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A Facile and Efficient Multi-Gram Synthesis of *N*-Protected 5-(Guanidinocarbonyl)-1*H*-pyrrole-2-carboxylic Acids

Carsten Schmuck,*[a] Volker Bickert,[a] Michael Merschky,[a] Lars Geiger,[a] Daniel Rupprecht,[a] Jürgen Dudaczek,[a] Peter Wich,[a] Thomas Rehm,[a] and Uwe Machon[a]

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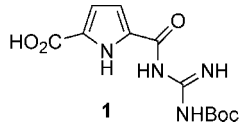
The synthesis of two versatile building blocks for supramolecular anion binding motifs, 5-(*N*-Boc-guanidinocarbonyl)-1*H*-pyrrole-2-carboxylic acid (**1**) and 5-(*N*-Cbz-guanidinocarbonyl)-1*H*-pyrrole-2-carboxylic acid (**2**) is reported. Using these building blocks, a guanidiniocarbonyl-pyrrole anion binding site can easily be introduced into more complex molecules by using standard amide coupling conditions. Both syntheses can be performed on a multi-gram scale. The products are obtained in pure form and can be stored as solids without decomposition.

Introduction

The guanidinium group is widely spread in nature i.e. mainly as part of the amino acid arginine, in which it is responsible for the interaction of proteins with carboxylates or other oxo-anions.[1] Guanidinium cations form directed bidentate ion pairs with oxo-anions which are, however, only stable under non-aqueous conditions.[2] For nature this does not cause problems because molecular recognition events can take place within the less polar microenvironment of a protein. Unfortunately, supramolecular model systems which use guanidinium ion pair interactions have to cope with the competing solvation of both substrate and host when applied to polar, especially protic solvents. Therefore, in the last few years a variety of modified guanidinium cations has been introduced with improved anion binding features.[3] One prominent example is the guanidiniocarbonyl-pyrrole cation.[4] Besides simple ion pairing additional H-bonds between the anion and the cationic binding motif (e.g. by the pyrrole NH) further increase complex stability. Hence, this building block has found wide application to study noncovalent interactions, for the design of receptors and sensors for anionic biomolecules[5] as well as the development of self-assembling nanomaterials.[6] However, all these applications depend on efficient synthetic protocols that enable the introduction of this building block under mild conditions into more complex molecules. Initially, we introduced the guanidino group by refluxing the corresponding methyl pyrrolecarboxylate with guanidinium chloride in sodium methoxide.[7] Only few molecules survive such harsh reaction conditions.

We have therefore developed a much more versatile and milder approach starting with the *N*-protected guanidinocarbonyl-pyrrolecarboxylic acids **1** and **2**, respectively. These building blocks can conveniently be introduced into nearly any molecule by standard amide coupling protocols with the only restriction that the most active coupling reagents such as PyBOP or HCTU give satisfactory yields (pyrrolecarboxylic acids are rather unreactive). We now report on the detailed syntheses of the *N*-protected guanidinocarbonyl-pyrrolecarboxylic acids **1** and **2**.



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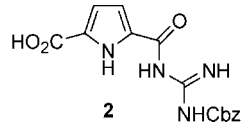

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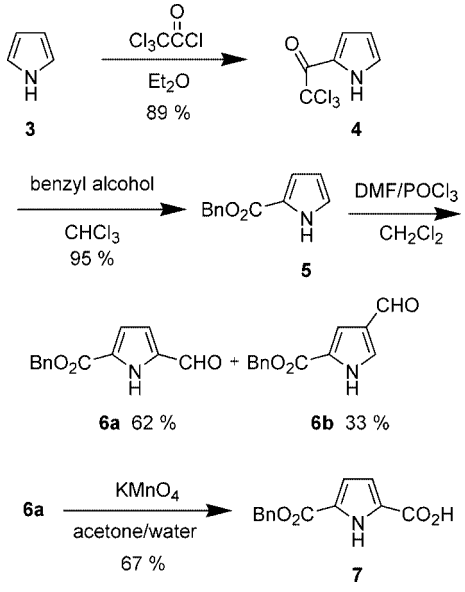
Results and Discussion

The synthesis of **1** and **2** starts in both cases from the commercially available pyrrole **3** (see Schemes 1 and 2 or 3). Pyrrole was first acylated with trichloroacetyl chloride in diethyl ether to give the trichloroacetyl-pyrrole **4** as a white solid in a yield of 89%. Upon standing with exposure to air, this compound rapidly turns into a grey metallic solid due to oxidation.[8] Trichloroacetyl-pyrrole **4** was then subjected to a haloform reaction with benzyl alcohol in chloroform in the presence of a catalytic amount of sodium. Attack of the benzylate and liberation of the trichloromethane anion directly yields the benzyl ester **5**. The released anion is immediately protonated by the benzyl alcohol regenerating the attacking nucleophile. During the work-up

