

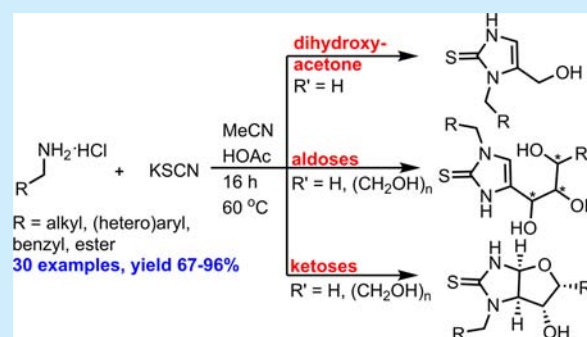
Sustainable Synthesis of Thioimidazoles via Carbohydrate-Based Multicomponent Reactions

Marcus Baumann and Ian R. Baxendale*

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

S 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.



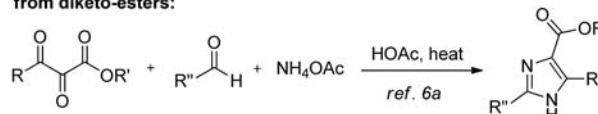
Multicomponent reactions represent some of the most versatile chemical transformations converting three or more simple starting materials into a complex molecule in a single cascade.¹ As such, these reactions continue to play a pivotal role in the assembly of complex molecular architectures for both 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).

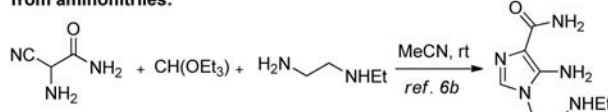
It was found that the heterogeneity of this reaction mixture was crucial for a successful outcome as otherwise competing Maillard processes⁹ would inevitably lead to numerous undesired condensation products, whereas in the heterogeneous scenario the desired product would precipitate once

Scheme 1. Representative Imidazole-Forming Multicomponent Reactions

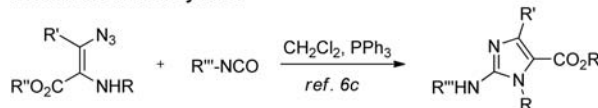
from diketo-esters:



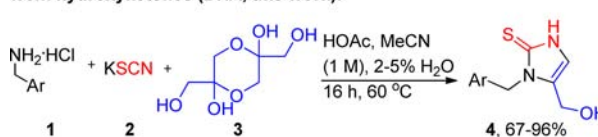
from aminonitriles:



from amino-azidoacrylates:



from hydroxyketones (DHA, this work):



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 (H_2SO_4 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

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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).

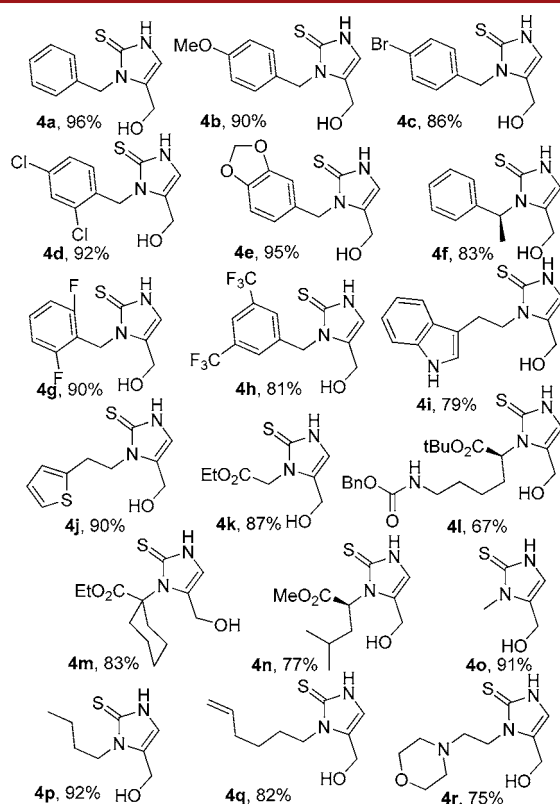


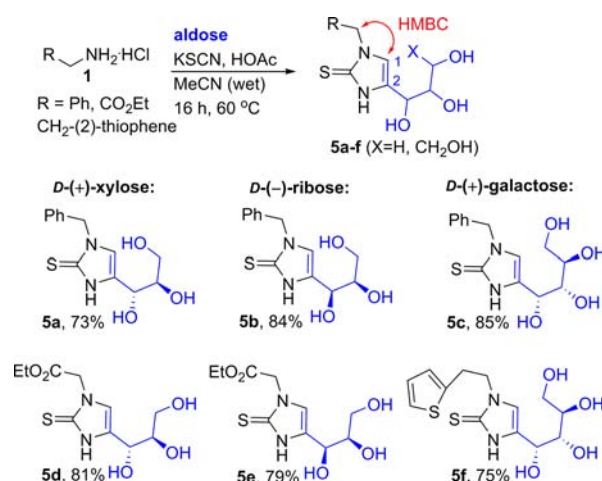
Figure 1. Extended scope of Marckwald thioimidazole synthesis (1–150 mmol scale).

