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Anchimeric Assistance With Intermediary N-Alkoxyaziridinium Salts. Formation of Vicinal Aminoalcohols and Derivatives.

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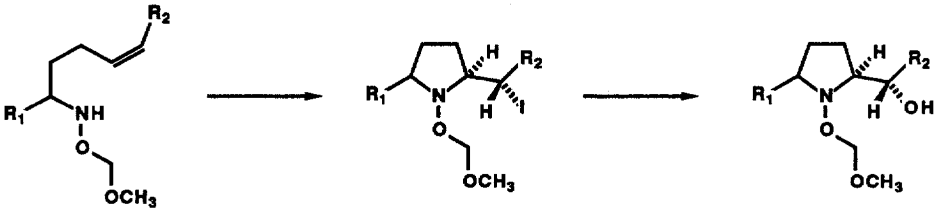
Summary: Intramolecular iodoaminations have afforded pyrrolidino iodides. Iodides are transformed to β-aminoalcohols with net retention of configuration. Intramolecular participation of proximate esters results in a double ring closure of cyclic amination and vicinal lactonization.

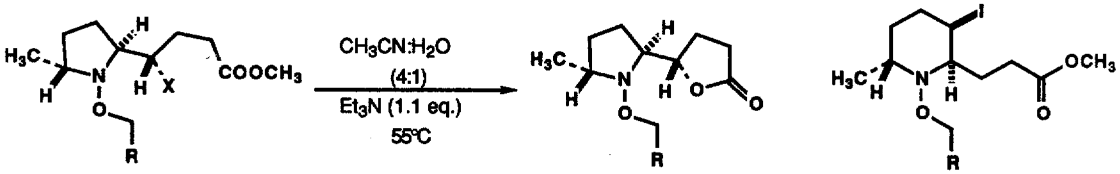
Studies of iodoaminations of bis-homoallylic-N-methoxymethyleneoxyamines 1 have been described as a route toward 2,3-and 2,5-disubstituted pyrrolidines.[1] Nucleophilic substitution reactions of β-aminoalkyl halides have long been recognized as important examples of anchimeric assistance stemming from their high reactivity as so called nitrogen mustards. In recent years a number of studies have examined the stereospecificity intrinsic in neighboring group participation as stereocontrolled pathways to saturated heterocycles.[2] Mechanistically, these substitution reactions pose questions of regiochemical, as well as, stereochemical control, which may be advantageously used for ring expansion and contraction processes.[3] As a part of our continuing investigations of *Stemona* alkaloids, we were in need of a strategy for the vicinal construction of *trans*-2,5-disubstituted pyrrolidino butyrolactones observed in these substances.[4] Our efforts have explored the consequences of anchimeric assistance within a series of 2-(α-iodoalkyl)-N-methoxymethyleneoxypyrrolidines 2 for production of the vicinal aminoalcohols 3 and nucleophilic intramolecular capture of the intermediate aziridinium salts to form butyrolactones.



1 2 3

Heating the individual diastereomeric iodides 4 and 5 under *anhydrous* conditions in refluxing acetonitrile (12 h) led to production of a single butyrolactone 6 and 7, respectively, in yields ranging from 22-45%.[5] Small amounts of starting pyrrolidines were recovered (8-10%), and in each case, single 3-iodopiperidines 8 and 9, respectively, were purified (yields 10-32%). The high degree of stereospecificity observed in these reactions implies a double displacement substitution via intermediacy of the N-alkoxyaziridinium salt 10, which offers two pathways for further reaction. Backside participation of the proximate carbonyl along pathway *(a)* affords the desired lactones. However, molecular models indicate a rather poor trajectory for intramolecular attack at site *(b)*, and no evidence for the isomeric 6,6-ring fused piperidino lactones was obtained. Competing S_N2 displacements along pathway *(b)* with iodide ion account for observation of 8 and 9, as well as the reisolation of small quantities of 4 and 5 (iodide substitution at site *(a)*). Resubmission of the 3-iodopiperidines 8 and 9 to the reaction conditions failed to demonstrate the reversibility we had expected, requiring slightly higher temperatures which produced only small amounts of lactones 6 and 7 with considerable decomposition.

