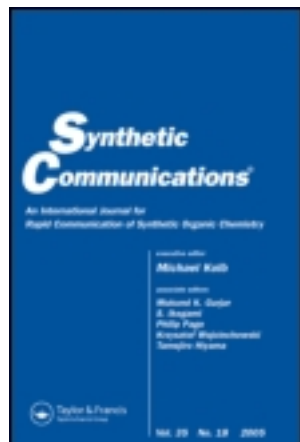


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Pranjal P. Bora ^a, Nabajyoti Baruah ^a, Ghanashyam Bez ^a & Nabin C. Barua ^b

^a Department of Chemistry, North Eastern Hill University, Shillong, India

^b Natural Product Chemistry Division, North Eastern Institute of Science and Technology, Jorhat, India

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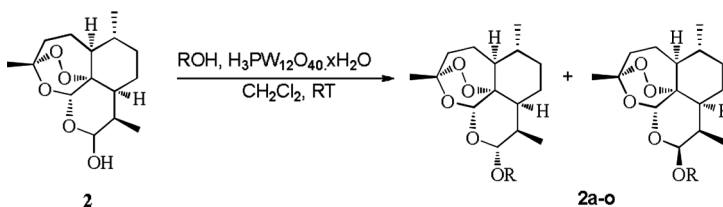
NEW METHOD FOR THE SYNTHESIS OF ETHER DERIVATIVES OF ARTEMISININ

Pranjal P. Bora,¹ Nabajyoti Baruah,¹ Ghanashyam Bez,¹ and Nabin C. Barua²

¹Department of Chemistry, North Eastern Hill University, Shillong, India

²Natural Product Chemistry Division, North Eastern Institute of Science and Technology, Jorhat, India

GRAPHICAL ABSTRACT



Abstract Dihydroartemisinin can be converted to its ether derivatives in good yields by reaction with different alcohols in the presence of a catalytic amount of dodecatungstophosphoric acid hydrate. Easy handling, trouble-free workup by filtration, excellent yields, and very short reaction times are some of the highlights of this protocol.

Keywords Antimalarial; dihydroartemisinin; dodecatungstophosphoric acid; ether

INTRODUCTION

In the world of drug development, derivatization of medicinally important natural products remains a challenging but rewarding endeavor for the synthetic chemist.^[1] Derivatization of any drug molecule requires mild yet efficient protocols, such that an attempt to introduce new functionality does not affect the pharmacophore. Artemisinin **1**, a clinically useful antimalarial agent isolated from the Chinese traditional medicinal plant *Artemisia annua*, has drawn tremendous attention from both chemists and pharmacologists because of its low toxicity and proven antimalarial activity.^[2] However, its practical utility is impaired by (i) low solubility in both oil and water,^[3] (ii) short plasma half-life,^[4] and (iii) the high rate of recrudescence in treated patients.^[5] Chemical modification has resulted in improved analogs artemether **2a** and arteether **2b**,^[6] which are active against both chloroquine-sensitive

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Address correspondence to Ghanashyam Bez, Department of Chemistry, North Eastern Hill University, Shillong 793022, India. E-mail: bez@nehu.ac.in

and chloroquine-resistant *P. falciparum* and are used clinically for the treatment of cerebral malaria (Figure 1).

The ether derivatives of artemisinin are usually synthesized from dihydroartemisinin **2** by reaction with the desired alcohol in the presence of acid catalysts such as HCl,^[7] *para*-toluenesulfonic acid (PTSA),^[8] $\text{BF}_3 \cdot \text{Et}_2\text{O}$,^[9] or Me_3SiCl ,^[10] but all these catalysts have very long reaction times and require aqueous workup. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ^[9] or Me_3SiCl ^[10] has the additional drawback of moisture sensitivity. In a bid to synthesize ether derivatives directly from artemisinin, Singh et al.^[11] carried out the reduction of artemisinin and subsequent etherification in one pot in the presence of a catalytic amount of Amberlyst-15 to achieve good yields, but results of this method in large-scale synthesis remain to be seen.

