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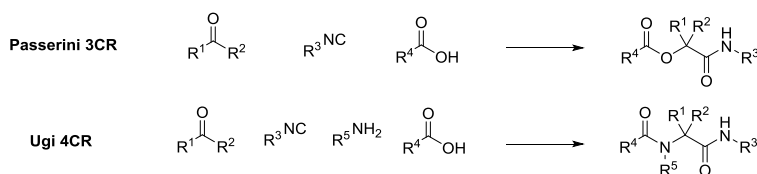
Summary

Off the Beaten Path:

Atypical Products of Ugi and Passerini Reactions

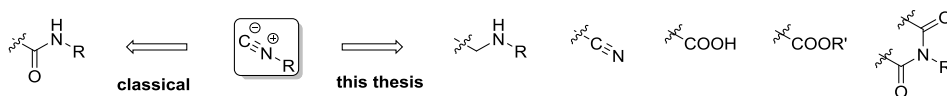
Summary

In 1921 Mario Passerini performed the reaction between acetone, acetic acid and *p*-isocyanobenzene, in what turned out to be the first isocyanide-based multicomponent reaction. Almost four decades later, Ivar Ugi took this reaction further by introducing a fourth component, the amine. Nowadays, these old reactions (Scheme 1) are recognized as essential synthetic tools and are widely applied in combinatorial and diversity-oriented synthesis, natural product synthesis, polymer science, etc.



Scheme 1. Isocyanide-based multicomponent reactions: Ugi and Passerini.

In this work the classical Ugi and Passerini reactions are given an upgrade: these valuable reactions are reinterpreted based on a rational design to afford atypical products for this chemistry. Several key concepts in the field of (isocyanide-based) multicomponent reactions have been used to access unconventional scaffolds: single-reactant replacement, post-condensation modification, bifunctional inputs, convertible isocyanides. Furthermore, based on sound mechanistic considerations, the normal course of the Passerini 3CR and Ugi 4CR has been manipulated towards different reaction pathways, and this only with subtle changes in reaction conditions and/or isocyanide design. Ultimately, the primary focus of this research was to move away from the classical conversion of the isocyanide group into a primary amide moiety and to provide access to other functionalities: primary amines, nitriles, carboxylic acids, esters, imides (Scheme 2).

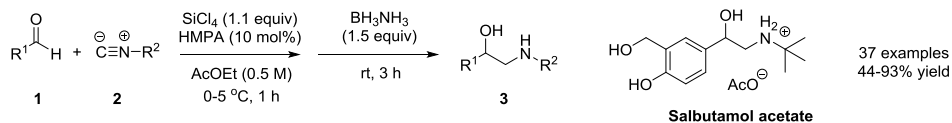


Scheme 2. Conventional and novel conversions of isocyanides.

Thus, after introducing the reader with the notions and concepts of the classical Ugi and Passerini reactions in **Chapter 1**, this thesis exemplifies in the following chapters how old chemistry can be reinvented for the improvement of the synthesis of valuable molecules. **Chapter 2** describes the combinatorial synthesis of medically relevant β -amino alcohols **3** from aldehydes and isocyanides. This protocol combines a Passerini-type reaction (in which the carboxylic acid component is replaced by silicon tetrachloride) with the one-pot ammonia-borane reduction to afford directly bioactive compounds in a straightforward

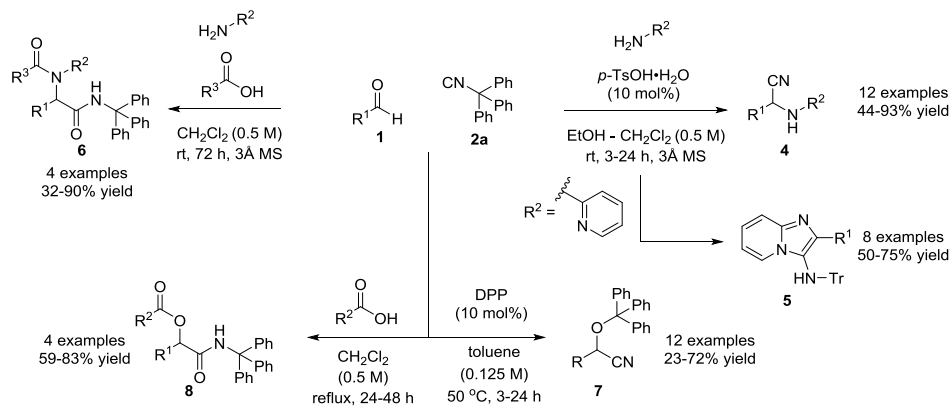
Summary

and general manner (Scheme 3). We demonstrated that this unusual retrosynthetic disconnection allows easy access to targets that are challenging for the conventional approaches based on substitution: the reaction tolerates steric bulk, unsaturated bonds and various functional groups. Importantly, the process can be upgraded by the introduction of a chiral catalyst to enable the catalytic enantioselective synthesis of β -amino alcohols through isocyanide addition. Finally, this new methodology was showcased by the preparation of the highly important anti-asthma drug Salbutamol.



Scheme 3. Synthesis of β -amino alcohols from aldehydes and isocyanides.

Next, in **Chapters 3 and 4** the multicomponent chemistry of triphenylmethyl (trityl) isocyanide **2a** was explored for the first time. Intriguingly, together with the expected reactivity, this simple isocyanide exhibits distinctive chemical behavior in interactions with imines or aldehydes and under determined conditions it allows the preparation of atypical Ugi and Passerini products. Thus, trityl isocyanide can be used as cyanide donor in the Strecker reaction (product **4**) and cyanohydrin (**7**) synthesis and serves as convenient convertible isocyanide in Ugi, Passerini and Groebke-Blackburn-Bienaymé reactions (Scheme 4).



