Organic Process Research & Development

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Streamlined Process for the Conversion of Artemisinin to Artemether

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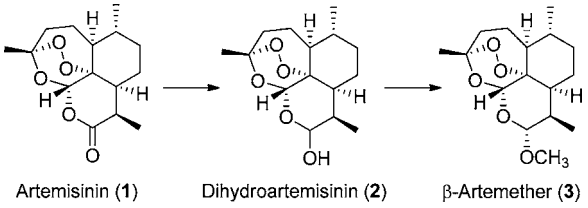
Supporting Information

ABSTRACT: We report an improvement to the previously published manufacturing process for artemether, a key antimalarial drug, utilizing readily available reagents, easily controlled manufacturing conditions, and a greatly simplified workup and isolation. New analytical methods and in-process controls allow for optimization of yield through control of side product formation. A 70% overall yield from the two-step conversion of naturally or synthetically derived artemisinin to pure β-artemether is obtained. This corresponds to a usage factor of 1.35 kg of artemisinin needed to produce 1 kg of β-artemether, compared to the current industry average of 1.59 kg.

INTRODUCTION

Artemisinin combination therapy (ACT) is the most effective treatment for malaria, with the artemether−lumefantrine combination being the most widely used. In a pair of manuscripts appearing in this journal,[1] the development group at Novartis graciously shared details of their improved processes for the manufacture of these active pharmaceutical ingredients (APIs). As a result, many Chinese and Indian generic API suppliers have adopted these processes. Artemether is prepared in two steps from artemisinin (Scheme 1). The

Scheme 1. Conversion of Artemisinin to Artemether

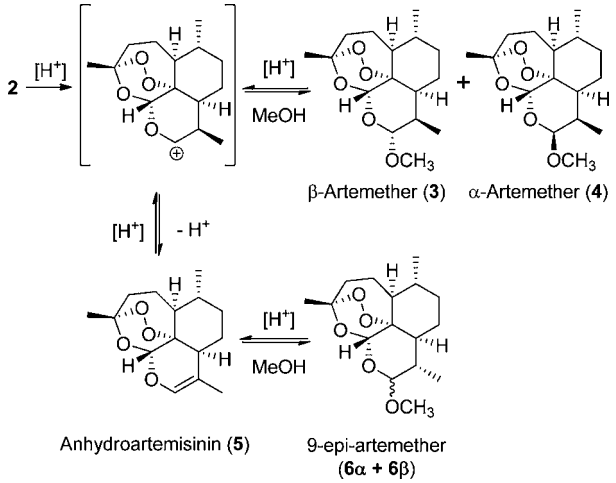


Novartis group reports historical yields of 79% and 74% for these steps, giving an overall yield of 58%, while their improved process claims 89% and 77% yields for an overall yield of 68%.

Artemisinin (**1**) is extracted from *Artemisia annua*. As an agriculturally derived product, its supply is subject to the effects of weather, competition with food crops for agricultural land, etc. Long lead times complicate matching supply with demand. In the past 2 years, prices have ranged from US$400 to $900/kg. At an average price of approximately US$600/kg, it is easily the most expensive raw material used in production of ACTs. As part of an effort to forecast needs for artemisinin to help supplier planning, the Clinton Health Access Initiative (CHAI) surveyed numerous API manufacturers to determine benchmark realized yields in artemether synthesis. Surprisingly the responses were consistently lower (58−62% overall) than those reported in the Novartis work. Included in the survey were manufacturers supplying Novartis using their specified process. It is not unusual for published yields to not be realized in practice, but the 10% discrepancy here is important. A higher, more consistent process yield—and therefore lower raw material consumption—would aid in stabilizing the volatile artemisinin market. For this reason, we decided to investigate the sources of discrepancies between claimed and realized yields. As well, we wished to consider additional avenues for process improvement to streamline production of the API.

The reduction of **1** to **2** as reported by Novartis is straightforward; most artemether suppliers are realizing 85−90% yields. The acid-catalyzed conversion of **2** to **3** using methanol in a cosolvent proves to be the problematic step. Reported impurities include α-artemether (**4**), anhydroartemisinin (**5**), and 9-*epi*-artemether (***6α*** and ***6β***). These impurities evoke a mechanism depicted in Scheme 2.

