

Pyrrolidinodiones in Enol-Ugi, Enol-Passerini and anomalous enol-Passerini condensations

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ABSTRACT: In continuation with our recent research in the development of novel multicomponent reactions with isocyanides, we have used for the first-time enols as the acid components in Ugi and Passerini-type reactions. Thus, electron-poor pyrrolidinodiones react with aldehydes, amines and isocyanides to give the enaminic four-component adducts. Conversely, in the absence of the amine component, careful control of the reaction conditions allows the involvement of one or two molecules of isocyanide to afford selectively, either Passerini-type or pseudo-enol-Ugi-type products. These unprecedented condensations of isocyanides, aldehydes, amines and 4-substituted pyrrolidine-2,3-diones constitute an excellent strategy for the preparation of new biologically relevant pyrrolidinones having peptidic or pseudo-peptidic groups on carbon 3.

Introduction

Pyrroles are important heterocycles, present in many biomolecules, such as hemo, chlorophyll, vitamin B₁₂ and the bile pigments. Nonaromatic pyrrolidinones are also found in the structure of many natural products and biologically active molecules, such as inhibitors of cAMP phosphodiesterase,¹ the vascular endothelial growth factor receptor (VEGF-R),² HIV integrase³ and xanthine dehydrogenase (Figure 1).⁴ Importantly, structure-based design has recently identified 1,5-dihydropyrrol-2-ones containing oxygen and nitrogen substituents in position 3 as potent inhibitors of p53-MDM2 protein-protein interactions, which proved selectively active against tumor cells with deleted p53 and tumor xenograft models.⁵ Although 3-substituted pyrrolidinones are readily accessible by the nucleophilic substitution on 2,3-diones,⁶ rather harsh conditions are required and only simple oxygen and nitrogen groups can be introduced.^{4-5,7} Thus, it is crucial to find mild and selective procedures to introduce complex substituents on position 3 of pyrrolidinones.

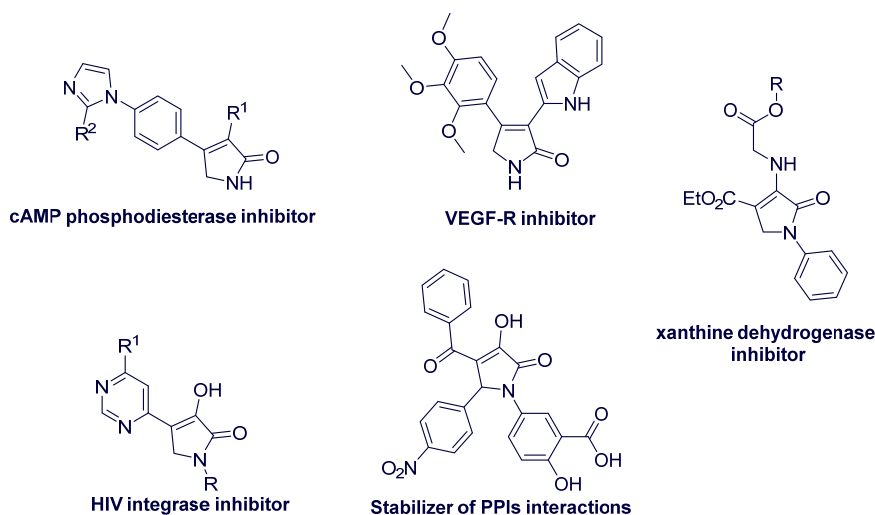
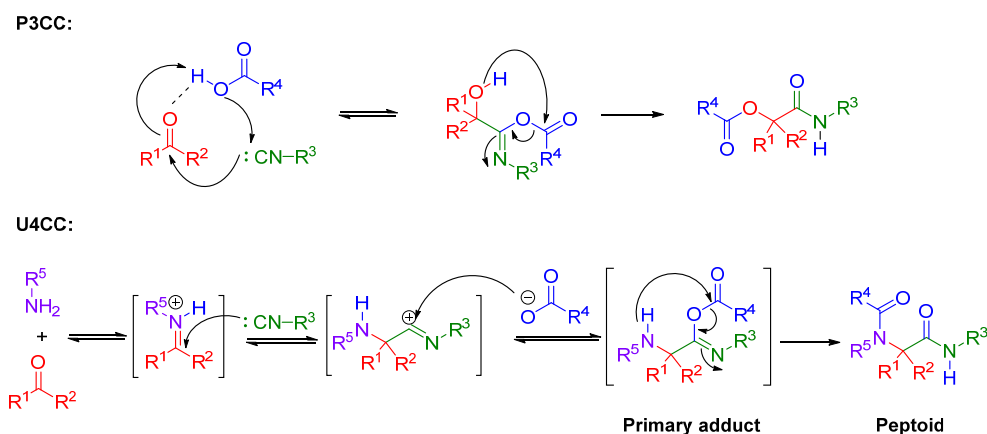


