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Synthesis of the hindered *N*,*N*,*N*′-trisubstituted guanidine moiety of martinelline and martinellic acid

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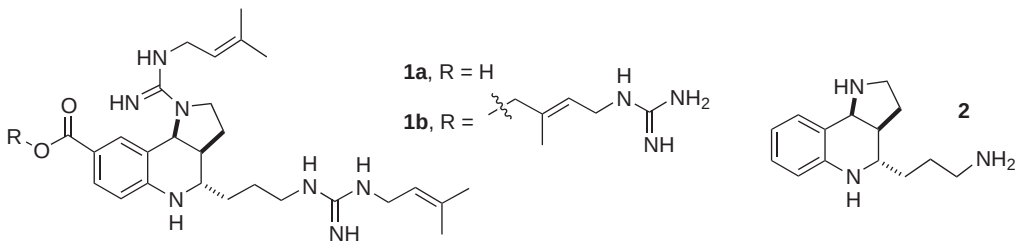
Abstract—Hindered guanidines can be prepared by reaction of cyanamides with amines in hexafluoroisopropanol at 90–120°C. This sequence was used for preparing guanidinium acid **21** as a model for martinellic acid.

Martinellic acid (**1a**) and martinelline (**1b**) were isolated by Witherup, Varga and co-workers at Merck Research Laboratories from the roots of the tropical plant *Martinella iquitosensis*.[1] These alkaloids are the first naturally occurring nonpeptide bradykinin B_1 and B_2 receptor antagonists. The novel tricyclic pyrrolo[3,2-*c*]quinoline core has been the object of intense synthetic effort.[2] We have developed an eight-step synthesis of the model triamine **2**, which proceeds in 11% overall yield from 2-hydroxymethylaniline.[3] Construction of the *N*,*N*′-disubstituted guanidine on the side chain of **2** could be easily achieved.[4] Formation of the *N*,*N*,*N*′-trisubstituted guanidine from the hindered pyrrolidine proved to be much more challenging.



We therefore chose to carry out model studies using 2-phenylpyrrolidine (**3b**)[5] as a model for the pyrrolidine of **2**. Guanidinylation of **3b** proved to be quite challenging despite the numerous methods developed to prepare *N*,*N*′-polysubstituted guanidines in the past decade.[6] For instance, reaction of **3b** with *N*-butyl-*N*′-(Boc)-thiourea using EDC[6b,m] afforded none of the guanidine, while use of $HgCl_2$ and Et_3N in THF[6i] afforded approximately 20% of the Boc-protected guanidine.

We decided to prepare the cyanamide from the hindered pyrrolidine with the expectation that this reaction would be clean because cyanogen bromide is both less hindered and more electrophilic than guanidinylating agents. However, addition of prenylamine to the cyanamide may not be straightforward. Although additions of amines to cyanamides to form guanidines have been known since the work of Von Braun, harsh conditions are usually required for this reaction.[7]

Reaction of pyrrolidine (**3a**) with a slight excess of cyanogen bromide and 3 equiv. of $NaHCO_3$ in EtOH for 2 h afforded 96% of crude cyanamide **4a**, which was used without purification. Reaction of *n*-$BuNH_2$ (**5a**) with **4a** was investigated in several solvents. No guanidine was formed in THF, MeOH, CH_3CN, *t*-BuOH, or CH_3NO_2 at reflux or in DMF at 100°C. We chose to investigate fluorinated alcohols since their polarity should facilitate the addition, while their lack of nucleophilicity should retard the formation of *O*-fluoroalkyl isoureas. Reaction of **4a** with *n*-$BuNH_2$

