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Regiocontrolled Synthesis of Pyrrole-2-carboxaldehydes and 3-Pyrrolin-2-ones from Pyrrole Weinreb Amides

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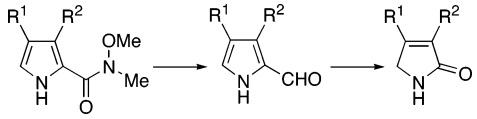
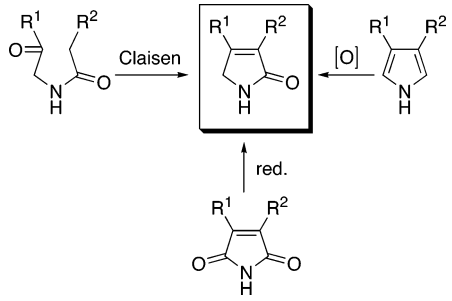


A regiocontrolled synthesis of 3,4-disubstituted pyrrole-2-carboxaldehydes was completed in two steps from acyclic starting materials. A Barton−Zard pyrrole synthesis between *N*-methoxy-*N*-methyl-2-isocyanoacetamide and α-nitroalkenes or *β*-nitroacetates provided *N*-methoxy-*N*-methyl pyrrole-2-carboxamides (pyrrole Weinreb amides), which were converted into the corresponding pyrrole-2-carboxaldehydes by treatment with lithium aluminum hydride. A regioselective oxidation of the pyrrole-2-carboxaldehydes gave the corresponding 3,4-disubstituted 3-pyrrolin-2-ones.

Pyrrole-2-carboxaldehydes and 3-pyrrolin-2-ones (1*H*-pyrrol-2(5*H*)-ones) are important heterocyclic building blocks utilized in the preparation of a wide array of biologically active compounds. Highly functionalized pyrrole-2-carboxaldehydes have been employed as key intermediates in the synthesis of oligopyrrole macrocycles,[1,2] linear oligopyrroles,[3] porphobilinogen analogues,[4] and kinase inhibitors.[5] The condensation of pyrrole-2-carboxaldehydes with 3-pyrrolin-2-ones provides dipyrrinones,[6] useful materials for the preparation of oligopyrrole plant pigments. Substituted 3-pyrrolin-2-ones have also been utilized as starting materials for the preparation of indolocarbazoles.[7] 5-Unsubstituted 3,4-diaryl-3-pyrrolin-2-ones have been synthesized and evaluated as COX-II inhibitors.[8] Furthermore, simple *N*-substituted 3-pyrrolin-2-ones have served as precursors to 2-silyloxypyrroles,[9] compounds that have been exploited for the preparation of complex nitrogen heterocycles.[10]

SCHEME 1. Selected Routes to 3-Pyrrolin-2-ones



Notable synthetic routes to 5-unsubstituted 3,4-disubstituted 3-pyrrolin-2-ones include intramolecular condensation reactions,[11,12] reductive cyclization of cyanoesters[13] (not shown), oxidation of a pyrrole moiety,[14] and reduction of a maleimide moiety[15] (Scheme 1). The first two strategies operate under complete regiocontrol but often require multiple steps and/or complex starting materials to prepare the acyclic substrates. The

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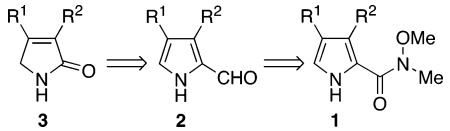
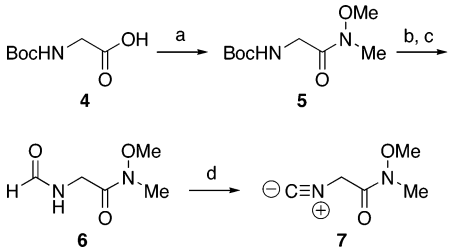
SCHEME 2. Retrosynthetic Approach



latter two strategies are well suited to the preparation of symmetrical substrates with respect to the substitution pattern at the 3- and 4-positions ($R^1 = R^2$), but both require a regioselective transformation in the event of nonsymmetrical substrates ($R^1 \neq R^2$) and this often proves to be dependent on steric and/or electronic factors. In the case of a reported total synthesis of the indolocarbazole natural product staurosporine, a regioselective reduction of a maleimide moiety proved to be problematic.[15bc] Similarly, the synthesis of pyrrole-2-carboxaldehydes utilizing either a Vilsmeier−Haack formylation[16] or metalation[17] often lead to mixtures of products when nonsymmetrical pyrrole substrates are involved.[18]