Figure 1. Biologically relevant pyrrolidinones

Multicomponent reactions (MCR) are highly convergent processes, in which three or more simple starting materials react to readily give complex products.⁸ They are characterized for their great efficiency, versatility and atom economy. Thus, MCR involving isocyanides (IMCRs), as the Passerini three-component condensation (P3CC; Scheme 1)⁹ and the Ugi four-component condensation (U4CC; Scheme 1)¹⁰ are extensively used to synthesize diversely functionalized substituted α -acyloxy- and α -acylamino amides, respectively.¹¹ Further structural diversity can be achieved through a wide variety of post-condensation transformations,¹² or by the replacement of one of the reactant components by a new reagent that mimics its reactivity and chemical behaviour.¹³



Scheme 1. Passerini and Ugi multicomponent condensations.

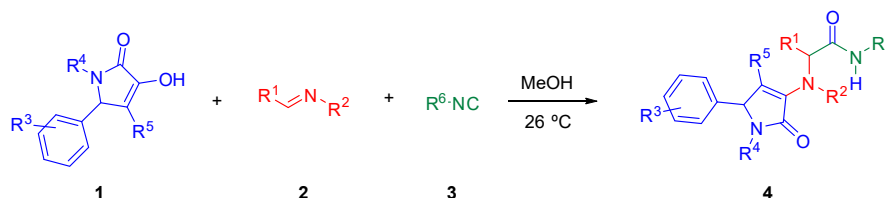
We have recently discovered that enols can be used as acid components in Passerini and Ugi-type multicomponent condensations.¹⁴ Here we describe the use of enolic pyrrolidinodiones in different types of IMCRs leading to pyrrolidinone-derived enol-ethers and enamines.

Results and Discussion

Thus, the reaction of 4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates with isocyanides and either aldehydes or imines have been explored.

Enol-Ugi condensations

Enolic pyrrolidine-2,3-diones (**1**), imines (**2**) and isocyanides (**3**) were mixed in methanol at rt to give the expected Ugi-type adducts (**4**, Scheme 2), which were isolated in very good to excellent yields. They were identified according to their spectral data, and the structure was further confirmed by X-ray diffraction analysis (Figure 2).^{14d}



Scheme 2. Enol-Ugi condensation of pyrrolidinodiones.

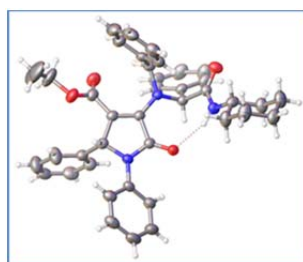


Figure 2. X-ray structure of the enol-Ugi adduct ethyl 4-(benzyl(2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate.^{14d}

The reaction shows a wide scope and has been performed with different combinations of imines, isocyanides and pyrrolidinodiones (Figure 3). We have also shown that it is possible to form the imines *in situ* from the corresponding amines and aldehydes, thus the four-component condensation can be accomplished.

