



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

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1. Introduction

2. Our proposal

3. Results

4. Conclusions

- **Isocyanides**
- **Multicomponent reactions of isocyanides**
- **Diversity of MCRI**

Isocyanides

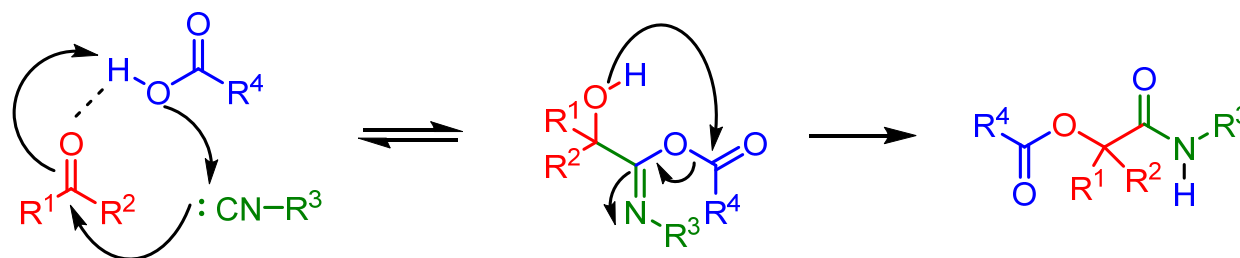


Reactions of isocyanides:

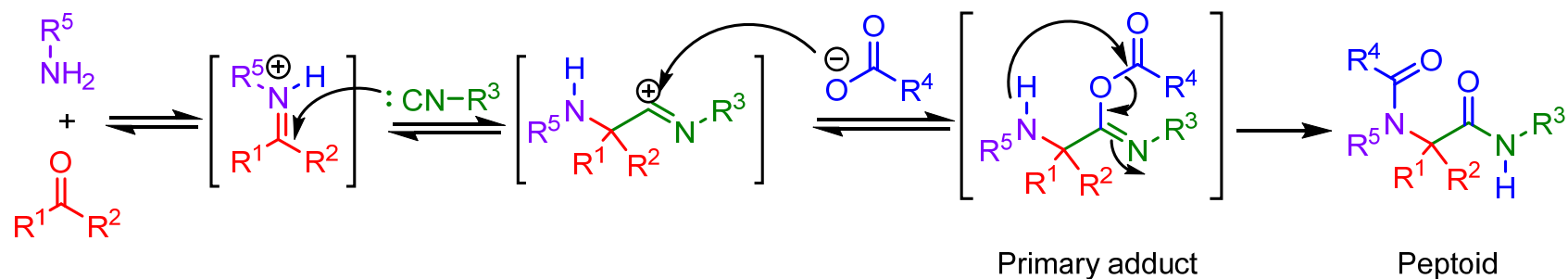
- Cycloadditions
- Insertions
- Multicomponent reactions (MCRIs)

Classic MCRI

Passerini three-component condensation



Ugi four-component condensation



Passerini, M. *Gazz. Chim. Ital* **1921**, 51, 126.

Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, 72, 267.

Advantages of MCRI

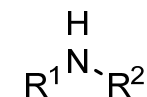
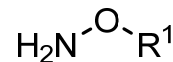
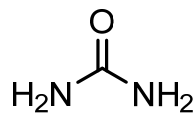
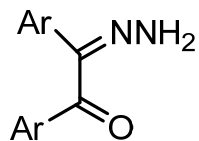
- Atom economy
- Efficient
- Sustainable
- Structural diversity
 - *Post-condensation transformations*
 - *Single replacement reactions (SRR)*

Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89; Ganem, B. *Acc Chem Res* **2009**, *42*, 463.