Scheme 2. Mechanism of Artemether Formation with Related Impurities



Novartis notes that reaction cosolvent and control of crystallization conditions may affect yields. The choice of reaction cosolvent affected the ratio of side products (**4**, **5**, **6**) formed. Their optimized process uses concentrated HCl as acid catalyst and cosolvent dichloromethane (or methyl acetate in

Received: February 10, 2012
Published: April 7, 2012

   dx.doi.org/10.1021/op300037e | *Org. Process Res. Dev.* 2012, 16, 764−768

an environmentally friendly substitution). The workup involved neutralization with aqueous base, phase separations, and concentration/solvent exchange to methanol prior to crystallization of artemether from methanol/water. A recrystallization from methanol/water was also described, which removed observed impurities.

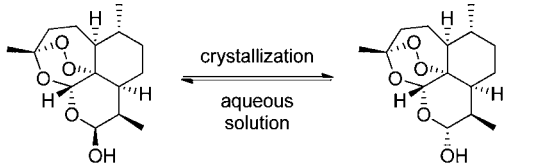
A review of patents and other publications shows that a wide variety of acid catalysts have been tested in preparing **3**. One patent[2] describes the preparation of arteether, the ethyl ether analogue of **3** (and, in a separate example, **3** itself), making use of solid acid catalysts including *p*-toluenesulfonic acid, $AlCl_3$, or a cation exchange resin. The reaction solvent consisted of the respective alcohol supplemented with the corresponding trialkyl orthoformate. The orthoformate was claimed to allow use of a lower amount of acid and to increase the reaction rate. As with the Novartis process, product isolation required extraction into an organic phase and concentrations. Another patent[3] describes a single pot conversion from **1** to **3**. The acid catalysts used included trimethylchlorosilane, trifluoroacetic acid, and a cation exchange resin. Product isolation required extraction and a chromatographic purification step. Other patents added sulfuric acid[4] to the list of acid catalysts used and advocated the use of acid precursor catalysts such as acetyl chloride.[5] The latter patent also made use of trialkyl orthoformate as a cosolvent.

Armed with this prior research, we wondered if the procedure might be further simplified, particularly in a way that eliminated the need for phase separations and/or solvent concentrations and exchanges. An ideal process for conversion of **2** to **3** would involve inexpensive, environmentally benign solvents and reagents, would provide a high conversion rate with minimal side product formation, and would have a simple, high-yielding isolation, ideally obviating the need for a recrystallization.

RESULTS AND DISCUSSION

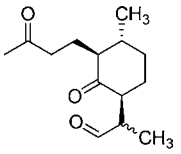
Reduction of Artemisinin (1). Informative analytical test methods are integral to productive process development. It was found that the HPLC conditions described in the International Pharmacopoeia monograph[6] for artemisinin (**1**) worked well for this application. Artemisinin is well resolved from dihydroartemisinin (**2**) within a reasonable analysis time. The α- and β-anomers of dihydroartemisinin (**2**α and **2**β) appear as two peaks with a raised baseline between the peaks, due to the *in situ* conversion during chromatography (Scheme 3; also see Supporting Information). The first peak corresponds to **2**α, the second peak to **2**β, and the area between to **2** undergoing the anomeric transition during the separation. Isolated **2** is almost completely in the β form. The conversion is affected by pH but cannot be completely stopped in solution. It is important to include both peaks and the area between when integrating **2**.

Scheme 3. Equilibration of Dihydroartemisinin Anomers



Reduction of **1** to a mixture of **2**α and **2**β is straightforward under the Novartis conditions, using either sodium or potassium borohydride. We found the reduction generally stalled just shy of completion when using 1.21 equiv of reductant; increasing the charge to 1.3 equiv resulted in a consistently clean reaction. Following isolation of the product, nearly exclusively as form **2**β, solids continued to crystallize from the mother liquors. These arise from conversion of soluble **2**α to the less soluble β form. Subsequent refinement of the isolation procedure—control of temperature during slow addition of water and inclusion of a maturation period—minimized the amount of **2**α remaining in the mother liquors and maximized the yield of **2**β as a single crop.