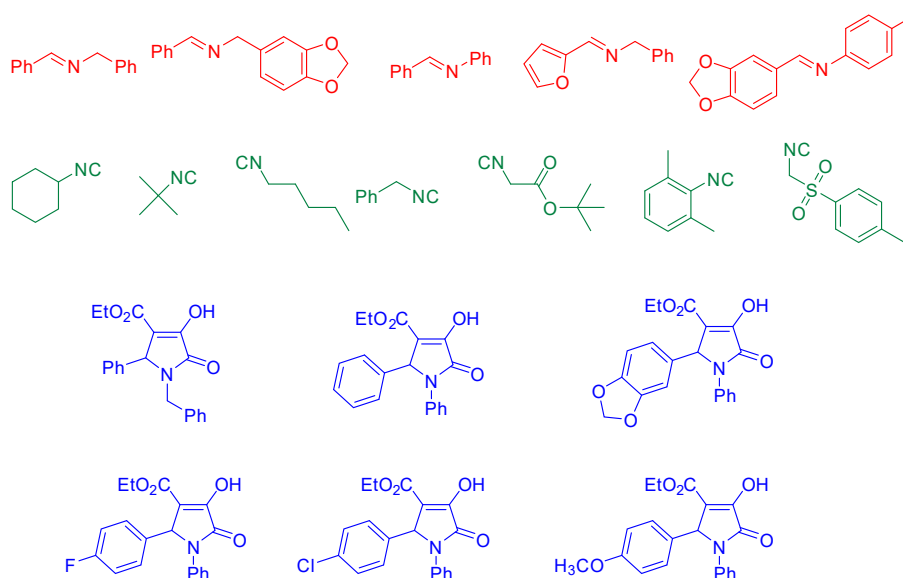
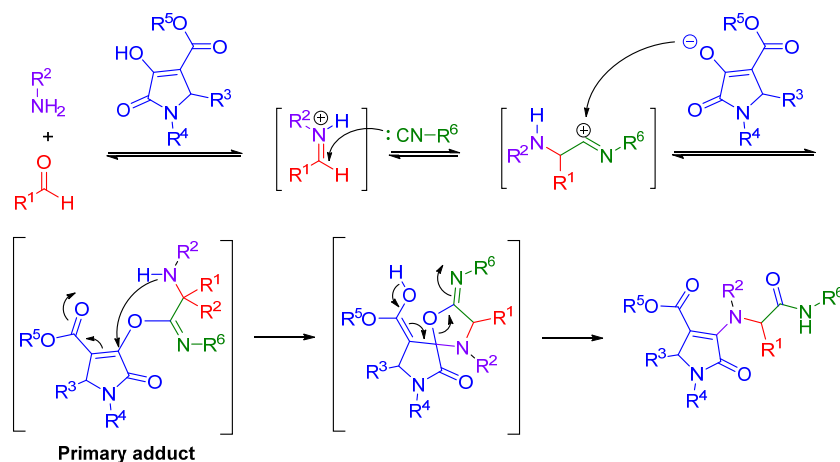


Figure 3. Scope of the enol-Ugi condensation with pyrrolidinodiones: different components used in the reaction.

The mechanism of the reaction can be explained by the protonation of the imine to form an iminium cation, which is attacked by the isocyanide to give a nitrilium cation intermediate. This then suffers the nucleophilic attack of the enolate, resulting in a primary adduct analogous to the primary adduct in the

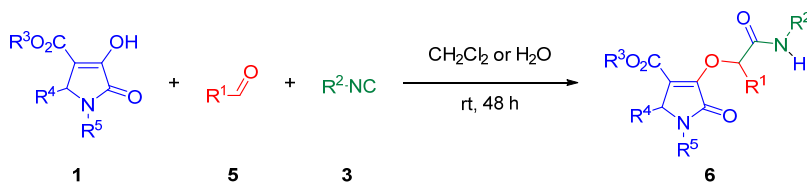
classical Ugi condensation. Thus, up to here, the reaction is mechanistically similar to the Ugi condensation with carboxylic acids. However, in the enol-Ugi condensation the primary adducts spontaneously evolve to a stable product by a Michael–retro-Michael rearrangement, instead of the Mumm rearrangement that takes place in the classic U-4CC (Scheme 3).



