

## Semi-synthesis of the anti-malarial artemisinin starting from dihydroartemisinic acid using natural and artificial photosensitizers

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### Highlights

- Utilization of former waste products as valuable starting materials and reagents
- Kinetic measurements in a continuous tubular mini-channel reactor
- Development of a kinetic model for a complex reaction network for natural product synthesis

### 1. Introduction

A major challenge in the fight against malaria is to make the highly efficacious artemisinin-based combination therapies widely available and affordable for the poor population of developing countries. The base compound, artemisinin, is a natural product whose state-of-the-art in production is the extraction from the leaves of *artemisia annua* [1]. A byproduct obtained from the extraction process is artemisinin's biological precursor dihydroartemisinic acid (DHAA), which can be converted into artemisinin via a regio- and stereo-selective reaction pathway (Figure 1) [2]. The starting point of the semi-synthesis is a light induced activation of oxygen catalyzed by a photo-active compound (photosensitizer). The formed singlet oxygen reacts with DHAA in an ene reaction, which is followed by a sequence of acid-catalyzed reactions to yield artemisinin. Thus, a complex natural product is formed simply by treating the precursor DHAA with light, oxygen, a catalytic amount of photosensitizer and acid. The existing process developed by Kopetzki et al. [3] utilizes blue LEDs with 9,10-dicyanoanthracene (DCA) as photosensitizer because of its high quantum yield and stability. However, a second waste product in the extraction stream, the leaf pigment chlorophyll, is known to possess a strong photosensitizing activity [4] and has been used to sensitize oxygen, albeit sparingly [5]. In this study pure chlorophyll as well as the crude extract were investigated regarding their potential as literally green sensitizers in comparison to conventional methods using both pure reagents and catalysts. In order to control the formation of byproducts optimizing for artemisinin, kinetic studies using conventional (DCA) and new (chlorophyll) photosensitizers were performed. Factors such as temperature, oxygen pressure and light emission were investigated for their effect on the reaction rate.

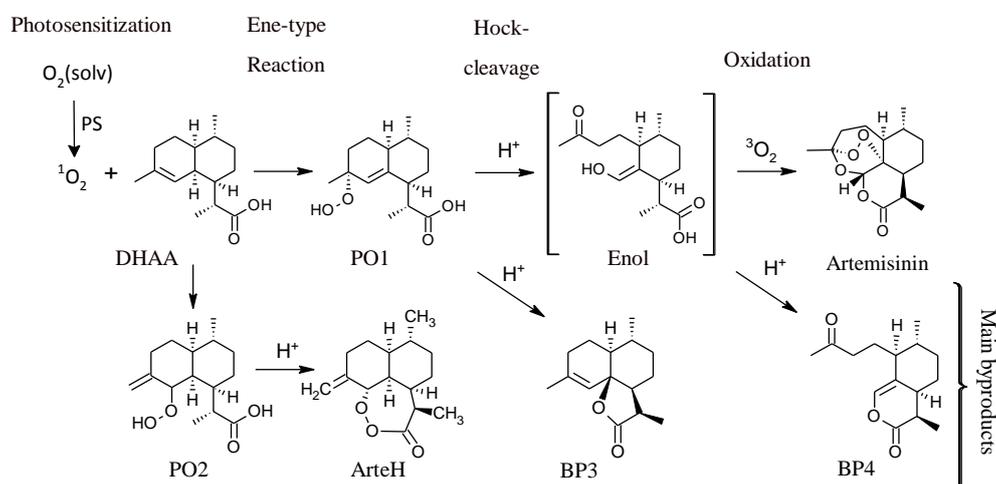


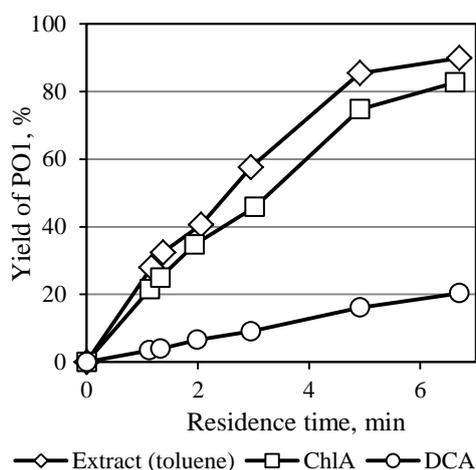
Figure 1. Schematic reaction network of the Artemisinin semi-synthesis with the main reaction pathways

## 2. Methods

The experiments were performed in a continuous tubular reactor consisting of transparent tubing with an inner diameter of 1.58 mm. The small dimensions of the reactor enable effective light penetration and fast gas-liquid mass transfer. The liquid and oxygen feed are mixed prior to the reactor resulting in a two-phase slug flow. The first reactor section is irradiated by a highly intensive LED lamp, which results in the continuous generation of the short-lived singlet oxygen. After passing the photoreactor, the reaction mixture enters a residence time module for the second reaction step to take place. Samples of the reactor outlet were collected in steady state and analyzed by HPLC and by qNMR.

## 3. Results and discussion

When pure chlorophyll A (ChlA) is compared directly with DCA (Figure 2), ChlA photosensitizes singlet oxygen much more efficiently than the artificial reagent. This high activity is exceeded by the performance of the crude plant extract itself. The enhanced effect may be the result of additional co-extracted plant metabolites which also act as photosensitizers. These results illustrate that plant extracts are promising renewable non-toxic agents for photochemical transformations, which can be applied in a variety of syntheses.



**Figure 2:** Yield of the intermediate PO1 formed by the photooxidation of DHAA with DCA, pure ChlA or crude plant extract (in toluene,  $-20^{\circ}\text{C}$ , 7 bar  $\text{O}_2$ )

In the next step the influence of other external parameters on the photooxidation with DCA or extract were investigated. In contrast to our expectations temperature and oxygen pressure did not affect the reaction rate of this first step. As a main governing effect the light intensity which is absorbed by the reaction solution was identified. Thus, the emitted light intensity and the reactor geometry are the main control parameters in the photooxidation. The acid-catalyzed reaction step is mainly controlled by the acid concentration and reaction temperature. Experiments with varied reactant concentration showed that the photooxidation proceeds with a fractional reaction order with respect to DHAA. The acid-catalyzed reaction sequence was confirmed to be first order with respect to the desired intermediate from the ene reaction (PO1). Based on these experimental results a simplified kinetic model was developed consisting of a set of rate equations for the main reactions and, further, of differential equations to describe the reactor behavior.

## 4. Conclusions

The semi-synthesis of artemisinin is an attractive extension of the conventional extraction process. The usage of co-extracted chlorophyll can substitute artificial photosensitizers leading to a simplification of the process and, thus, a decrease in operation cost. The developed kinetic model provides the basis for further quantitative optimization of the single semi-synthesis step as well as of the overall process ranging from extraction to the final separation.

## References

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## Keywords

Artemisinin; natural product synthesis; photosensitization; chlorophyll