In older samples of **2**, an additional pair of peaks eluting before **2**α is observed by HPLC. These peaks correspond to isomers of degradation product **7** (Figure 1).[7] The formation of this degradant is accelerated by heat (whether in solution or solid state) and under basic aqueous conditions; careful sample preparation is needed to avoid obtaining misleading results. Notably, we observed 8% area (5% by mass) formation of **7** under the drying conditions (50 °C) listed in the Novartis work.[1] Vacuum drying without heat proved sufficient to remove both methanol and water from **2** with negligible formation of **7**.



7

Figure 1. Degradation product of dihydroartemisinin **7**.

The final conditions developed for the conversion of **1** to **2** are presented below. These conditions differ from those reported by Novartis in that (i) Sodium borohydride is used in place of potassium borohydride.[8] (ii) Sodium borohydride equivalents are increased from 1.21 to 1.3. (iii) Isolated **2** is dried under vacuum without heat.

Conversion of Dihydroartemisinin (2) to Artemether (3). In general **2** is stirred with methanol, generally with a cosolvent, in the presence of an acid to effect conversion to **3**. The WHO monograph purity test method for **3**[9] was found to be suitable for reaction monitoring. Under reaction conditions used by Novartis and others, the reaction mixture, initially a slurry, clears prior to reaction completion, allowing easy sampling for confirming the reaction end point. To ensure reproducible analytical results, reaction aliquots must be neutralized prior to dilution to prevent altering the proportion of side products. Previous reports[1] utilized TLC for assessing reaction completion. Using HPLC for in-process control monitoring allowed informed evaluation of reaction conditions.

Our baseline trials using the Novartis conditions indicated that reaction slowed after about 3 h with 2−3% of **2** remaining, with α-artemether (**4**) and anhydroartemisinin (**5**) formed at about 12% and 6%, respectively, representing a significant loss of yield.[10] Our goal for optimizing this reaction was to improve selectivity for **3** at a conversion rate that allowed for both a suitable in-process control and a stable product mixture. Practically speaking, conversion over 1−2 h was deemed optimal.

Reaction Optimization. A variety of cosolvents were examined for their effect on reaction selectivity, as shown in

dx.doi.org/10.1021/op300037e | Org. Process Res. Dev. 2012, 16, 764−768

Table 1.[11] Notably, the reaction with trimethyl orthoformate (TMOF) cleared immediately and was found to be complete in 15 min. In addition to reaching completion much more rapidly, use of TMOF provided much better selectivity than the other solvents.

Table 1. Cosolvent Effect on Formation of 3[a]

cosolvent	%2	%3	%4	%5	selectivity[b]
CH_2Cl_2	11.2	70.0	14.4	4.5	78.7
MeCN	0.6	77.1	18.1	4.3	77.5
NMP	94.6	3.8	0.9	0.7	70.4
MTBE	15.3	66.3	14.2	4.2	78.3
MeOAc	2.6	78.3	15.0	4.0	80.5
Me_2NAc	98.2	1.3	0.3	0.3	68.4
TMOF[c]	0.0	85.6	10.8	3.6	85.6

[a]Trial conditions: 300 mg of **2**, 1.0 mL of MeOH, 0.75 mL of cosolvent, 25 μL of conc HCl, 3 h reaction. Structures are shown in Scheme 2. [b]Selectivity is defined as %**3** of the total **3** + **4** + **5**. [c]Trimethyl orthoformate.

With TMOF selected as an obvious choice for further optimization, we examined the methanol/TMOF ratio, the reaction molarity, catalyst composition and charge, and reaction temperature.

With respect to the methanol/TMOF ratio and TMOF stoichiometry (if considered a reagent), volume ratios from 19:1 to 3:2 were trialed at two reaction molarities, ranging from near-stoichiometric TMOF charges (1.7 equiv) to large excess (13.8 equiv). Results indicated that the volume ratio with methanol was more important than the stoichiometry relative to **2**. The optimum conversion (giving both rapid reaction and high selectivity) was 2:1 methanol/TMOF.

