STEREOSELECTIVE SYNTHESIS OF MEDICINALLY-RELEVANT DIHYDROISOQUINOLINONES

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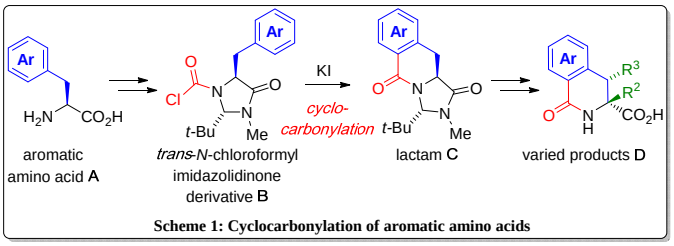
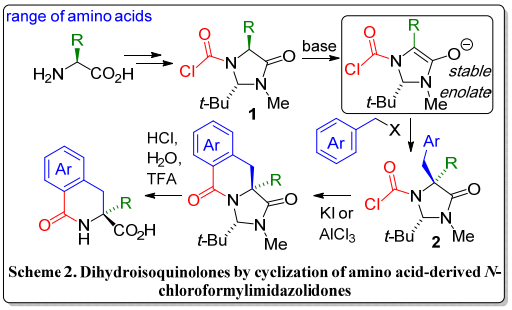
The dihydroisoquinoline ring system is found in some key biologically active compounds, not least among them the Amaryllidaceae alkaloids such as narciclasine and pancratistatin [1].

Part 1: Imidazolidinone derivatives of a range of aromatic α-amino acids [2], on treatment with phosgene and potassium iodide, undergo a mild Bischler-Napieralski-style cyclocarbonylation reaction that generates a tricyclic lactam by insertion of a C=O group between the amino acid nitrogen and the *ortho* position of the aryl substituent [3]. Regio- and diastereoselective functionalization of the lactam generates a library of substituted dihydroisoquinolinones and their congeners in enantioenriched form (Scheme 1).



Scheme 1: Cyclocarbonylation of aromatic amino acids

Part 2: Remarkably, the enolate of the imidazolidinone 1 can be generated in the presence of the reactive, electrophilic chloroformyl group (Scheme 2) [4]. The enolate functions as a formal 1,3-dipole: alkylation of the nucleophilic enolate with benzylic electrophiles, followed by electrophilic cyclization of the *N*-chloroformylimidazolidinone 2 provides a dihydroisoquinolone in a formal [3+3] annulation. Introducing the nucleophilic aromatic component of the cyclization after formation of the *N*-chloroformyl imidazolidinone enables the synthesis of a much wider range of cyclized products, leading to dihydroisoquinolones bearing a variety of functionality on the aryl ring.



Scheme 2. Dihydroisoquinolones by cyclization of amino acid-derived *N*-chloroformylimidazolidones

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[2] D. J. Leonard, J. W. Ward, J. Clayden, *Nature* **2018**, *562*, 105.

[3] **M. M. Amer**, A. C. Carrasco, D. J. Leonard, J. W. Ward, J. Clayden, *Org. Lett.* **2018**, *20*, 7977.

[4] H. Abas‡, **M. M. Amer‡**, O. Olaizola, J. Clayden, *Org. Lett.* **2019**, *21*, 1908. [‡Joint first authorship]