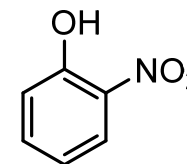
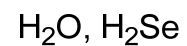
Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

Single replacement reactions (SRR)

Amine

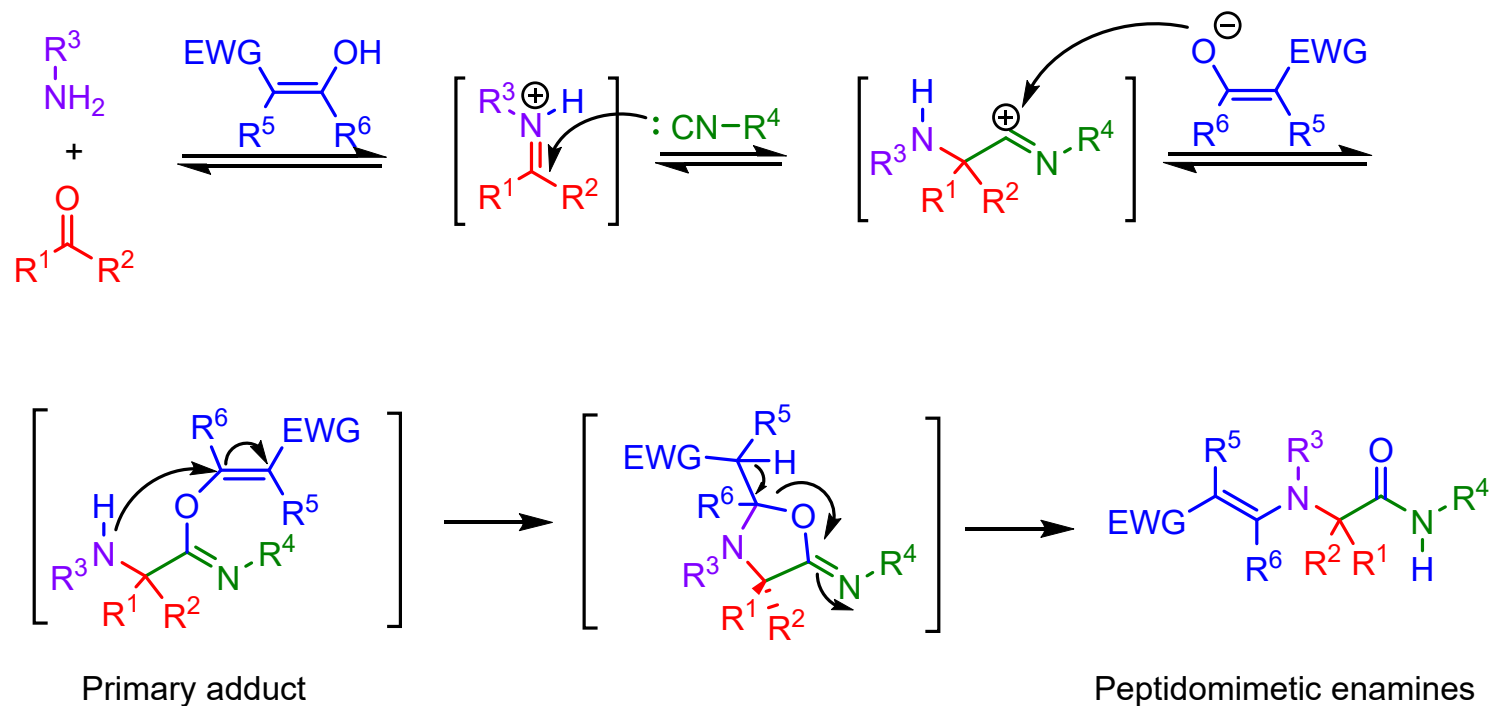


Acid

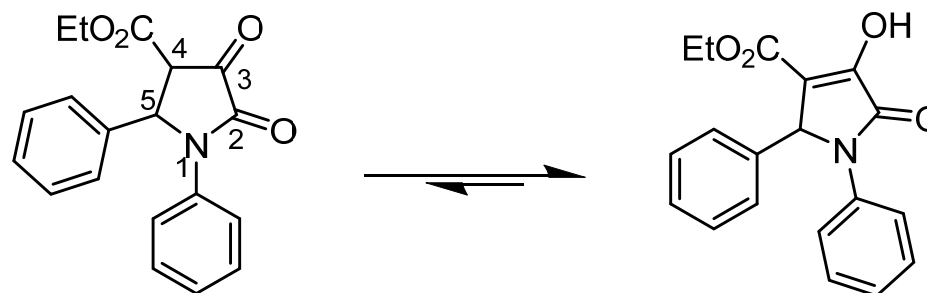


Single replacement reactions (SRR)

