Summary

Multicomponent approaches towards both C2-functionalized 2-imidazolidines and 2-imidazolines

This thesis describes the synthesis of both C2-functionalized 2-imidazolidines and 2-imidazolines. The synthetic strategies are based on MCRs of in situ formed imines and α-acidic components (Scheme 1). In Chapter 2, respective selective C2-oxidation and C2-thionation protocols of 2-imidazolinium halides (G) towards imidazolidine-2-thiones (B) and imidazolidine-2-ones (A) are discussed. The synthetic sequence is based on the Orru-3CR. In chapter 3 multicomponent synthesis of imidazolidine-2-thiones (C), utilizing α-acidic isothiocyanates, is presented. In chapter 4, synthesis of C2-arylated 2-imidazolines (D) through Liebeskind-Srogl reactions of arylboronic acids with imidazolidine-2-thiones is presented. This chapter was directed towards synthesis of Nutloids, potential MDM2-p53 PPI inhibitors. In Chapter 5 synthetic investigations towards synthesis of novel NK1 receptor antagonists (E) is discussed, of which the synthetic strategy was based on the α-acidic isothiocyanate MCR. Chapter 6 deals with the synthesis of 2-imidazolinium halides (G), contrary to chapter 3, this work was focused towards synthesis of NCH precursors. Finally, in chapter 7, explorative investigations towards a single-step multicomponent synthesis of C2-arylated 2-imidazolines (D) is discussed.

Scheme 1 Multicomponent approaches towards both C2-functionalized 2-imidazolidines and 2-imidazolines
Chapter 2

Chapter 2 describes a scope-study of selective oxidation and thionation protocols of 2-imidazolinium halides of which the synthetic strategy is depicted in Scheme 2. The Orru-3CR products, the 2-imidazolines, were generally obtained in good to excellent yield, although application of isocyanides with weaker electron-withdrawing substituents at the α-position provided these products in a somewhat lower yield. Alkylation towards the 2H-imidazolinium halides was generally achieved in good to quantitative yield by either direct alkylation or utilizing Finkelstein conditions. The imidazoline-2-ones were generally obtained in good yields with the C2 selective oxidation protocol; The imidazoline-2-thiones were generally obtained in good yields utilizing the C2 selective thionation protocol.

Scheme 2  Synthetic strategy: Selective C2-oxidation and C2-thionation protocols

Chapter 3

In chapter 3, MCR synthesis of imidazoline-2-thiones is discussed. This protocol was developed employing α-acidic isothiocyanates, as a single reactant replacement approach (SRR) starting from the Orru-3CR (Scheme 3). While this approach was successful for syntheses of imidazolidine-2-thiones, efforts in a SRR-approach towards imidazolidine-2-ones, utilizing α-acidic isocyanates, failed.
Conclusive evidence of this approach came from crystallographic analysis of imidazolidine-2-thione A1, proving final establishment of the imidazolidine-2-thione scaffold as well as assignment of the respective diastereoisomers.

Experimental results of a scope expansion study of the α-acidic isothiocyanate component, showed that the MCR requires the use of quite α-acidic derivatives since inputs to the MCR of type II and III failed to provide the desired heterocyclic scaffold (Figure 2), which was supported by a DFT computational study.
A DFT computational study into the mechanism of the MCR indicated a Mannich type mechanism, which is favored over the alternative ‘first b then a’-type mechanism (Scheme 4). Additionally, decisive factors were assigned to explain the observed reactivity of the utilized α-acidic isocyanates.

![Scheme 4](image)

Additionally, explorative experimental investigations into the kinetics of the MCR were performed. This showed the MCR to possess a temperature based ‘on – off’-type properties. Mechanistic details and kinetics of the MCR are currently under investigation.

**Chapter 4**

Chapter 4 describes our synthetic efforts towards synthesis of C2-arylated 2-imidazolines. The synthetic sequence is based on the α-acidic isothiocyanate MCR presented in chapter 3. The sequence provides synthesis of the desired heterocyclic scaffold in two synthetic steps, which is a reduction of four synthetic steps in comparison with the Orru-3CR based strategy. Research is focused towards synthesis of nutloids. Therefore, a scope study of the Liebeskind-Srogl reaction was performed utilizing both α-substituted and α,α-disubstituted arylboronic acids (Scheme 5). Although the desired products were isolated in modest yields, corresponding C2-unsubstituted 2-imidazoline was also isolated as a thus far not reported type of side product of the Liebeskind-Srogl cross-coupling.
Chapter 5

In chapter 5 synthetic investigations towards synthesis of imidazolidine-2-one NK1 receptor antagonists is presented. The synthetic strategy, based on the α-acidic isothiocyanate MCR discussed in chapter 3, includes reduction of the C4-ester moiety and alkylation of the resulting alcohol. While these steps need to be performed in the abovementioned order, necessary S/O-exchange was envisioned to be possible during various stages of the sequence (Scheme 6).

Scheme 6  Synthetic strategy towards imidazolidine-2-one NK1 receptor antagonists

Both MCR synthesis of the imidazolidine-2-thione scaffold, and reduction of the ester moieties proceed in excellent yield. However, S/O-exchange in the MCR stage of the sequence was until now unsuccessful. Additionally, synthesis of the ether linkage proved a real challenge, since both under basic and neutral coupling conditions S-alkylation instead of O-alkylation was observed. Next, both efforts through generation of a dianion, approaches ‘A’ and ‘C’, proved unsuccessful. Application of approach ‘C’ synthesis of 2-(methylthio)-2-imidazolines and was achieved though sequential S- and O-alkylation. However, all efforts into hydrolytic cleavage of the SR functionality failed.
Chapter 6

In chapter 6, synthesis of 2-imidazolinium iodides, based on the Orru-3CR followed by alkylation under Finkelstein conditions, is described (Scheme 8). Contrary to chapter 2, synthesis was focused towards synthesis of NHC precursors as ligands in homogeneous catalysis. The Orru-3CR products were either synthesized according to literature or afforded in excellent yield, while alkylation towards the 2-imidazolinium iodides was achieved in excellent to quantitative yields.