In response to the reports of a wide variety of acid catalysts used for this reaction, we compared the effects of concentrated HCl, anhydrous HCl in 2-propanol, methanesulfonic acid, sulfuric acid, trimethylsilyl chloride, and acetyl chloride. None of these catalysts offered improvement over concentrated HCl, so the readily available concentrated HCl was selected for continued development. Notably we found no significant difference in reaction rate or selectivity in using concentrated aqueous HCl compared to anhydrous HCl or acid precursors (such as acetyl chloride/methanol). Additionally we found that addition of small amounts of water slowed the reaction but did not affect the selectivity. This may be due to the water-scavenging effects of the TMOF.

We then examined the quantity of acid catalyst needed. Reactions were run at 2.8, 2.3, and 1.7 mol % acid relative to **2**, which gave complete consumption of **2** within about 45, 60, and 150 min, respectively. Reaction selectivity at completion did not change with acid level at these levels. However, extended reaction times (significantly beyond the time required for consumption of **2**) resulted in slow conversion of **3** to **4** and thus a degradation of selectivity (and hence reduction of yield). As such, the acid catalyst concentration is then tunable, moderating the reaction rate and facilitating quench at the maximum in-process level of **3**. A concentration of 2.3 mol % acid was selected for further use, giving complete reaction in the optimum time frame while allowing suitable time for in-process control without degradation of selectivity.[12] It should be noted that the critical effect of acid level confounded attempts to telescope the reduction and ether formation steps: quenching of the reduction step (preparation of **2**) requires excess acid, which is detrimental to the selectivity of the conversion to **3**.

Reactions were run at 5, 25, and 40 °C to determine if selectivity might be further improved. It was found that temperature affected the reaction rate but not the selectivity. No benefit to the use of alternate reaction temperatures was found; the reaction may be conveniently performed at ambient temperature.

As noted above, the optimum methanol/TMOF ratio was selected as 2:1. Optimization of the reaction concentration showed that there was little change in selectivity over a range from 3.8 L solvent mix/kg of **2** up to 7.5 L/kg. At the highest concentration, the reaction mixture never cleared, even though the reaction reached completion. While further optimization is possible, the reaction is conveniently run at a 5× solvent volume concentration (0.70 mol/L). This corresponds to 4 equiv of TMOF relative to **2**.

Isolation of β-Artemether (3). With optimized reaction conditions in hand, we sought an optimized workup procedure. The reaction solvents used in our revised process are miscible with an aqueous quench solution, so we anticipated that we could avoid organic-aqueous extractions and solvent distillations. Initial attempts to isolate product by simple addition of dilute aqueous base (to quench the acid catalyst) gave gummy intractable solids. It was apparent that TMOF, used at these levels, interferes with crystal formation. Fortunately, we found that addition of methanol to the reaction mixture upon completion, diluting from a 2:1 ratio to a 3:1 methanol/TMOF ratio, prior to addition of dilute aqueous base greatly improved crystal formation. A well-stirred reactor was also essential for good crystal formation. Washing the filter cake with cold water removed any remaining TMOF (as analyzed by HPLC); fairly pure material was isolated in good yield in this greatly simplified workup. This process is then well-suited for production: the reaction may be executed in a smaller vessel and transferred to a larger vessel using methanol as rinse, and the product crystallized by addition of dilute aqueous base.

Scale-up Results. The developed conditions were used to perform scale up experiments at 10- and 40-g scale. This scale allowed careful analysis of process streams to account for mass balance (see Table 1 in the Supporting Information). In several trials at these scales, the yield for the conversion of **1** to **2** is around 89−90%, consistent with reports from API manufacturers. The yield for the conversion of **2** to **3** is 76−80%, in line with that previously reported but considerably better than the yield realized by manufacturers. The crude wet **3** showed a purity of 99.4% with impurities **4** and **5** at 0.27 and 0.36%, respectively. At these impurity levels, the material does not meet current International Pharmacopoeia limits, but the quality is easily improved with recrystallization as described by Novartis to give material meeting specifications. Given the high quality of the crude material, recrystallization results in a yield loss of only 1−2% and provides material of >99.9% purity. The overall two-stage yield is 70−71%.