In recent years, organic reactions catalyzed by cheap, operationally simple, and environmentally friendly catalyst have become desirable to meet environmentally friendly challenges. Industries prefer reaction protocols that give the product just by filtration with no aqueous workup using hazardous organic solvents. Heteropoly acids^[12] are such catalysts and are finding enormous applications for acid-catalyzed reactions. Their noncorrosive and environmentally compatible properties (as compared to the mineral acids), high structural and thermal stability, and well-defined redox and acidic properties make them unique among the acid catalysts. Nevertheless, they give fewer side reactions as compared to mineral acids, are recyclable, and can be equally effective both in homogeneous as well as in heterogeneous systems. Here, we are reporting an efficient method for conversion of dihydroartemisinin **2** to its ether derivatives by reaction with corresponding alcohols in the presence of a catalytic amount of dodecatungstophosphoric acid hydrate, a heteropoly acid (Scheme 1).

Initially, we added 1.25 equiv. of methanol to a solution of dihydroartemisinin^[9b] in dichloromethane and stirred it at rt in the presence of 0.10 equiv. of dodecatungstophosphoric acid hydrate. Upon monitoring with thin-layer chromatography (TLC), it was observed that no starting material was left after 3 h and two less-polar products were formed. The reaction mixture was filtered through ordinary filter paper, and the filtrate was concentrated under reduced pressure to get the crude. Chromatographic separation gave the products in a 1:3 ratio of α - and β -isomers of artemether^[11] with quantitative overall yields. Having obtained this highly anticipated and encouraging result, we wanted to try out the same reaction in non-halogenated solvents. As evident from the results shown in Table 1, to our dismay, it is clear that the reaction works best when CH_2Cl_2 is used as the reaction

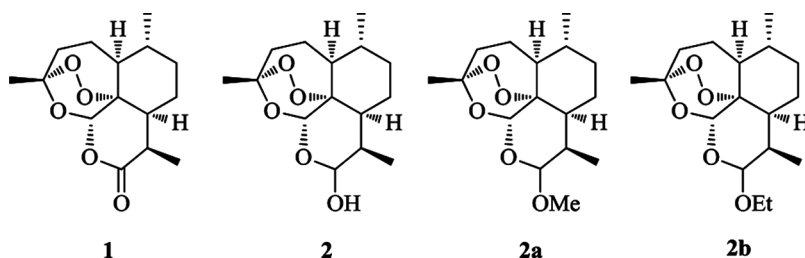
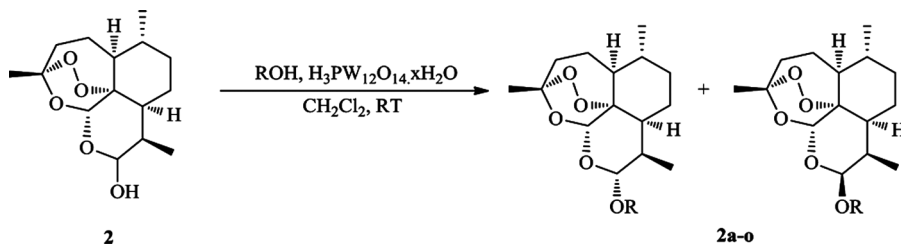


Figure 1. Artemisinin derivatives.



Scheme 1. Synthesis of ether derivatives.

medium. In almost all the other nonhalogenated solvents, the reaction did not go to completion and unreacted starting material was recovered even after running the reactions up to 72 h.

Then we wanted to optimize the amount of catalyst required for the reaction. The reaction took almost the same time when 0.05 equiv. of the catalyst was used, but lowering the amount of catalyst to 0.03 equiv. resulted in complete conversion after 5 h. The same catalyst can be used twice without losing any catalytic activity, but use of the recovered catalyst for a third time resulted in longer reaction time and poor reactivity. We could achieve only 72% yield of the product by using the catalyst after the second recovery and unreacted starting material was observed even after 10 h.

