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Synthesis and characterization of Boc-protected 4-amino- and 5-amino-pyrrole-2-carboxylic acid methyl esters☆

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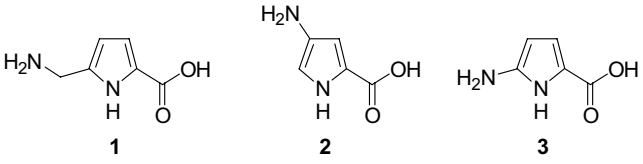
Abstract—Syntheses of Boc-protected 4-amino- and 5-amino-pyrrole-2-carboxylic acid methyl esters have been achieved and the structures of these compounds have been fully characterized by detailed NMR studies.

A common approach to restrict the conformational degrees of freedom in small peptides involves the design and synthesis of structurally rigid non-peptide scaffolds which, when inserted in the appropriate sites in peptides, produce the specific secondary structures required for binding to their receptors. This has led to an exponential growth in the number of reports on the development of large varieties of constrained peptidomimetic scaffolds.[1] Many of these designer templates are based on de novo structural entities with several functional groups anchored on a single ensemble. 5-(Aminomethyl)-pyrrole-2-carboxylic acid **1** is one such structure that has been used as a dipeptide isostere in synthetic peptides[2] and in the development of new DNA-binding agents.[3] In continuation of our work on the development of new pyrrole-based monomeric building blocks, we were interested in the synthesis of 4-amino-pyrrole-2-carboxylic acid **2** and its 5-amino congener **3**. The synthesis of compound **2** has been reported[4] and it has been used recently to develop novel guanidinium-based carboxylate receptors.[5] We were interested in developing an alternative route based on our earlier synthesis of 5-(aminomethyl)-pyrrole-2-carboxylic acid.[2a] The results of this study are described here.



Vilsmeier–Haack reaction of pyrrole-2-carboxylic acid methyl ester **4** gave a mixture of 4-formyl and 5-formyl products, **5** and **6**, respectively, in 2:3 ratio and in 95% total yield, which could be separated easily by standard silica gel column chromatography (Scheme 1).[6] Compound **5** was oxidized to an acid **7** in 92% yield. The acid was treated with diphenyl phosphoryl azide (DPPA) in the presence of Et_3N and the intermediate isocyanate was reacted with *t*-butanol to furnish the 4-*t*-butylcarbamate **8** in 50% yield.[7,8] Aldehyde **6** was similarly converted to the 5-substituted product **9**.[8]

To our surprise, compound **8**, and not **9**, was found to be identical with the product synthesized by us following the method reported earlier by Dervan et al.[4] with a slight modification that was also followed by Schmuck et al.,[5] that is, using MeONa/MeOH instead of EtONa/EtOH to get the methyl ester. It is to be noted here that this step in Dervan's method is inconsequential as far as the question of whether the 4- or 5-isomer is formed is concerned, which is settled in the previous step.

To confirm the structures of the two products, **8** and **9**, detailed NMR experiments were carried out at 30 °C in DMSO-d_6. For the spectral assignments, decoupling and nuclear Overhauser effect spectroscopy (NOESY)

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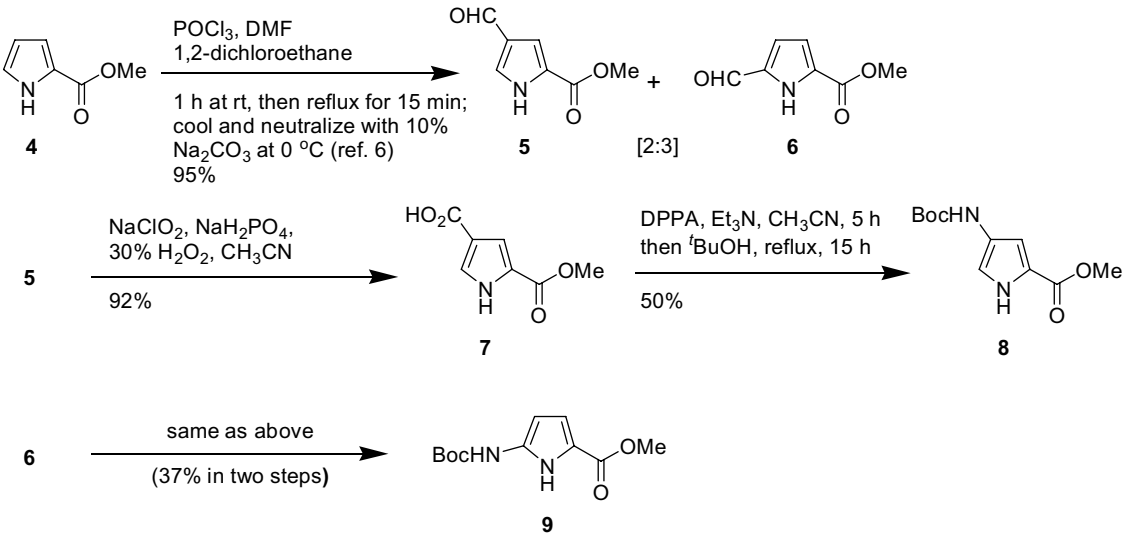

Scheme 1.

