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A simple approach for the synthesis of new pyrimidinyl α-amino acids

Abdelatif Elmarrouni, Mireia Güell, Cristina Collell, Montserrat Heras *

Department of Chemistry, Faculty of Science, University of Girona, Campus de Montilivi, Girona E-17071, Spain

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ABSTRACT

A simple synthetic method for the preparation of optically active pyrimidinyl α-amino acids is presented. A nucleophilic *ipso*-substitution reaction between 2-(benzylsulfonyl)-4-isopropoxypyrimidines and a nucleophilic side chain of several protected natural α-amino acids is investigated to obtain new pyrimidin-2-yl α-amino acids. A detailed optimisation study of this reaction is discussed. Moreover, the selective *O*-alkylation of 2-(benzylsulfanyl)-4(3*H*)pyrimidinones with a hydroxylic side chain of some natural α-amino acids under Mitsunobu conditions is studied as a method to prepare new pyrimidin-4-yl α-aminoesters.

1. Introduction

In drug discovery, interest in non-proteinogenic amino acids is increasing as a result of their intrinsic biological properties—antibiotic, antiviral and antitumour[1]—and their utility as building blocks and molecular scaffolds in the synthesis of combinatorial libraries of non-peptidic compounds.[2] Many of these non-proteinogenic amino acids are also critical components in pharmaceuticals and developmental drugs.[3] Furthermore, their incorporation into biologically active peptides has been used to improve the activity, stability, bioavailability and selectivity of peptides in their use as a therapeutic agents.[4] For these reasons, research into methods that will allow the efficient synthesis of novel non-proteinogenic amino acids is crucial.[5] From among the various non-proteinogenic amino acids, such as α,α-disubstituted α-amino acids,[6] arylglycines,[7] β and γ-amino acids,[8] proline derivatives[9] and conformationally restricted amino acids[10] we have focused our attention on the heterocyclic amino acids type I (Fig. 1), a class of non-proteinogenic α-amino acids, substituted on the side chain by an heterocyclic ring.[11] Many of these compounds are natural and have been discovered and isolated from natural sources.[12] Examples include willardiine,[13] discadenine,[14] L-azatyrosine[15], L-lathyrine[16] and ibotenic acid[17] (Fig. 1), which all displayed a wide range of biological properties such as antibacterial or antitumour activities. Moreover, in recent years a number of stereoselective methods for rendering new synthetic enantiopure heterocyclic α-amino acids have been reported.[18] These methods are mainly based on the enantioselective transformation of prochiral starting materials or on chiral pool synthesis by transformation of natural α-amino acids.

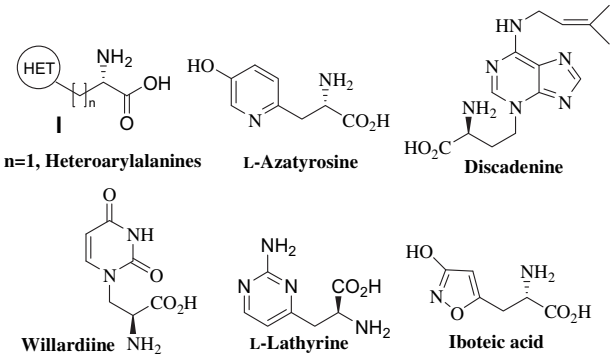

Figure 1. Examples of heterocyclic α-amino acids.

Pyrimidine rings are present in some important natural biologically active compounds[19] and synthetic pyrimidine derivatives have important pharmaceutical and agrochemical properties.[20] Apart from willardiine[13] and lathyrine analogues[16,21] only a small number of synthetic methods for obtaining new unnatural pyrimidinyl α-amino acids are reported in the literature.[22]

One of our research interest lies in the development of efficient methods for the preparation of pyrimidinyl compound libraries with a high degree of molecular diversity through solution or solid-

* Corresponding author. Tel.: +34 972418274; fax: +34 972418150.
E-mail address: montserrat.heras@udg.edu (M. Heras).

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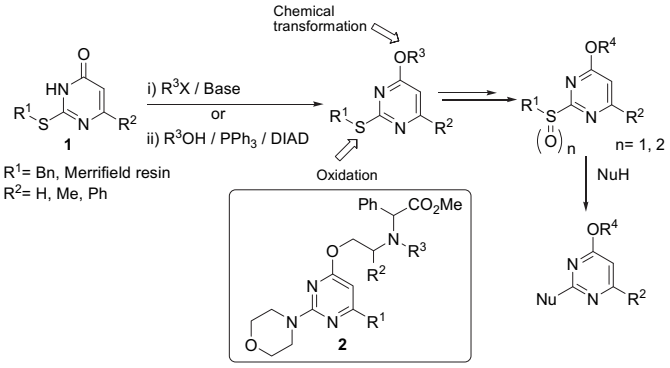
phase synthesis.[23] The highlight in our synthetic sequences include selective O-alkylation of 2-(alkylsulfanyl)-4(3*H*)pyrimidinones **1** with alkyl halides under basic conditions or with alcohols under Mitsunobu conditions, followed by chemical transformations at position 4 of the pyrimidine ring and a final nucleophilic *ipso*-substitution step of the oxidised sulfur with a variety of nucleophiles (Scheme 1). This last step is used not only for introducing molecular diversity but also as cleavage reaction in solid-phase synthesis. Both nucleophilic *ipso*-substitution reaction of alkylsulfonyl groups and Mitsunobu reaction are versatile and useful methods currently employed in the development of synthetic strategies for the construction of highly functionalised pyrimidines.[24] In this connection, we have recently described the synthesis of novel *N*-pyrimidinyl arylglycines type **2** through subsequent Mitsunobu, Petasis and *ipso*-substitution reactions[25] (Scheme 1).



