



University
of Victoria

Graduate Studies

Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

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MPhil (Queen's University Belfast, 2013)
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“Applications of Thiele’s Ester Derivatives from Biological to Material”

Department of Chemistry

Wednesday, May 2, 2018
9:30 A.M.
Elliott Building
Room 305

Supervisory Committee:

Dr. Jeremy Wulff, Department of Chemistry, University of Victoria (Supervisor)
Dr. Natia Frank, Department of Chemistry, UVic (Member)
Dr. Dave Berg, Department of Chemistry, UVic (Member)
Dr. Alisdair Boraston, Department of Biochemistry and Microbiology, UVic (Outside Member)

External Examiner:

Dr. Graham J. Bodwell, Department of Chemistry, Memorial University of Newfoundland

Chair of Oral Examination:

Dr. Jen Bornemann, Department of Electrical and Computer Engineering, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

Building upon existing synthetic methods, we have optimized the synthesis of Thiele's methyl ester to an efficient and scalable methodology. As part of a study of chemo- and regioselective transformations within the Thiele's ester scaffold, we designed and synthesized a new suite of molecular scaffolds incorporating a broad range (from 123° to 176°) of cleft angles.

In addition to this, we compared two competing conceptual models for their ability to rationalize the selective formation of Thiele's ester and two minor regioisomers which arise during the formation of the target product. We found that radical stabilization arguments (based on Deslongchamps' seminal work) outperformed the classic frontier molecular orbital theory model in predicting the regioselectivity of Thiele's ester dimerization. When this method was combined with simple steric arguments, we arrived at a general algorithm to rationalize Thiele type dimerization, including all the known homo- and heterodimerizations in the literature as well as a novel phosphine oxide-containing Thiele acid analogue discovered as part of this thesis work.

In order to stimulate the use of Thiele's ester chemistry in a diverse range of applications, we took advantage of our Thiele's ester methodology to achieve a mono ester-substituted dicyclopentadiene (colloquially referred to as a "half" Thiele's ester), and used this as the precursor of a novel functionalized polydicyclopentadiene ROMP polymer. The resulting *p*PDCPD has the highest glass-transition temperature reported for any polydicyclopentadiene material and allows for the facile manipulation of the surface chemistry through alteration of the embedded functional group.

A long-term goal in the Wulff lab is to use Thiele's ester as a scaffold for the generation of conformationally restricted ("peramivir-like") neuraminidase inhibitors. Setting the groundwork for this, we explored the selectivity of various peramivir derivatives toward group-1 vs. group-2 neuraminidase enzymes. To this end, we coupled a wide range of alkyl chains and aromatic rings with different length and size parameters onto the primary amine of peramivir. We found that our de-guanidinylated peramivir analogues showed a rare target selectivity against group-2 neuraminidases instead of group-1 neuraminidases, which might due to the ring geometry of peramivir as well as the reduced electrostatic interaction between the amino group from our analogues and the Asp147-His150 residues from the enzyme. This suggested that it is possible for group-2 neuraminidases to have a more open 150-cavity state than group-1 neuraminidases. Additionally, the respectable IC₅₀ values for these compounds, together with their significantly reduced polarity (relative to peramivir itself) may prove advantageous from a bioavailability standpoint.