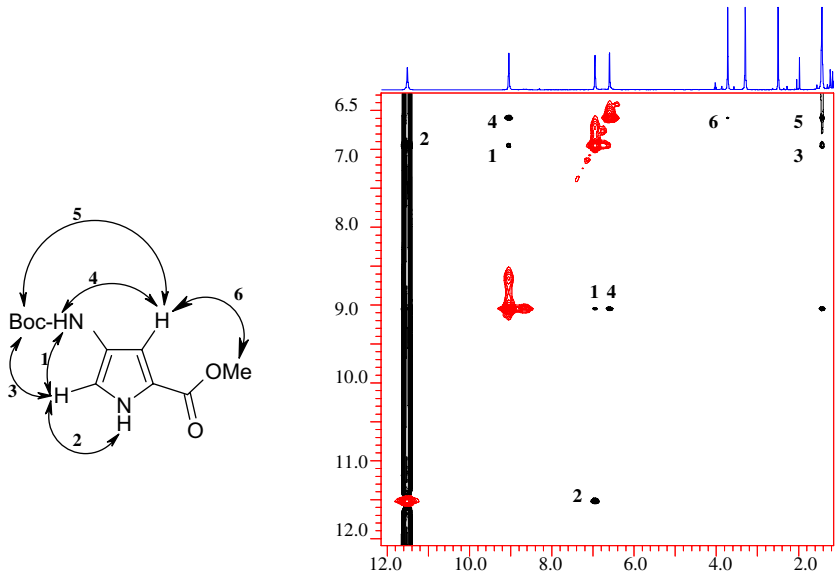

Figure 1. NOE correlation and NOESY spectrum for **8**.

experiments were carried out. NOESY experiments, in addition, provided crucial information about the proximity of the protons. The aromatic C–H signals for both **8** and **9** appeared as a dd with $J = 2.6$, 1.8 Hz for the former and $J = 4.0$, 2.3 Hz for the latter. D_2O exchange studies transformed them into doublets with 2.6 Hz coupling in **8** and 4.0 Hz in **9**. In view of the range reported for the unsubstituted pyrrole,[9] only $^3J_{H(3)–H(4)}$ has a value of about 3.5 Hz, whereas all other couplings are about 2.6 Hz or smaller. This suggests a 2,4-substitution pattern for **8** and a 2,5-substitution pattern for **9**. Further support for these observations was obtained from $^1J_{H–C}$ couplings. In pyrrole, one bond proton–carbon couplings are distinctive with $^1J_{H(3)–C(3)} \sim 170$ Hz and $^1J_{H(2)–C(2)} \sim 182$ Hz.[10] Our experiments show that for **8** they are 190.3 and 174.7 Hz whereas for **9** the $^1J_{H–C}$s have values of 174.0 and 175.4 Hz., further confirming a 2,4-substitution pattern for **8** and 2,5-substitution in **9**.

Consolidation of the above spectral data along with the heteronuclear single quantum correlation spectroscopy (HSQC) experiments, allows us to assign H(3), H(5/4), C(3) and C(5/4) at 6.60, 6.96, 105.5 and 112.7 ppm for **8** and at 6.70, 5.78, 115.8 and 95.1 ppm for **9**, respectively. To arrive at an unambiguous structure for **8** and **9**, NOESY experiments were additionally performed.

NOE studies on **8** confirmed that our findings on its structure are at variance to those of Dervan et al. The low-field pyrrole proton H(5) ($\delta = 6.96$ ppm) shows NOE correlations with both the NH protons as well as the Boc–CH_3 group (Fig. 1), while the other pyrrole proton H(3) ($\delta = 6.60$ ppm) shows NOEs with NH–Boc, Boc–CH_3 and OMe protons. These observations give conclusive proof for **8** as *N*-Boc-4-amino-pyrrole-2-carboxylic acid methyl ester.