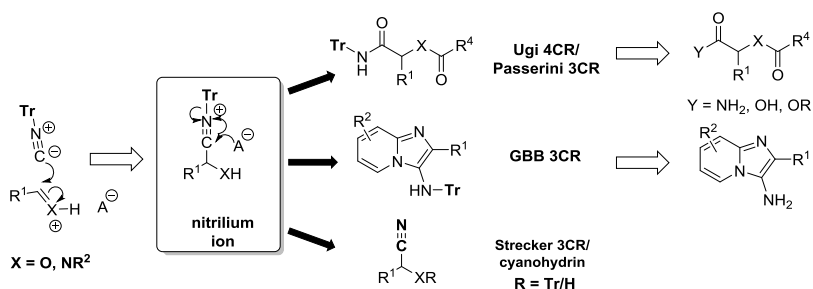
Scheme 4. Ugi and Passerini-type additions with trityl isocyanide.

The mechanisms of these classical MCRs intersect in the common trityl nitrilium ion intermediate whose predictable reactivity can be exploited towards chemoselective

Summary

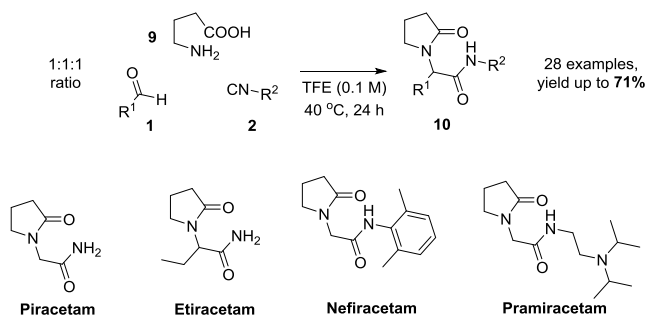
transformations. Specifically, this reactive species can undergo fragmentation (*Strecker* pathway), intramolecular addition (*Groebke-Blackburn-Bienaymé* pathway) or intermolecular addition (*Ugi/Passerini* pathways), as shown in Scheme 5. A great variety of products is thus accessible from simple inputs in a divergent way, particularly since the *N*-trityl amide derivative can be transformed further into interesting scaffolds.

This unique chemical behavior of trityl isocyanide can be exploited in many other ways; some suggestions were provided in **Chapter 7**.



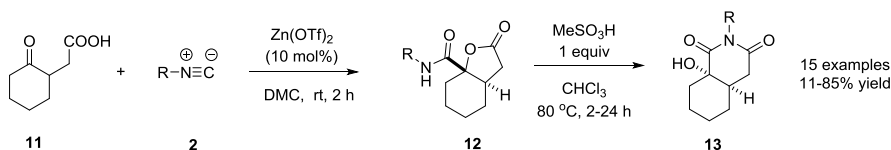
Scheme 5. Reactivity of the *N*-trityl nitrilium ion.

Continuing on the topic of combinatorial synthesis of bioactive compounds, **Chapter 5** describes the direct Ugi four center-three component reaction involving γ -aminobutyric acid **9** towards racetam derivatives **10**. These compounds find wide application in the treatment of various medical conditions and represent therefore highly relevant targets for synthesis. Substantial optimization efforts were required to improve the selectivity for the desired product in this novel Ugi reaction but gratifyingly under the optimal conditions the transformation proved to be general. Thus, this method provides rapid access towards novel racetam derivatives as well as commercial drug molecules: no less than four clinically important racetams were prepared using this approach (Scheme 6).



Scheme 6. Ugi approach towards clinically-relevant racetams.

Finally, in **Chapter 6** we returned to the Passerini reaction and attempted to tackle a difficult problem in isocyanide chemistry, namely the stereocontrol of the isocyanide addition. Thus, we were able to add a new entry to the brief list of diastereoselective Passerini reactions by employing a bifunctional input, keto acid **11**. *Trans*-fused bicyclic lactones **12** can be generated with *dr* of up to 90:10 and the isocyanide scope of this intramolecular Passerini reaction is broad. Interestingly, this scaffold was shown to rearrange towards α -hydroxy imide **13** under acidic conditions, which is unprecedented in Passerini chemistry.



Scheme 7. Diastereoselective intramolecular Passerini reaction.

In summary, the work described in this thesis represents an attempt to expand the highly diverse chemistry of isocyanides in new directions, going beyond the classical primary amide products. Building on well-established concepts of isocyanide chemistry and reaction mechanisms, novel transformations were designed to access unconventional products. Thus, the new entries added to the list of Passerini and Ugi products are the β -amino alcohols, α -amino nitriles, *O*-trityl cyanohydrins, 2-pyrrolidone-1-acetamides and α -hydroxy imides. The protocols towards these structures generally feature attractive characteristics for applications in organic synthesis: high atom economy, high selectivity, mild reaction conditions, short reaction times, broad scope. Moreover, the chemistry developed herein is divergent, in the sense that typically both the classical (*i.e.* Passerini and Ugi) as well as the novel reactivity can be pursued in the same system, under rationally adapted conditions.

In conclusion, isocyanides are highly versatile building blocks for synthesis and this thesis testifies that despite the decades of intense exploration, the possibilities of developing novel chemistry with these reagents are far from exhausted.