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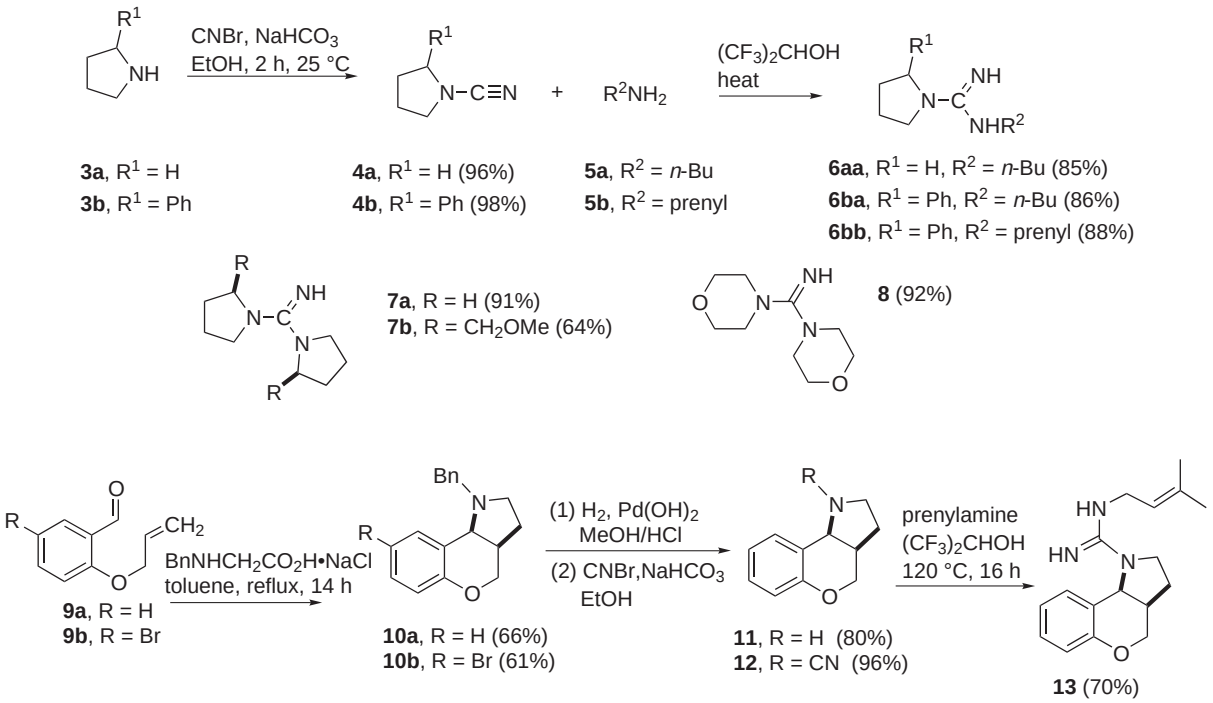
in trifluoroethanol in a sealed tube at 90°C for 17 h afforded a 2:1:2 mixture of the desired guanidine **6aa**, the *O*-trifluoroethyl isourea and recovered **4a** indicating the validity of this approach. Optimal results were obtained with the more polar, less nucleophilic solvent, hexafluoroisopropanol (HFIP). Reaction of **4a** with 1.1 equiv. of *n*-$BuNH_2$ as a 0.1 M solution in HFIP in a sealed tube at 90°C for 12 h afforded 85% of pure guanidine **6aa**. The guanidine was easily purified by dissolution in aqueous citric acid and extraction of the non-basic impurities into ether. The aqueous layer was basified with 20% aqueous KOH solution and the guanidine was extracted into CH_2Cl_2 to give **6aa** that was >95% pure by ^1H NMR spectroscopy.

Guanidines **7a** (80°C, 12 h, 91%), **7b** (130°C, 18 h, 64%), and **8**[11] (100°C, 14 h, 92%) were prepared by heating the appropriate cyanamide and amine in HFIP.

