BIOTRANS
LA ROCHELLE 2023

N°1696 / PC
TOPIC(s) : (Chemo)enzymatic strategies / Reaction design

Combining Bio- and Organocatalysis for the Synthesis Of Piperidine Alkaloids.

AUTHORS
Adam O'CONNELL / UNIVERSITY COLLEGE DUBLIN, UCD SCIENCE CENTRE SOUTH, ROEBUCK, DUBLIN
Corresponding author : Elaine O'REILLY / elaine.oreilly@ucd.ie

PURPOSE OF THE ABSTRACT
2-Subtituted piperidine alkaloids are a class of naturally occurring nitrogen-containing heterocyclic compounds that are key components in many traditional medicines, toxins, and modern-day substances of abuse.[1] Due to their low natural abundance and interesting biological properties, development of chemical routes towards the total synthesis of these highly stereospecific compounds has gained much interest. However, these pathways often require the use of expensive metal catalysts and environmentally un-friendly solvents.[2] To circumvent these undesirable components, the introduction of a biocatalytic step would be favorable as it provides a potentially greener way of producing alkaloids and their derivatives, using milder reaction conditions in aqueous solvents.

Inspired by the work carried out in the Bella and Turner groups,[3,4] a hybrid bio-organocatalysed approach for the synthesis of 2-subtituted piperidines was developed involving a ω-transaminase enzyme (TA) and the organocatalyst L-proline. The TA mediates the conversion of cadaverine 1 to the reactive intermediate Δ1-piperideine 4, which then undergoes a Mannich-type reaction with an activated methyl ketone (Scheme 1). This novel approach utilises the ketone's ability to take on a dual role within the cascade, acting as the transaminase acceptor substrate as well as the nucleophile in the Mannich-type reaction. Conversions of up to 75 % were achieved using this methodology and the preparative scale synthesis of the natural product (±)-pelletierine (60 % yield, 85 mg) is reported.[5]

FIGURES

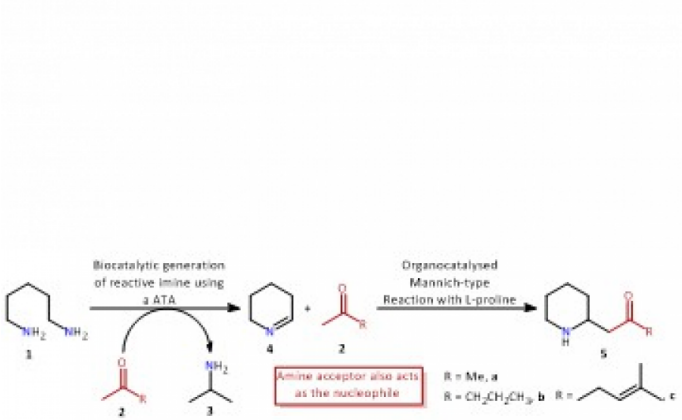

FIGURE 1
Hybrid bio-organocatalytic approach for the synthesis of 2-subtituted piperidines.

FIGURE 2

KEYWORDS
Organocatalysis | Transaminase | Piperidine Alkaloids | Mannich

BIBLIOGRAPHY

[1] B. Debnath, W. S. Singh, M. Das, S. Goswami, M. K. Singh, D. Maiti, K. Manna, Materials Today Chemistry, 2018, 9, 56-72.
[2] A. Bari, A. Iqubal, Z. A. Khan, S. A. Shahzad, M. Yar, Syn. Comm., 2020, 50, 2572-2589.
[3] M. R. Monaco, P. Renzi, D. M. Scarpino Schietroma, M. Bella, Organic Letters, 2011, 13, 4546-4549.
[4] J. L. Galman, I. Shabu, F. Parmeggiani, N. J. Turner, Chem. Comm., 2018, 54, 11316-11319.
[5] F. Taday, R. Cairns, A. O'Connell, E. O'Reilly, Chem. Comm., 2022, 58, 1697-1700.