Scheme 8 Synthetic sequence towards 2-imidazolinium iodides
Also, in chapter 6, two synthetic strategies towards bis-(2-imidazolinium) iodides are described; a sequence of (i) the Orru-3CR, followed by bis-alkylation of a bridging bis-electrophile and (ii) a double Orru-3CR by utilizing a diamine followed by bis-alkylation (Scheme 9). Strategy (i) proved successful, affording the 2-imidazolinium iodides in good yields over two steps. All efforts employing strategy (ii) however, surprisingly failed, even though Bon et al. reported the utilization of bis-functional components in the Orru-3CR. Therefore, additional investigations into strategy (ii) are desired.

Scheme 9  Synthetic strategies towards bis-(2-imidazolinium) iodides

(i)  
\[
\begin{align*}
\text{Orru-3CR} & \quad \rightarrow \quad \begin{array}{c}
\text{(i)} \\
\text{Bridge, rt, Nal}
\end{array} \\
(R)_n N & \rightarrow \quad \begin{array}{c}
\text{Aceton, rt, Nal}
\end{array} \\
\end{align*}
\]

(ii)  
\[
\begin{align*}
\text{Orru-3CR} & \quad \rightarrow \quad \begin{array}{c}
\text{Bridge, rt, Nal}
\end{array} \\
(R)_n N & \rightarrow \quad \begin{array}{c}
\text{Aceton, rt, Nal}
\end{array} \\
\end{align*}
\]

Chapter 7

In chapter 7, explorative investigations towards the synthesis of C2-arylated 2-imidazolines, through 1,3-dipolar cycloadditions by reactions of imines and imidoyl chlorides, is presented (Scheme 10). Contrary to chapter 4, research is focused towards methodological development.

Scheme 10  Synthetic strategy towards C2-arylated 2-imidazolines

\[
\begin{align*}
\begin{array}{c}
\text{Ar}^1 \quad \text{Ar}^2 \quad \text{Ar}^3 \\
\text{N} \\
\end{array} & \quad \rightarrow \quad \begin{array}{c}
\text{Cl} \\
\text{Ar}^3 \\
\text{Ar}^2 \quad \text{Ar}^3 \\
\end{array} \\
\end{align*}
\]

Experimentation was directed to the optimization of the 1,3-dipolar cycloaddition, which was found to proceed both under base- and TMSOTf-promoted conditions. We were able to reduce reaction times dramatically from 7 days to 5 hours in the order of NEt₃ → lutidine → TMSOTf. However, TMSOTf-promoted conditions facilitated isolation of regioisomer instead (Scheme 11).
Formation of this regioisomeric product may originate from nitrile ylide interconversion as a result of a formal hydride shift (Scheme 12).

Furthermore, assignment of the respective diastereoisomers was accomplished through measurement of the relative air oxidation rates (Scheme 13). In analogy with the work of Bon et al. the *trans*-derivatives possessed much greater stability to air oxidation.

Finally, in this chapter an initial MCR approach is described, which proceeds through a 1,3-dipolar cycloaddition of an imidoyl chloride and an *in situ* formed imine (Scheme 14).
References

Samenvatting (Summary in Dutch)

**Multicomponent strategieën voor de synthese van C2-gefunctionaliseerde 2-imidazolidines en 2-imidazolines**

In dit proefschrift word de synthese beschreven van zowel C2-gefunctionaliseerde 2-imidazolines als 2-imidazolidines. De synthetische strategieën zijn gebaseerd op MCRs van *in situ* gevormde imines en α-zure componenten (Schema 1). In **hoofdstuk 2** wordt respectievelijk de selectieve C2-oxidatie en C2-thionatie protocollen van 2-imidazolinium halides (G) besproken voor de synthese van imidazolidine-2-onen (A) en imidazolidine-2-thionen (B). The synthetische sequentie is gebaseerd op de Orru-3CR. In **hoofdstuk 3** wordt, gebruik makend van α-zure isothiocyanaten, de synthese van imidazolidine-2-thionen (C) gepresenteerd. **Hoofdstuk 4** beschrijft de synthese van C2-gearyleerde 2-imidazolines (D) door Liebeskind-Srogl reacties van boorzuren en imidazolidine-2-thionen. In dit hoofdstuk was het onderzoek toegespitst op de synthese van Nutloids, potentiele inhibitoren van MDM2-p53 eiwit-eiwit interactie. In **hoofdstuk 5** wordt het onderzoek naar de synthese van NK1 receptor antagonisten (E) gepresenteerd, waarvan de synthetische sequentie gebaseerd is op de MCR van imines met α-zure isothiocyanaten. In **hoofdstuk 6** wordt de synthese van imidazolinium halides (G) beschreven. In tegenstelling tot hoofdstuk 3, was dit onderzoek gericht op de synthese van intermediairs van NHCs. Als laatste wordt in **hoofdstuk 7** exploratief onderzoek gepresenteerd naar de MCR synthese van C2-gearyleerde 2-imidazolines (D).