Application to Semisynthetic Artemisinin. Artemisinin isolated from plant sources has a surprisingly consistent impurity profile, containing trace levels of artemisitene and 0.2−0.5% 9-*epi*-artemisinin.[6b,c] Artemisinin may also be produced by synthesis from artemisinic acid produced by yeast fermentation. Such artemisinin typically contains a higher level of the 9-*epi* isomer. Semisynthetic **1** containing 0.7% 9-*epi*-artemisinin was subjected to the described process, resulting in

dx.doi.org/10.1021/op300037e | Org. Process Res. Dev. 2012, 16, 764−768

artemether of comparable yield and purity to material derived from natural **1**.

CONCLUSION

A simplified process for the conversion of artemisinin to β-artemether was developed on the basis of existing manufacturing processes, resulting in significant yield improvements. The consumption rate is thereby reduced from 1.59 to 1.35 kg of **1** required to produce 1 kg of **3**. Careful analysis of process streams showed that these gains were achieved primarily in solution and isolation yields in the second step.

The key finding in the reduction of **1** to **2** was the use of a lower drying temperature to minimize product degradation.

In the conversion of **2** to **3**, use of a methanol/trimethyl orthoformate solvent mixture afforded a faster reaction with high selectivity. Controlling the level of acid catalyst controls the reaction rate so that the undesired conversion of **3** to **4** may be minimized. Improved in-process controls allow the quench to be performed at the proper time to obtain the maximum yield. An 87% solution yield (area% **3**) is routinely obtained through these improvements. A facile quench and isolation lead to high-quality crude product, and the previously reported recrystallization provides an upgrade if required. The process requires no extractions and no concentrations, and it generates less hazardous waste. The use of cosolvent dichloromethane is eliminated; substitution with TMOF has a negligible raw material cost impact given the improved yield and the high cost of **1**.[13]

While our resources have not allowed us to execute this improved process at greater than 40 g scale, we are confident that the process is robust and scalable. Indeed, we find the conversion of **2** to **3** performs well over a moderately broad range of temperatures, concentrations, and catalyst amounts. In particular, manufacturers will be able to control the reaction rate and selectivity by using in-process controls to tune the acid catalyst charge to optimize processing. The critical crystallization of **3** may be executed even more effectively at manufacturing scale, where well-stirred vessels and controlled cooling profiles are routinely employed. We are in the process of sharing this procedure with manufacturing partners in our global fight to combat malaria.

EXPERIMENTAL SECTION

Preparation of Dihydroartemisinin (2). To a solution of artemisinin (**1**, 40 g, 0.141 mols) and methanol (400 mL) was added calcium chloride (5.32 g, 0.048 mol, 0.34 equiv). This mixture was cooled to ∼ −1.5 °C. Sodium borohydride (6.89 g, 0.182 mol, 1.3 equiv) was added in five portions over about 1 h, controlling the temperature below 5 °C. The reaction was stirred at 0−4 °C for 1 h. A sample (20 μL) was added to 20 μL of 10% HCl in an autosampler vial. This was diluted with water to 0.5 mL and with acetonitrile to about 1.0 mL to give a clear solution. Failure to quench prior to dilution gives misleading results, as the **2** formed otherwise degrades in the sample. No **1** was observed, indicating 100% conversion.

The reaction mass was quenched with concentrated HCl (13.91 mL, 0.169 mol, 1.2 equiv). A minor temperature rise (∼3−4 °C) was observed. Water (480 mL, 5 °C) was added over 45 min at <10 °C. The resulting mixture was stirred at 5−10 °C for 20 min. Solid **2** was collected by filtration and the cake rinsed with chilled water (120 mL). The cake was dewatered for 10 min and dried overnight under vacuum at 15−25 °C, providing 35.97 g (89.7% yield) of **2** with >99.9% purity by HPLC and <0.1% water.

