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Evaluation and Optimization of Synthetic Routes from Dihydroartemisinin to the Alkylamino-artemisinins Artemiside and Artemisone: A Test of *N*-Glycosylation Methodologies on a Lipophilic Peroxide.[†]

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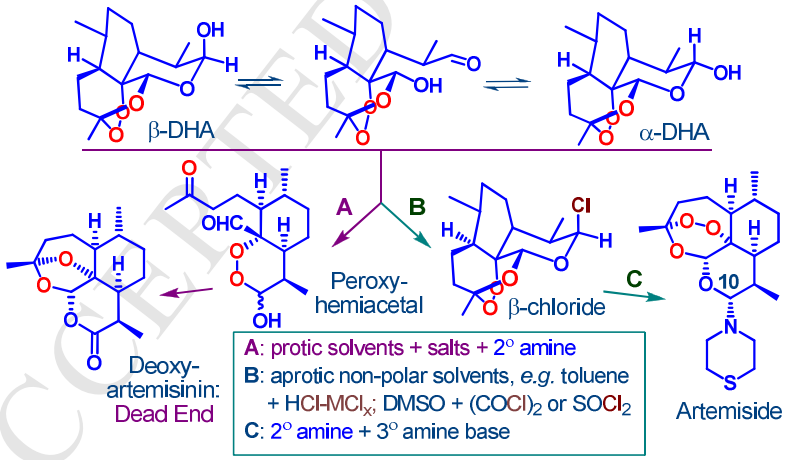
Abstract

10-Alkylamino-artemisinins including artemiside and artemisone display enhanced activities against malaria. Earlier, dihydroartemisinin (DHA) TMS ether was converted by trimethylsilyl bromide into the 10-β-bromide that with amine nucleophiles provided the amino-artemisinins. In an attempt to develop more economic approaches, direct *N*-glycosylation of DHA was examined but 2-deoxyartemisinin was invariably obtained. However, hydroxyl group activation by conversion into the 10β-halide in non-polar solvents with anhydrous HCl and Group I and II metal halides, oxalyl chloride or thionyl chloride with catalytic DMSO, and oxalyl bromide did succeed. The β-halides were converted *in situ* by thiomorpholine into artemiside, and by thiomorpholine-1,1-dioxide into artemisone respectively in scalable reactions. Hydrogen peroxide-acetonitrile or the urea-hydrogen peroxide complex efficiently oxidized the sulfide artemiside to the sulfone artemisone. Overall, a generalized approach to 10-alkylamino-artemisinins is now available.

Graphical Abstract



Keywords: Malaria, Antimalarial Drugs, Artemisinins, *N*-Glycosylation, Amino-artemisinins, Artemisone

[†] Dedicated to the memory of Professor Sir Derek Barton, one of the greatest of organic chemists of the 20th Century and a master of all trades within the profession of organic chemistry. He was an inspiring mentor who graciously and enthusiastically shared his knowledge, and he effectively imparted the sense of foresight and introspection required for the conception and successful execution of the varied and potent research projects in which the members of his research groups were engaged. The art and form thereof represented the ideal models upon which to base our activities once we had moved on to become engaged in the complicated tasks of conceiving and then supervising our own research projects. The time at Imperial College was indeed the high point in my early career path.