Enols act as the acid component in the Ugi reaction



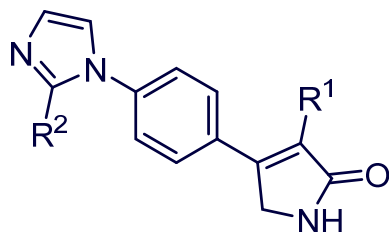
Pyrrolidinodiones in MCRI



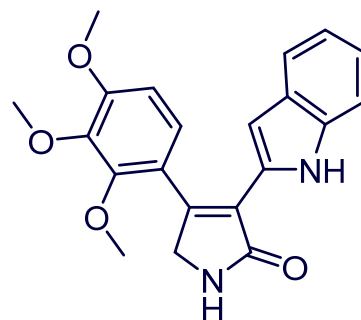
1. **Predominant enolic form**
2. **pKa < 5**
3. **Michael acceptor**

Vaughan, W. R.; Covey, I. S. *J. Am. Chem. Soc.* **1958**, *80*, 2197.

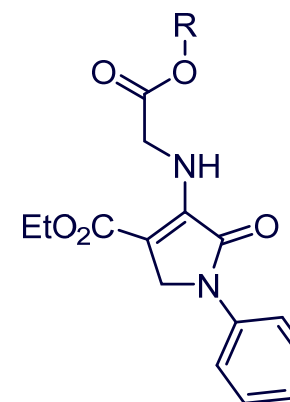
Biologically relevant pyrrolidinones



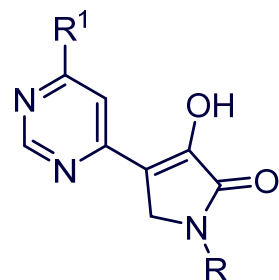
cAMP phosphodiesterase inhibitor



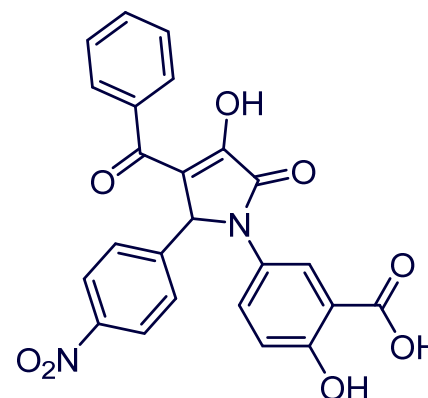
VEGF-R inhibitor



xanthine dehydrogenase inhibitor



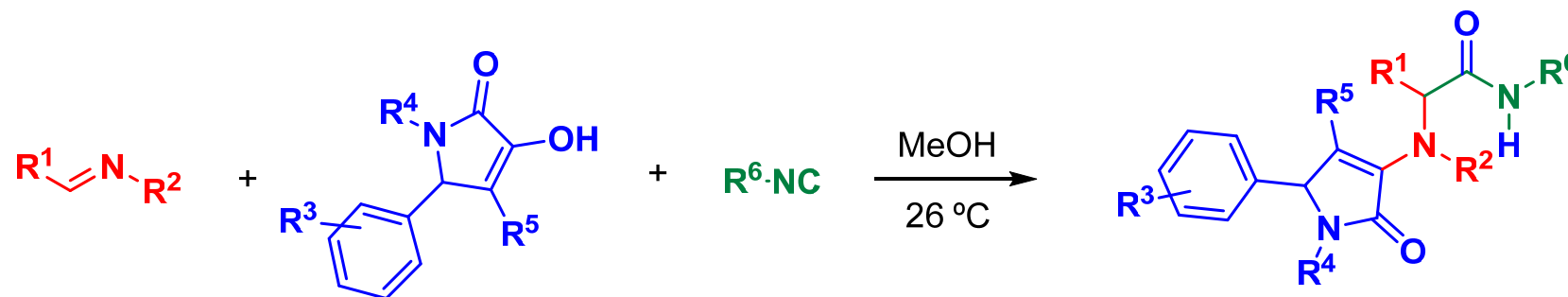
HIV integrase inhibitor



Stabilizer of PPIs interactions

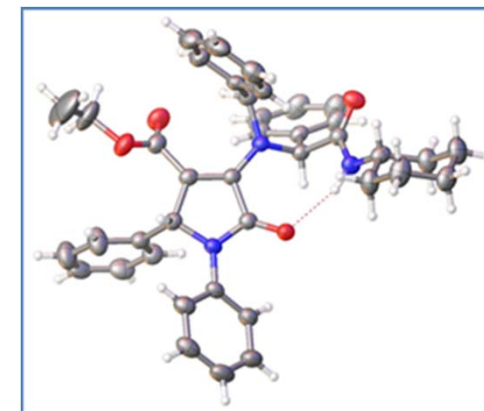
Peifer, C et al. *J. Med. Chem.* **2008**, *51*, 3814; Lampe, J. W et al. *J. Med. Chem.* **1993**, *36*, 1041; Rose, R. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 4129; Jourdan, F. et al. *ChemInform* **2006**, *37*.