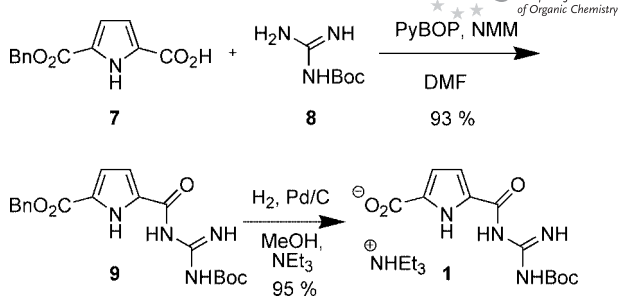
[a] Universität Würzburg, Institut für Organische Chemie, Am Hubland, 97074 Würzburg, Germany
Fax: +49-931-8884626
E-mail: schmuck@chemie.uni-wuerzburg.de

procedure of this reaction, care has to be taken that the benzyl ester is not hydrolyzed. Therefore, too basic reaction conditions have to be avoided. In the literature this kind of cleavage is well known, even in a two-phase mixture with potassium carbonate as base.[9] Hence, an equimolar amount of hydrochloric acid was added to quench the base. Separation of the phases is very difficult at this stage due to the deep black color of the reaction mixture, so we decided to directly evaporate the organic solvent from the aqueous reaction mixture under reduced pressure. The resulting aqueous mixture, which still contains benzyl alcohol, was then lyophilized to obtain a crude solid product. This crude benzyl ester **5** was then purified via flash column chromatography to give pure **5** in 95% yield. Compound **5** was then subjected to Vilsmeier–Haack formylation. The Vilsmeier reagent, preformed from phosphoryl chloride and dimethylformamide, was added slowly at –15 °C to **5**. During this reaction two regioisomers are formed (substitution in positions 4 and the 5 of the pyrrole ring). Both isomers can be separated by chromatography. Purification via chromatography resulted in the 2,4-substituted product **6b** (33%) and in the desired 2,5-substituted product **6a** (62%). The aldehyde **6a** was then oxidized with potassium permanganate in a mixture of acetone and water. The reaction was worked up by filtration under basic conditions through a celite pad and then the carboxylic acid was precipitated by acidification. After filtration and drying the mono benzyl ester **7** of 1*H*-pyrrole-2,5-dicarboxylic acid was obtained in 67% yield as a colorless powder.

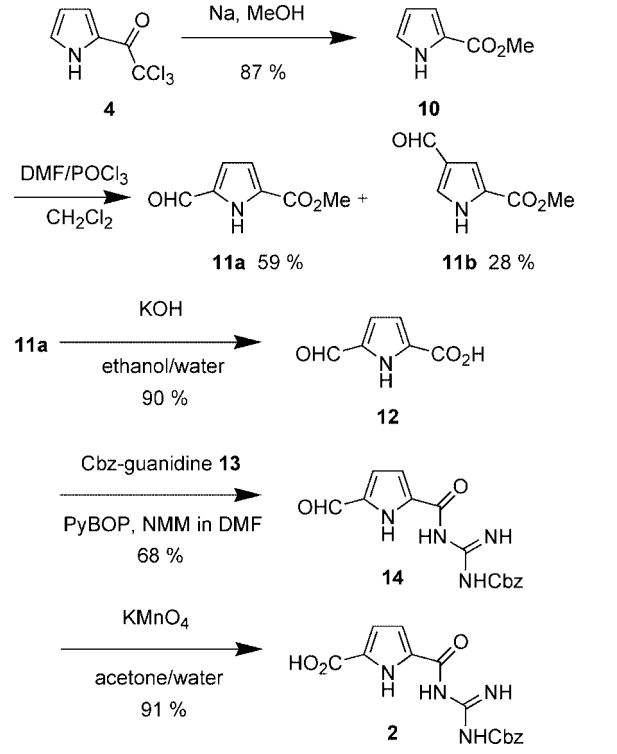


Scheme 1. Synthesis of the mono benzyl ester **7**.

The acidic function of **7** can now be reacted with *N*-protected guanidines. On the one hand, the advantage of this procedure is the easy purification of the *N*-protected compounds via chromatography on silica gel, which is nearly impossible with the free guanidine base. On the other hand, the formation of a guanidiniocarbonyl-pyrrolecarboxylate zwitterion in subsequent reaction steps is avoided. Such



Scheme 2. Synthesis of the 5-(*N*-Boc-guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylic acid (**1**).



Scheme 3. Synthesis of the 5-(*N*-Cbz-guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylic acid **2**.

zwitterions are known to form very stable dimers with poor solubility in nearly any solvent.[7]