We envisioned a new regiocontrolled route to 5-unsubstituted 3,4-disubstituted pyrrole-2-carboxaldehydes **2** and 3-pyrrolin-2-ones **3** starting from the corresponding pyrrole Weinreb amides **1** (Scheme 2).[19] First, compounds **1** could be converted to pyrrole-2-carboxaldehydes **2** by reduction of the Weinreb amide.[20] Second, a precedented regiospecific oxidation[21] of the formyl group of **2** followed by hydrolysis of the intermediate formate esters would lead to the desired 3-pyrrolin-2-ones **3**. The requisite pyrrole Weinreb amides **1** could be obtained by utilizing the Barton−Zard pyrrole synthesis,[22,23] a cyclocondensation reaction between an α-nitroalkene or *β*-nitroacetate and an activated isocyanide. This reaction has received much attention for the preparation of 3,4-disubstituted pyrrole-2-carboxylates suitable for the preparation of porphyrins and related macrocyclic pyrrole-containing materials,[23ab] although it has not been utilized for the synthesis of pyrrole Weinreb amides.[24] Overall, this synthetic route to pyrrole-2-carboxaldehydes and 3-pyrrolin-2-ones is attractive as a result of the flexibility afforded by incorporating readily available starting materials that include nitroalkanes[25] and aldehydes (Henry reactions of which give α-nitroalkenes[26] or *β*-nitroacetates[22a]) along with known isocyanide **7**.[27] Notably, related syntheses of 3-pyrrolin-2-ones have been reported[28] that involve the regioselective introduction of oxygen onto α-tosylpyrroles.

SCHEME 3. Preparation of Isocyanide 7[a]



[a] Reagents and conditions: (a) MeONHMe, DCC, CH_2Cl_2, 0 °C → rt (78%); (b) HCO_2H, 80 °C; (c) HCO_2Et, Et_3N, Δ (65%, two steps); (d) $POCl_3$, Et_3N, THF (70%).

The synthesis of known isocyanide **7**[27] was achieved in four steps from Boc-glycine (**4**) utilizing a procedure that differed from the literature[29] (Scheme 3). DCC coupling of **4** with freshly distilled *N*,*O*-dimethylhydroxylamine gave **5** in 78% yield. Removal of the Boc group and formylation gave **6** in 65% yield (two steps) after a modified workup. Finally, dehydration of the formamide **6** with phosphorus oxychloride gave the desired isocyanide **7** in 70% yield, which represents an improvement over the literature yield of 50% for the same transformation.[27b] The yield for this dehydration reaction appears to be dependent on the purity of the formamide substrate, and thus an extra workup step of the crude formamide **6** proved to be beneficial.

The synthesis of pyrrole Weinreb amides **1** was simultaneously investigated with both *β*-nitroacetates **8** and α-nitroalkenes **9**. The cyclocondensation reaction between isocyanide **7** and **8** or **9** in the presence of DBU led to the corresponding pyrrole Weinreb amides **1** in good yields when the reaction conditions were kept mild (0 °C → rt) (Table 1). With nonsymmetrical pyrroles **1b** and **1c**, the expected regiochemistry was confirmed by their subsequent conversion to the corresponding known pyrrole-2-carboxaldehydes **2b** and **2c** and known 3-pyrrolin-2-ones **3b** and **3c**, respectively.

The pyrrole Weinreb amides **1** were then converted into the corresponding known pyrrole-2-carboxaldehyes **2** by reduction with lithium aluminum hydride[30] in THF (Table 2). The yields obtained were moderate, and no major byproducts were isolated.