Preparation of Artemether (3). To a solution of dihydroartemisinin (**2**, 35.9 g, 0.126 mols) in methanol (123 mL) and trimethyl orthoformate (61.4 mL) was added concentrated HCl (0.23 mL, 2.8 mmol, 0.022 equiv), and the reaction was stirred at room temperature. The slurry cleared after 60 min and was sampled for completion at 90 min. A 50-μL aliquot of the reaction solution was quenched with 50 μL of 0.2% aqueous sodium bicarbonate in an autosampler vial (producing a white precipitate) and diluted with 0.5 mL of acetonitrile to give a clear solution. Analysis by HPLC showed less than 0.5% **2** remaining with 87.1% β-artemether (**3**) along with 9.0% of **4** and 3.5% of **5**.

The reaction solution was diluted by addition of 60 mL of methanol, followed by quenching by the steady addition of 0.2% aqueous sodium bicarbonate (233 mL, 5.56 mmol, 0.044 equiv), giving well-stirred solids.[14] The slurry was stirred in an ice bath stir for 1 h and allowed to settle for 30 min. Solid crude **3** was collected by filtration, and the cake was washed with 2 × 120 mL of chilled (5 °C) water (passing the wash through the reactor as a rinse). HPLC analysis of the crude cake showed a purity of 99.4% **3** with impurities **4** and **5** at 0.3% and 0.4%, respectively. This material could be dried before recrystallization, if required, but is conveniently recrystallized as a moist cake after dewatering.

The solids were transferred back to the reactor and suspended in methanol (240 mL).[15] The mixture was heated to 40 °C to effect dissolution. Water (about 120 mL) was charged slowly at 40 °C over about 15 min, until the onset of crystallization. The batch was held for about 30 min to allow equilibration of solubility. The remainder of the water (240 mL total) was added over about 10 min, maintaining the temperature at 40 °C. The batch temperature was reduced in steps to 20 °C, then chilled to 5 °C, and held for 30 min. The product was isolated by filtration and washed with 20 mL prechilled (5 °C) methanol/water (1:4) and then 2 × 120 mL chilled water. The product was dried under vacuum at ambient temperature, providing 29.6 g (78.8% yield) of **3** (>99.9% purity, with no impurities >0.02%; mp 90−91 °C; assay >100% against reference material).

ASSOCIATED CONTENT

Supporting Information

Mass balance table for conversion of **2** to **3**, and HPLC conditions and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Bill and Melinda Gates Foundation, DFID, and other Clinton Health Access Initiative donors for financial support. We thank Uday Gokhale and Kamal Vashi of Mangalam Drugs & Organics Ltd. for helpful discussions regarding scale-up. Semisynthetic artemisinin was graciously supplied by Sanofi. The table of contents photograph was supplied courtesy of Birgit Betzeit, www.stopmalarianow.org.

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(8) While the reasons Novartis presents for selection of this reagent appear valid, the higher cost and reduced availability of potassium borohydride may direct manufacturers toward use of sodium borohydride.

(9) http://apps.who.int/phint/en/p/docf/, search "artemetherum".

(10) Putative side products ***6α*** and ***6β*** either are not formed in significant quantities or are not detected by our analysis.

(11) While trimethyl orthoformate (and perhaps even methyl acetate) is a likely participant in the reaction (perhaps as a scavenger of adventitious water), it is discussed here as a cosolvent.

(12) We noted, however, with one supplier's lot of TMOF that higher levels of acid (as much as 10 mol%) were required for effective reaction progress. This lot appears to contain low levels of an uncharacterized basic impurity. We suggest that manufacturers conduct use tests to confirm the needed catalyst level. When the reaction using this TMOF was dosed with sufficient acid to achieve reaction completion in 1 h, product yield and quality were unaffected.

(13) TMOF costs approximately US$4/kg at bulk scale and is used at 1.5× by weight vs **1** at a cost of approximately US$600/kg.

(14) These solids may be gummy in reactors with insufficient stirring. At 500-mL scale, a baffle was added to the reactor to improve agitation.

(15) Again, a well-stirred reactor is essential for good crystallization.