The acid **7** was therefore reacted with *N*-Boc-guanidine **8** with *N*-methylmorpholine as a base and PyBOP as the coupling reagent (Scheme 2). This was necessary due to the low reactivity of a pyrrolecarboxylic acid derivative like **7**. Coupling attempts with DCC failed and activation of the acid with oxalyl chloride caused cleavage of the *N*-Boc group in the subsequent coupling step. Another coupling reagent that can be used is HCTU, approximately 10% lower yields have to be envisaged. The guanidinocarbonyl-pyrrolecarboxylate **9** directly precipitated when water was added to the reaction mixture. For further work-up this precipitate was redissolved in diethyl ether and the organic phase was extracted several times with water. Finally, the ester **9** was obtained as a colorless crystalline powder in 93% yield. The benzyl ester group in **9** was then cleaved off by hydrogenation with a catalytic amount of palladium on

activated charcoal in methanol. Because of the low solubility of the deprotected carboxylic acid we initially carried out a hot filtration through a celite pad which was washed extensively with warm DMF. The acid **1** could then be precipitated by the addition of water. However, the yields were not satisfactory and the procedure was very tedious. A better way of isolation is to make use of the good solubility of the ammonium salt of the acid **1** in methanol. So we performed the hydrogenation of **9** in the presence of triethylamine in methanol. This way the ammonium salt of **1** is formed directly which is well soluble under these conditions. Afterwards the reaction mixture was filtered through a celite pad and the ammonium salt of **1** was isolated after evaporation of the solvent in nearly quantitative yield.

The *N*-Boc-protected acid **1** is a versatile compound which allows introducing this building block in a variety of different compounds. However, with some reaction conditions that might show up later on in subsequent syntheses a acid-labile Boc-protecting is not compatible. We therefore also synthesized the *N*-Cbz-protected analogue **2**. The Cbz group is much more stable under acidic conditions but can be easily cleaved off by hydrogenation. For the synthesis of the Cbz analogue **2** we choose a different approach compared to the *N*-Boc-protected compound **1** using the reaction sequence shown in Scheme 3. The synthesis starts with the methyl ester **10** instead of the benzyl ester **5** mainly for two reasons: on the one hand, a benzyl ester next to a Cbz-protecting group in one molecule can not be cleaved off by hydrogenation selectively and quantitatively. On the other hand, basic saponification of the benzyl ester in the presence of a *N*-Cbz guanidinocarbonyl pyrrole is not possible. The *N*-protected guanidine is a rather good leaving group under nucleophilic conditions so that treatment with base not only leads to cleavage of the ester but also of the guanidinocarbonyl amide bond. We have already observed this problem in the past when trying to cleave a methyl ester with lithium hydroxide in the presence of a *N*-protected guanidinocarbonyl-pyrrole. The yield of this hydrolysis was less than 25% and only the use of trimethyltin hydroxide[10] gave satisfactory yields. This reagent is, however, very expensive and thus not suited for large-scale multi-gram syntheses. So we changed the reaction sequence for the *N*-Cbz-protected acid **2** as shown above (Scheme 3). Starting from 2-(trichloroacetyl)pyrrole (**4**), we synthesized the methyl ester **10** in 87% yield by reacting **4** with sodium methoxide in methanol. Analogously to the formation of the benzyl ester described above, sodium methoxide was used only in a catalytic amount. However, the work-up was now much easier than in the case of the benzyl ester. Extraction of the product with diethyl ester from the aqueous mixture after quenching and recrystallization gave the white product **10** in 87% yield. The Vilsmeier–Haack formylation was done in the same way as described before in the case of **5** and also the ratio of the regioisomeric aldehydes obtained was similar. The desired aldehyde **11a** was isolated in 59% yield after chromatography compared to 62% for **6a**. Now we decided not to oxidize the aldehyde to the carboxylic acid at this stage but first to cleave off the methyl ester. This way we could avoid the necessity for methyl ester hydrolysis after the introduction of the *N*-protected guanidine with the problems mentioned above. The methyl ester in **11a** was hydrolyzed with potassium hydroxide in an ethanol/water mixture and the free carboxylic acid **12** was obtained in 90% isolated yield. Then the Cbz guanidine **13** was coupled to this carboxylic acid group using PyBOP in DMF as coupling reagent and *N*-methylmorpholine as base. This way the *N*-Cbz-protected guanidinocarbonyl-pyrrolecarbaldehyde **14** was prepared in 68% yield. Finally, this compound was oxidized under the same conditions used before ($KMnO_4$ in acetone/water) to give the *N*-Cbz-protected 5-(guanidinocarbonyl)pyrrole-2-carboxylic acid **2** in 91% yield. The *N*-Boc-protected guanidine **8** can also be used in this synthesis, so that **1** can be synthesized accordingly. However, the yields are significantly lower than with *N*-Cbz-guanidine **13** (40% for the coupling and 55% for the oxidation), most likely due to problems in the isolation and purification of the carboxylic acid as it can not be as easily precipitated with strong acids due to the *N*-Boc protection group. Therefore, especially for large-scale synthesis, route 1 as described in Scheme 1 is preferred for compound **1**.

Conclusions

The *N*-Boc-protected 5-(guanidinocarbonyl)-1*H*-pyrrole-2-carboxylic acids **1** and **2** can be synthesized with overall yields of 31% and 25%, respectively. The two synthetic routes allow multi-gram syntheses of these versatile building blocks for supramolecular anion binding motifs. Both products can easily be stored and handled in subsequent reactions without additional precautions.

Experimental Section

General Remarks: Solvents were dried and distilled before use. The starting materials and reagents were used as obtained from the commercial suppliers. All reactions were carried out in oven dried glassware. Column chromatography was done on columns packed with silica gel of 60 Å with a spherical size of 32–63 mm. The IR spectra were recorded on a JASCO FT-IR 410 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at ambient temperature. The chemical shifts are reported relative to the deuterated solvents $CDCl_3$ or $[D_6]$-DMSO. HR-EI mass spectra were received by using a Finnigan MAT 90, HR-ESI-mass spectra by using a Bruker micro TOF focus.