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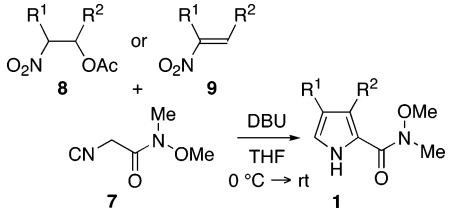
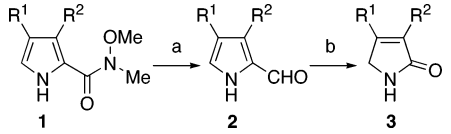
TABLE 1. Preparation of Pyrrole Weinreb Amides 1



substrate	R^1	R^2	product	(%)
8a	Me	Me	**1a**	89
9a	Me	Me	**1a**	89
8b	Et	Me	**1b**	95
9b	Et	Me	**1b**	92
8c	Me	Et	**1c**	85
9c	Me	Et	**1c**	90
9d	-$[CH_2]_4$-	-$[CH_2]_4$-	**1d**	84
9e	Ph	Ph	**1e**	71

TABLE 2. Preparation of Pyrrole-2-carboxaldehydes 2 and 3-Pyrrolin-2-ones 3[a]



substrate	R^1	R^2	**2** (%)[b]	**3** (%)[c]
1a	Me	Me	84	50
1b	Et	Me	69	73
1c	Me	Et	65	67
1d	-$[CH_2]_4$-	-$[CH_2]_4$-	59	56
1e	Ph	Ph	72	80

[a] Reaction conditions: (a) $LiAlH_4$, THF, 0 °C; (b) H_2O_2, $NaHCO_3$, MeOH, rt. [b] Yields of **2** are reported for isolated, chromatographed materials. [c] Yields of **3** are reported for isolated, recrystallized materials.

The identity of **2** was confirmed by comparison to reported spectral data.[31] This reduction was also investigated using DIBAL[32] with **1c**, but unexpectedly, none of the desired product **2c** was formed. Importantly, this sequence allows for the preparation of pyrrole-2-carboxaldehydes where the substitution pattern can be controlled by the appropriate choice of starting material.

Finally, oxidation of the pyrrole-2-carboxaldehydes **2** to the corresponding known 3-pyrrolin-2-ones **3** was accomplished utilizing hydrogen peroxide and sodium bicarbonate as described by Scott and Pichon-Santander.[21] This reaction presumably proceeds via a Baeyer−Villiger-type oxidation of the formyl group followed by hydrolysis of the intermediate formate ester. Again, the identity of **3** was confirmed by comparison to reported spectral data.[31]

In conclusion, we have demonstrated a novel synthetic route to 3,4-disubstituted pyrrole-2-carboxaldehydes **2** and 3-pyrrolin-2-ones **3** from readily available acyclic starting materials as follows: (1) Barton−Zard pyrrole synthesis leading to pyrrole Weinreb amides **1**; (2) reduction to pyrrole-2-carboxaldehydes **2**; and (3) a regioselective oxidation to 3-pyrrolin-2-ones **3**. Significantly, this work allows for the preparation of nonsymmetrical pyrrole-2-carboxaldehydes and 3-pyrrolin-2-ones with respect to substituents located in the β-positions, and this might prove useful for the preparation of oligopyrroles and related compounds. Furthermore, by taking advantage of the chemistry associated with the Weinreb amide functionality,[33] **1** could prove to be useful precursors to 2-ketopyrroles.

Experimental Section

General Method. Synthesis of Pyrrole Weinreb Amides 1 from α-Nitroalkenes 9. To a 0 °C stirred solution of isocyanide **7** (0.51 g, 4.0 mmol) and DBU (0.84 mL, 5.6 mmol) in THF (10 mL) was added a solution of α-nitroalkene **9** (5.6 mmol) in THF (10 mL) dropwise via syringe. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. The solvent was then removed in vacuo, and the crude material obtained was purified by flash chromatography (ethyl acetate/petroleum ether gradient).

***N*-Methoxy-*N*-methyl-3,4-diphenylpyrrole-2-carboxamide (1e).** The product was obtained as a white amorphous solid (71% yield). Recrystallization (ethyl acetate) gave the analytical sample as white prisms: mp 137−140 °C; R_f = 0.16 (1:2 ethyl acetate/petroleum ether); IR (film) 3470, 3220, 3025, 2990, 1610, 1470, 1425, 1380, 1265, 1070, 1020, 965, 940, 895, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.01 (br s, 1 H), 7.03−7.26 (m, 10 H), 7.06 (d, 1 H, J = 3.0 Hz), 3.59 (s, 3 H), 2.98 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 135.5, 135.1, 130.5, 128.7, 128.33, 128.26, 127.5, 126.9, 126.1, 125.5, 121.6, 119.9, 61.0, 35.2 ppm; MS *m*/*z* 276, 275 (M^+ − OMe), 246 (M^+ − NMeOMe), 245, 217, 216, 190, 189. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.25; H, 5.92; N, 9.14.