Having optimized different parameters such as the substrate catalyst ratio, solvent, and reaction time, we wanted to explore the efficacy of our catalyst for synthesis of other ether derivatives of artemisinin (Table 2). Because artemisinin is known for its poor solubility in lipid, we wanted to see the efficiency of our protocol for the formation of ethers having long hydrocarbon chains, which may impart better lipophilicity and hence improve the antimalarial activity. It was heartening to observe that the reactions (entries 3–6) went to completion in shorter times for long-chain alcohols. As the ether derivatives of dihydroartemisinin are believed to generate neurotoxin dihydroartemisinin under physiological conditions, we planned to synthesize benzyl ethers of dihydroartemisinin (DHA) that may offer stability against the cleavage of ether bond and reduce the formation of DHA.^[13] They are more selective toward the formation of the β -isomer and take almost the same time to generate their ether derivatives with DHA (entries 12–16) in excellent yields. It has

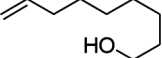
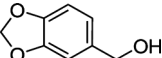
Table 1. Optimization of solvent for synthesis of artemether from dihydroartemisinin^a

Solvent	Temp. (°C)	Time (h)	Yield (%) ^b
Diethyl ether	25	72	58
Tetrahydrofuran	25	48	77
Acetonitrile	25	72	53
1,2-Dimethoxyethane	25	48	71
Dioxane	25	72	48

^a10 mol% of the catalyst was used.

^bUnreacted starting materials were recovered.

Table 2. Etherification of DHA via Scheme 1^a

Entry	Substrate	Product	Time (h)	Yield ^b (%) (α/β)
1	MeOH	2a	3	99 (1/3)
2	EtOH	2b	6	98 (1/3)
3	CH ₃ (CH ₂) ₆ CH ₂ OH	2c	1	97 (1/2)
4	CH ₃ (CH ₂) ₁₀ CH ₂ OH	2d	1.2	91 (1/2.5)
5	CH ₃ (CH ₂) ₁₄ CH ₂ OH	2e	1.5	89 (1/2)
6		2f	2	90 (1/3)
7	PhCH ₂ CH ₂ OH	2g	3	98 (1/3)
8	Cholesterol	2h	5	88 (0/1)
9	Propargyl alcohol	2i	1.5	95 (1/3)
10	CH ₂ =CHCH ₂ OH	2j	1.5	92 (1/2)
11	Cinnamyl alcohol	2k	2.5	92 (1/2)
12	PhCH ₂ OH	2l	3	98 (1/2.5)
13	<i>p</i> -MeOC ₆ H ₄ CH ₂ OH	2m	3	92 (0/1)
14		2n	3	93 (0/1)
15	<i>p</i> -ClC ₆ H ₄ CH ₂ OH	2o	3	88 (1/3)
16	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂ OH	2p	3	86 (1/3)

^aConditions: dihydroartemisinin/ alcohol/H₃PW₁₂O₄₀·xH₂O = 1:1.25:0.05 CH₂Cl₂, rt.

^bIsolated yield.

been observed that methoxy (entry 13) and methylenedioxy (entry 14) groups are unaffected under this reaction condition. The presence of the methoxy group in the ether derivative could be confirmed from the singlet integrating to three protons at δ 3.78 ppm in its ¹H NMR spectra, while the existence of the methylenedioxy group was evident from the singlet integrating to two protons at δ 5.95 ppm. Interestingly, the benzyl groups having methoxy and methylenedioxy groups showed selective formation of only the β -isomers, as evident from their *J* values of the protons on C-10 in the ¹H NMR spectra. The presence of a doublet at δ 4.88 ppm in 10 β -[(4/-methoxyphenyl)methoxy]dihydroartemisinin (entry 14) with *J* = 3.2 Hz integrating one proton suggests the formation of a β -derivative, while a doublet integrating to one proton at δ 5.39 ppm with *J* = 3.5 Hz showed the formation of a β -derivative of anisyl ether of DHA (entry 13). We could not find any explanation to justify the experimental findings that favor β -selectivity of the aforementioned compounds. *p*-Chloro- and *p*-nitro substituted benzyl ethers (entries 15 and 16) showed the only preferential formation of the β -isomers to the α -isomers.

CONCLUSION

To sum up, we have demonstrated a simple and efficient method for the synthesis of ether derivative of artemisinin catalyzed by dodecatungstophosphoric acid, a heteropoly acid. As simple filtration is enough to remove the catalyst and hence quench the reaction rather than the generally used aqueous workup, the protocol may find application in large-scale synthesis of ether derivatives of artemisinin.

EXPERIMENTAL

The dihydroartemisinin and the substituted benzyl alcohols were synthesized by reduction of artemisinin and the substituted benzaldehydes with sodium borohydride in methanol. Dodecaphosphotungstic acid was purchased from Sigma-Aldrichs Chemicals Pvt. Ltd. and were used without any processing. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 on Bruker DRX 400 NMR machines with tetramethylsilane (TMS) as internal standard while infrared (IR) spectra (Perkin-Elmer) were recorded as thin films unless otherwise stated.

