Chemical Engineering Journal 294 (2016) 83–96

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

Optimisation of the photochemical oxidation step in the industrial synthesis of artemisinin

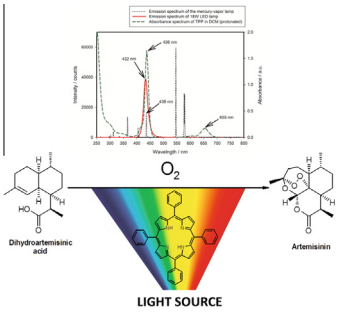
Andreas Burgard [a,*], Tile Gieshoff [a], Alexander Peschl [b], Dirk Hörstermann [a], Claus Keleschovsky [a], Roberto Villa [c], Silvana Michelis [c], Martin P. Feth [a,*]

[a] Sanofi-Aventis Deutschland GmbH, Chemistry & Biotechnology Development (C&BD) Frankfurt Chemistry, 65926 Frankfurt, Germany
[b] Peschl Ultraviolet GmbH, 55130 Mainz, Germany
[c] Sanofi-Aventis S.p.A., 12075 Garessio (Cuneo), Italy

HIGHLIGHTS

- Artemisinin synthesis: photooxidation with mercury lamp or LED technology.
- Safety aspects considerations due to the sensitive endoperoxide containing structure.
- Implementation of PAT (process analytical technology): IR and UV/Vis spectroscopy.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 16 November 2015
Received in revised form 17 February 2016
Accepted 19 February 2016
Available online 27 February 2016

Keywords:
Artemisinin
Photooxidation
Singlet and Triplet Oxygen
Process analytical tools (PAT)
Peroxide chemistry
Safety aspects

ABSTRACT

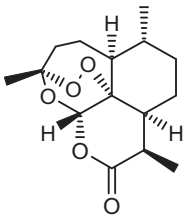
The photooxidation process to artemisinin was studied in detail using different types of light sources by conversion of dihydroartemisinic acid (DHAA) or related derivative into artemisinin using tetraphenylporphyrin (TPP) as photosensitizer in the presence of oxygen. The pivotal singlet oxygen was generated by illumination of the reaction mixture during bubbling ambient air by means of either a mercury vapour lamp or light emitting diodes with appropriate wavelengths focusing on the absorption maximum of the TPP. Both light sources resp. methods were compared in efficiency, yield and resulting quality of isolated artemisinin. These photooxidation studies in laboratory scale were investigated and kinetically monitored using ATR-MID-IR- and UV/Vis spectroscopy as process analytical tools (PAT). Due to the sensitive endoperoxide containing structure of artemisinin and potential peroxide containing by-products the safety aspect was intensively examined particularly with regard to scaling up the photooxidation process. Beyond technical requirements for future realisation of LEDs as light source in production scale were considered.

1. Introduction

Artemisinin (**1**) is a sesquiterpene lactone endoperoxide (refer to Scheme 1) which is a component of the traditional Chinese medical herb *Artemisia annua*. It has been utilised for controlling symptoms of fever in China for over 1000 years. In 2001 WHO has recommended the use of artemisinin based combination therapies

* Corresponding authors.
E-mail addresses: Andreas.Burgard@sanofi.com (A. Burgard), Martinphilipp.Feth@sanofi.com (M.P. Feth).

http://dx.doi.org/10.1016/j.cej.2016.02.085
1385-8947/



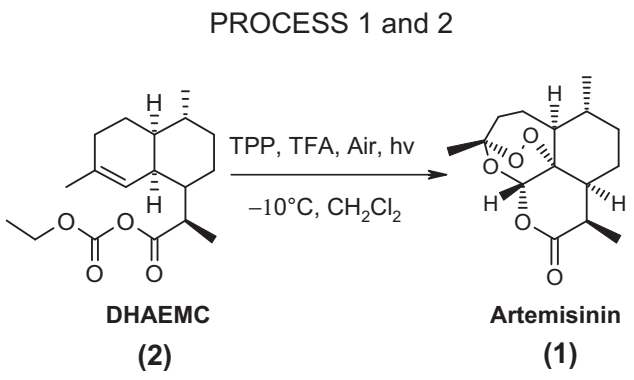
Scheme 1. Structure of artemisinin (**1**).

(ACTs) in countries where *Plasmodium falciparum* malaria is resistant to chloroquine, sulfadoxine–pyrimethamine and amodiaquine [1]. Artemisinin and its derivatives not only have an excellent antimalarial effect, but have also an effective anti-parasitic activity towards other parasites such as *Schistosoma japonicum* causing the *Schistosomiasis japonica*, which is beside malaria a major neglected parasitic disease in the tropical and subtropical regions [2]. Moreover artemisinin and its derivatives possess potent inflammatory properties and have been found to be immunosuppressive with therapeutic effects in the treatment of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis and collagen-induced arthritis [3–5]. In addition artemisinin and its derivatives have been studied for cancer treatment since at least ten years [6,7].