2-(Trichloroacetyl)-1*H*-pyrrole (4):[8] To a solution of trichloroacetyl chloride (200 g, 1.10 mol, 1.1 equiv.) in dry diethyl ether (220 mL) freshly distilled pyrrole **3** (67.1 g, 1.00 mol, 1 equiv.) was added over 3 h. The mixture was stirred for an additional hour at room temperature and afterwards neutralized with an aqueous potassium carbonate solution (85.0 g, 0.62 mol, 0.62 eq in 300 mL of water). The organic phase was separated and dried with $MgSO_4$. Activated charcoal was added to the solution which was then filtered through a celite pad after stirring for 10 min. Solvent evaporation and crystallization from hexane resulted in a white solid (189 g, 89%). R_f = 0.49 (SiO_2, dichloromethane); m.p. 75–75.5 °C. FT-IR (KBr): $\tilde{\nu}$ = 3323 (br. s), 2921 (w), 1656 (s), 1536 (w), 1425

(w), 1387 (m), 1137 (m), 1112 (m), 1064 (m), 1036 (m), 843 (w), 756 (m), 740 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.37–6.34 (m, 1 H, CH), 7.16–7.17 (m, 1 H, CH), 7.38–7.40 (m, 1 H, CH), 9.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 95.1 (C_q), 112.0, 121.3 (both CH), 123.1 (C_q), 127.2 (CH), 173.3 (C_q) ppm. HR-MS (EI): *m*/*z* calcd. for $C_6H_4Cl_3NO^{\cdot+}$ ($M^{\cdot+}$) 210.9361, found 210.9358.

Benzyl 1*H*-Pyrrole-2-carboxylate (5):[8] A sodium benzylate solution, prepared from Na (1.08 g, 47.0 mmol, 0.2 equiv.) in freshly distilled benzyl alcohol (26.8 mL, 259 mmol, 1.1 equiv.), was added to a solution of **4** (50.0 g, 235 mmol, 1 equiv.) in chloroform (50 mL). The resulting dark mixture was stirred for one hour at room temperature and then 1 N hydrochloric acid (50 mL, 50.0 mmol, 0.2 equiv.) was added. After stirring for ten minutes the organic solvent was first evaporated under reduced pressure and the remaining aqueous reaction mixture was lyophilized after the addition of another 100 mL of water to help remove the remaining benzyl alcohol upon lyophilization. The crude black solid product was purified by flash chromatography on silica gel (hexane/ethyl acetate/dichloromethane, 70:15:15) to give the slightly yellow benzyl ester **5** (44.9 g, 95%). R_f = 0.55 (SiO_2, hexane/ethyl acetate/dichloromethane, 70:15:15); m.p. 55 °C. FT-IR (KBr): $\tilde{\nu}$ = 3310 (s), 3190 (s), 2325 (m), 2320 (m), 1696 (s), 1420 (s), 1320 (s), 1190 (s), 1130 (s), 735 (m), 745 (m), 765 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.32 (s, 2 H, CH_2), 6.26–6.28 (m, 1 H, pyrrole-C*H*), 6.94–6.97 (m, 1 H, CH), 6.98–6.99 (m, 1 H, CH), 7.32–7.44 (m, 5 H, CH), 9.19 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.1 (CH_2), 110.7, 115.8 (both CH), 122.8 (C_q), 123.1 (CH), 128.3, 128.4, 128.7 (all CH), 136.3 (C_q), 161.0 (C_q) ppm. HR-MS (EI): *m*/*z* calcd. for $C_{12}H_{11}NO_2^{\cdot+}$ ($M^{\cdot+}$) 201.0790, found 201.0793.

Benzyl 4-/5-Formyl-1*H*-pyrrole-2-carboxylates 6a and 6b:[11] Phosphoryl chloride (11.0 mL, 0.12 mol, 2 equiv.) was added drop wise to dimethylformamide (23.4 mL, 0.3 mol, 5 equiv.) at 5–10 °C. Stirring for 30 min produced the Vilsmeier reagent. The benzyl pyrrolecarboxylate **5** (12.1 g, 0.06 mol, 1 equiv.) was dissolved in 250 mL of dichloromethane and cooled to –15 °C, and the Vilsmeier reagent was added drop wise over 15 min. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 24 h. A saturated aqueous sodium hydrogen carbonate solution (150 mL) was added, and the mixture was refluxed for 15 min. After filtering the resulting solution, the organic layer was separated, washed twice with brine (50 mL) and dried with $MgSO_4$. The solvent was evaporated first under reduced pressure and afterwards in high vacuo to remove the DMF. Purification of the brown oil by flash chromatography on silica gel (cyclohexane/ethyl acetate/dichloromethane, 70:15:15) gave the white to yellow 2,5-substituted product **6a** (8.45 g, 62%) and the red 2,4-substituted side product **6b** (4.50 g, 33%).

