Regioselective Cyclic Iminium Formation of Ugi Intermediates: Rapid Access to 3,4-Dihydropyrazin-2(1*H*)-ones and Other Heterocycles

Naděžda Cankařová,*[,1] Viktor Krchňák[1,2]

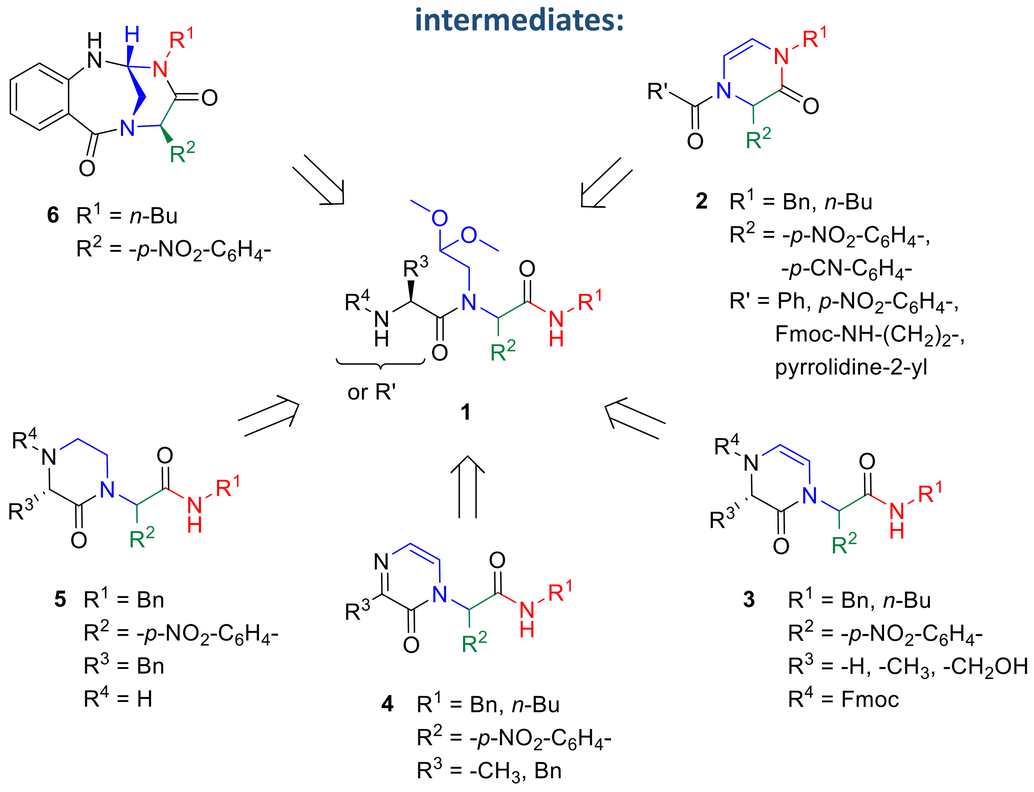
[1]*Department of Organic Chemistry, Faculty of Science, Palacký University, 17. listopadu 12, 771 46 Olomouc*
[2]*Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Center, Notre Dame, Indiana 465 56, United States*
e-mail: Nadezda.Cankarova@upol.cz

1. INTRODUCTION

Multicomponent reactions (MCRs) represent remarkable synthetic strategies providing access to compounds with three or more diversity positions in one step. MCRs have been applied to synthesize a variety of structural types, including pharmacologically relevant compounds.

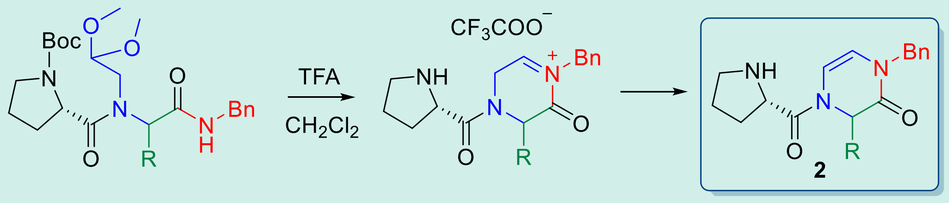
Ugi four-component reaction (U-4CR)[1] led to the formation of linear dipeptide intermediates, Ugi advanced intermediates **1**. The presence of a masked aldehyde enabled acid-mediated deprotection and subsequent cyclization. Utilizing *N*-protected amino acid as a carboxylic acid component, appropriate dipeptide amides **1** could be cyclized from two possible directions to diverse heterocycles containing a 3,4-dihydropyrazin-2(1*H*)-one core **2** and **3**,[2] pyrazin-2(1*H*)-one **4**, and piperazin-2-one **5**, as well as a tricyclic framework with a 3D architecture **6**.