Enol-Ugi condensation of pyrrolidinodiones



39 examples

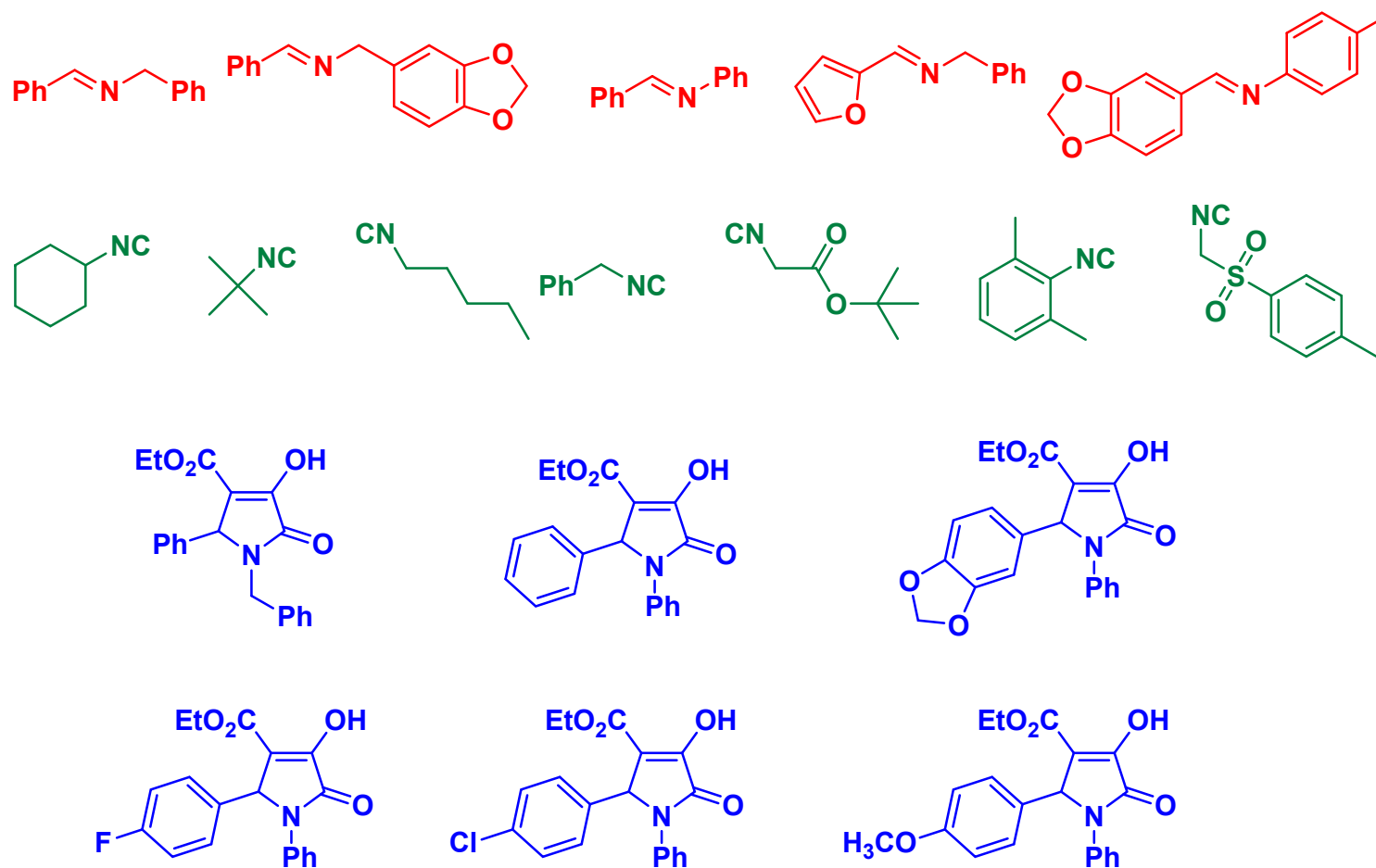
Yields up to 95%



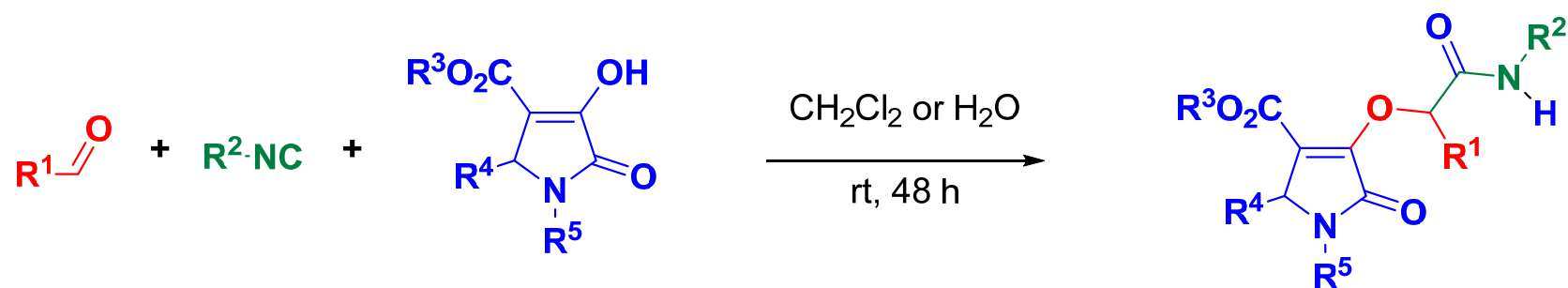
Castellano, T. G.; Neo, A. G.; Marcaccini, S.; Marcos, C. F. *Org. Lett.* **2012**, *14*, 6218.