Phosphotungstic acid hydrate (0.253 g, 0.05 equiv) was added to a solution of dihydroartemisinin (0.5 g, 1.76 mmol) in dry DCM (20 ml), and the reaction mixture was stirred at room temperature for 5 min. To the mixture, MeOH (70 mg, 2.18 mmol, 1.25 equiv.) was added, and the reaction mixture was further stirred for 3 h. The catalyst was removed by filtration, the filtrate was concentrated, and the crude product was chromatographed by TLC to obtain 0.52 g of artemether (1.74 mmol, 99% yield) with α - and β -isomers isolated in a 1:3 ratio (26% α -isomer and 73% β -isomer).

^1H and ^{13}C NMR Data of Selected Compounds

10 α -(Non-8-enyloxy)dihydroartemisinin, α -2f. ^1H NMR (400 MHz, CDCl_3): δ 0.84 (d, $J=6.8$ Hz, 3H), 0.91 (d, $J=6.0$ Hz, 3H) 1.19–1.74 (m, 17H), 1.42 (s, 3H), 1.81–1.87 (m, 1H), 1.95–2.01 (m, 3H), 2.29–2.41 (m, 3H), 3.35 (m, 1H), 3.91 (m, 1H), 4.76 (d, $J=9.2$ Hz, 1H), 4.92 (m, 2H), 5.29 (s, 1H), 5.77 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 12.6, 20.2, 24.4, 24.7, 25.9, 26.0, 28.8, 29.0, 29.3, 29.4, 29.5, 32.6, 33.8, 34.3, 36.3, 37.3, 45.3, 51.6, 69.2, 80.3, 91.1, 101.0, 104.2, 114.1, 139.2 ppm.

10 β -(Non-8-enyloxy)dihydroartemisinin, β -2f. ^1H NMR (400 MHz, CDCl_3): δ 0.86 (d, $J=6.8$ Hz, 3H), 0.91 (d, $J=6.4$ Hz, 3H) 1.21–1.89 (m, 16H), 1.45 (s, 3H), 1.95–2.07 (m, 4H), 2.25–2.45 (m, 3H), 2.53–2.66 (m, 1H), 3.35 (m, 1H), 3.81 (m, 1H), 4.76 (d, $J=3.2$ Hz, 1H), 4.95 (m, 2H), 5.37 (s, 1H), 5.78 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 13.0, 20.3, 24.4, 24.6, 26.2, 26.2, 28.9, 29.0, 29.2, 29.4, 29.6, 30.9, 33.8, 34.6, 36.4, 37.4, 44.4, 52.5, 68.4, 81.1, 87.8, 101.9, 104.0, 114.1, 139.1 ppm.

10 α -(Prop-2-ynyloxy)dihydroartemisinin, α -2i. ^1H NMR (400 MHz, CDCl_3): δ 0.90 (d, $J=6.8$ Hz, 3H), 0.96 (d, $J=6.0$ Hz, 3H), 0.98–1.05 (m, 1H), 1.23–1.61 (m, 5H), 1.44 (s, 3H), 1.68–2.05 (m, 4H), 2.34–2.45 (m, 3H), 4.39 (dd, $J=16$, 2.4 Hz, 1H), 4.56 (dd, $J=16$, 2.0 Hz, 1H), 4.69 (d, $J=9.2$ Hz, 1H), 5.35 (s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 12.4, 20.3, 22.2, 24.6, 29.7, 32.3, 34.2, 36.2, 37.3, 45.4, 51.5, 55.0, 74.2, 79.6, 80.3, 91.2, 97.5, 104.3 ppm.

10 β -(Prop-2-ynyloxy)dihydroartemisinin, β -2i. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (d, $J=7.4$ Hz, 3H), 0.95 (d, $J=6.8$ Hz, 3H), 1.20–1.54 (m, 1H), 1.23–1.61 (m, 4H), 1.44 (s, 3H), 1.62–2.06 (m, 4H), 2.33–2.41 (m, 3H), 2.63–2.69 (m, 1H), 4.31 (d, $J=2.0$ Hz, 2H), 4.98 (d, $J=3.2$ Hz, 1H), 5.41 (s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 12.8, 20.3, 24.4, 24.6, 25.8, 26.1, 30.5, 34.5, 36.3, 37.3, 44.3, 52.5, 54.9, 73.9, 79.7, 81.0, 88.0, 100.5, 104.1 ppm.

