From nitriles to nitrogen heterocycles; chemoenzymatic approaches toward diversely substituted enantiopure building blocks

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SUMMARY
FROM NITRILES TO NITROGEN HETEROCYCLES

CHEMOENZYMATIC APPROACHES TOWARD
DIVERSELY SUBSTITUTED ENANTIOPURE BUILDING BLOCKS

Natural compounds containing a cyano group are commonly found in nature, mainly as part of the defense mechanism of plants and microorganisms. In addition, the cyano group is a versatile functionality in organic synthesis, since it can be easily introduced and converted into an amine, amide or acid. Nature has developed efficient enzymatic methods to introduce or convert nitriles and it is not more than logical that synthetic organic chemists have applied these methods for similar purposes. In this thesis, the application of nitrile hydrolyzing enzymes and a hydroxynitrile lyase in the preparation of nitrogen heterocycles is detailed. Subsequently, these compounds were further functionalized via N-acyliminium ion chemistry, a powerful tool for CC bond formation. In this way, the combination of organic synthesis and biocatalysis has proven to be an effective combination for the efficient preparation of a wide range of target molecules.

In chapter 1, the biosynthesis of some nitriles is discussed. The most widely occurring class of natural compounds containing a cyano group are cyanogenic glucosides (1, figure 1) that originate from amino acids. Another source of nitriles are the glycosinolates (2), which also find their origin in amino acids.

![Figure 1](image)

Obviously, nature has developed methods to transform the highly toxic cyano group into less harmful functionalities. Nitrile hydrolyzing enzymes convert nitriles into amides or acids and three types of enzymes may be involved (scheme 1).

![Scheme 1](image)
In chapter 2, the application of *Rhodococcus erythropolis* NCIMB 11540 that possesses nitrile hydrolyzing activity is discussed. This bacterium was incubated with a wide variety of nitriles, including aliphatic, aromatic and dinitriles. Interestingly, all types of substrates were hydrolyzed and the dinitriles were selectively monohydrolyzed. The hydrolysis of 3-hydroxyglutaronitriles (3, scheme 2) led to cyano acids 4, in modest to good selectivity. On the other hand, malononitriles (5) – which were mainly dihydrolyzed by enzyme systems reported in literature — were converted to cyano amides 6 in e.e.s up to 98%.

The results indicated that this enzyme system is significantly different from what has been known in literature, and attempts were made to identify and isolate the responsible enzymes. Unfortunately, screening of enzyme libraries has not yet led to the identification of one enzyme that shows high selectivity and is genetically different from the ones known in literature.

In order to develop follow-up chemistry, a racemic route was developed to arrive at the same products that were formed in the enzyme catalyzed hydrolysis of 3-substituted glutaronitriles (scheme 3).

The results of this research are presented in chapter 3. Transformation of cyano acid 8 into lactam 9 provided a building block that could be further functionalized. Using two different pathways, lactam 9 was converted into two different N-acyliminium ion precursors (10 and 11, scheme 4) allowing the preparation of a modest collection of piperidine-derived compounds (viz. 12 and 13). Interestingly, the routes afforded different selectivity for the introduction of the nucleophile with respect to the O-substituent.
In addition to nitrile hydrolyzing enzymes, a hydroxynitrile lyase was used for the preparation of cyanohydrin 15, which is discussed in chapter 4. Cyanohydrin 15 (scheme 5) should give access to hydroxylactam 16 analogous to the preparation of lactam 9.

However, our initial attempts did not lead to the expected product, but to N,N-acetals 18 (scheme 6). This surprising and unprecedented result made us explore the applicability of this conversion resulting in a novel route to bicyclic N,N-acetals.

Chapter 5 details the preparation of morpholinone derived compounds, using our previously developed chemistry (scheme 7).

Starting from mandelic acid (19), a novel route towards morpholinone structures 21 was developed. In addition, benzaldehyde was converted into N,N-acetal 24 via cyano ester 23. So far, we have only been able to prepare bicycle 23 by hydrogenation of cyano ester 23 in the
presence of ethylenediamine. However, further optimization of the reaction conditions should allow formation of related bicyclic systems.

Finally, in chapter 6 the findings are applied in a synthetic approach toward (racemic) febrifugine, an anti-malaria agent, and a total synthesis of pseudoconhydrine (scheme 8).

Scheme 8

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\text{pseudoconhydrine} \quad \xleftrightarrow{} \quad \text{9} \quad \rightarrow \quad \text{25} \quad \text{lit.} \quad \text{febrifugine}
\]