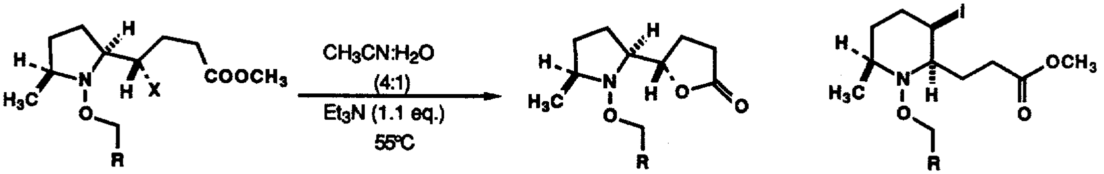
Fortunately a more advantageous protocol was found for transformation of the starting iodopyrrolidines to the desired butyrolactones by heating in aqueous acetonitrile (1:4 by volume) at 55°C with inclusion of triethylamine (1.1 equiv). These conditions provided cleaner, more consistent results with total isolated yields ranging from 83-97% as summarized below. Interestingly, the *cis*-2,5-disubstituted pyrrolidines 5a and 5b afforded better conversion to their corresponding lactones 7a (90%) and 7b (91%), at the expense of formation of the 3-iodopiperidines 9a (2%) and 9b (6%), respectively, compared to the *trans*-2,5-disubstituted cases 4a and 4b, which led to 6a (60%) and 6b (70%).[6] Overall these conditions greatly improved the production of lactones compared to iodopiperidines with ratios ranging from of 45:1 (7a:9a) for the best case to 2.5:1 (6a:8a) with consumption of all starting material.



4a X = I ; R = OCH_3
4b X = I ; R = Ph
11 X = OH ; R = OCH_3

6a R = OCH_3 ; (60%)
6b R = Ph ; (70%)

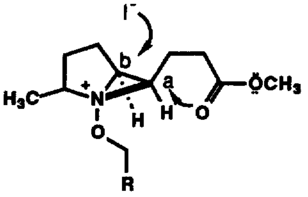
8a R = OCH_3 (24%)
8b R = Ph (19%)



5a X = I ; R = OCH_3
5b X = I ; R = Ph
12 X = OH ; R = OCH_3

7a R = OCH_3 (90%)
7b R = Ph (91%)

9a R = OCH_3 (2%)
9b R = Ph (6%)



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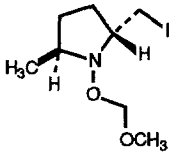
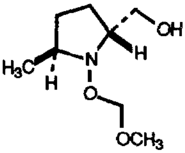
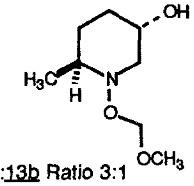
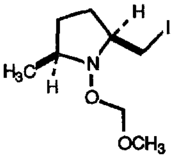
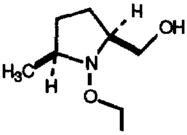
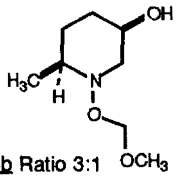
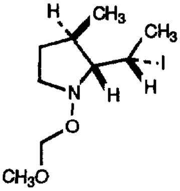
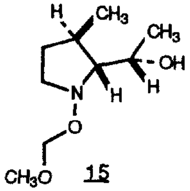
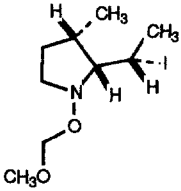
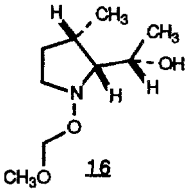
One can also minimize the involvement of nucleophilic iodide ion by conducting reactions with silver tetrafluoroborate (1.2-1.5 equiv.) in aqueous acetone (1:4 by volume). At room temperature these reactions were complete in fifteen to thirty minutes, yielding a separable mixture of alcohol 11 (41%) and lactone 6a (49%) from iodide 4a. Similar conversion of 5a to its corresponding alcohol 12 (39%) and 7a (56%) was observed with isolated yields totalling 90-95%. The alcohols 11 and 12 were quantitatively converted into their respective lactones 6a and 7a upon stirring with a catalytic amount of *p*-toluenesulfonic acid in methylene chloride.[7] The stereochemistry of alcohols 11 and 12 was assigned after lithium borohydride reductions (ether, 0°C, 98% yield) of 6a and 11, and 7a and 12 gave identical pairs of diols.

The silver tetrafluoroborate procedure afforded an efficient route to vicinal aminoalcohols as summarized by further examples in Table I. Note that our *cis* and *trans*-2,3-disubstituted pyrrolidines (entries 3 and 4) led to nucleophilic replacement with complete regiocontrol in addition to the expected stereospecificity.[8]

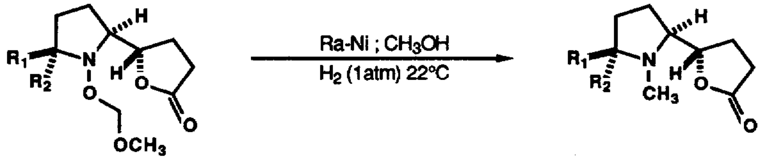
TABLE I

	Starting Material	Conditions	Products	Yield (%)
1.		A or B	  13a:13b Ratio 3:1	79%
2.		A or B	  14a:14b Ratio 3:1	77%
3.		A	 15	78%
4.		A	 16	70%

(A) $AgBF_4$ *(1.1 equiv); 10% aqueous acetone; 5-10 mins*

(B) $CH_3CN:H_2O$ (9:1 by volume); reflux; these slow, incomplete reactions gave the same product ratios

Finally we note that the facile reduction of the N-O bond suggests the utility of various N-alkoxy blocking units for preparation of a series of vicinal aminoalcohols. Interestingly, we have found that Raney-nickel (1 atm H_2, MeOH, 22°C) treatment of lactones 6a and 7a provides reductive N-methylation in addition to the anticipated N-O bond cleavage.