Scheme 3. Possible mechanism of the enol-Ugi condensation.

Enol-Passerini condensations

In this case, the reaction is performed by mixing enolic pyrrolidine-2,3-diones (**1**), aldehydes (**5**) and isocyanides (**3**). The reaction takes place optimally at room temperature in dichloromethane, readily affording the corresponding pyrrolidinone amido ethers (**6**) in good to excellent yields.^{14a} The reaction is also possible in on-water conditions, i.e. using water as the solvent (Scheme 4).



Scheme 4. Enol-Passerini condensation of pyrrolidinodiones.

The reaction has been also shown to be quite general, allowing the use of diverse aromatic aldehydes, pyrrolidinodiones and both aliphatic and aromatic isocyanides (Figure 4).

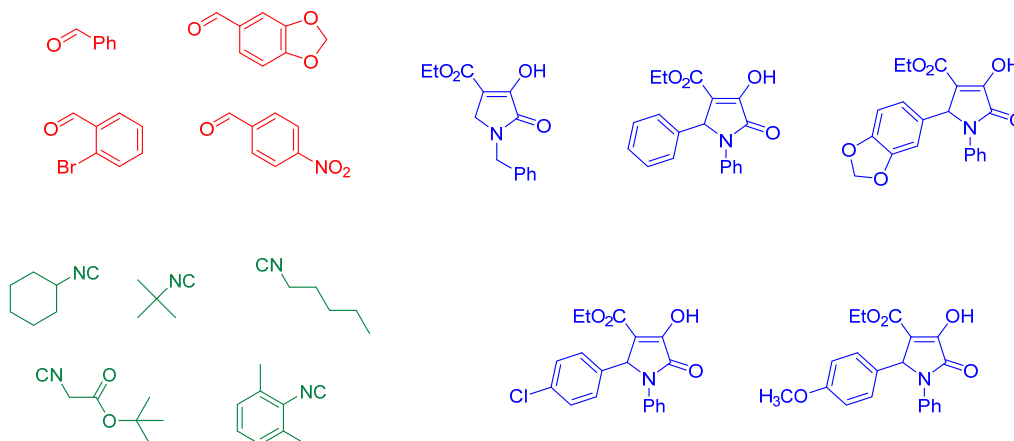
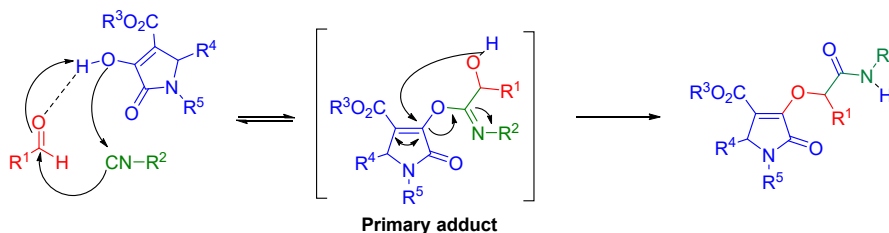


Figure 4. Scope of the enol-Passerini condensation with pyrrolidinodiones: different components used in the reaction.

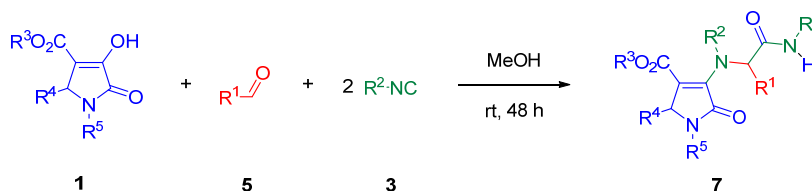
A mechanism in which the pyrrolidinodione acts as the acid component of the condensation can be envisaged. In parallelism with the classical Passerini condensation, the reaction purportedly takes place in a concerted manner, as show in Scheme 5.



Scheme 5. Possible mechanism of the enol-Passerini condensation.

