A Modified Procedure for the Preparation of 2,5-Dihydropyrrole (3-Pyrroline)

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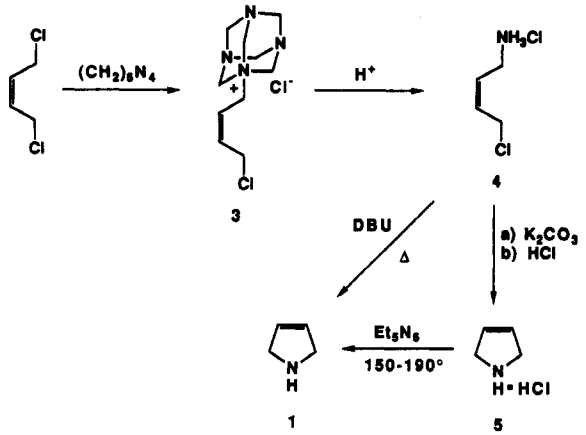
During our studies of elaborating chiral 3-pyrrolines containing the formamidine moietys into various 2-substituted pyrrolidines,[1] we required considerable quantities of 2,5-dihydropyrrole 1 (Scheme I).

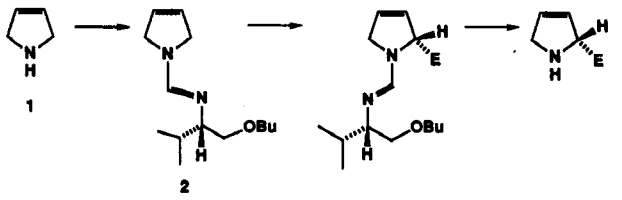
We had previously utilized commercially available 3-pyrroline which contained 15% pyrrolidine,[2] and this required chromatographic separation at the formamidine stage to reach pure 2. More recently, however, 1 is available in only 65% purity,[2] and it is possible to purchase 97% material at a prohibitive cost ($45/g). The separation of 3-pyrroline from the saturated derivative, pyrrolidine, is quite tedious as they differ by only 1.5 deg in their boiling points.[3] Recently,[4] Brandänge reported a very nice, efficient route to the title compound, and it appeared to have the potential for producing multigram quantities of material. However, upon attempting to repeat the procedure, we encountered some difficulty and, after some trivial modification, now find the route to be indeed viable for the acquisition of 3-pyrroline.



As reported, the reaction of *cis*-1,4-dichloro-2-butene with hexamethylenetetramine proceeds to the chloroallyl ammonium salt 3 in excellent yield. Hydrolysis to the allylic amine as its hydrochloride also proceeded in excellent yield as described.[4] However, in contrast to the earlier report, we were able to obtain 4 as a stable, pure, crystalline material (mp 117–119 °C).

The earlier synthesis[4] proceeded in an unusual manner which included neutralization of the amine hydrochloride 4 with potassium carbonate to effect cyclization and

Scheme I



subsequent addition of HCl to form the pyrroline hydrochloride, 5. "The deprotonation (of 5) with pentaethylenehexamine at 150–190 °C to afford 1" seemed to us to be a bit harsh, and when we repeated this step as described, we did not obtain 1, but only recovered 4. Thus, the addition of K_2CO_3 merely neutralized the hydrochloride and the addition of HCl merely returned 4 and not the stated hydrochloride of 1. No spectroscopic or other physical data for the pyrroline hydrochloride 5 was reported.[4]

When we continued the earlier procedure, as written—addition of pentaethylene hexamine and distillation of the resulting mixture—we obtained only a small quantity of the pyrroline, 1. We subsequently found that mixing the chloroallylamine hydrochloride 4 with 2.0 equiv of diazabicyclo[5.4.0]undec-7-ene (DBU) and heating the mixture with a heat gun produced pyrroline 1 as a clear distillable oil in 63–65% yield.

In summary, Brandänge's synthesis[4] of 3-pyrroline was modified so that a route to this important pheromone starting material[5] is now in hand.

