohydride[7]. However, 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 for the process. Recently years, we developed an efficient phase transfer catalyst induced reduction preparation process for dihydroartemisinine. In this process, KBH_4 was used for the reductant instead of $NaBH_4$, the reaction runs smoothly at room temperature. Herein, we are glad to report some of our results, further work on artemether, artether, artesunate etc. are under progress in our laboratory.

RESULTS AND DISCUSSION

Dihydroartemisinine was given readily by reduction of artemisinine with KBH_4 in the presence of phase transfer catalyst(e.g. HDTMAB). Experiment results show that reductant, catalyst, reaction temperature as well as reaction time could influence the reaction(TABLE 1).

TABLE 1 showed that PTA catalyst plays an important role in this reduction process. In the presence of phase transfer catalyst HDTMAB (Hexa-Dexyl-Tri-Methyl-Ammonium Bromide), artemisinine underwent the reduction reaction smoothly, conducted the reaction at room temperature for 5 h, 91.4% yield of dihydroartemisinine was obtained(Entry 3, TABLE 1). While in the presence of other phase transfer catalyst, the yields for the reactions decreased obviously, e. g. in the presence of TEBAB (benzyl-triethylammonium bromide), 83.6% yield of dihydroartemisine was obtained (Entry 9, TABLE 1), similarly, the yield for tetrabutylammonium bromide (TBAB) or PEG-400 induced reaction decreased to some extent (Entries 6-7, TABLE 1). Noteworthy was that in the absence of phase transfer catalyst, the yield for the reaction declined sharply (49.3%, Entry 8, TABLE 1).

The amount for the reductant KBH_4 could also influence the reaction, experiments showed that 0.18 mol KBH_4 for 0.81 mol artemisinine starting material would be the optimum ratio (Entries 1-5, TABLE 1).

The reaction time (Entries 15-17, TABLE 1) together with reaction temperature(Entries 10-14, TABLE 1) were also found influence the reaction to a certain extent. Conducted the reaction at lower or higher temperature did not lead to optimum results.

In Summary, we have developed a phase transfer catalyst HDTMAB induced reduction reaction (by the reductant KBH_4) of artemisinine to prepare dihydroartemisinine conveniently, the optimum re-

TABLE 1: Reduction preparation of dihydroartemisinine[a]

Entry	KBH_4[b]	PTA catalyst	Time/h	T/°C	Yield/ % [b]
1	0.32	HDTMAB	5	20	86.8
2	0.25	HDTMAB	5	20	88.6
3	0.18	HDTMAB	5	20	91.4
4	0.11	HDTMAB	5	20	80.1
5	0.8	HDTMAB	5	20	52.5
6	0.18	TBAB	5	20	79.3
7	0.18	PEG-400	5	20	82.3
8	0.18	-[c]	5	20	49.3
9	0.18	TEBAB	5	20	83.6
10	0.18	HDTMAB	5	5	78.5
11	0.18	HDTMAB	5	10	86.2
12	0.18	HDTMAB	5	15	87.2
13	0.18	HDTMAB	5	30	81.1
14	0.18	HDTMAB	5	40	79.6
15	0.18	HDTMAB	1	20	40.2
16	0.18	HDTMAB	3	20	72.5
17	0.18	HDTMAB	6	20	90.1

[a]**Reaction conditions: The mixture of artemisinine (0.81 mol), KBH_4 and PTA (0.05 mol) was stirred in ethyl alcohol (200ml) at 20°C for desired time; [b]Yields determined by GC analysis; [c] In the absence of PTA catalyst.**

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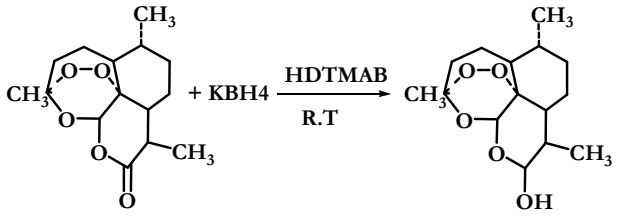

Artemisinine Dihydroartemisinine

SCHEME 1

action might be: the mixture of artemisinine (0.81 mol), KBH_4 (0.18 mol) and PTA (0.05 mol) were stirred in ethyl alcohol (200ml) at 20°C for 5 h. Further investigation on application for this reaction are underway in our laboratory.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Brucker AC 400 spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were obtained with WQF-410 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 dihydroartemisinine

The mixture of artemisinine (0.81 mol), KBH_4, PTA (0.05 mol) in ethyl alcohol (200ml) was stirred at 20°C 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 products. The products were then purified by flash column chromatography to afford the product (hexane).

Dihydroartemisinine

Hexane:EtOAc (9:1) was used as the eluent: solid, White cream crystalline powder, mp 145.0~150.0°C; ^1H NMR d 0.96919 (d, 9H), 1.44109(m, 6H), 1.74196 (m, 4H), 2.06826(s, 1H), 2.39765(t, 1H), 3.03861(s, 1H), 5.31372 (s, 1H), 5.62907(s, 1H); ^{13}C NMR d 13.1, 20.2, 22.1, 24.6, 24.7, 25.9, 26.0, 34.2, 34.8, 34.9, 44.4, 45.5, 51.6, 52.6, 76.7, 77.3, 80.4, 81.1, 87.6, 91.3, 94.7, 96.4, 104.1, 104.4; IR (KBr): 3379.3, 2986.7, 2946.2, 2853.4, 1445.5, 1378.0, 1227.05, 1201.4, 1188.9, 1134.7, 1093.0, 1027.7, 1013.7, 986.2, 969.2, 957.9, 876.0, 847.0, 731.6, 699.0, 488.3 cm^{-1}; MS m/z 284.35 (M^+), 283.35, 265.98, 238.97, 221.08, 203.13, 191.20, 189.10, 163.11,149.10, 124.22,107.02, 74.05.

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