Enol-Ugi condensation of pyrrolidinodiones

Scope



Enol-Passerini condensation



14 examples

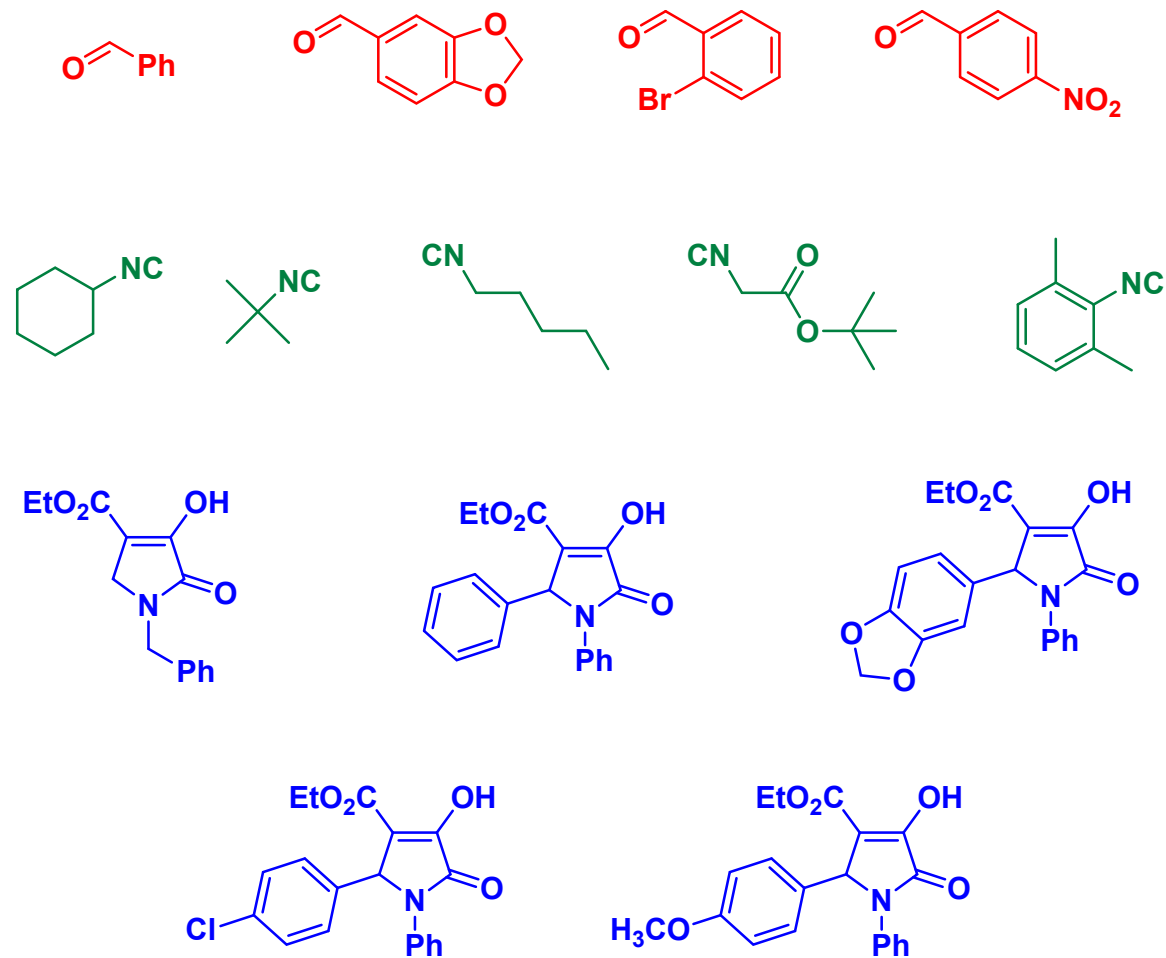
Yields up to 92%

Neo, A. G.; Marcos, C. F. *Org. Lett.* **2018**, *20*, 3875.

