



A Simple, High Yield Route to *cis*-4-(N-Alkylamino)-L-Prolines

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Abstract: Reaction of 1 equivalent of N- α -acetyl-*cis*-4-azido-L-proline with 1 equivalent of an aldehyde and a catalytic amount of Pd-C under an H₂ atmosphere cleanly and efficiently yields the corresponding N- α -acetyl-*cis*-4-(N- γ -alkylamino)-L-proline derivative.

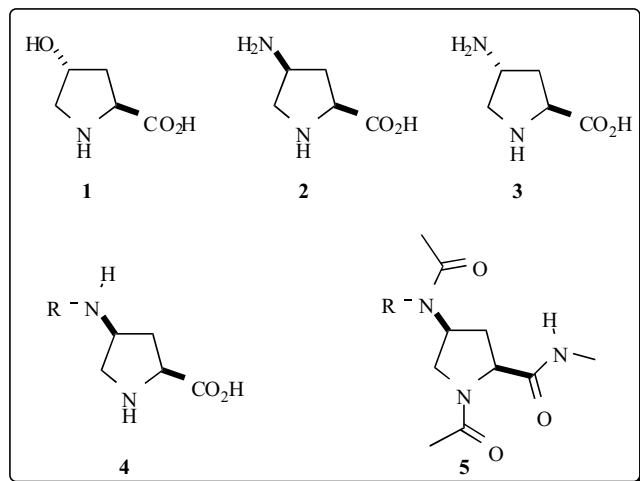
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Derivatives of *trans*-4-hydroxy-L-proline (**1**) [1] bearing an amine group (see structures **2** and **3**) in place of the hydroxyl group are being used in many areas of current research. In medicinal chemistry such compounds have found use as antisickling agents [2], as inhibitors of angiotensin converting enzyme for use as hypertensive agents [3], as inhibitors of matrix metalloprotease for use as a treatment for osteoarthritis [4], as inhibitors of calpain I [5], and as antifungal agents [6]. Aminoprolines also have been used to construct conformationally constrained molecules such as diethylenetriaminepentaacetic acid (DTPA) analogs [7], spermine analogs [8], arginine analogs [9], and a scaffold for the synthesis of chemical libraries [10]. Other reported uses for aminoprolines include formation of chiral peptide nucleic acids [11], formation of a synthetic receptor protein [12], stabilization of the collagen triple helix [13], and novel ligands for transition metal complexes [14]. In our own work we have found that *cis*-4-amino-L-proline can serve as a γ -turn mimetic [15].

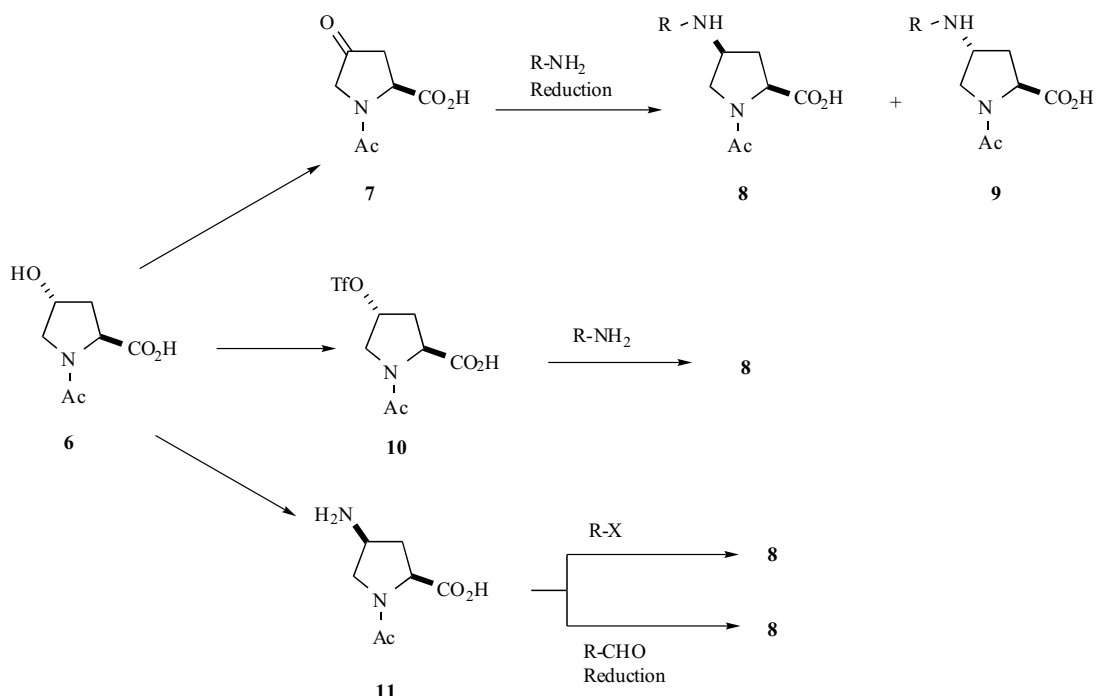
As part of our work we also explored the conformational properties of acyl derivatives (**5**) of *cis*-4-(N-alkylamino)-L-proline (**4**). Although these compounds do not adopt a turn structure, our work did lead us to develop a simple and direct route for preparing these compounds. This method is elaborated below.

