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Intramolecular Cyclizations from N-Alkoxyamines. Formation of Dialkylsubstituted Pyrrolidines and Piperidines.

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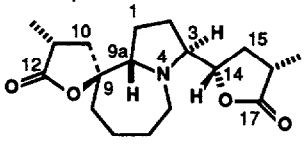
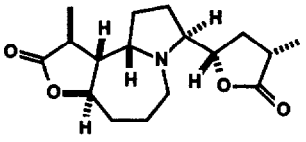
Summary: Iodine-induced cyclizations of *bis*-homoallylic N-alkoxyamines generally favor formation of *trans*-2,3 and 2,5 disubstituted pyrrolidino iodides. Studies of carbon-13 data are important for stereoassignments of *cis* and *trans*-diastereoisomers within this series, as well as for the corresponding 2,6-dialkylpiperidines.

In recent years studies of intramolecular cyclizations of olefinic precursors by amidomercuration,[1] amidoselenation,[2] and amidohalogenation[3] have been reported as preparative routes toward nitrogen heterocycles. Although some variations in regioselectivity for such cyclizations may be anticipated in accord with changes in the substitution pattern of the carbon double bond,[4] ring closures in the five-*exo*-mode affording pyrrolidines, and examples of the six-*exo*-mode providing piperidines, are most commonly observed. The stereochemical selectivity of these reactions is more difficult to predict. Harding has shown that amidomercuration providing 2,5-disubstituted pyrrolidines proceeds with *trans*-selectivity,[5] however, his recent studies suggest that the observed stereocontrol in these cyclizations is dependent on conditions which prescribe kinetic versus thermodynamic control.[6] On the other hand, Clive has demonstrated formation of *cis*-2,6-disubstituted piperidines by amidoselenation.[7] A survey of the literature reveals far fewer examples of aminoselenation, halogenation, or mercuration.[8] In connection with our interest in the *Stemona* alkaloids, croomine and stemonine, we have studied iodoamination of acyclic bis-homoallylic N-alkoxyamines as a strategy for construction of *trans*-2,5-dialkylpyrrolidine butyrolactones (for example $C_{9a} \rightarrow C_{17}$ and $C_3 \rightarrow C_{12}$ of croomine) as observed in these natural products.[9]



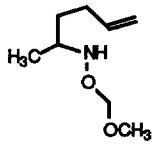
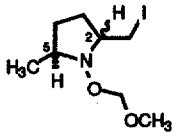
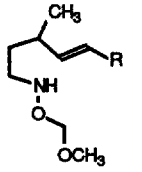
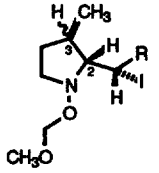
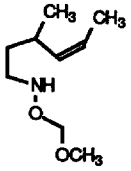
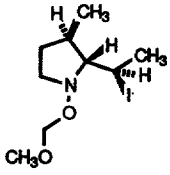
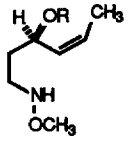
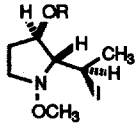
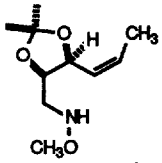
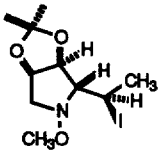
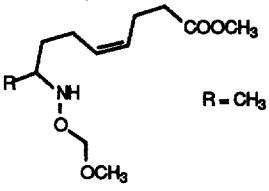
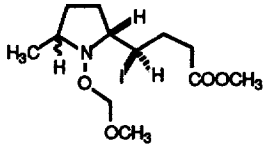
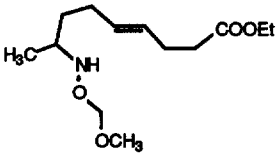
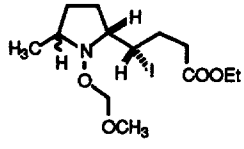
Croomine



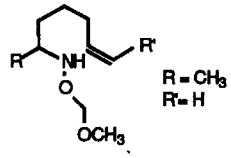
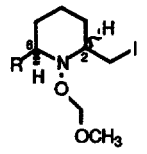
Stemonine

