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A General Stereocontrolled Synthesis of *cis*-2,3 Disubstituted Pyrrolidines and Piperidines

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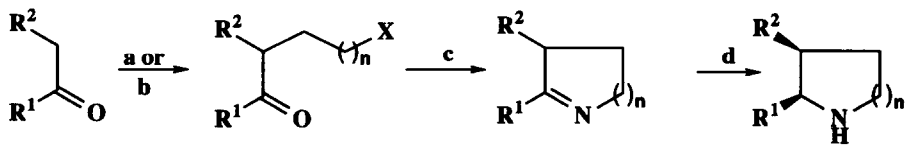
Abstract: A general synthetic method is reported for the preparation of *cis*-2,3-disubstituted pyrrolidines and piperidines from readily available acyclic precursors. The key reaction involves the stereoselective reduction of a cyclic imine controlled by the *C-3* substituent.

As part of an ongoing research program, we needed to prepare a variety of *cis*-2,3-disubstituted pyrrolidines and piperidines. An important consideration in our retrosynthetic analysis was the ability to easily assemble different analogs possessing the desired *cis* stereochemistry. A key feature of our synthetic strategy (Eq. 1) is the use of the *C-3* substituent to direct the reduction of the cyclic imines **3** from the less hindered face of the heterocycle thus ensuring formation of the desired *cis* disubstituted amine **4**. The cyclic imines can be easily prepared from acyclic aminoketones, which can in turn be obtained by reduction of the corresponding nitro or cyano precursors **2**.[1] These compounds can be prepared by the alkylation of readily available ketones **1** with either nitroethylene or acrylonitrile. A particularly attractive feature of our synthetic plan is that the nature of either the *C-2* or *C-3* substituent on the pyrrolidine or piperidine ring may be easily controlled by the choice of an appropriate ketone precursor.



Eq. 1

1 **2a X=NO_2, n=1** **2b X=CN, n=1** **3a n=1** **3b n=2** **4a n=1** **4b n=2**

a. LDA, $ZnCl_2$, nitroethylene, -30°C, THF; b. *t*-BuOK, acrylonitrile, 0°C, THF; c. RaNi, EtOH, 50 psi H_2; d. $NaBH_3CN$, HOAc, 0°C, EtOH.

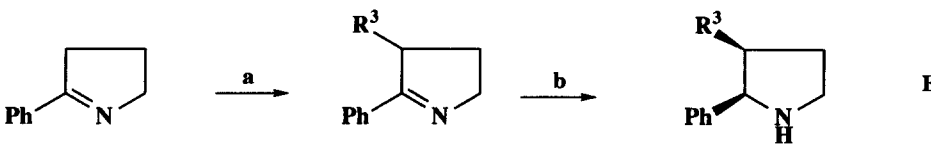
The synthesis of the pyrrolidine systems begins with the alkylation of ketone **1** with nitroethylene.[2] The success of this reaction is critically dependent on the formation of the zinc enolate prior to the Michael reaction with the nitroethylene.[3] The initially formed lithium enolate can be readily transmetallated to the corresponding zinc species by treatment of the lithium enolate with anhydrous zinc chloride. In the absence of the transmetallation step, low yields of the Michael adduct are obtained, presumably due to the well precedented polymerization of the intermediate lithium nitronate anion.[4] Alkylation with nitroethylene proceeds in good yield

to produce the intermediate nitroketones (Table 1). It should be noted that in the cases where either R^1 or R^2 is a simple alkyl group, the alkylation reaction does not proceed efficiently; however, an alternative procedure has been developed to address these cases (*vide infra*).

Table 1: Synthesis of *cis*-2,3-disubstituted pyrrolidines and piperidines

	1	2	3	4
$R^1 = R^2 = Ph$	n = 1	77%	95%	100
	n = 2	80%	90%	95%
R^1 = 2-Pyridyl, R^2 = 4-F-Ph	n = 1	74%	90%	100
	n = 2	63%	63%	91%

It was envisioned that the nitroketone could then be transformed to the desired *cis* 2,3-disubstituted pyrrolidine in a two step sequence involving the initial reduction of the nitro group to the amine and concomittant cyclization to the Δ^1-pyrroline, followed by reduction of the Δ^1-pyrroline to the desired *cis* pyrrolidine. In the event, reduction of nitroketones **2a** was effected with a catalytic amount of Raney Nickel in ethanol at 50 psi H_2 which resulted in the formation of the desired Δ^1-pyrrolines **3a** in 90-95% yield. While further hydrogenation produced the desired *cis*-2,3-disubstituted pyrrolidine **4a**, low mass recovery often resulted due to hydrogenolysis at the benzylic position. Instead, after purification, the Δ^1-pyrrolines were immediately reduced with sodium cyanoborohydride to provide essentially quantitative yields of the desired *cis*-2,3-disubstituted pyrrolidines.[5] We next explored alternate reduction conditions that would allow conversion of the nitroketones to the desired pyrrolidines in one step.[6] A number of different heterogenous catalysts, metal hydride reductants, transfer hydrogenation methods, and metal reductions were examined; however, the two step process was generally found to give superior results.



5 6 7

R^3= Me, Et, *n*-Pr, *i*-Pr

Eq. 2

a. LDA, 0°C, R^3X; b. $NaBH_3CN$, HOAc, 0°C, EtOH.