Benzyl 5-Formyl-1*H*-pyrrole-2-carboxylate (6a): R_f = 0.55 (SiO_2, cyclohexane/ethyl acetate/dichloromethane, 70:15:15); m.p. 105 °C. FT-IR (KBr): $\tilde{\nu}$ = 3280 (s), 2320 (m), 2350 (m), 1690 (s), 1700 (s), 1550 (s), 1390 (s), 1340 (s), 1220 (s), 780 (m), 770 (m), 700 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.35 (s, 2 H, CH_2), 6.93–6.98 (m, 2 H, CH), 7.36–7.44 (m, 5 H, CH), 9.66 (s, 1 H, CH), 9.84 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.2 (CH_2), 116.1, 119.9 (both CH), 128.3 (CH), 128.6, 128.7, 128.8 (all CH), 134.7 (C_q), 135.4 (C_q), 160.3 (C_q), 180.5 (C_q) ppm. HR-MS (EI): *m*/*z* calcd. for $C_{13}H_{11}NO_3^{\cdot+}$ ($M^{\cdot+}$) 229.0741, found 229.0739.

Benzyl 4-Formyl-1*H*-pyrrole-2-carboxylate (6b): R_f = 0.13 (SiO_2, cyclohexane/ethyl acetate/dichloromethane, 70:15:15); m.p. 99 °C. FT-IR (KBr): $\tilde{\nu}$ = 3138 (m), 2990 (m), 1707 (s), 1636 (s), 1567 (m), 1502 (m), 1452 (m), 1416 (m), 1383 (m), 1344 (m), 1268 (m), 1202 (s), 1152 (m), 1113 (m), 953 (w), 909 (w), 810 (w), 788 (w), 759 (m), 693 (m), 615 (w), 584 (w), 536 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.3 (s, 2 H, CH_2), 7.32–7.41 (m, 6 H, CH), 7.52–7.54 (m, 1 H, CH), 9.80 (s, 1 H, CH), 10.20 (NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.7 (CH_2), 114.7, 127.5 (both CH), 128.2, 128.5, 128.6 (all CH), 128.7, 135.4, 160.7, 185.7 (all C_q) ppm. HR-MS (EI): *m*/*z* calcd. for $C_{13}H_{11}NO_3^{\cdot+}$ ($M^{\cdot+}$) 229.0741, found 229.0739.

5-(Benzyloxycarbonyl)-1*H*-pyrrole-2-carboxylic Acid (7): To a solution of the aldehyde **6a** (17.2 g, 75.0 mmol, 1 equiv.) in acetone (100 mL) a solution of $KMnO_4$ (23.7 g, 150 mmol, 2 equiv.) in acetone/water (1:1, 300 mL) was added drop wise over a period of 1 h. The solution was heated to 40 °C for 1 h and stirred at room temperature for an additional hour. Sodium dithionite (1.31 g, 7.50 mmol, 0.1 equiv.) was added, stirred for ten minutes and then filtered through a celite pad. The celite pad was thoroughly washed with a 1 M aqueous sodium hydroxide solution (150 mL) and the combined filtrates were acidified with 2 M hydrochloric acid. A colorless precipitate formed which was filtered off, washed with cold 2 M hydrochloric acid and dried with phosphorus pentoxide to give the carboxylic acid **7** as a colorless powder (12.3 g, 67%). R_f = 0.59 (SiO_2, dichloromethane/ethyl acetate + triethylamine, 5:5 + 1%); m.p. 234 °C (decomp.). FT-IR (KBr): $\tilde{\nu}$ = 3287 (s), 2360 (m), 2350 (m), 1731 (s), 1730 (s), 1684 (m), 1557 (m), 1277 (s), 770.4 (m), 770.3 (m) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 5.29 (s, 2 H, CH_2), 6.75–6.77 (m, 1 H, CH), 6.83–6.85 (m, 1 H, CH), 7.32–7.47 (m, 5 H, CH), 12.54 (s, 1 H, NH), 12.83 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 65.5 (CH_2), 115.1, 115.6 (all CH), 125.9, 127.9 (both C_q), 128.0, 128.0, 128.4 (all CH), 136.2, 159.6, 161.2 (all C_q) ppm. HR-MS (EI): *m*/*z* calcd. for $C_{13}H_{11}NO_4^{\cdot+}$ ($M^{\cdot+}$) 245.0687, found 245.0688.

***N*-Boc-Guanidine (8):**[12] A cooled solution of Boc_2O (12.0 g, 55.0 mmol, 1 equiv.) in dioxane (100 mL) was added drop wise within 8 h at 0 °C (ice bath) under vigorous stirring to a mixture of guanidinium chloride (26.3 g, 275 mmol, 5 equiv.) in an aqueous sodium hydroxide solution (12.1 g, 303 mol, 5.5 equiv. NaOH in 50 mL of water). The resulting suspension was stirred at room temperature for additional 20 h and then extracted with ethyl acetate (3 times with 100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting white crystals were dried in vacuo to yield **8** (8.51 g, 97%). R_f = 0.25 (SiO_2, dichloromethane/methanol + triethylamine, 5:1 + 1%); m.p. 165 °C (decomp.). FT-IR (KBr): $\tilde{\nu}$ = 3408 (s), 1650 (s), 1540 (s), 1450 (m), 1311 (s), 1253 (m), 1142 (s), 1066 (s), 950 (w), 806 (m) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.34 (s, 9 H, CH_3), 6.82 (br. s, 4 H, NH_2) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 28.4 (CH_3), 75.8, 162.8, 163.4 (all C_q) ppm. HR-MS (EI): *m*/*z* calcd. for $C_6H_{13}N_3O_2^{\cdot+}$ ($M^{\cdot+}$) 159.101, found 159.101.