Our studies have examined haloaminations using N-methoxymethyleneoxyamine precursors to prepare a series of five and six-membered heterocycles as illustrated in Table I.[10] Cyclizations affording N-alkoxypyrrolidines rapidly occurred at 0°C upon addition of iodine in acetonitrile in the presence of sodium bicarbonate (Method A). However, ring closures to the analogous piperidines were sufficiently slower under these conditions giving rise to numerous side reactions, including oxidation to provide acyclic oxime ethers and cleavage of the MOM unit.[11] These complications were avoided when reactions were undertaken in methylene chloride-ether (2:1 by volume) at 0°C, without addition of solid sodium bicarbonate (Method B).[12] Yields consistently ranged from 79% to 87% after flash chromatography on silica gel. As summarized, pyrrolidines (entries 1-10) were generally formed favoring a trans orientation of ring substituents. Purified individual diastereoisomers were resubmitted to the reactions conditions without detectable isomerization, and variations in reaction times did not alter trans/cis ratios. Trans selectivity was only slightly increased when reactions were conducted at lower temperatures (entry 8 afforded the largest gain). These observations suggest conditions of kinetic control. The geometry of the starting olefin may significantly affect the degree of stereoselectivity as observed in entries 3 through 7. As we have previously reported for an analogous study of tetrahydrofurans,[13] the Z-alkene provides complete stereocontrol to yield *trans*-2,3-dialkylpyrrolidines (entries 4, 5, 6, 7), owing to unfavorable steric interactions in transition states leading toward the corresponding cis isomers. Such allylic encumbrance is relieved in the transition state available from the E-olefin (entry 3). Additionally 8-9% yields of endo cyclizations to piperidine diastereomers were obtained for entries 3 and 4. In contrast, ring closure in the six-exo mode (entries 11, 12, and 13) proceeded more slowly, and predominantly generated the *trans*-2,6-disubstituted piperidine isomers as the major products for entries 11 and 12 rather than the *cis* isomers as expected by amidoselenation.[7] Note that the steric demands of substituents located at C-6 and C-5 for the piperidines and pyrrolidines, respectively, assert little influence on the stereochemical outcome (compare entries 8/9, and 11/12).

TABLE I

	Substrate		Conditions	Products		Ratio (trans/cis)	Yield (%)
1.			A; 0° C (1/2 h) A; -35° C (1 h)		1a/1b	67:33 [a] 75:25 [a]	87 81
2.		R=H	A; 0° C (1/2 h)		2a/2b	50:50 [b]	84
3.	Entry 2: R = CH_3		A; 0° C (1/2 h)		3a/3b	67:33 [a]	79
4.			A; 0° C (1/2 h)		4a	100:0 [a]	81
5.		R=H	B; 0° C (1 h)		5a	only [d]	69
6.	Entry 5: R = CH_2OCH_3		B; 0° C (1 h)		6a	100:0 [a]	79
7.			A; 0° C (1/2 h)		7a	100:0 [a]	83
8.		R=CH_3	A; 0° C A; -20° C A; -40° C (8 h)		8a/8b	56:44 [a] 68:32 72:28	85
9.	Entry 8: R = $(CH_3)_2CH$		A; -40° C (12 h)		9a/9b	77:23 [a]	85
10.			A; -40° C (8 h)		10a/10b	39:61 [a]	83

(CONTINUED)

	Substrate	Conditions	Products	Ratio (trans/cis)	Yield (%)
11.	 R = CH_3, R' = H	B; 0° C (2 h)		11a/11b 65:35 [c]	83
12.	Entry 11: R = $(CH_3)_2CH$, R'=H	B; 0° C (2 h)		12a/12b 63:37 [c]	81
13.	Entry 11: R = CH_3, R' = $CH_2CH_2COOCH_3$	B; 20° C (6 h)		13a/13b 33:67 [a]	80

A = iodine in acetonitrile, solid $NaHCO_3$ B = iodine in methylene chloride-ether (2:1)

(a) Ratios determined by ^{1}H-NMR integration and by chromatographic purification of individual diastereoisomers. (b) Ratio determined by ^{1}H-NMR integration and purification of individual *cis* and *trans*-2-3-dimethyl-N methoxymethyleneoxypyrrolidines from $LiHBEt_3$ reduction. (c) Ratios determined by ^{1}H-NMR integration and capillary glpc. (d) Product undergoes decomposition: 4a was efficiently converted to 5a using MOMCl and Hunig's base/CH_2Cl_2.