10 β -[(4'-Methoxyphenyl)methoxy]dihydroartemisinin, β -2m. ^1H NMR (400 MHz, CDCl_3): δ 0.98 (d, $J=6.0$ Hz, 3H), 1.04 (d, $J=7.5$ Hz, 3H), 0.97–1.05 (m, 1H), 1.44 (s, 3H), 1.28–1.73 (m, 5H), 1.87–2.09 (m, 4H), 2.35–2.45 (m, 1H), 2.74–2.84 (m, 1H), 3.78 (s, 3H), 4.48 (d, $J=12.4$ Hz, 1H), 4.86 (d, $J=12.4$ Hz, 1H), 5.39 (d, $J=3.5$ Hz, 1H), 5.55 (s, 1H), 6.80–7.09 (m, 4H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 12.9, 20.2, 24.3, 24.6, 26.0, 31.0, 34.5, 36.3, 37.3, 44.4, 52.5, 55.6, 80.9, 88.0, 101.5, 104.1, 114.5, 118.0, 151.6, 154.6 ppm.

10 β -[(2',3'-Methylenedioxy)phenyl)methoxy]dihydroartemisinin, β -2n. ^1H NMR (400 MHz, CDCl_3): δ 0.91–0.95 (m, 6H), 1.23–1.34 (m, 1H), 1.45 (s, 3H), 1.40–1.93 (m, 5H), 2.01–2.06 (m, 4H), 2.34–2.38 (m, 1H), 2.64–2.70 (m, 1H), 4.42 (d, $J=12.0$ Hz, 1H), 4.78 (d, $J=12.0$ Hz, 1H), 4.88 (d, $J=3.2$ Hz, 1H), 5.45 (s, 1H), 5.95 (s, 2H), 6.77 (m, 2H), 6.81 (s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 13.0, 20.3, 24.5, 24.6, 26.2, 30.8, 34.5, 36.4, 37.3, 44.3, 52.5, 69.5, 81.1, 88.0, 100.9, 101.0, 104.1, 108.0, 108.0, 120.8, 132.1, 146.8, 147.5 ppm.

10 β -[(4'-Chlorophenyl)methoxy]dihydroartemisinin, β -2o. ^1H NMR (400 MHz, CDCl_3): δ 0.91–0.95 (m, 6H), 1.22–1.34 (m, 1H), 1.45 (s, 3H), 1.42–1.91 (m, 5H), 2.01–2.07 (m, 4H), 2.34–2.42 (m, 1H), 2.65–2.69 (m, 1H), 4.48 (d, $J=12.4$ Hz, 1H), 4.86 (d, $J=12.4$ Hz, 1H), 4.89 (d, $J=3.6$ Hz, 1H), 5.44 (s, 1H), 7.23–7.31 (m, 4H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 13.0, 20.3, 24.5, 24.6, 26.1, 30.8, 34.5, 36.3, 37.4, 44.3, 52.5, 68.9, 81.1, 88.0, 101.3, 104.1, 128.4, 128.5, 133.1, 136.8 ppm.

10 α -[(4'-Chlorophenyl)methoxy]dihydroartemisinin, α -2o. ^1H NMR (400 MHz, CDCl_3): δ 0.86–0.95 (m, 6H), 1.20–1.30 (m, 1H), 1.42 (s, 3H), 1.42–1.92 (m, 5H), 2.01–2.06 (m, 4H), 2.34–2.43 (m, 1H), 2.44–2.56 (m, 1H), 4.49 (d, $J=8.8$ Hz, 1H), 4.59 (d, $J=12.8$ Hz, 1H), 4.94 (d, $J=12.8$ Hz, 1H), 5.33 (s, 1H), 7.23–7.31 (m, 4H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 12.7, 20.2, 24.5, 24.7, 26.0, 32.6, 34.1, 36.2, 37.3, 45.3, 51.6, 69.0, 80.3, 91.2, 98.9, 104.3, 128.3, 128.9, 133.1, 136.7 ppm.

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