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Chemical Papers 67 (1) 92–100 (2013)
DOI: 10.2478/s11696-012-0246-z

ORIGINAL PAPER

A concise synthesis of enantiomerically pure aroyl-L-alanines and dihydroaroyl-L-alanines

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Received 31 March 2012; Revised 26 June 2012; Accepted 2 July 2012

Dedicated to Professor Štefan Toma on the occasion of his 75th birthday

Straightforward preparation of enantiomerically highly enriched *N*-substituted aroylalanines has been developed. This process involves the combination of crystallization-induced asymmetric transformation and a conjugate addition of *N*-nucleophiles to the corresponding aroylacrylic acids. Further transformations to 3,4-dichlorobenzoylalanine and aroyl-L-alanines via periodate oxidation and stereoselective reduction to *N*-substituted *syn*-4-aryl-4-hydroxy-2-aminobutanoic acids are also described.

Keywords: crystallization-induced asymmetric transformation, periodate degradation, aroylalanine, amino acid

Introduction

The kynurenine pathway (KP) represents a major route for the catabolism of tryptophan (Trp). Metabolites in KP, generated by the Trp degradation, are thought to play an important role in a wide range of diseases and disorders including infectious diseases, neurodegenerative disorders (e.g. Alzheimer's and Huntington's disease), and also affective disorders (e.g. schizophrenia, depression and anxiety, and autoimmune disorders) (Myint et al., 2012; Stone et al., 2012; Zwilling et al., 2011).

From the known enzyme inhibitors of KP, substituted aroylalanines – structural analogues of kynurenine, represent the intensively studied derivatives (Fig. 1). Among them, *m*-nitrobenzoylalanine (*m*-NBA) and 3,4-dichlorobenzoylalanine (FCE28833) possess kynurenine 3-monooxygenase (3-KMO) inhibition activity (Natalini et al., 1995; Pellicciari et al., 1994), and 4-ethylsulfonylbenzoylalanine (ESBA) demonstrates kynurenine aminotransferease II (KAT II) inhibition activity (Pellicciari et al., 2006, 2008). (4*R*)-5-Bromodihydro-L-kynurenine was found to be one of the most potent inhibitors of kynureninase (Heiss et al., 2003).

In all cases, (*S*)-enantiomers were found to be active stereoisomers. Several synthetic methods for the synthesis of enantiomerically pure aroylalanines have been developed based on different variants of enantioselective alkylation of α-imino esters (Barfoot et al., 2005; Ferraris et al., 2001; Nakamura et al., 2003) or the chiron approach using amino acid derivatives as chiral templates (Lin et al., 2001; Natalini et al., 1995). The enantioselective *N*-heterocyclic carbene-catalyzed intermolecular Stetter reaction has been applied recently (Jousseaume et al., 2011).

Our research program is focused on the synthesis and stereoselective transformations of substituted γ-oxo and γ-hydroxy-α-amino acids via the application of crystallization-induced asymmetric transformation (CIAT) (Anderson, 2005; Brands & Davies, 2006; Yoshioka, 2007). Highly diastereomerically enriched *N*-substituted γ-oxo-α-amino acids can be easily isolated from the equilibrated heterogeneous reac-

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