Diversity-oriented synthesis of nitrogen heterocycles from Ugi advanced intermediates:

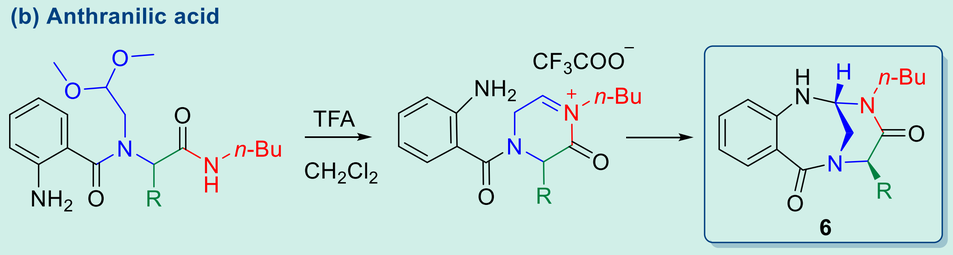


EASTBOUND CYCLIZATION

(a) Boc-Pro-OH



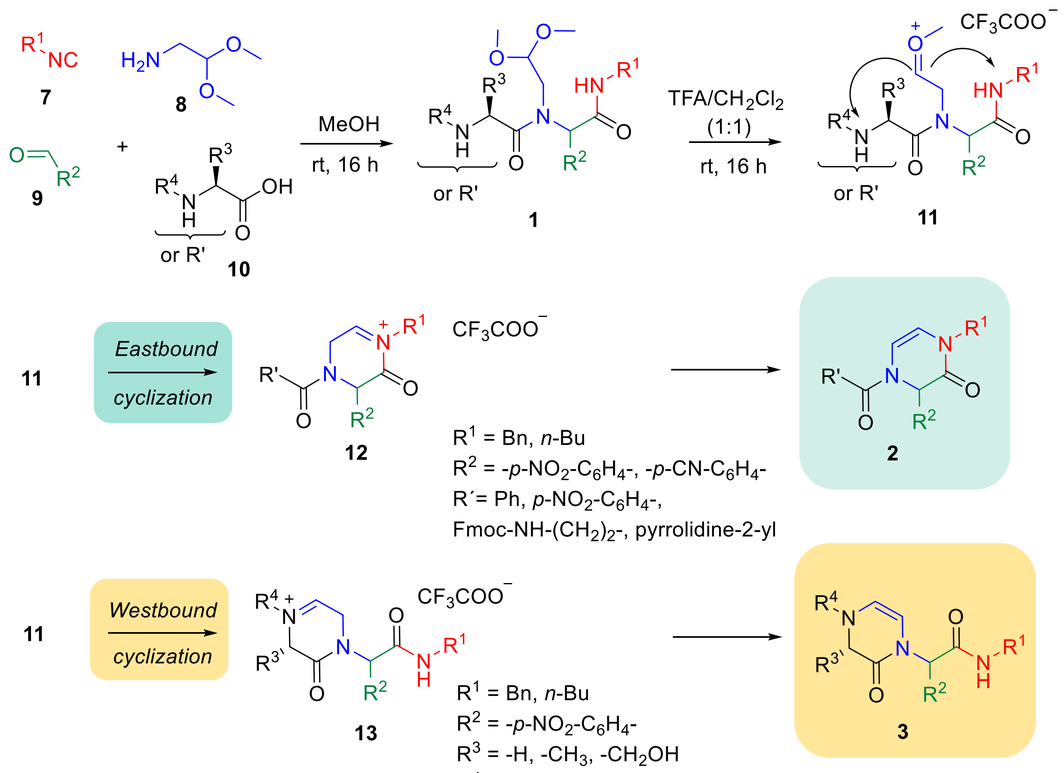
(b) Anthranilic acid



2. SYNTHESIS

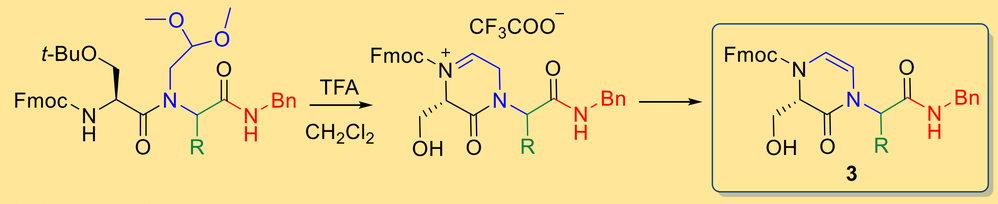
- Target 3,4-dihydropyrazin-2(1*H*)-ones and their derivatives were prepared by one-pot reaction sequence, including U-4CR followed by acid-mediated cyclization *via* iminium salts **12** and **13**.[3]
- Deliberate selection of building blocks drove the cyclization regioselectively and yielded diverse heterocycles.
- Cyclization to the peptide carboxyl terminus (eastbound) and to the peptide amino terminus (westbound) was demonstrated.[2]

Formation of 3,4-dihydropyrazin-2(1*H*)-ones 2 and 3 from Ugi adducts 1:

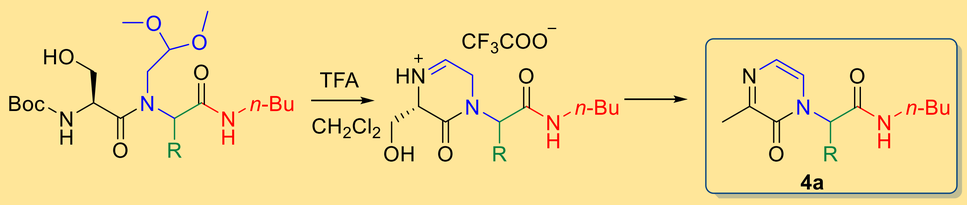


WESTBOUND CYCLIZATION

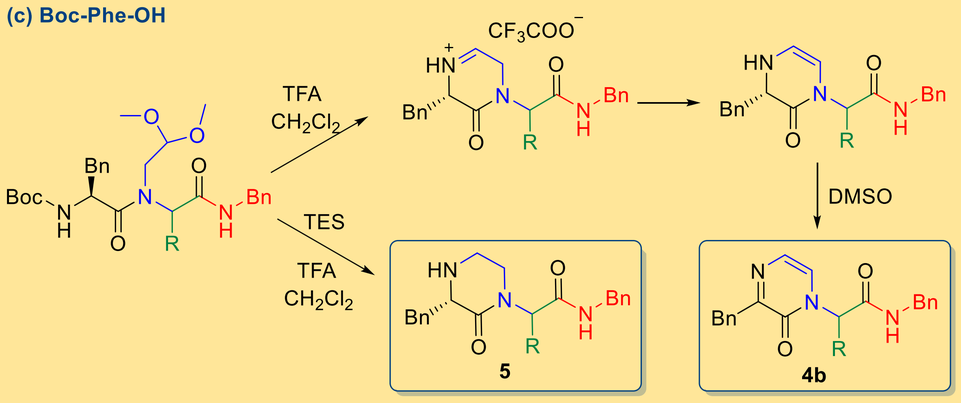
(a) Fmoc-Ser(*t*-Bu)-OH



(b) Boc-Ser-OH



(c) Boc-Phe-OH



3. CONCLUSION

- U-4CR of isocyanides, aldehydes, masked amino aldehydes, and carboxylic acids resulted in formation of Ugi advanced intermediates, which were further reacted without isolation.
- Following treatment with trifluoroacetic acid resulted in cascade reaction. Masked amino aldehyde was deprotected and trapped with one of the two internal *N*-nucleophiles.
- The cyclization proceeded regioselectively. Both eastbound and westbound cyclizations were demonstrated; westbound cyclization was preferable.
- In addition, we prepared a tricyclic framework with a 3D architecture, which was achieved diastereoselectively.
- The yields were in range of 10 - 69%.

4. REFERENCES

[1] (a) Dömling, A. *Chem. Rev.* **2006**, 106, 17; (b) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, 112, 3083; (c) Cankařová, N.; Krchňák, V. *Int. J. Mol. Sci.* **2020**, 21, 9160.
[2] La Venia, A.; Lemrová, B.; Krchňák, V. *ACS Comb. Sci.* **2013**, 15, 59–72.
[3] Cankařová, N.; Krchňák, V. *Molecules* **2023**, 28 *(7)*, 3062 (1-17).

orgchem.upol.cz koch_upol koch_prf