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

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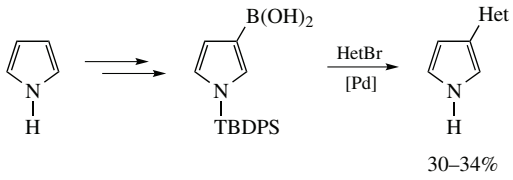
1-[*tert*-Butyl(diphenyl)silyl]pyrrol-3-ylboronic acid was obtained from pyrrole in three steps. Its Suzuki–Miyaura cross-coupling with functionalized pyridinyl and pyrimidinyl bromides afforded new promising 3-hetaryl-1*H*-pyrroles.



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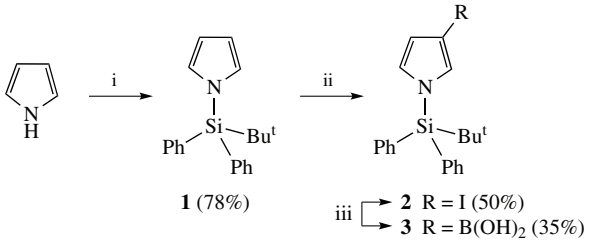
Heterocyclic aromatic compounds are extremely important for drug discovery.[1–3] In particular, bicyclic heteroaromatic compounds containing five- and six-membered fused ring systems are considered as excellent analogues of the purine bases.[4–6] Many modified heterobases can serve as substrates of purine 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 enzymes[14] 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]

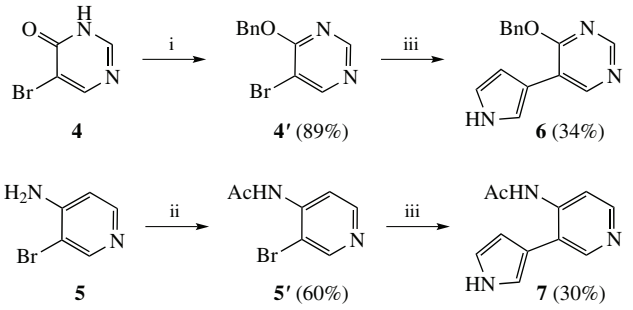
This work describes a convenient synthesis of 3-hetaryl-1*H*-pyrroles. We anticipate that these new flex-base analogues can demonstrate biological activity by themselves or find application as intermediates in organic synthesis and medicinal chemistry, including the chemical and enzymatic preparation of the corresponding 'fleximer' nucleosides. Effective methods for the formation of the C–C bond between heterocyclic/aromatic compounds either are based on palladium catalysis[17] or can be 'metal free'.[18] For introducing 4-(3*H*)-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 triisopropylsilyl[20,26,27] 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 Br_2 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, Bu^tPh_2SiCl, THF, 0 °C; ii, NIS, acetone, –78 °C; iii, BuLi, THF/PhMe (1 : 4), $B(OPr^i)_3$, –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^tMe_2SiCl (BuLi, THF, –78 °C), 55%, 25%; Bu^tPh_2SiCl (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



Scheme 2 *Reagents and conditions*: i, $PhCH_2OH$, PPh_3, DIAD, DMF, 0 → 20 °C; ii, Ac_2O, acetone, room temperature; iii, **3**, $Pd(PPh_3)_4$, $NaHCO_3$(sat.), DME, reflux, 4 h.

Initially, the Suzuki–Miyaura cross-coupling reaction was attempted with the N-unprotected bromo hetarenes **4** and **5**[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 **4′**,[30] and aminopyridine **5** was N-acetylated to give 3-bromo-4-(acetylamino)pyridine **5′**.[31] The subsequent cross-coupling reaction with pyrrolylboronic acid **3** (see Scheme 2) using $Pd(PPh_3)_4$ gave the desired pyrrolylhetarenes **6** and **7** in 34 and 30% yields, respectively.[§] As expected TBDPS protecting group was removed under the basic conditions of the cross-coupling procedure.

To conclude, the use of *tert*-butyl(diphenyl)silyl group to protect the pyrrole increased the regioselectivity of the iodination at C-3, which provides easy access to pyrrol-3-ylboronic derivatives, valuable components for the Suzuki–Miyaura cross-coupling. This group is spontaneously eliminated in the course of the cross-coupling reaction, thus negating the need for a deprotecting step. Thus, two new 3-hetarylpyrroles were obtained for the synthesis of the corresponding 'fleximer' nucleoside analogues, which will be further studied for potential biological activity, the results of which will be reported elsewhere in due time.

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a dry ice bath to –78 °C. Then, BuLi (1.6 M in hexane, 6.4 ml, 10.2 mmol) was added dropwise in an argon stream over 2 h, and the mixture was left overnight at room temperature. Next day, 1 M HCl (50 ml) was added, and the mixture was stirred for 1 h and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 and extracted. The organic layer was dried with anhydrous sodium sulfate, filtered and then evaporated. The resulting product **3** (1.4 g, 35%) was used in subsequent reactions without further purification. HRMS, *m*/*z*: 350.1716 [M+H] (calc. for $C_{20}H_{24}BNO_2Si$: 350.1742).

§ *4-Benzyloxy-5-(1*H*-pyrrol-3-yl)pyrimidine* **6**. 4-Benzyloxy-5-bromopyrimidine **4′** (230 mg, 0.85 mmol) was dissolved in 1,2-dimethoxyethane (20 ml) in a two-necked flask, then $Pd(PPh_3)_4$ (5 mol%) was added under argon atmosphere, and this was stirred for 15 min. A solution of pyrrolylboronic acid **3** (350 mg, 1 mmol) in 1,2-dimethoxyethane (20 ml) and saturated sodium bicarbonate (10 ml) were added. The mixture was refluxed at 90 °C for 4 h. Column chromatography on silica gel (eluent $CDCl_3$/MeOH, 95 : 5) afforded product **6** as a white powder (75 mg, 34%). ^{1}H NMR ($CDCl_3$) δ: 8.28 (m, 1H, NH), 8.13 (s, 1H), 7.95 (s, 1H), 7.26–7.12 (m, 5H, Ph), 6.76–6.74 (m, 2H), 6.53–6.51 (m, 1H), 5.12 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 149.44, 148.06, 146.82, 145.22, 135.30, 129.06 (2C), 128.45, 128.37, 128.27, 128.07 (2C), 120.19, 118.61, 50.08. HRMS, *m*/*z*: 252.1130 [M+H], 274.0953 [M+Na] (calc. for $C_{15}H_{13}N_3O$: 252.1131 [M+H], 274.0951 [M+Na]).

4-Acetylamino-5-(1*H*-pyrrol-3-yl)pyridine **7** was synthesized from 4-acetylamino-4-bromopyridine **5′** in a similar manner (for details, see Online Supplementary Materials).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.034.

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