Stereochemical assignments in the series of 2,5-dialkylsubstituted pyrrolidines were unambiguously resolved by single crystal X-ray diffraction studies of the cis-isomer 8b (mp 29-30° C).[14] Characteristically , the ^{13}C-NMR data demonstrated chemical shifts of C_2 and C_5 for the cis-pyrrolidines which were downfield when compared to their corresponding trans-isomers.[15] Furthermore, the proton NMR spectra were well defined for cis compounds, but displayed considerable line broadening for the trans cases as a result of slowly interconverting populations of conformers by ring flipping and nitrogen inversion. The 2,3-dialkyl pyrrolidines (entries 2, 3, 4, 5, 6, 7) were assigned on the basis of proton and carbon NMR data. Although the cis and trans isomers of entry 2 were chromatographically indistinguishable, reduction with superhydride ($LiHBEt_3$) in tetrahydrofuran led to pure samples of each diastereomer for comparison with carbon-13 spectral data for *cis*- and *trans*-2,3-dimethylpyrrolidine. Throughout the series, steric compression results in an upfield chemical shift for the methyl carbon of all *cis*-2,3-disubstituted cases relative to their trans isomers.[16] Additionally, we have observed shielding effects in the ^{1}H-NMR spectra for ring hydrogens H_A and H_B, resulting in upfield chemical shifts of 0.4 to 0.5 ppm for trans-compounds compared to the cis examples [2a; δ 2.2 (H_A), 1.9 (H_B). 2b; δ 3.2 (H_A), 2.4 (H_B). 4a; δ 2.6 (H_A), 2.0 (H_B). 3a; δ 1.85 (H_A), 2.0 (H_B). 3b; δ 3.3 (H_A), 2.5 (H_B).].

In the piperidine series (entries 11-13), both the ^{1}H-NMR and ^{13}C-NMR spectra were clearly resolved for the *cis*-2,6-dialkylpiperidines. The trans-isomers did not exhibit such behavior, and gave rise to severely broadened proton coupling patterns as well as broad signals in the carbon spectra. Reduction of the mixture of iodides 11ab with $LiHBEt_3$ (THF, 22° C) gave the *cis* and *trans*-dimethyl-N-methoxymethyleneoxypiperidines. A diagnostic indication of stereochemistry, resulting from the plane of symmetry available in the *cis* compound, affords a singlet for the methylene of the OMOM unit (δ 4.81), whereas the trans isomer provides the expected AB system (δ 4.77, J_{AB} = 7.5 Hz, $\Delta\upsilon$ = 48.3 Hz).[17] Further distinguishing features of the ^{1}H-NMR and ^{13}C-NMR data for this series were consistent with literature.[18] While the pyrrolidine iodides were thermally labile, decomposing at temperatures exceeding about 80° C, the corresponding *cis* and *trans*-2,6-piperidine iodides were recovered unchanged from acetonitrile-water at reflux (2h). Proton spectra of the conformationally fluxional trans isomers 11a and 12a were fully resolved (coalesence) at 120° C in *ortho*-xylene d_{10}.

In summary, this work is the first report of successful iodoaminations of N-alkoxyamines. The intramolecular reactions readily provide pyrrolidines and piperidines without conflicting amine oxidations. We have documented carbon-13 spectra data throughout the series, which are diagnostic for identification of cis and trans-dialkylsubstituted diastereomers in these heterocycles.

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10. Yields are reported for purified samples, characterized by IR, ^{1}H-NMR, ^{13}C-NMR and high resolution mass spectra.
11. However, the cyclization products were shown to be stable to these reaction conditions.
12. Inclusion of sodium bicarbonate led to increased yields of the acyclic oxime ethers.
13. Williams, D.R.; Grote, J.; Harigaya, Y. *Tetrahedron Lett.* **1984**, *25*, 5231.
14. Single crystal X-ray diffraction at -155° C located all atoms, including hydrogens. Complete data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 87195.
15. Partial characterizations by ^{13}C-NMR ($CDCl_3$, 125.7 MHz) as follows. 1a; δ 9.4, 16.3, 27.0, 27.8, 56.0, 60.3 (C_5), 65.2 (C_2), 99.6. 1b; δ 10.6, 18.7, 27.2, 27.4, 56.1, 64.0 (C_5), 67.7 (C_2), 100.5. 8a; δ 17.5, 24.1, 28.5, 29.4, 34.3, 37.9, 51.6, 56.1, 61.9 (C_5), 70.1 (C_2), 100.0, 173.1. 8b; δ 18.7, 22.7, 27.9, 34.5, 36.4, 51.6, 55.9, 64.4 (C_5), 72.9 (C_2), 100.6, 173.3. 10a; δ 14.2, 15.3, 26.3, 28.1, 32.6, 34.6, 43.7, 56.2, 60.5 (C_5), 68.8 (C_2), 99.9, 172.6. 10b; δ 14.2, 18.5, 24.9, 27.9, 32.5, 34.7, 44.5, 56.3, 60.5, 62.7 (C_5), 71.1 (C_2), 100.6, 172.5.
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