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Synthesis of 3-hetarylpyrroles by Suzuki–Miyaura cross-coupling

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1-[tert-Butyl(diphenyl)silyl]pyrrol-3-ylboronic acid was obtained from pyrrole in three steps. Its Suzuki–Miyaura cross-coupling with functionalized pyridyl and pyrimidinyl bromides afforded new promising 3-hetaryl-1H-pyrroles.

Keywords: heterocyclic aromatic compounds, fleximers, Suzuki–Miyaura cross-coupling, pyrrole, iodination, silyl protection.

Heterocyclic aromatic compounds are extremely important for drug discovery.1–3 In particular, bicyclic heteroaromatic compounds containing five- and six-membered fused ring systems are considered as excellent analogues of the purine bases.4–6 Many modified heterobases can serve as substrates of purine nucleoside phosphorylase (PNP) and in the course of PNP-catalyzed trans-glycosylation can be converted into the corresponding analogues of ribo- and 2′-deoxyribonucleosides.7,8 Until recently, this reaction was limited to bicyclic heteroaromatic compounds.

Recently, it was shown that the ‘split’ analogues of fused heterocyclic bases consisting of two separate fragments and named ‘flex-bases’, could also be recognized by PNP and converted to their corresponding 2′-deoxyribonucleoside forms.9–11 Such structurally unusual nucleosides called as ‘fleximers’ were synthesized both chemically and enzymatically.12,13 They were recognized by enzymes14 and showed activity against a number of viruses, including Ebola, Marburg, Middle East Respiratory Syndrome (MERS-CoV), Dengue, and Yellow Fever. The rotational and conformational properties of the ‘fleximers’ allow them to overcome mutations as well as to undergo more favorable interactions in biological significant enzymatic systems.15,16

This work describes a convenient synthesis of 3-hetaryl-1H-pyrroles. We anticipate that these new flex-base analogues can demonstrate biological activity by themselves or find application as intermediates in organic synthesis and medicinal chemistry, including the chemical and enzymatic preparation of the corresponding ‘fleximer’ nucleosides. Effective methods for the formation of the C–C bond between heterocyclic/ aromatic compounds either are based on palladium catalysis17 or can be ‘metal free’.18 For introducing 4-(3H)-pyrimidone or 4-aminopyridine residues at C-3 of the pyrrole ring, Suzuki–Miyaura cross-coupling reaction seems to be a method of choice.19–24 Synthesis of pyrroles substituted at the position 3 has been the subject of extensive research.21,25,26 Electrophilic substitution preferably occurs at C-2 of the unprotected pyrrole ring. In addition, 2,5-dihalogeno derivatives can also be formed. For selective halogenation of the less reactive C-3 of the pyrrole, the more reactive C-2 should be blocked, for example, by protecting the NH group with a bulky substituent. The selectivity of substitution at C-3 can be significantly increased by the use of the triisopropylsilyl20,26,27 protective group, however, small amount of the 2-substituted product is still observed.26 As a result, to provide the required hindrance for better regioselectivity, a tert-butyl(diphenyl)silyl protection group was herein applied (Scheme 1). In addition, we expected that this protective group would be eliminated under basic conditions of the cross-coupling reaction, thereby circumventing the final deprotection step. The subsequent iodination of compound 1 with N-iodosuccinimide (NIS) proceeded exclusively at C-3 of pyrrole with the formation of only a monoiodo derivative 2.† The bromination of pyrrole 2 with Br2 or NBS was not clean and gave, along with the target 3-bromo derivative, a significant amount of 3,4-dibromopyrrole. Finally, standard boronation of iodide 2 [BuLi, then (Pr iO)3B] afforded 1-[tert-butyl(diphenyl)silyl]pyrrol-3-ylboronic acid 3 in satisfactory yield (see Scheme 1).‡

Scheme 1 Reagents and conditions: i, NaH, BuPh2SiCl, THF, 0 °C; ii, NIS, acetone, –78 °C; iii, BuLi, THF/PhMe (1 : 4), B(OPri)3, –78 °C, then 1 M HCl.

† The use of other protective groups or reaction conditions provided poorer yields at both stages of N-protection and 3-iodination (see Table S1 in the Online Supplementary Materials). For the given reagents and conditions, the yields were as follows: TsCl (Bu tOK, DMF, 0 °C), 23%, 11%; Bu tMe2SiCl (BuLi, THF, –78 °C), 55%, 25%; Bu tPh2SiCl (BuLi, THF, –78 °C), 42%, 27%, respectively.
‡ 1-[tert-Butyl(diphenyl)silyl]pyrrol-3-ylboronic acid 3. Iodopyrrole 2 (1.75 g, 4.06 mmol) was dissolved in a 4:1 toluene/THF mixture, triisopropyl borate (1.8 ml, 8.1 mmol) was added, and this was cooled in
Initially, the Suzuki–Miyaura cross-coupling reaction was attempted with the N-protected bromo hetarenes 4 and 5\textsuperscript{28,29} (Scheme 2), however the desired cross-coupling products were formed only in trace amounts and most of starting materials were recovered. Compound 4 was then O-benzylated to provide 4-benzyloxy-5-bromopyrimidine 3\textsuperscript{27} and aminopyridine 5 was N-acetylated to give 3-bromo-4-(acetylamino)pyridine 6. \textsuperscript{30} The subsequent cross-coupling reaction with pyrrolboronic acid \textsuperscript{3} in 34 and 30% yields, respectively. \textsuperscript{3}\§ As expected TBDPS protecting group was removed under the basic conditions of the cross-coupling procedure.

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