Anomalous enol-Passerini condensations

Finally, the reaction of pyrrolidine-2,3-diones (**1**), aldehydes (**5**) and two equivalents of isocyanides (**3**) in polar solvents, such as methanol, yields a pseudo-enol-Ugi four-component adduct (**7**; Scheme 6).^{14a}



Scheme 6. Anomalous enol-Passerini condensation of pyrrolidinodiones.

In this case, the reaction admits diverse aldehydes and pyrrolidinodiones, but it is not possible with bulky isocyanides (Figure 5).

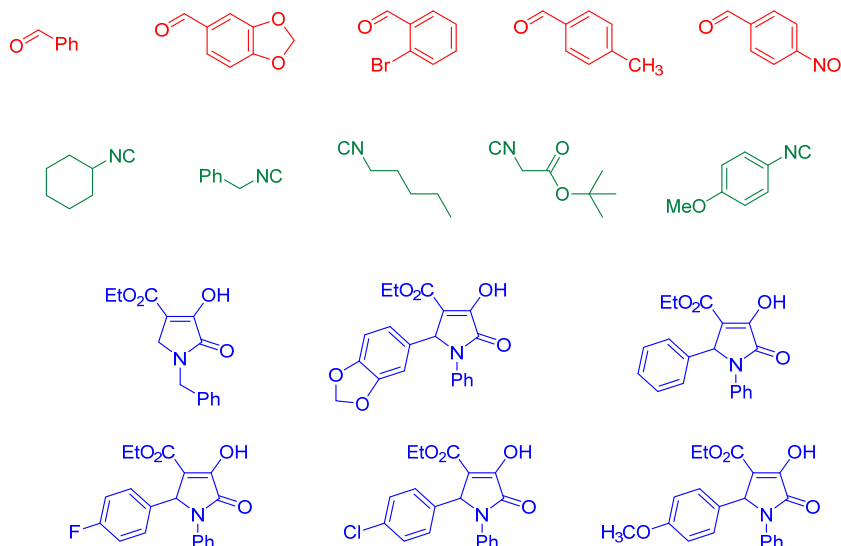
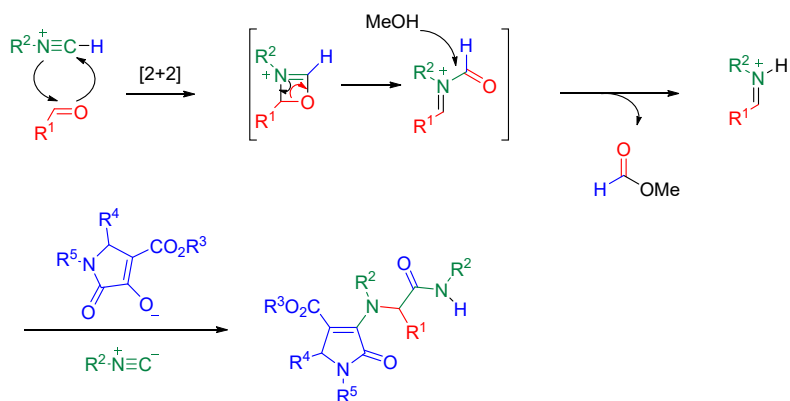


Figure 5. Scope of the anomalous enol-Passerini condensation with pyrrolidinodiones: different components used in the reaction.

The mechanism can be rationalized considering that a [2+2] cycloaddition of an aldehyde and a protonated isocyanide, followed by the cycloreversion and transfer of a formyl group to the solvent to give methyl formate and an intermediate iminium ion. This can then participate in a subsequent enol-Ugi reaction (Scheme 7). It had been previously observed that isocyanides and aldehydes can react to give imines, in the presence of Brønsted¹⁵ or Lewis acids.¹⁶



Scheme 7. Possible mechanism of the anomalous enol-Passerini condensation.

Conclusion

In summary, we have used enols for the first time as the acid component in Ugi and Passerini-type reactions. Careful control of the reaction conditions allows us to obtain Ugi, Passerini or pseudo-enol-Ugi products selectively. The use of enols as acidic partners in MCRI is an excellent strategy for the preparation of new pyrrolidinones having peptidic or pseudo-peptidic groups on carbon 3.

Acknowledgements

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