Scheme 1. Synthesis of highly functionalised pyrimidines.

As a part of our research aimed at synthesising novel, modified antimicrobial peptides by incorporation of unnatural α-amino acids, we centred our attention on the synthesis of novel, unnatural pyrimidinyl α-amino acids. Specifically, we prepared a series of pyrimidines substituted at position 2 and/or 4 with an α-amino acid residue, following the method described by our research group. The results of this investigation are disclosed herein.

2. Results and discussion

Consistent with our goal, we reasoned that the incorporation of an α-amino acid residue at position 2 of a pyrimidine ring could be achieved by nucleophilic *ipso*-substitution of the sulfones **3** with a nucleophilic side chain of several protected natural α-amino acid. For this purpose, the easily available 2-(benzylsulfonyl)-4-isopropoxypyrimidines[23c] **3** were treated under basic conditions, with N^{α}-Boc-aminoesters **4** with an amine (lysine), an heteroaryl (histidine and tryptophan), an alcohol (serine) or a phenol (tyrosine) functions in the side chain in order to obtain the corresponding pyrimidinyl α-aminoesters type **5** (Table 1, entries 1–32).

When a ring nitrogen of the imidazole of the N^{α}-Boc-histidine methyl ester **4a** was employed as a nucleophile the best results were obtained using DBU as a base and heating at 50 °C (Table 1, entries 2–5). Under these conditions all compounds **5a–c** were isolated in good yields and without appreciable racemisation except for compound **5c**, which contained a phenyl group at position 6 of pyrimidine ring that showed a substantial degree of racemisation (Table 1, entry 4). It proved possible to avoid racemisation of **5c** carrying out the reaction at room temperature (Table 1, entry 5). The two nitrogen atoms of the imidazole ring of histidine are not equivalent. The nucleophilic attack could, in principle, take place by

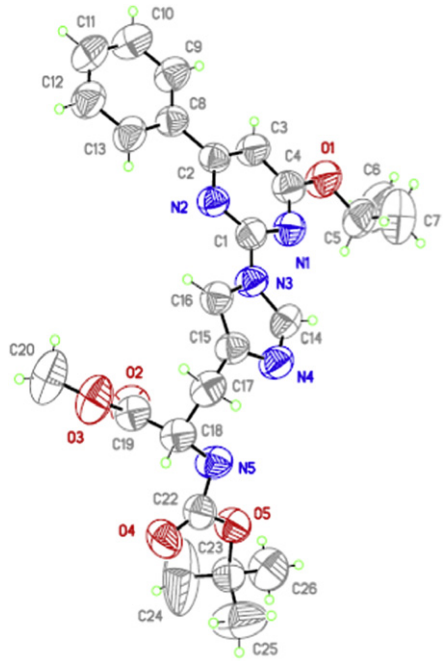


Figure 2. X-ray crystal structure of compound **5c**.

N(π) or N(τ) atoms and consequently two regioisomers would be isolated. Although the N(τ) derivative is often the major product resulting from steric factors, it is rarely exclusive. However, in all cases (Table 1, entries 1–5) the reaction was completely regioselective in favour of the N(τ) derivative. The unambiguous assignment of the structures **5a–c** was achieved by X-ray analysis of compound **5c**. As evidenced in Figure 2, the histidine residue is attached to position 2 of the pyrimidine ring by the N(τ) of the imidazole ring.

In our initial experiments with N^{α}-Boc-tyrosine methyl ester **4b**, we first studied the nucleophilic *ipso*-substitution reaction by employing several bases and starting from 2-benzylsufonylpyrimidine **3a**. No reaction took place when potassium *tert*-butoxide was used as a base (Table 1, entry 6). Better results were obtained using both NaH and potassium carbonate affording pyrimidinyl amino ester **5d** without appreciable racemisation (Table 1, entries 7 and 8). In the case of potassium carbonate, reaction required heating at 50 °C for completion. These reaction conditions were then extended to 2-benzylsufonylpyrimidines **3b** and **3c**, which afforded the corresponding pyrimidinyl aminoesters **5e** and **5f** in good yields (Table 2, entries 9 and 10). Unfortunately compound **5f** was obtained with a high degree of racemisation (60:40 enantiomeric ratio). In order to avoid racemisation the temperature reaction was decreased. When this reaction was carried out at 40 °C a substantial reduction in racemisation was observed (87:13 enantiomeric ratio) whereas at room temperature pyrimidinyl amino ester **5f** was obtained without appreciable racemisation but with a lower yield (Table 1 entries 11 and 12). It was possible to obtain an X-ray analysis of structure **5f** (Fig. 3) in which the tyrosine residue links to position 2 of the pyrimidine ring by the phenoxy group could be seen.

In the case of N^{α}-Boc-lysine methyl ester (Table 1, entries 9–12) we used the commercially available N^{α}-Boc-lysine methyl ester acetate salt **4c**. For this reason the *ipso*-substitution reaction between 2-benzylsulfonylpyrimidines **3** and amino ester **4c** also needed basic conditions. The reaction was not complete even after several days heating at 50 °C when Et_3N and DIEA were employed as a base and the corresponding pyrimidinyl amino ester **5g** was isolated in poor yield (Table 1, entries 13 and 14). It