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One-Pot Diastereoselective Synthesis of Highly Functionalized γ-Lactams via Sequential Ugi-4CR and Intramolecular Michael Addition

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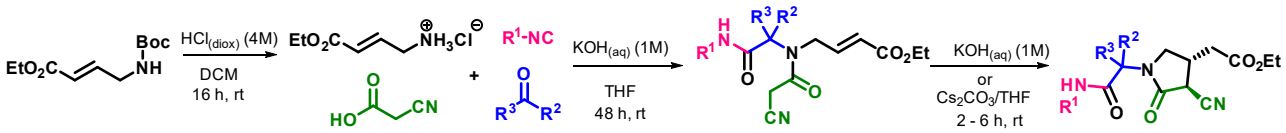
ABSTRACT

The γ-lactam is a conspicuous scaffold in medicinal chemistry, and due to their important properties, the synthesis of this ring has attracted the attention of the scientific community.[1] In this sense, we have recently reported a simple one-pot diastereoselective synthesis of new γ-lactams from ketoaziridines, via the Horner-Wadsworth-Emmons reaction.[2] The range of γ-lactams includes the 2-oxopyrrolidine-3-carbonitrile derivatives, a versatile synthon in organic chemistry that can be easily converted into other functionalities such as carboxylic acids, amines, amines, and aldimines, for instance.

Herein, an efficient one-pot diastereoselective protocol for the synthesis of highly substituted γ-lactams is described. The Ugi reaction was carried out with an appropriated γ-amino α,β-unsaturated ester, 2-cyanoacetic acid and different isonitriles and carbonyl compounds. The Ugi product was then cyclized via a Michael addition using a base. By employing the optimized conditions, a representative reaction scope was performed with 10 different isocyanides being the desired γ-lactams obtained in moderate to good overall yields over three steps. For our delight, only one diastereoisomer was observed and the relative configuration was determined by x-ray crystallography of one of the γ-lactams. However, when different carbonyl compounds were used only the Ugi products were isolated. We have then screened other bases to promote the 1,4-addition of the isolated Ugi products and Cs_2CO_3 showed the best result, providing the desired γ-lactams in good yields.



Next, we will investigate the intramolecular asymmetric Michael addition by screening different chiral organocatalysts.[3]

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REFERENCES

[1] Caruano, J.; Muccioli, G. G. Robiette, R. *Org. Biomol. Chem.*, **2016**, *14*, 10134.
[2] Martelli, S. R. L.; Da Silva, O. A. M.; Zukerman-Schpector, J.; Correa, A. G. *Org. Biomol. Chem.*, **2023**, *21*, 9128.
[3] Gayen, P.; Sar, S.; Ghorai, P. *Angew. Chem. Int. Ed.* **2024**, *63*, e202404106.