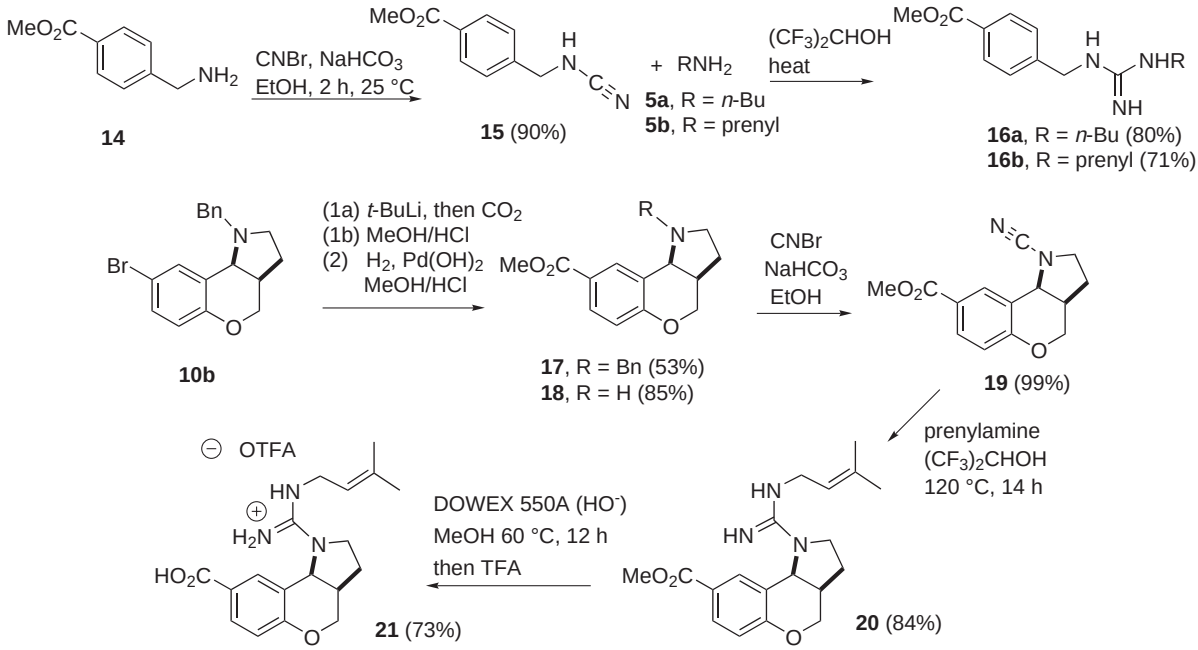
Tricyclic pyrrolidine **11** was prepared as a better model for **2** by condensation of 2-allyloxybenzaldehyde (**9a**) with *N*-benzylglycine·NaCl to give 66% of **10a**.[4,12] Hydrogenolysis over $Pd(OH)_2$ afforded 80% of **11**.[4,12c] Condensation of **11** with CNBr and $NaHCO_3$ in EtOH afforded 96% of cyanamide **12**. Reaction of **12** with prenylamine in HFIP at 120°C for 16 h provided 70% of the required guanidine **13** indicating the suitability of this method for the synthesis of the trisubstituted guanidine of martinelline and martinellic acid.



Fortunately, comparable results were obtained with more hindered 2-phenylpyrrolidine (**3b**). Condensation of **3b** with cyanogen bromide and $NaHCO_3$ in EtOH afforded 98% of cyanamide **4b**.[8] Reaction of **4b** with *n*-$BuNH_2$ in HFIP at 90°C for 11 h gave 86% of pure guanidine **6ba**. We were initially surprised to find that **4b** did not react with prenylamine (**5b**)[9] under these conditions. However, the allylic double bond is electron-withdrawing making allylamine 15 times less basic than propylamine.[10] Therefore prenylamine should be less nucleophilic than *n*-$BuNH_2$. Guanidine formation was achieved by heating **4b** with prenylamine in HFIP at 130°C in a sealed tube for 18 h to give 88% of the pure model guanidine **6bb**.[8] Attempted preparation of guanidines **6ba** and **6bb** by reaction of the cyanamide prepared from **5a** or **5b** with **3b** in HFIP at 90–120°C for 12–48 h proceeded in only 25–50% yield, indicating that the hindered secondary amine, rather than the primary amine, should be converted to the cyanamide. *N*,*N*,*N*′,*N*′-tetrasubstituted guanidines can be prepared by addition of secondary amines to cyanamides.