ECSOC 22

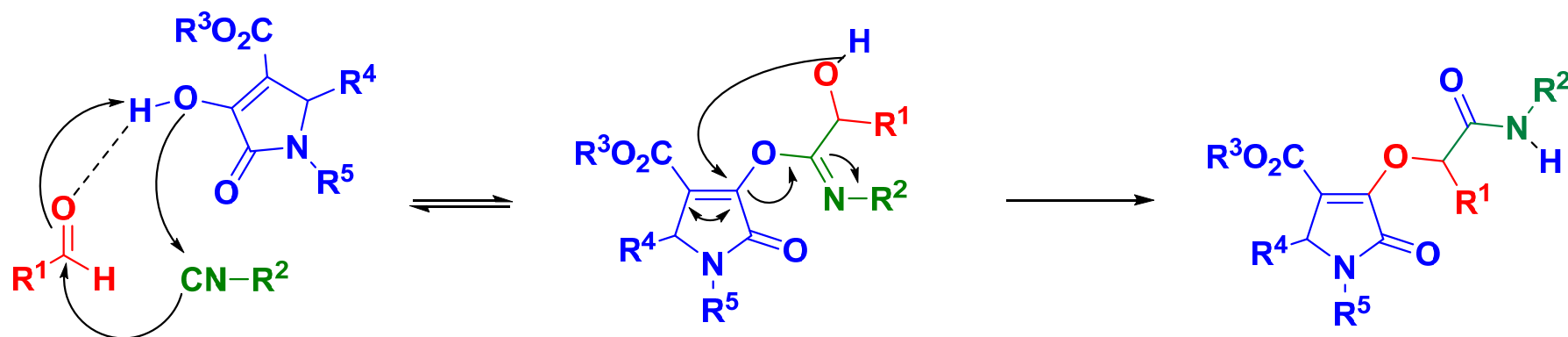
Enol-Passerini condensation

Scope

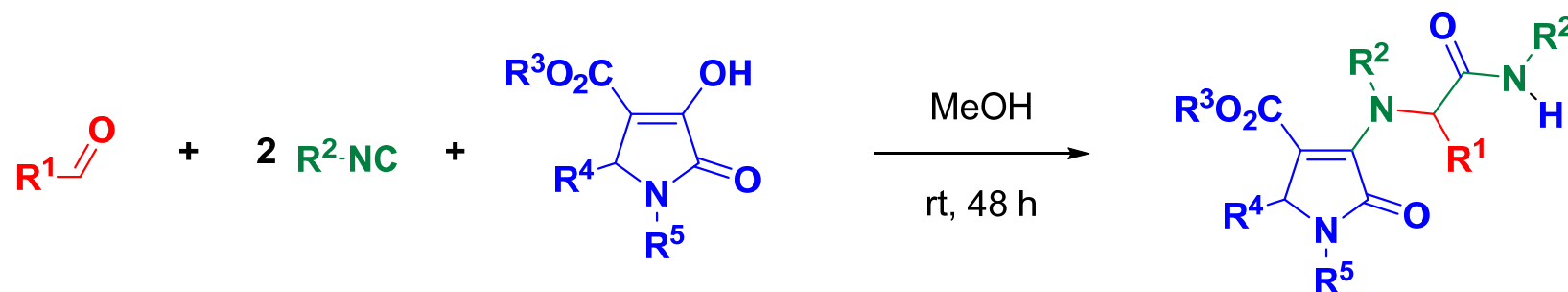


Enol-Passerini condensation

Mechanism



Anomalous enol-Passerini condensations



17 examples

