Sustainable Synthesis of Thioimidazoles via Carbohydrate-Based Multicomponent Reactions

Marcus Baumann and Ian R. Baxendale*

Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, United Kingdom

Supporting Information

ABSTRACT: The synthesis of diversely functionalized thioimidazoles through a modern variant of the Marckwald reaction is presented. This new protocol utilizes unprotected carbohydrates as well as simple amine salts as sustainable and biorenewable starting materials. Importantly it was discovered that a bifurcated reaction pathway results from using aldoses and ketoses respectively, yielding distinct reaction products in a highly selective manner.

Multicomponent reactions represent some of the most versatile chemical transformations converting three or more simple starting materials into a complex molecule in a single cascade.1 As such, these reactions continue to play a pivotal role in the assembly of complex molecular architectures for both natural product and medicinal chemistry programs.2 Despite the structural diversity resulting from these atom- and step-economical reactions,3 sourcing the appropriately prefunctionalized substrates can be cumbersome as this commonly adds extra steps to the final synthetic route. We therefore sought to address this generic problem by making use of diverse yet highly abundant biorenewable starting materials such as carbohydrates and amino acid derivatives.4 We reasoned that combining these readily available inputs with potassium isothiocyanate (KSCN) would yield structurally diverse sets of thioimidazoles based on the overlooked Marckwald thioimidazole synthesis.5 Importantly, this would allow for an efficient and highly sustainable access into the important imidazole motif, which can be found in numerous biologically active molecular structures.6,7

We set out preparing several trisubstituted thioimidazoles using different benzylamine hydrochloride salts (1), KSCN (2), and dihydroxyacetone dimer (3, DHA) which are the common inputs for this multicomponent reaction.8 Pleasingly, when heating the combined starting materials in wet acetonitrile (1 M, 2–5% water content) and glacial acetic acid (1 equiv) a light colored suspension resulted allowing for a very high yielding synthesis of products 4 (Scheme 1).

It was found that the heterogeneity of this reaction mixture was crucial for a successful outcome as otherwise competing Maillard processes9 would inevitably lead to numerous undesired condensation products, whereas in the heterogeneous scenario the desired product would precipitate once formed enabling simple product isolation through filtration. Early investigations into the nature of the amine salt component had also revealed that other salts are tolerated although either lower yields (HOAc salts) or ester hydrolysis/lactonization (H2SO4 salts) might result. Encouraged by these results we decided to study the scope of this reaction by varying the nature of the amine salt component and found that various benzylamine derivatives as well as aliphatic

Scheme 1. Representative Imidazole-Forming Multicomponent Reactions

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amines as their corresponding HCl salts give the desired thioimidazole products in high isolated yields. More importantly, employing several amino ester salts was found to also deliver the desired thioimidazole products (Figure 1).

While the variation of the amine component had reliably delivered the desired thioimidazole products tolerating many (hetero)aromatic moieties as well as potentially labile esters and carbamates (e.g., 4I), we decided to next challenge this transformation by substituting dihydroxyacetone with highly abundant carbohydrates such as tetroses, pentoses, and hexoses. As such we chose to submit different amine hydrochloride species (1) to our multicomponent protocol with L-(+)-erythrulose, D-(+)-xylose, D-(−)-ribose, D-(+)-galactose, or D-(−)-fructose as the carbohydrate component.

Pleasingly, the various thioimidazole structures were obtained in high yield as reaction products when using aldoses (e.g., D-(+)-xylose, D-(−)-ribose, and D-(+)-galactose) as carbohydrate components (Scheme 2). Further analysis of 2D-NMR data (e.g. HMBC, see SI for details) revealed the presence of a different regioisomeric thioimidazole product in these cases.

The fact that these reactions consistently produced single diastereomers (5a–f) prompted us to consider a mechanism in which epimerization through enolization pathways would only affect C1 and C2 of the acyclic carbohydrate substrates (Scheme 3). The assumption that C3 is not undergoing epimerization is furthermore supported by the fact that the 1H and 13C NMR data for C3-epimeric product pairs such as 5a and 5b are not identical (see Supporting Information for details). We thus propose that an imine species 6b is initially formed prior to its reaction with KSCN. The transient adduct can undergo an Amadori rearrangement10 allowing a subsequent cyclocondensation to furnish the thioimidazole scaffold (6e) upon elimination of water. Based on this reasoning and confirmed by polarimetric experiments, aldose-derived Markwald reaction products are optically active entities.

Intriguingly, when subjecting ketoses to the same reaction conditions a very different outcome was observed delivering bicyclic 6-hydroxytetrahydro-1H-furo[2,3-d]imidazole-2(5H)-thiones (Figure 2, 7a–f) as major products. It is noteworthy that although the bicyclic framework of compounds 7a–f is predecented in carbohydrate literature,11 its conventional synthesis typically starts from protected 2-aminosugars and various isothiocyanates representing a more laborious and cost-intensive synthesis than the transformation reported here via a one-step multicomponent route.

Being a much more attractive route into these bicyclic structures we decided to further study the mechanism of this unexpected substrate-specific transformation.

We propose that under the mildly acidic reaction conditions both erythrulose and fructose exist in their acyclic keto-forms analogous to the aldoses. This allows for a ketimine product 8a to form with the amine component prior to the reaction of this species with KSCN (Scheme 4).

Once the resulting ternary adduct 8b is generated two separate Amadori rearrangement pathways can occur leading to either aldehyde 8c or ketone 8e. Aldehyde 8c can undergo subsequent ring closure furnishing the cyclic thiourea 8d, which provides the main reaction product 7a–c via 5-exo-trig

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**Figure 1.** Extended scope of Markwald thioimidazole synthesis (1–150 mmol scale).

**Scheme 2.** Polyhydroxyl-thioimidazoles Generated from Different Aldoses

**Scheme 3.** Proposed Reaction Mechanism for Aldoses (Shown for D-(+)-Xylose)
interesting entities will spark renewed interest in this that our simple and high yielding synthetic routes to these ess starting from aldoses and ketoses, respectively. We believe tetrahydro-1 of either monocyclic thioimidazoles or bicyclic 6-hydroxy- we discovered and exploited the substrate-speci
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scale. Importantly, the developed procedures rely on
can generate isolable byproducts such as 8g and 8h indicating the presence of different concurrent reaction pathways. Overall, the dynamic nature of this proposed mechanism explains the observed product outcome and appears to be controlled by thermodynamic elements.

In conclusion, we have developed a modern variant of the overlooked Markwald multicomponent reaction that can deliver diverse sets of thioimidazoles products on multigram scale. Importantly, the developed procedures rely on biorenewable starting materials such as various carbohydrates and amino acid derivatives providing a cheap and sustainable access to these structures. During the course of our studies, we discovered and exploited the substrate-specific generation of either monocyclic thioimidazoles or bicyclic 6-hydroxy-tetrahydro-1H-furo[2,3-d]imidazole-2(5H)-thiones in a process starting from aldoses and ketoses, respectively. We believe that our simple and high yielding synthetic routes to these interesting entities will spark renewed interest in this transformation as well as further green applications of related chemistries.

ASSOCIATED CONTENT
Supporting Information
Experimental procedures, spectroscopic characterization of the products, and CIF data for 7b (CCDC 1020070) and (OAc)₃-7f (CCDC 1020071). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION
Corresponding Author
E-mail: i.r.baxendale@durham.ac.uk.
Notes
The authors declare no competing financial interest.

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REFERENCES

(12) These minor products were isolated by column chromatography of the crude material obtained after evaporating the mother liquors, from which the main product had been triturred.