We investigated the preparation of guanidine **16** to determine whether an ester was stable to the high temperature needed for the addition of the amine to the cyanamide. Reaction of **14** with CNBr afforded 90% of cyanamide **15**, which was treated with *n*-$BuNH_2$ (90°C, 17 h) or prenylamine (105°C, 14 h) to give ester guanidines **16a** (80%) and **16b** (71%), respectively. This indicates that aminolysis of the methyl ester to give the amide does not occur at 90–105°C.

Pyrrolidine ester **18** was prepared to complete the model study. Condensation of 2-allyloxy-5-bromobenzaldehyde (**9b**)[13] with *N*-benzylglycine·NaCl gave 61% of **10b**. Halogen–metal exchange with *t*-BuLi and trapping with CO_2[14] gave the acid, which was refluxed in HCl/MeOH to give 53% of ester **17**. Hydrogenolysis afforded 85% of pyrrolidine **18**,[8] which was condensed with CNBr to give 99% of cyanamide **19**.[8] Reaction of **19** with prenylamine in HFIP at 120°C for 14 h afforded 84% of the desired ester guanidine **20**,[8] indicating that this procedure is compatible with the ester of martinelline.



We needed to hydrolyze the ester of **20** to complete the model study. Since guanidines are stable in acid, but hydrolyze to ureas in base we initially investigated acid cleavage of the methyl ester. Unfortunately, no hydrolysis occurred after 2.5 h in 1:1 CH_2Cl_2/TFA at reflux, but the double bond was partially decomposed. Heating a solution of **20** in 9:1 1 M HCl/MeOH at 60°C for 2 h completely decomposed the double bond without hydrolyzing the ester. Basic hydrolysis of the ester is complicated by the problem of separation of a guanidino acid from inorganic salts. We therefore hydrolyzed **20** by heating with Dowex 550A resin in the hydroxide form[15] in MeOH at 60°C for 12 h. The MeOH was discarded and the resin, to which was complexed the carboxylate salt of **21**, was suspended in D_2O. The solution was acidified with TFA, stirred for 45 min, filtered and concentrated to afford 73% of pure acid guanidinium salt **21**[8] with spectral data similar to those of martinellic acid.

In conclusion, we have developed a general new method for the synthesis of hindered guanidines by reaction of cyanamides with amines in HFIP at 90–120°C and shown that this procedure can be used to prepare the hindered *N*,*N*,*N*′-trisubstituted guanidine of martinellic acid and martinelline.