Benzyl 5-(*N*-Boc-Guanidinocarbonyl)-1*H*-pyrrole-2-carboxylate (9): A mixture of the mono ester **7** (2.45 g, 10.0 mmol, 1 equiv.), PyBOP (5.72 g, 11.0 mmol, 1.1 equiv.) and *N*-methylmorpholine (2.45 mL, 22.0 mmol, 2.2 equiv.) was stirred in DMF (50 mL) at room temperature for 30 min. Boc-Guanidine **8** (3.19 g, 20.0 mmol, 2 equiv.) was added and the resulting solution stirred overnight. The yellow solution was slowly poured into vigorously stirred water (150 mL) causing the formation of a white solid precipitate which was dissolved in diethyl ether (150 mL). After phase separation the water/DMF phase was extracted twice with diethyl ether (150 mL) the solvent was evaporated and the crude product was further purified by flash chromatography yielding a colorless powder **9** (3.59 g, 93%). R_f = 0.51 (SiO_2, hexane/ethyl acetate + triethylamine,

3:2+1%); m.p. 88 °C. FT-IR (KBr disk): $\tilde{\nu}$ = 3393 (m), 3256 (m), 2360 (s), 2340 (m), 1719 (s), 1717 (s), 1635 (s), 1540 (s), 1286 (s), 1149 (s), 842 (w) cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.46 (s, 9 H, CH_3), 5.31 (s, 2 H, CH_2), 6.85 (m, 2 H, CH), 7.30–7.46 (m, 5 H, CH), 8.58 (br. s, 1 H, NH), 9.31 (br. s, 1 H, NH), 10.74 (br. s, 1 H, NH), 11.62 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 27.7 (CH_3), 65.5 (CH_2), 81.2 (C_q), 113.84 115.75 (both CH), 124.52 (C_q), 127.88, 128.02, 128.44 (all CH), 133.97, 136.22, 155.56, 158.30, 159.77, 168.04 (all C_q) ppm. HR-MS (pos. ESI): *m*/*z* calcd. for $C_{19}H_{22}N_4NaO_5^+$ [M + Na^+] 409.146, found 409.149.

1*H*-Pyrrole-5-*N*-Boc-guanidinocarbonyl-2-carboxylic Acid (1): A mixture of the benzyl ester **9** (1.94 g, 5.00 mmol, 1 equiv.), a catalytic amount of Pd/C (≈200 mg) and triethylamine (1.05 mL, 7.50 mmol, 1.5 equiv.) in methanol (30 mL) was vigorously stirred at 40 °C for 5 h under hydrogen atmosphere. The resulting solution was filtered through a celite pad which was washed several times with methanol containing 3% triethylamine. The solvent was evaporated under reduced pressure. After adding water (10 mL) to the resulting oil, the solution was lyophilized yielding the product **1** as a white solid (1.89 g, 95%). R_f = 0.64 (SiO_2, dichloromethane/methanol + triethylamine, 8:2+1%); m.p. > 300 °C. FT-IR (KBr disk): $\tilde{\nu}$ = 3393 (m), 2958 (w), 1650 (s), 1542 (s), 1319 (s) cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.08 (t, ^3J(H,H) = 7.20 Hz, 9 H, NEt_3-CH_3), 1.45 (s, 9 H, CH_3), 2.79 (q, ^3J(H,H) = 7.20 Hz, 6 H, NEt_3-CH_2), 6.47 (d, ^3J(H,H) = 3.64 Hz, 1 H, CH),6.77 (d, ^3J(H,H) = 3.68 Hz, 1 H, CH), 8.58 (br. s, 1 H, NH), 9.31 (br. s, 1 H, NH); 10.84 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 9.7 (NEt_3-CH_3), 27.8 (CH_3), 45.2 (NEt_3-CH_2), 80.2 (C_q), 112.1, 114.1 (both CH), 128.8, 133.0, 158.5, 160.6, 163.9, 167.2 (all C_q) ppm. MS (neg. ESI): *m*/*z* calcd. for $C_{12}H_{15}N_4O_5^-$ [M – H^+] 295.1048, found 295.1048.