The production of artemisinin can be accomplished through several routes: by extracting artemisinin from *A. annua* [8,9] or by extracting the biosynthetic precursor molecule artemisinic acid from *A. annua* and then synthetically converting this molecule in several synthetic steps to artemisinin.

A new commercial-scale alternative manufacturing process to produce a complementary source of artemisinin to supplement the plant-derived supply is described by conversion of biosynthetic artemisinic acid into semisynthetic artemisinin using diastereoselective hydrogenation and photooxidation as pivotal steps [10]. This manufacturing process was accepted by Prequalification of Medicines Programme (PQP) in 2013 as a first source of nonplant derived-artemisinin in industrial scale from Sanofi production facility in Garessio, Italy.

The Seeberger group described a useful extension of this chemistry by performing the photooxidation step in a full flow system in lab scale starting from dihydroartemisinic acid [11], rather than in the semibatch process that Sanofi implemented in the factory (refer to Scheme 2: Process 1 (**a**)). As described by Seeberger et al. at least 1500 photoreactors should be employed in parallel to convert in each photoreactor 2.95 g dihydroartemisinic acid in 25 ml dichloromethane (which corresponds to appr. 8 V) at 60 °C with 11.5 bar oxygen in the presence of tetraphenylporphyrin (TPP) into the linear hydroperoxide of dihydroartemisinic acid which is converted subsequently by continuous addition of trifluoroacetic acid to result after a reaction cascade in artemisinin, which could be isolated after work-up and chromatography. Tetraphenylporphyrin absorbs light at 420 nm, as soon as trifluoroacetic acid is added, the absorption maximum of the protonated TPP is shifted to 435 nm.



Scheme 2. Reaction scheme for the photo-oxidation of DHAEMC (**2**) to artemisinin (**1**) in the presence of trifluoroacetic acid (TFA) and tetraphenylporphyrin (TPP), called Process 1 (**a**) (10 V) and 2 (**a**) (5 V).

A mercury vapour lamp was used as light source for this continuous photooxidation method. One year later Seeberger et al. [12] published the application of monochromatic light emitting diodes (LEDs) with 420 nm emission wavelength as light source to perform the artemisinin photooxidation in different organic solvents upon others as e.g. dichloromethane or toluene. The same principle was utilised as published before keeping approximately the same dilution (8 V) of the reaction mixture, introducing the linear peroxide with subsequent addition of trifluoroacetic acid to accomplish the reaction. For the work-up the crude artemisinin was solubilised with acetonitrile and subsequently filtered through a PTFE syringe filter with 0.45 μm cutoff to remove the photosensitizer DCA (9,10-dicyanoanthracene). Using two recrystallization steps in cyclohexane/ethanol 9/1 solvent mixture artemisinin was isolated as white needles in a yield of 46% based on initial DHAA. The described work-up by Seeberger group with respect to purification of artemisinin by filtration via PTFE syringe filter with 0.45 μm cutoff and elaborate recrystallization using several organic solvents is sincerely an appropriate method on lab scale but would be too costly on industrial scale which is always the major target of our development.

Applying green chemistry to the photochemical route to artemisinin was published by Poliakoff et al. [13] with either liquid carbon dioxide and ethanol water mixtures as reaction media in a continuous process. For the photooxidative conversion of DHAA into artemisinin light emitting diodes were used as light source with a broad visible wavelengths spectrum investigating the application of different photosensitizers pending on photooxidation strategy.

There is a growing interest in applying light emitting diodes (LEDs) as alternative to traditional mercury vapour lamps due to their low energy consumption and potential for high efficiency and long lifetime. Modern, high-intensity LEDs is revolutionizing horticultural lighting. With well-developed light recipes focusing on appropriate wavelength ranges pending on absorption maxima by the chlorophylls of the plants, growers are realising increased growth rates and yields while reducing operating costs [14,15]. The emitted wavelengths of the Hg vapour lamp meet only with significant less than 10% of the energy input in total the absorption maximum area of protonated tetraphenylporphyrin at 435 ± 20 nm, which prompted us to apply light emitting diodes focusing on appropriate wavelengths at 435 nm.

This study investigate the different photooxidation strategies to manufacture artemisinin with respect to comparison of dihydroartemisinic acid (DHAA) and its activated derivative (refer to the Schemes 2–4), concentration limit of the photoreaction mixture and application of light emitting diodes with proper wavelengths compared to mercury vapour lamp with broad unspecified spectrum as light source. All considerations are closely associated with safety aspects which are essential before any lab development can be scaled up industrially.

To better understand the photochemical processes involved in the synthesis of artemisinin, online-spectroscopic methods were used beside conventional off-line analytical methods (like HPLC and NMR). Online ATR-MID-IR- and UV/Vis spectroscopy have