In prior work, four approaches have been employed to prepare 4-(N-alkylamino)-L-prolines (see Scheme (1)). In the first route, a suitably protected derivative of **1** (**6**) is converted to the ketone **7**, and **7** is then converted to the secondary amines **8** and **9** via a reductive amination [6, 16]. In the second route, **6** is converted to the triflate **10**, and **10** then undergoes nucleophilic substitution to yield the *cis* secondary amine **8** [7]. In the third route, **6** is converted to the primary amine **11**, and **11** is then alkylated with a primary halide in order to obtain the *cis* secondary amine **8** [2, 4]. Alternatively, in the fourth route **11** can undergo a reductive amination with an aldehyde to yield **8** [6]. The first route was unattractive because it has the potential to yield both the *cis* (**8**) and *trans* (**9**) diastereomers during the reductive amination. Thus, initial attempts to prepare **8** focused on using either the second or third routes, because they would presumably yield only the desired *cis* secondary amine. However, neither alkylation of a triflate similar to **10** with ethylamine, nor alkylation of a primary amine similar to **11** with ethyl iodide, yielded appreciable quantities of the desired product.

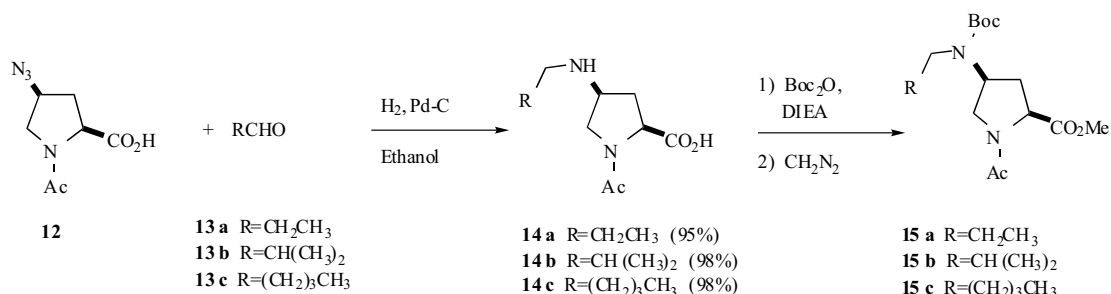
With the failure of these two routes the direct reductive amination of **11** with an aldehyde was explored. However, **11** is hygroscopic and proved difficult to isolate and manipulate. In order to avoid handling **11** we explored whether it could be prepared and reacted in the same reaction vessel as the reductive amination. The direct intramolecular reduction/coupling/reduction of an azide to an aldehyde or ketone has been demonstrated previously for intramolecular reactions [17]. Here, (Scheme (2)) one equivalent of azide **12** [15, 18] dissolved in methanol was reacted with one equivalent of propanal (**13a**) with a catalytic amount of Pd-C



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Scheme 1.



Scheme 2.

under an H₂ atmosphere. After 16 h the catalyst was removed by vacuum filtration and the filtrate was evaporated. Analysis of the crude product by ¹H NMR showed it to be pure secondary amine **14a**, obtained in 95% yield. Since **14a** was hygroscopic, it was converted to the N-Boc methyl ester **15a** for elemental analysis characterization [19].

The generality of this transformation was tested by running the reaction with two other aldehydes. Thus, **12** was reacted with 2-methylpropanal (**13b**) and hexanal (**13c**) under similar reaction conditions. In both cases the expected 4-(N-alkylamino)-L-proline product (**14b**, **14c**) was cleanly obtained in greater than 95% yield. Both **14b** and **14c** were hygroscopic, and were characterized by elemental analysis as their N-Boc methyl ester derivatives **15b** and **15c**, respectively.

These results show that the direct reaction of a *cis*-4-azido-L-proline derivative with an aldehyde in the presence of H₂ and Pd-C catalyst cleanly provides the corresponding *cis*-4-(N-alkylamino)-L-proline derivative. The ease and versatility of this method should facilitate ongoing research into the many uses of 4-(N-alkylamino)-L-prolines. It also illustrates that the direct reaction of an azide with an aldehyde can be used to prepare amino acid derivatives (or

other topical molecules) possessing secondary amine functional groups.

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- [19] **Representative Procedure for Preparation of *N*- α -Acetyl-4-(*N*- γ -propylamino)-*L*-proline (**14a**).** To a solution of 0.440 g (2.22 mmol) of **12** in 18 mL MeOH was added 30 mg of 5% Pd-C followed by 162 L (2.22 mmol) of propanal (**13a**). The resulting mixture was hydrogenated on a Parr apparatus. After 18 h the reaction mixture was removed from the hydrogenation apparatus and the catalyst removed by vacuum filtration through celite. The filtrate was evaporated to yield 0.449 g (95%) of **14a** as a clear, hygroscopic oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.42-4.29 (1H, m), 4.21-4.16 (1H, m), 3.82-3.63 (2H, m), 3.05-2.88 (2H, m), 2.64-2.36 (2H, m), 2.15, 2.11 (3H, 2s), 1.93-1.79 (2H, m), 1.04 (3H, t, $J = 7.3$ Hz). Compound **14a** was further characterized as its *N*- γ -Boc methyl ester, **15a**: TLC, R_f 0.28 (2:1 EtOAc/hexanes); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.70-4.30 (1H, br s), 4.50-4.10 (1H, m), 3.90-3.70 (1H, m), 3.83, 3.80 (3H, 2s), 3.60-3.30 (1H, m), 3.20-3.00 (2H, m), 2.70-2.40 (1H, m), 2.20-1.90 (1H, m), 2.12, 1.98 (3H, 2s), 1.70-1.40 (2H, m), 1.51, 1.50 (9H, 2s), 0.92, 0.91 (3H, 2t, $J = 7.3$ Hz). Anal. Calcd for $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_5$: C, 58.51; H, 8.59; N, 8.53. Found: C, 58.59; H, 8.69; N, 8.27.