Methyl 1*H*-Pyrrole-2-carboxylate (10): In dry methanol (640 mL) sodium (2.23 g, 97.0 mmol, 0.14 equiv.) was dissolved and **4** (147 g, 692 mmol, 1 equiv.) was added in small quantities over a period of 30 min. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the resulting solid was dissolved in diethyl ether (800 mL). The ether solution was washed with 3 N hydrochloric acid (50 mL) and a sodium hydrogen carbonate solution (50 mL). The ether phase was dried ($MgSO_4$) and concentrated in vacuo to ca. 300 mL. Charcoal (2.30 g) was added and the suspension was filtered hot through a bed of celite. The solution was cooled and the colorless crystals which formed were filtered and washed with cold diethyl ether. The product **10** (75.3 g, 602 mmol) was isolated in 87% yield. R_f = 0.32 (SiO_2, hexane/ethyl acetate, 6:4); m.p. 73 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, CH_3), 6.26–6.28 (m, 1 H, CH), 6.91–6.93 (m, 1 H, CH), 6.95–6.97 (m, 1 H, CH), 9.27 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.6 (CH_3), 110.6, 115.4 (both CH), 122.8 (C_q), 123.0 (CH), 161.8 (C_q) ppm. HR-MS (EI): calcd. for $C_6H_7NO_2^{\cdot+}$ ($M^{\cdot+}$) 125.0470, found 125.0471.

Methyl 4-/5-Formyl-1*H*-pyrrole-2-carboxylates 11a and 11b: Phosphoryl chloride (5.59 mL, 59.9 mmol, 1.5 equiv.) was added drop by drop to DMF (4.64 mL, 59.9 mmol, 1.5 equiv.) at 5–10 °C. Stirring for 15 min produced the Vilsmeier reagent. A portion of **10** (5.00 g, 40.0 mmol, 1 equiv.) was dissolved in DCM (50 mL) the solution was cooled to –10 °C and the Vilsmeier reagent was added over a period of 30 min. The reaction mixture was stirred at –10 °C for 1 h then at 0 °C for 1 h and at room temperature for an additional hour. Afterwards the solution was stirred for 30 min at 40 °C. Aqueous sodium hydrogen carbonate (350 mL) was added until pH was neutral. The mixture was refluxed for 15 min. The organic layer was separated, washed twice with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give a yellow solid. Flash chromatography on silica gel (hexane/ethyl acetate, 6.5:3.5) yielded in the colorless product **11a** (3.61 g, 23.6 mmol, 59% yield) and the side product **11b** (1.71 g, 11.2 mmol, 28% yield).

Methyl 5-Formylpyrrole-2-carboxylate (11a): R_f = 0.37 (SiO_2, hexane/ethyl acetate, 6.5:3.5); m.p. 96 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, CH_3), 6.94 (d, ^3J(H,H) = 2.5 Hz, 2 H, CH), 9.67 (s, 1 H, CH), 9.88 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4 (CH_3), 115.8, 119.8 (both CH), 128.3, 134.6, 161.0, 180.5 (all C_q) ppm. HR-MS (neg. ESI): *m*/*z* calcd. for $C_7H_6NO_3^-$ [M – H^+] 152.035, found 152.035.

Methyl 4-Formylpyrrole-2-carboxylate 11b: R_f = 0.15 (SiO_2 hexane/ethyl acetate, 6.5:3.5); m.p.104 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, CH_3), 7.31 (m, 1 H, CH), 7.58–7.59 (m, 1 H, CH), 9.85 (s, 1 H, CH), 9.97 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3 (CH_3), 114.5 (CH), 125.0, 127.9 (both C_q), 128.7 (CH), 161.6, 185.8 (both C_q) ppm. HR-MS (pos. ESI): *m*/*z*: calcd. for $C_7H_7NNaO_3^+$ [M + Na^+] 176.032, found 176.032.

5-Formylpyrrole-2-carboxylate (12): A solution of **11a** (10.0 g, 65.3 mmol, 1 equiv.) and potassium hydroxide (4.03 g, 71.8 mmol, 1.1 equiv.) in ethanol (80 mL) and water (20 mL) was refluxed for 3 h. The solvent was evaporated and the residue was dissolved in water (80 mL). The solution was acidified with conc. hydrochloric acid. The precipitate was filtered, washed with water and dried in vacuo affording the pale yellow product **12** (8.13 g, 58.4 mmol, 90% yield). R_f = 0.44 (cyclohexane/ethyl acetate + trifluoro acetic acid, 1:1+1%); m.p. > 188 °C (decomp.). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 6.82–6.84 (m, 1 H, CH), 6.93–6.95 (m, 1 H, CH), 9.69 (s, 1 H, CH), 12.85 (br. s, 1 H, NH), 13.06 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 115.4, 116.4 (both CH), 129.1, 135.3, 161.4, 181.3 (all *C*q) ppm. HR-MS (EI): calcd. for $C_6H_5NO_3^{\cdot+}$ ($M^{\cdot+}$) 139.0264, found 139.0266.