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., **4l**), 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-(+)-erythrose, D-(+)-xylose, D-(–)-ribose, D-(+)-galactose, or D-(–)-fructose as the carbohydrate component.

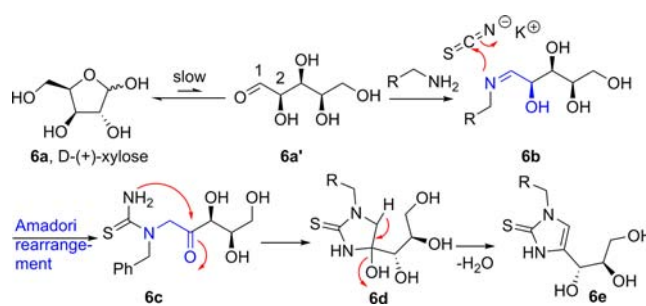
Pleasingly, the various thioimidazole structures were obtained in high yield as reaction products when using aldoses (e.g., D-(+)-xylose, D-(–)-ribose, and D-(+)-galactose) as carbohydrate components (Scheme 2). Further analysis of 2D-NMR data (e.g. HMBC, see SI for details) revealed the presence of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

Scheme 2. Polyhydroxyl-thioimidazoles Generated from Different Aldoses



Scheme 3. Proposed Reaction Mechanism for Aldoses (Shown for D-(+)-Xylose)



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 Marckwald 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 preceded 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 erythrose 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

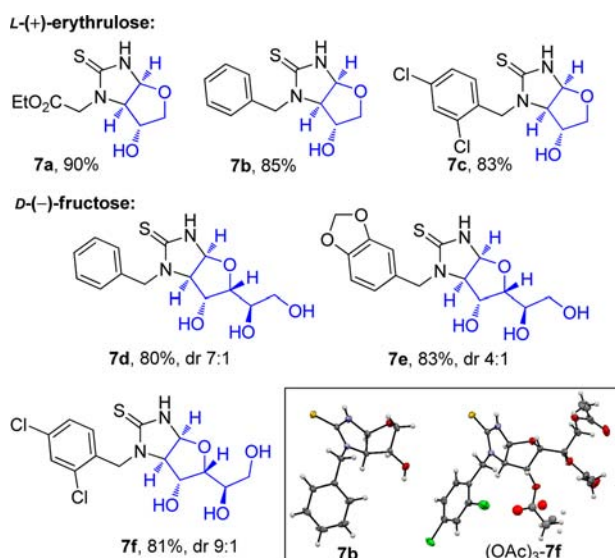
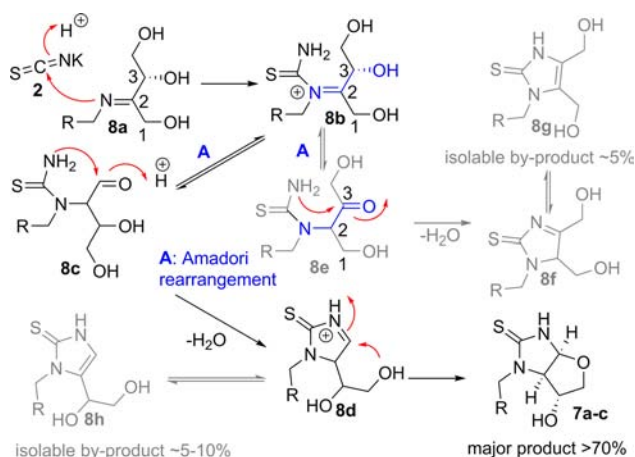


Figure 2. Ketose-based reaction products and X-ray structures of **7b** and (OAc)₃-**7f**.

Scheme 4. Proposed Reaction Mechanism for the Formation of Bicyclic Reaction Products from Ketoses (Shown for L-(+)-Erythrose)



cyclization. Alternatively, competing pathways (shown in gray) can generate isolable byproducts such as **8g** and **8h** indicating the presence of different concurrent reaction pathways.¹² 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 Marckwald multicomponent reaction that can deliver diverse sets of thioimidazole 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-1*H*-furo[2,3-*d*]imidazole-2(*SH*)-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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(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 triturated.