<u>6a</u> $R_1 = H ; R_2 = CH_3$
<u>7a</u> $R_1 = CH_3 ; R_2 = H$

<u>17</u> (88%)
<u>18</u> (92%)

In summary, we have investigated the use of N-alkoxyamines as participants for intramolecular electrophilic cyclizations, and subsequently for stereospecific nucleophilic substitutions via anchimeric assistance. Further studies directed toward highly oxygenated alkaloids are in progress.

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<u>References</u>

1. Williams, D.R.; Osterhout, M.H.; McGill, J.M. *Tetrahedron Lett.* **1988**, *29*, preceding paper.
2. Horning, D.E.; Muchowski, J.M. *Can. J. Chem.* **1974**, *52*, 1321.
   Heathcock, C.H.; Von Geldern, T.W. *Heterocycles* **1987**, *25* (Special Issue), 75.
   Bartlett, P.A.; Ting, P.C. *J. Org. Chem.* **1986**, *51*, 2230.
   Williams, D.R.; Phillips, J.G.; Barner, B.A. *J. Am. Chem. Soc.* **1981**, *103*, 7398.
3. For an expansion of the pyrrolidine nucleus to piperidine: Harding, K.E.; Burks, S.R. *J. Org. Chem.* **1984**, *49*, 40. From studies of lasalocid A: Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933.
   Other examples include: Ting, P.C.; Bartlett, P.A. *J. Am. Chem. Soc.* **1984**, *106*, 2668.
4. For a leading reference: Xu, R.-S.; Lu, Y.-J.; Chu, J.-H.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1982**, *38*, 2667. Williams, D.R.; Brown, D.L.; Benbow, J.W. *J. Am. Chem. Soc.* **1989**, *111*, in press.
5. Our stereoassignments, which confirm this double inversion of stereochemistry in the lactonization process, were unambiguously determined by a single crystal X-ray diffraction study of lactone <u>7b</u> (mp 96-8°C (EtOH)). All atoms were located, including hydrogens, and refined to final residues of $R_F = 0.04$ and $R_{w(F)} = 0.0394$. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 88161.
6. Our molecular models indicate that the *cis*-2,5-disubstituted pyrrolidines <u>5</u> may give more efficient conversion to the butyrolactones <u>7</u> as a result of restricted rotation of the methyl ester chain in the intermediate aziridinium salt and subsequent relief of 1,3 diaxial steric compression with the C_5 methyl.
7. These alcohols were also resubmitted to the conditions of aqueous acetonitrile at 55°C for 2 hours in the presence of triethylamine to generate the lactones (82% yield). However, the alcohols have not been detected as intermediates in the previous cyclizations of <u>4</u> and <u>5</u>.
8. All yields are reported for purified samples, characterized by infrared, ^1H NMR, ^{13}C-NMR and high resolution mass spectral data. Carbon-13 are particularly helpful for recognition of related stereoisomers. Partial characterizations are as follows. ^{13}C NMR (125.7 MHz, $CDCl_3$) for <u>6a</u>: δ 15.2 (q), 24.5 (t), 24.8 (t), 28.6 (t), 29.8 (t), 56.1 (q), 63.1 (d), 69.6 (d), 81.7 (d), 99.9 (d), 177.3 (s). For <u>7a</u>: δ 18.4 (q), 21.3 (t), 23.4 (t), 28.2 (t), 28.5 (t), 56.1 (q), 63.7 (d), 68.6 (d), 81.4 (d), 100.4 (t), 177.2 (s). For <u>13a</u>: δ 15.7 (q), 24.2 (t), 29.3 (t), 56.2 (q), 61.1 (d), 63.4 (t), 67.4 (d), 99.5 (t). For <u>13b</u>: δ 19.2 (q), 29.7 (t), 33.1 (t), 56.1 (q), 61.3 (d), 65.1 (t), 67.1 (d), 99.6 (t). For <u>14a</u>: δ 18.5 (q), 22.2 (t), 27.9 (t), 56.2 (q), 63.6 (d), 63.9 (t), 67.8 (d), 100.6 (t). For <u>14b</u>: δ 19.7 (q), 28.7 (t), 33.1 (t), 56.2 (q), 62.3 (d), 63.5 (t), 67.6 (d), 99.8 (t). For <u>15</u>: δ 18.1 (q), 22.4 (q), 27.9 (t), 29.5 (d), 55.2 (q), 55.9 (t), 65.0 (d), 78.7 (d), 99.3 (d). For <u>16</u>: δ 14.6 (q), 20.7 (q), 29.3 (t), 30.9 (d), 55.6 (q), 57.9 (t), 63.3 (d), 72.5 (d), 99.8 (t).

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