This approach was found not to be acceptable for the preparation of pyrrolidines with an alkyl substitutent at the *C-3* position. Instead, 2-phenyl-1-pyrroline **5** was prepared in moderate yield by the reaction of phenylmagnesium bromide with 4-chlorobutyronitrile according to the procedure of Kemppainen.[7] This material can be easily lithiated at the *C-3* position (LDA, THF, 0°C) and then treated with an appropriate electrophile to obtain the requisite 3-alkyl-2-phenyl-Δ^1-pyrrolines **6** in modest yields (Eq. 2). By this strategy, substrates with varying steric requirements at *C-3* were prepared allowing a systematic evaluation of the

stereoselectivity of the key reduction step (see Table 2). All reductions were carried out with sodium cyanoborohydride and acetic acid in ethanol. The stereoselectivity of the reaction proved to be quite dependent upon both the substrate and reaction conditions. As expected, the *cis* stereoselectivity improved with increasing steric requirements of the *C-3* substituent. Thus only an 80:20 *cis:trans* ratio was observed when the *C-3* substituent was a methyl group. However, the stereoselectivity could be increased to 99:1 in favor of the *cis* isomer for the substrate with an isopropyl group in the *C-3* position. In addition to the steric bulk of the substrates, the stereoselectivity could also be influenced by varying the temperature of the reaction. As would be expected, greater *cis* stereoselectivity was observed at lower temperatures. Consequently, at -78°C, reduction of 3-methyl-2-phenylpyrroline produced only the *cis* product, while in refluxing ethanol the amount of the *trans* product could be increased to about one half of the product mixture.

Table 2. Synthesis of 3-alkyl-2-phenyl pyrrolidines

	6	**7**	***cis:trans***
R = Me	55%	77%	80:20
R = Et	62%	91%	85:15
R = *n*-Pr	58%	94%	90:10
R = *i*-Pr	40%	95%	99:1

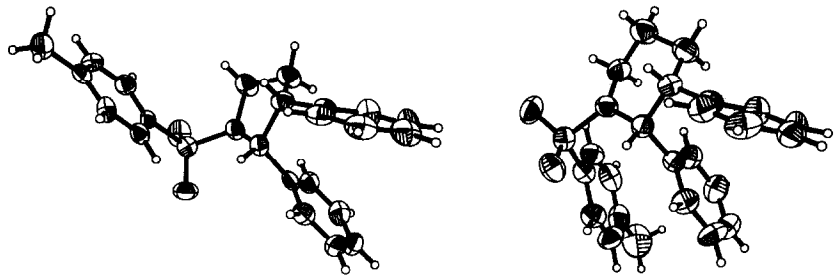
The synthesis of the *cis*-2,3-disubstituted piperidines was performed in a manner analogous to that of the pyrrolidines, with the exception that acrylonitrile was employed as the Michael acceptor. In this case, the use of a catalytic amount of *tert*-butoxide as the base was sufficient to promote the alkylation reaction. Addition of a solution of acrylonitrile to an ice-cold solution of the enolate resulted in a rapid reaction, affording the alkylated products **2b** in moderate yields (63-80%) after chromatographic purification. This reaction was also found to be limited to the sterically hindered ketones used in the pyrrolidine synthesis. As before, the use of less sterically demanding substrates resulted in a poor yield of the desired product, the main product being the dialkylated material.

Catalytic hydrogenation (RaNi, 50 psi H_2, EtOH) of the cyanoketones **2b** for 17 hours resulted in the formation of the desired *cis*-2,3-disubstituted piperidines **4b** directly. Alternatively, the intermediate 3,4,5,6-tetra-hydropyridines **3b** could be isolated if shorter reaction times (2-4 hours) were used. Reduction of **3b** with sodium cyanoborohydride and acetic acid in ethanol at 0°C afforded the desired *cis* piperidine. Interestingly, only the *cis* piperidine was observed regardless of which reduction protocol was employed. The various reduction conditions which were attempted in the preparation of the pyrrolidines were also examined with these substrates; however, improvements over the Raney Nickel procedure were not obtained.

The pyrrolidines and piperidines were found to be of limited stability; consequently, they were used immediately or were converted to the *p*-toluenesulfonamide for further characterization. While consistent spectroscopic evidence was obtained to establish the *cis* stereochemistry of the *C-2* and *C-3* substituents, X-ray crystal structures of the *p*-toluenesulfonamide derivatives of 2,3-diphenyl pyrrolidine and 2,3-diphenyl piperidine were determined to conclusively establish the *cis* stereochemistry of the substituents. The ORTEP

diagrams (Fig. 1) clearly indicate that the *C-2* and *C-3* substituents in both cases are indeed on the same side of the heterocyclic ring.

Figure 1. ORTEP Diagrams of N-tosyl-*cis*-2,3-diphenyl pyrrolidine (left) and N-tosyl *cis*-2,3-diphenyl piperidine (right)



In conclusion, we have reported a short stereocontrolled synthesis of *cis*-2,3-disubstituted pyrrolidines and piperidines. The *cis* stereochemistry is established by the directed reduction from the less hindered face of the cyclic imine intermediate **3**. The scope of this reaction and the application of this methodology is currently under investigation.

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5 The *cis* and *trans* pyrrolidines can be easily distinguished by the characteristic chemical shift for the *C-2* proton. Typically the *C-2* proton appears at lower field and with a larger coupling constant for the *cis* pyrrolidine. For example, for N-tosyl-*cis*-3-methyl-2-phenyl pyrrolidine, the *C-2* proton appears at 4.4 ppm with a coupling constant of 8.2 Hz and for the corresponding *trans* compound the *C-2* proton appears at 4.1 ppm with a coupling constant of 6.1 Hz. The ratios of *cis:trans* were determined by integration of the *C-2* methine signals in the crude 270 MHz NMR spectrum.

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