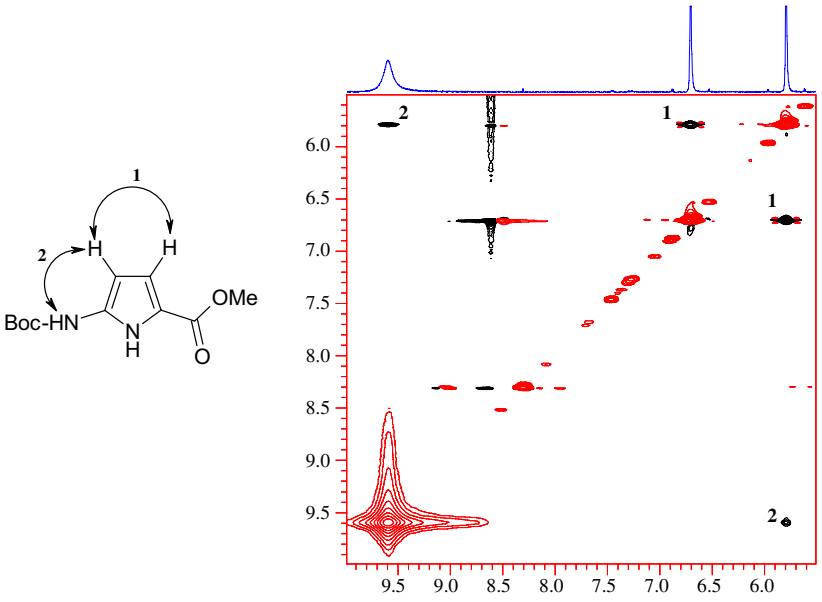

Figure 2. NOE correlation and NOESY spectrum for **9**.

For compound **9**, the two aromatic protons in the pyrrole ring show strong NOE correlations in the NOESY spectrum (Fig. 2). Further, observation of a NOE cross peak between H(4)–BocNH, in addition to confirming the assignments for H(3) and H(4) at $\delta = 6.70$ ppm and $\delta = 5.78$ ppm, respectively, provides emphatic evidence for their vicinal disposition, and confirms **9** as *N*-Boc-5-amino-pyrrole-2-carboxylic acid methyl ester.

In addition, compound **8** was transformed into its ethyl ester **10** by a base-catalyzed *trans*-esterification process. The spectral data of **10** matched exactly those of the compound reported by Dervan et al.[11] These findings imply that the reported structure of the compound prepared by Dervan et al. is likely to be different. Based on the NMR studies described here, we conclude that the amino-substituted pyrrole-2-carboxylic acid reported earlier[4] was actually the 4-amino isomer.

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8. Selected physical data of **8**: white solid; mp 185–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.65 (br, 1H, pyrroleN*H*), 9.09 (br, 1H, BocN*H*), 6.96 (dd, $J = 2.6$, 1.8 Hz, 1H, 5-*H*), 6.60 (dd, $J = 2.6$, 1.8 Hz, 1H, 3-*H*), 3.73 (s, 3H, CO_2CH_3), 1.44 (s, 9H, Boc); ^{13}C NMR (150 MHz, DMSO-d_6): δ 160.8, 152.8, 125.1, 119.0, 112.7, 105.5, 78.5, 51.1, 28.2; MS (FAB): *m*/*z* (%) 240 (50) $[M]^+$.
Selected physical data of **9**: white solid; mp 118 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (br, 1H, pyrroleN*H*), 9.57 (br, 1H, BocN*H*), 6.70 (dd, $J = 4.0$, 2.3 Hz, 1H, 3-*H*), 5.78 (dd, $J = 4.0$, 2.3 Hz, 1H, 4-*H*), 3.71 (s, 3H, CO_2CH_3), 1.45 (s, 9H, Boc); ^{13}C NMR (150 MHz, DMSO-d_6): δ 160.4, 152.5, 133.7, 115.8, 115.2, 97.0, 80.2, 50.9, 28.0; MS (FAB): *m*/*z* (%) 241 (48) $[M+H]^+$.
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11. Selected physical data of **10**: white solid; mp 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H, pyrrole-N*H*), 9.04 (s, 1H, BocN*H*), 6.94 (br, 1H, 5-*H*), 6.60 (br, 1H, 3-*H*), 4.20 (q, $J = 7.3$ Hz, 2H, $CO_2CH_2CH_3$), 1.44 (s, 9H, Boc), 1.26 (t, $J = 7.3$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 152.6, 124.8, 119.2, 112.4, 105.3, 78.3, 59.3, 28.1, 14.3; MS (FAB): m/z (%) 254 (34) $[M]^+$.