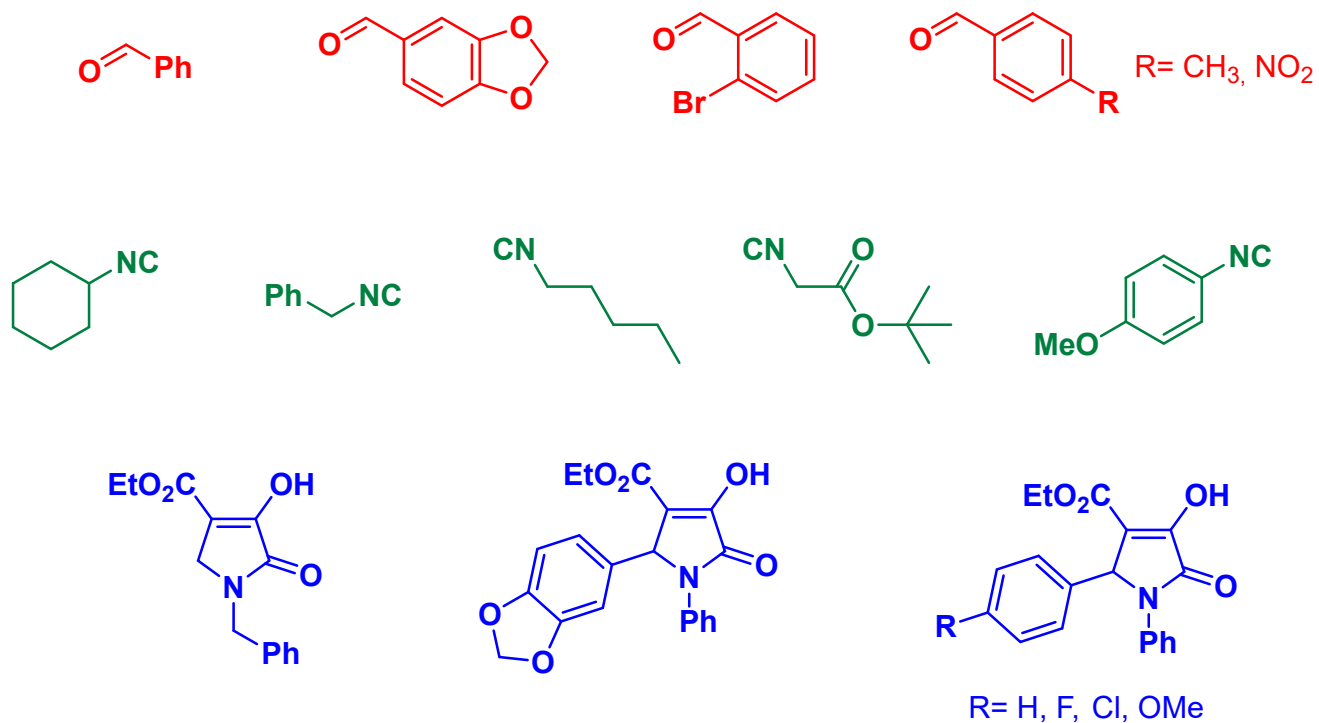
Yields up to 67%

Neo, A. G.; Marcos, C. F. *Org. Lett.* **2018**, *20*, 3875.

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Anomalous enol-Passerini condensation

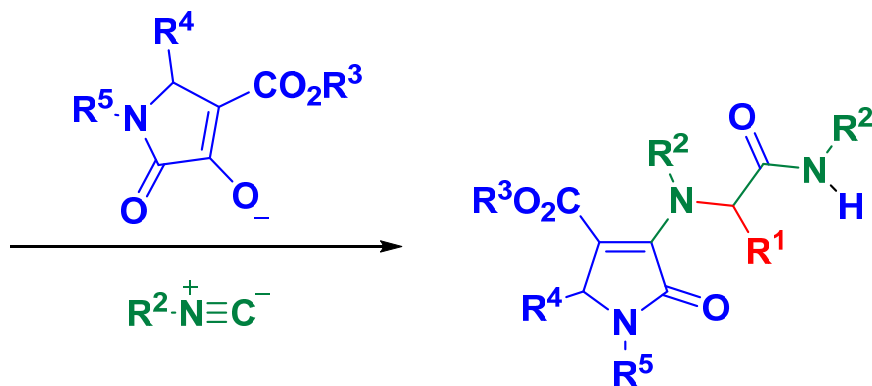
