SYNTHESIS OF (PURIN-6-YL)AMINO ACIDS

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(Purin-6-yl)alanines and 4-(purin-6-yl)phenylalanines, two novel amino acid–spurine conjugates, were synthesized. Palladium catalyzed cross-coupling reactions of organometals derived from amino acid with diverse 6-halopurines were used as key step in the synthesis of both types of derivatives. Iodozincalanines were used in synthesis of (purin-6-yl)alanines, and 4-boronophenylalanines or 4-(trimethylstanyl)phenylalanines for preparation of 4-(purin-6-yl)phenylalanines. Free purine bases and nucleosides bearing alanine or phenylalanine in position 6 were obtained after complete deprotection of the products of cross-coupling reactions.

INTRODUCTION

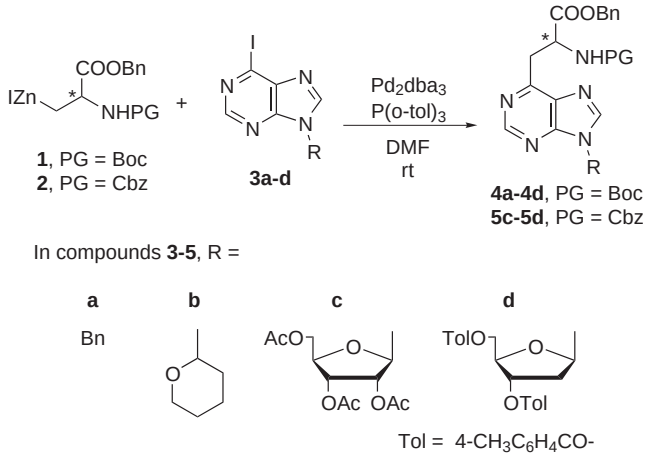
Purines bearing carbon substituents attached to carbon atoms of purine ring (positions 2, 6 and/or 8) are of great interest due to potential applications in medicinal chemistry and chemical biology. Several examples of this class of compounds were reported to possess cytostatic[1], antimicrobial[2] and A_2-receptor agonist activity[3], and some of them were used as artificial nucleobases in the extension of the genetic alphabet[4]. Cross-coupling reactions are a powerful tool[5] for the synthesis of these compounds but, in most cases, were only used for an introduction of simple unfunctionalized alkyl, alkenyl, alkynyl, aryl and hetaryl substituents. Therefore, an extension of this methodology to functionalized C-substituents is a very challenging target. One of the prominent functionalized substituents of high biological relevance is undoubtedly an amino acid residue. Our goal is to develop approaches towards the synthesis of a novel class of compounds: carbon–carbon linked conjugates of amino acids and purines. Such compounds may display biological activity and be used as building blocks in the synthesis of chemically and enzymatically stable nucleic acids–peptide/protein conjugates. This communication reports on the synthesis of (purin-6-yl)alanines[6] and 4-(purin-6-yl)phenylalanines[7], two examples of this novel type of compounds.

RESULTS AND DISCUSSION

Our synthesis of (purin-6-yl)alanines as well as 4-(purin-6-yl)phenylalanines is based on Pd(0)-catalyzed cross-coupling reactions of protected organometals derived from amino acids with diverse 6-halopurines.

(Purin-6-yl)alanines

(Purin-6-yl)alanines **4** and **5** were prepared by cross-coupling reactions of iodozincalanines[8] **1** or **2** with 6-iodopurines **3** (Fig. 1). Iodozincalanines **1** and **2** were prepared by sonication of the solution of β-iodoalanines in DMF at room temperature with Zn dust activated by trimethylsilyl chloride. These organozinc reagents were used in palladium catalyzed cross-coupling reactions with 6-iodopurines **3a**–**3d** (Scheme 1). The reactions were carried out in DMF at ambient temperature with palladium(0) catalyst prepared from tris(dibenzylidene-acetone)dipalladium and tri-*o*-tolylphosphine to give the (purin-6-yl)alanines **4a**–**4d**, **5c**, **5d**, in excellent yields (80–95%).



SCHEME 1
Synthesis of (purin-6-yl)alanines

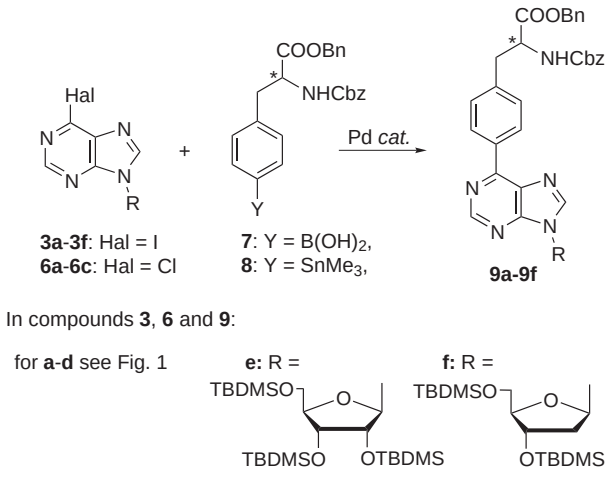
Finally, protecting groups of cross-coupling products **4b**, **5c** and **5d** were cleaved to give free purine base and nucleosides bearing alanine in position 6. **4a** was deprotected by Pd/C catalyzed hydrogenolysis followed by treatment of the product with HCl in ethyl acetate to give (9*H*-purin-6-yl)alanine. Basic hydrolysis of compounds **5c** and **5d** by aqueous sodium hydroxide (0.8 eqiv. for one ester), was followed by Pd/C catalyzed hydro-

genolysis to afford free nucleoside and 2'-deoxynucleoside, respectively. Above described synthetic route was carried out with racemic amino acids at first. However, starting from (*S*)-iodozincalanine **2** optically pure compounds (*S*)-**5c** and (*S*)-**5d** and subsequently optically pure free nucleosides were prepared under the same conditions.

4-(Purin-6-yl)phenylalanines

Synthesis of 4-(purin-6-yl)phenylalanines **9a**–**9f** was based on palladium catalyzed cross-coupling reactions of 6-halopurines **3** or **6** with organoboron reagent[9] **7** or organostannane[10] **8** derived from phenylalanine (Scheme 2). Reaction conditions for both reagents were optimized to give desired 4-(purin-6-yl)phenylalanines **9a**–**9f** in good yields (70–75%). However, when enantiomerically pure amino acids were used, reactions of organostannane **8** with 6-iodopurines **3a**–**3f** in presence of 1.2 eqiv. of CuI and catalytic system based on $Pd_2dba_3/AsPh_3$ in DMF was shown to be superior in terms of optical purity of cross-coupling products (>99.8% *ee*/*de*). On the other hand, methodology based on boronic acid **7** gave only enantiomerically enriched products (about 80% *ee*/*de*) due to presence of base in reaction mixture causing partial racemization.

Free purine base and nucleosides bearing phenylalanine in position 6 were prepared by cleaving of protecting groups of compounds **9b**, **9e** and **9f**. Derivative **9b** was treated by TFA followed by Pd/C catalyzed hydro-



SCHEME 2
Synthesis of 4-(purin-6-yl)phenylalanines

genolysis of intermediate to give 4-(9*H*-purin-6-yl)phenylalanine. Treating of nucleosides **9e** and **9f** by $Et_3N{\cdot}3HF$ followed by Pd/C catalyzed hydrogenolysis furnished free nucleoside and 2'-deoxynucleoside. Starting from (*R*)- and (*S*)-amino acids, two series of optically pure derivatives varying in configuration on phenylalanine were prepared.

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