General Method. Synthesis of Pyrrole-2-carboxaldehydes 2. To a 0 °C stirred mixture of lithium aluminum hydride (57 mg, 1.5 mmol) in THF (5 mL) was added a solution of pyrrole Weinreb amide **1** (1.0 mmol) dissolved in THF (10 mL) dropwise via addition funnel. The reaction mixture was stirred at 0 °C for 2−4 h and monitored by TLC (1:4 ethyl acetate/petroleum ether). Upon completion, the reaction mixture was treated with an aqueous solution of $KHSO_4$ (0.82 g, 6.0 mmol) in deionized water (20 mL) dropwise via addition funnel followed by dilution with ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with aqueous citric acid (5% w/v, 50 mL), aqueous sodium bicarbonate (saturated, 50 mL), and brine (50 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a crude material that was purified by flash chromatography (ethyl acetate/petroleum ether gradient).

3,4-Diphenylpyrrole-2-carboxaldehyde (2e).[34] The product was obtained as a red amorphous solid (72% yield): mp 168−172 °C (lit.[34] mp 168−170 °C); R_f = 0.30 (1:4 ethyl acetate/petroleum ether); ^1H NMR (d_6-DMSO, 300 MHz) δ 12.40 (br s, 1 H), 9.30 (s, 1 H), 7.11−7.49 (m, 11 H) ppm; ^{13}C NMR (d_6-DMSO, 75 MHz) δ 179.2, 134.0, 132.8, 130.4, 130.0, 128.4, 128.3, 127.8, 127.4, 126.1, 125.2, 125.0, 124.7 ppm; MS *m*/*z* 248, 247 (M^+), 246, 218, 189, 165, 152, 140, 123, 115, 108.

General Method. Synthesis of 3-Pyrrolin-2-ones (1*H*-Pyrrol-2(5*H*)-ones) 3. A modification of a reported procedure was utilized.[21] To a room temperature stirred solution of pyrrole-2-carboxaldehyde **2** (2.0 mmol) in methanol (50 mL) was added sodium bicarbonate (1.7 g, 20 mmol) followed by hydrogen peroxide (30% w/v, 2.3 mL, 20 mmol). The reaction mixture was stirred for 3−7 d, and additional hydrogen peroxide was added periodically until TLC (4:1 ethyl acetate/petroleum ether, visualiza-

(31) See Supporting Information for references regarding known pyrrole-2-carboxaldehydes **2** and known 3-pyrrolin-2-ones **3**.

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tion with Ehrlich's reagent) showed complete conversion (total hydrogen peroxide, 30−60 mmol). The solvent was then removed in vacuo, and the crude material obtained was treated with deionized water (30 mL) and aqueous HCl (0.1 M, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The organic layer was concentrated in vacuo, giving a crude material that was purified by flash chromatography (gradient ethyl acetate/petroleum ether).

3,4-Diphenyl-1*H*-pyrrol-2(5*H*)-one (3e).[35] The product was obtained as a yellow amorphous solid (80% yield): mp 182−183 °C (lit.[35] mp 192−193 °C); R_f = 0.56 (4:1 ethyl acetate/petroleum ether); ^{1}H NMR (d_6-DMSO, 300 MHz) δ 8.62 (br s, 1 H), 7.33−7.36 (m, 10 H), 4.41 (s, 2 H) ppm; ^{13}C NMR (d_6-DMSO, 75 MHz) δ 172.4, 150.4, 133.3, 132.3, 131.7, 129.3, 129.0, 128.6, 128.1, 127.7, 127.5, 47.5 ppm; MS *m*/*z* 235 (M^+), 206, 191, 178.

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Supporting Information Available: General methods, experimental procedures (**5**−**7**), and spectral data (**1**−**3**, **5**−**7**). This material is available free of charge via the Internet at http://pubs.acs.org.

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