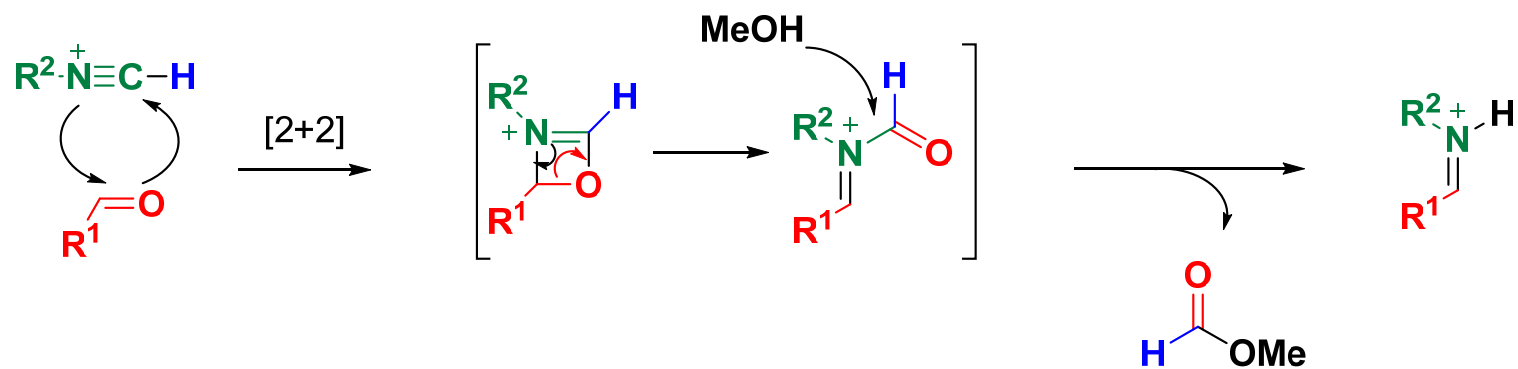
Scope



Bulky isocyanides do not react

Anomalous enol-Passerini condensations

Mechanism



- ✓ 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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