Experimental Section

1-[(*Z*)-4-Chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo-[3.3.1.1]decane Chloride (3). To a solution of hexamethylenetetramine (34.4 g, 0.24 mmol) in 500 mL of $CHCl_3$ in a 1-L flask was added *cis*-1,4-dichloro-2-butene (30.2 g, 0.24 mmol), and the mixture was heated at reflux for 4 h, after which the reaction mixture was cooled to rt and filtered through a sintered-glass funnel. The solid was washed with $CHCl_3$ (2 × 50 mL). The filtrate was refluxed for an additional 18 h, cooled, and filtered. The solids were washed with $CHCl_3$ (2 × 25 mL), and the combined solids were dried in a dessicator under vacuum (1 mm) to afford 58.6 g (91%) of 3: mp 160–170 °C dec; ^1H NMR (D_2O) δ 6.23 (complex m, 1 H), 5.67 (complex m, 1 H), 5.01 (s, 6 H), 4.58 (d, 3 H, J = 12.9 Hz), 4.43 (d, 3 H, J = 12.9 Hz), 4.10 (dd, 2 H, J = 8.1, 0.5 Hz), 3.54 (dd, 2 H, J = 7.9, 0.5 Hz).

[(*Z*)-4-Chloro-2-butenyl]ammonium Chloride (4). In a 1-L flask were mixed 400 mL of 95% EtOH and 70 mL of concd HCl (slightly exothermic). To the still warm solution was added 3 (58.5 g, 0.22 mmol) in one portion. The reaction became homogeneous and slightly orange in color, and a precipitate began to form after 45 min. The reaction mixture was allowed to stir at rt for 18 h, at which point it was cooled to 0 °C and the solid (NH_4Cl) was removed by filtration. The solid was washed with cold EtOH (2 × 100 mL), and the filtrate was concentrated on a rotary evaporator. The semisolid residue was taken up in 40 mL of cold EtOH, and the NH_4Cl was removed by filtration and washed with cold EtOH (2 × 20 mL). This procedure was then repeated again.

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The solid left from concentration of the filtrate was dissolved in 80 mL of warm EtOAc. Upon cooling, the product crystallized. Hexane was added (30 mL), and the crystals were collected on a 10–20-μm sintered-glass funnel. The solid was washed with 60 mL of hexane. The filtrate was concentrated on a rotary evaporator to give a small amount of solid which was recrystallized from a minimum amount of EtOAc. The combined solids were dried in a dessicator under vacuum (1 mm) for 2 h giving 30.5 g (97%) of **4** as a light yellow crystalline solid: mp 117–119 °C deg; ^{1}H NMR (D_2O) δ 5.89 (complex m, 1 H), 5.58 (complex m, 1 H), 4.07 (d, 2 H, J = 8.0 Hz), 3.63 (d, 2 H, J = 7.3 Hz).

2,5-Dihydropyrrole (3-Pyrroline) (1). DBU (66.4 g, 0.44 mmol) in a 250-mL flask was cooled to 0 °C in an ice bath as **4** (30.3 g, 0.21 mmol) was added in portions. Toward the end of the addition, the slurry became orange, gas evolved, and the mixture started to reflux. The remaining **4** was added, and a short-path distillation apparatus was put in place. A 50-mL receiving flask was totally immersed in a −78 °C bath (CO_2/iPrOH). The orange solid was heated with a heat gun, causing the solid to liquify and 3-pyrroline (**1**) to distill (80–85 °C). Some foaming occurred initially but subsided during the distillation. Heating was continued until no more pyrroline distilled, affording 9.5 g (63%) of the 3-pyrroline as a clear oil: ^{1}H NMR ($CDCl_3$) δ 5.84 (br s, 2 H), 3.71 (s, 4 H), 1.93 (br s, NH, 1 H).

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Note Added in Proof. After this manuscript was submitted the synthesis of various N-substituted 3-pyrrolines came to our attention. Tufariello, J.; Ding, M. *Synth. Commun.* **1990**, *20*, 227.