Acknowledgements

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8. **4b**: ^{1}H NMR: 7.38 (dd, 2, J=7.2, 7.2), 7.33–7.29 (m, 3), 4.66 (dd, 1, J=7.3, 7.3), 3.72 (ddd, 1, J=7.2, 7.2, 6.8), 3.62–3.57 (m, 1), 2.38–2.30 (m, 1), 2.10–1.95 (m, 2), 1.92–1.83 (m, 1); ^{13}C NMR: 139.7, 128.8 (2 C), 128.2, 126.3 (2 C), 116.9, 65.9, 51.4, 35.5, 24.8; IR 2211. **6bb**: ^{1}H NMR: 7.35–7.31 (m, 2), 7.27–7.23 (m, 3), 5.07 (br t, 1, J=6.7), 4.75 (dd, 1, J=7.9, 3.2), 3.68–3.55 (m, 2), 3.61 (br d, 2, J=6.7), 2.40–2.31 (m, 1), 2.00–1.81 (m, 3), 1.64 (s, 3), 1.52 (s, 3); ^{13}C NMR: 157.9, 144.0, 135.4, 128.7 (2 C), 127.2, 125.6 (2 C), 121.2, 61.2, 47.8, 40.2, 36.3, 25.5, 22.9, 17.7; IR 1591; HRMS (DEI) calcd for $C_{16}H_{23}N_3$ (M^+) 257.1892, found 257.1889. **18**: mp 77.5–78.5°C; ^{1}H NMR: 8.09 (s, 1), 7.84 (br d, 1, J=8.5), 6.90 (d, 1, J=8.5), 4.16 (dd, 1, J=11, 4.3), 4.00 (d, 1, J=6.1), 3.87 (s, 3), 3.64 (dd, 1, J=11.0, 11.0), 3.10 (ddd, 1, J=10, 9, 5), 2.97 (ddd, 1, J=9, 9, 9), 2.56–2.47 (m, 1), 2.19–2.07 (m, 1), 2.07 (s, 1, NH), 1.58–1.50 (m, 1); ^{13}C NMR: 166.8, 158.9, 132.8, 130.1, 123.3, 122.9, 117.0, 66.7, 55.6, 51.8, 44.9, 35.4, 27.9; IR 1714. **19**: ^{1}H NMR: 8.16 (d, 1, J=2.4), 7.95 (dd, 1, J=8.5, 2.4), 6.94 (d, 1, J=8.5), 4.55 (d, 1, J=6.1), 4.20 (dd, 1, J=11.0, 4.2), 3.89 (s, 3), 3.85 (dd, 1, J=11.0, 9.8), 3.57 (apparent t, 2, J=6.7), 2.72–2.62 (m, 1), 2.32–2.23 (m, 1), 1.95–1.87 (m, 1); ^{13}C NMR: 166.3, 158.0, 132.9, 131.8, 123.5, 118.4, 117.3, 116.4, 65.1, 57.5, 52.1, 48.5, 35.3, 26.0; IR 2208, 1714. **20**: ^{1}H NMR: 8.50 (br s, 1, J=8.5), 7.80 (dd, 1, J=8.5, 1.8), 6.79 (d, 1, J=8.5), 5.49 (d, 1, J=7.3), 5.30 (br t, 1, J=6.7), 4.29 (dd, 1, J=11.6, 2.4), 4.24 (dd, 1, J=11.6, 2.4), 3.89 (s, 3), 3.77 (d, 2, J=6.7), 3.43 (ddd, 1, J=8.5, 8.5, 8.5), 3.36–3.31 (m, 1), 2.62–2.55 (m, 1), 2.14–2.07 (m, 2), 1.76 (s, 3), 1.73 (s, 3); ^{13}C NMR: 166.9, 157.5, 132.9, 129.9, 123.4, 120.9, 116.6, 65.7, 53.2, 51.8, 46.1, 40.5, 36.5, 25.81, 25.71, 18.0 (four quaternary carbons were not observed); HRMS (DCI, NH_3) calcd for $C_{19}H_{26}N_3O_3$ (MH^+) 344.1974, found 344.1977. **21**: ^{1}H NMR (D_2O, HDO at 4.79, 500 MHz): 7.93 (d, 1, J=1.0), 7.75 (dd, 1, J=8.5, 1.0), 6.91 (d, 1, J=8.5), 5.37 (br t, 1, J=7), 5.32 (d, 1, J=6.9), 4.40 (dd, 1, J=12.2, 2.4), 4.36 (dd, 1, J=12.2, 2.0), 3.99 (dd, 1, J=15.2, 7), 3.96 (dd, 1, J=15.2, 7), 3.63–3.45 (m, 2), 2.85–2.77 (m, 1), 2.30–2.22 (m, 1), 2.16–2.05 (m, 1), 1.79 (s, 3), 1.75 (s, 3); ^{13}C NMR: 157.8, 154.8, 131.4, 131.2, 120.6, 120.1, 117.7, 117.5, 65.1, 54.4, 46.6, 40.1, 36.2, 24.9, 23.9, 17.3 (2 quaternary carbons were not observed); HRMS (FAB, DMSO/NBA) calcd for $C_{18}H_{24}N_3O_3$ (MH^+) 330.1818, found 330.1818.
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15. A column of Dowex 550A resin was pretreated with 20 volumes of 20% NaOH followed by 5 volumes of H_2O and 5 volumes of MeOH. The resin was dried under a flow of air for 1 h.