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# An efficient synthesis of substituted prolines by the selective reduction and reductive cyanation of 2-pyrrolidones

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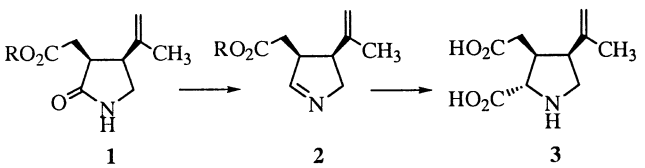
**Abstract**—Substituted pyrrolidones undergo selective reduction using $Cp_2ZrHCl$ (Schwartz's reagent) to form $\Delta^1$-pyrrolines, which can be isolated or directly cyanated and hydrolyzed to the corresponding proline. Short syntheses of glutamic semialdehyde (ethyl ester), the marine metabolite (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid, and the conformationally constrained amino acid 5,5-dimethylproline, are reported. 

New methods for controlling the geometry of peptide bonds are of interest in connection with the design of discrete protein[1] or protein-like (i.e. foldamer)[2] architectures. Because proline confers unusual conformational properties on peptides and proteins, often resulting in biological and therapeutic utility, substituted analogs and congeners of this amino acid have been synthesized and studied.[3,4] Versatile strategies for assembling functionalized proline derivatives are therefore desirable.

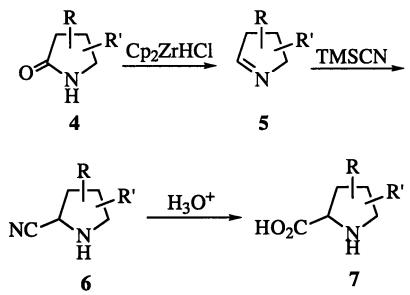
Several years ago, our laboratory developed a procedure for reducing secondary amides and lactams selectively to imines using $Cp_2ZrHCl$ (Schwartz's reagent).[5] That methodology enables the conversion of amides to amines under mild conditions, and has further been extended to the transformation of tertiary amides to aldehydes.[6] Most recently, in an application to the total synthesis of (−)-α-kainic acid **3**, we demonstrated that pyrrolidone **1** (Eq. (1)) could be reduced to **2**, which underwent smooth addition of cyanotrimethylsilane (TMSCN) to afford **3** after hydrolysis.[7]




(1)

We now report that this process of reductive cyanation, in which a secondary amide group is transformed into an α-amino acid, represents a useful extension of the Strecker reaction. When applied to substituted 2-pyrrolidones, e.g. **4**, the procedure leads to pyrrolidine-2-carboxylic acids, e.g. **7** by way of intermediates **5** and **6** (Scheme 1). Moreover, the hydrolytically unstable 2-pyrrolines **5** are in some cases biologically interesting metabolic intermediates, and can be isolated and characterized. The scope and limitations of the method are reported herein.

Reduction of the known[8] L-(−)-pyroglutamic acid ethyl ester **8** (Scheme 2) with $Cp_2ZrHCl$ (1.6 equiv., THF, −20 to 20°C, 3 h) and nonaqueous work-up (dilution of the reaction mixture with hexane and filtration) led to **9**, which is of biological interest since the corresponding carboxylic acid, L-glutamic acid semialdehyde,[9] is a key intermediate in both L-proline[10] and chlorophyll[11] biosynthesis. Imine **9** could be isolated pure (47% after flash chromatography), or reacted directly with TMSCN (2.1. equiv.) to afford the readily separable α-aminonitriles **10** (45% from **8**) and **11** (9% from **8**). Acidic hydrolysis (6N HCl) of **10** gave (2*S*,5*S*)-pyrrolidine-2.5-dicarboxylic acid (−)-**12** (91%), a constituent




**Scheme 1.**

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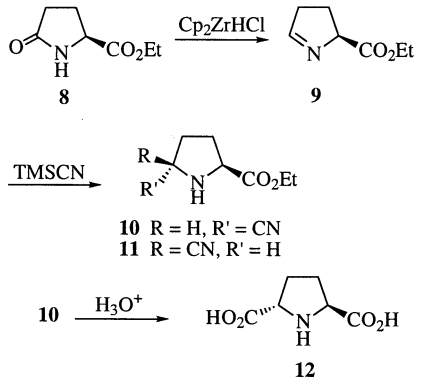


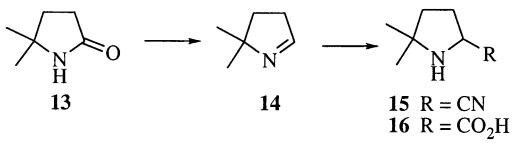

**Scheme 2.**

of the red alga *Schizymenia dubyi*.[12] The route to **12** described here is significantly shorter than an earlier-reported five-step synthesis.[13]

The new methodology also affords a convenient synthesis of the unnatural amino acid 5,5-dimethylproline **16** (Scheme 3),[14] which forms amide bonds that are locked in the *cis*-form, and is thus of interest in studying the conformationally constrained peptides and proteins.[4a,15]

Starting from the known[16] dimethylpyrrolidone **13**, which is readily prepared from the inexpensive reactants 2-nitropropane and methyl acrylate, reduction using $Cp_2ZrHCl$ gave imine **14**. Cyanation of **14** and hydrolysis of the incipient nitrile **15** afforded racemic **16** (52% yield), which has previously been resolved to obtain the pure L-enantiomer.[15,17]

In summary, we have shown that the reduction of 2-pyrrolidones selectively to $\Delta^1$-pyrrolines can be generally and conveniently achieved using $Cp_2ZrHCl$. Moreover, cyanation of such imines provides access to a variety of differentially substituted proline analogs and congeners that may be of interest as natural products, biosynthetic intermediates, or as probes of macromolecular structure and function.




**Scheme 3.**

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17. *Representative procedure*: A solution of **13** (3.1 g) in THF (50 mL) was added dropwise to $Cp_2ZrHCl$ (1.3 equiv., 9.7 g in THF (50 mL)) at −20°C. The mixture warmed slowly to rt for 3 h, then TMSCN (1.1 equiv.) was added with stirring for 1 h. Addition of 6N HCl (100 mL) formed a suspension that was washed once with $CH_2Cl_2$ (50 mL), then heated at reflux for 12 h. After cooling and washing with $CH_2Cl_2$ (50 mL), the aqueous layer was concentrated. The residue was dissolved in $H_2O$ (10 mL), and purified over Dowex (50Wx8-400 mesh), eluting with 1N $NH_4OH$. The residue was dissolved in $EtOH/Et_2O$ and filtered to remove impurities (three times). Recrystallization ($EtOH/Et_2O$) afforded **16**: colorless crystals (2.1 g, 52%), mp 194–197°C, lit.[14] mp 194–196°C. See supplementary material for additional procedures (available upon request).