***N*-Cbz-Guanidine 13:** A solution of benzyl chloroformate (21.4 mL, 150 mmol, 1 equiv.) in dioxane (170 mL) was added slowly (15 h) at 5 °C under vigorous stirring to a mixture of guanidine hydrochloride (89.4 g, 936 mmol, 6.25 equiv.) and sodium hydroxide (41.5 g, 1.04 mol, 6.93 equiv.) in water (200 mL). The resulting suspension was stirred at room temperature for additional 10 h. The reaction mixture was extracted with ethyl acetate (4 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried with Na_2SO_4. The organic solvent was evaporated in vacuo to give the pure compound **13** in 89% yield (25.7 g, 133 mmol). R_f = 0.33 (SiO_2 dichloromethane/methanol, 9:1); m.p. 140–142 °C. FT-IR (KBr): $\tilde{\nu}$ = 3420 (s), 3309 (m), 3205 (m), 1665 (s), 1631 (s), 1598 (s), 1541 (s), 1454 (m), 1378 (m), 1292 (s), 1134 (m), 950 (m), 847 (w), 798 (m), 747 (m), 697 (m). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 4.96 (s, 2 H, CH_2), 6.96 (br. s, 4 H, NH), 7.22–7.36 (m, 5 H, CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 64.9 (CH_2), 127.3, 127.3, 128.2 (all CH), 138.1, 162.8, 163.0 (all C_q) ppm. HR-MS (pos. ESI): *m*/*z* calcd. for $C_9H_{12}N_3O_2^+$ [M + H^+] 194.092, found 194.092.

5-(*N*-Cbz-Guanidinocarbonyl)-1*H*-pyrrole-2-carbaldehyde (14): A mixture of **12** (2.91 g, 20.9 mmol, 1 equiv.), PyBOP (16.3 g, 31.3 mmol, 1.5 equiv.) and NMM (4 mL) in dry DMF (40 mL) was stirred for 10 min at room temperature. Cbz-Guanidine **13** (6.04 g, 31.3 mmol, 1.5 equiv.) was added and the resulting solution was stirred overnight. The solution was hydrolyzed with water (300 mL) and extracted with dichloromethane (3 × 100 mL). After washing the combined organic layers with brine (50 mL) and drying with sodium sulfate the crude product was purified via column chromatography (SiO_2, ethyl acetate/dichloromethane, 3:7) to ob-

tain the light yellow coupling product **14** (4.43 g, 14.1 mmol, 68% yield). R_f = 0.50 (SiO_2, dichloromethane/ethyl acetate, 7:3); m.p. 143–145 °C. FT-IR (KBr pellet): $\tilde{\nu}$ = 3392 (m), 3273 (m), 1733 (m), 1671 (s), 1643 (s), 1532 (m), 1339 (m), 1277 (m), 1217 (s) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 5.18 (s, 2 H, CH_2), 6.95–6.99 (m, 2 H, CH), 7.34–7.42 (m, 5 H, CH), 8.75 (br. s, 1 H, NH), 9.44 (br. s, 1 H, NH), 9.68 (s, 1 H, CH), 11.11 (br. s, 1 H, NH), 12.41 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 66.5 (CH_2), 114.7, 117.1 (both CH), 127.8, 128.0, 128.4 (all CH), 134.8, 136.2, 158.6, 181.3 (all C_q) ppm. HR-MS (pos. ESI): *m*/*z* calcd. for $C_{15}H_{14}N_4NaO_4^+$ [M + Na^+] 337.091, found 337.091.

5-(*N*-Cbz-Guanidinocarbonyl)-1*H*-pyrrole-2-carboxylic Acid (2): To the solution of **14** (320 mg, 1.02 mmol, 1 equiv.) in acetone (5 mL) a suspension of potassium permanganate (322 mg, 2.04 mmol, 2 equiv.) in acetone/water (1:1; 20 mL) was added over a period of 1 h. The solution was heated for 1 h at 40 °C and stirred at room temperature for an additional hour. Sodium dithionite (17.7 mg, 0.10 mmol, 0.1 equiv.) was added and the reaction mixture was filtered through a bed of celite. The celite pad was thoroughly washed with aqueous sodium hydroxide solution (30 mL, 5%). The combined filtrates were acidified with hydrochloric acid (5%). The resulting colorless precipitate was filtered off, washed with hydrochloric acid (5%) and dried in vacuo to give **2** as a colorless powder in 91% yield (307 mg, 0.93 mmol). R_f = 0.4 (SiO_2, dichloromethane/methanol, 9:1); m.p. > 250 °C. FT-IR (KBr pellet): $\tilde{\nu}$ = 3355 (m), 3330 (s), 3238 (w), 2980 (m), 2589 (w), 1755 (m), 1697 (s), 1643 (s), 1591 (s), 1351 (w), 1288 (w), 1233 (s), 1179 (s), 764 (s) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 5.27 (s, 2 H, benzyl-CH_2), 6.82 (d, ^3J(H,H) = 4.0 Hz, 1 H, CH), 7.37–7.44 (m, 6 H, CH), 9.46 (br. s, 1 H, NH), 9.97 (br. s, 1 H, NH), 12.57 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 68.0 (CH_2), 115.3, 116.5 (both CH), 127.3 (C_q) 128.3, 128.5, 128.6 (all CH), 129.7, 135.0, 153.4, 154.7, 160.6, 161.0 (C_q) ppm. HR-MS (neg. ESI): *m*/*z* calcd. for $C_{15}H_{13}N_4O_5^-$ [M – H^+] 329.089, found 329.089.

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