

AMINYL RADICAL CYCLIZATION BY MEANS OF ANODIC OXIDATION.
STEREOSELECTIVE SYNTHESIS OF cis-1-METHYL-2,5-DISUBSTITUTED PYRROLIDINES

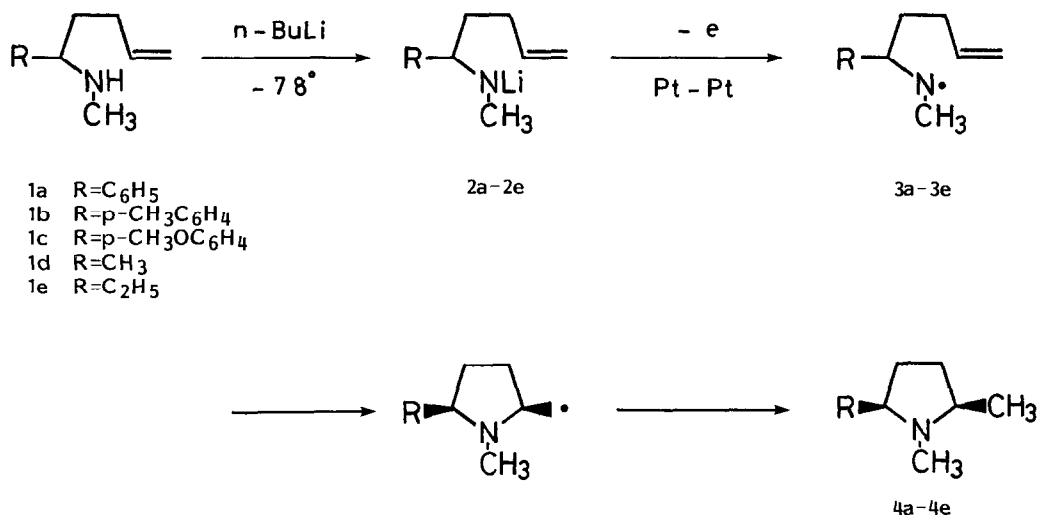
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Summary: Neutral aminyl radicals generated by anodic oxidation of lithium alkenylamides 2 undergo a stereoselective cyclization to give cis-1-methyl-2,5-disubstituted pyrrolidines 4. Their cis stereochemistry was confirmed by a comparison with trans-1,2-dimethyl-5-phenylpyrrolidine, the structure of which was established by X-ray crystallographic analysis of its quaternary ammonium bromide 6.

The potential of carbon radical cyclization for organic synthesis has recently been studied by several groups of investigators.¹ These investigations have demonstrated that the carbon radical cyclizations are useful for the preparation of some of the five-membered alicyclic¹ and even for some of the heterocyclic compounds.² On the other hand, although there are numerous accounts of examples of the cyclizations of aminyl radicals complexed to metal ion or protonated aminyl radicals (aminium radicals),³ only a few examples of neutral aminyl radical cyclization have been reported.⁴ Since neutral aminyl radicals can be generated by an anodic oxidation of lithium alkylamides,⁵ we decided to investigate the cyclization of those species which are generated by electrolysis of lithium alkenylamides. In this communication, we wish to report the exclusive formation of several cis-1-methyl-2,5-disubstituted pyrrolidines by means of the cyclization of those neutral aminyl radicals which are generated by electrolysis of lithium alkenylamides.

We found that the alkenylamines⁶ 1a, 1b, 1c, 1d, and 1e could be converted into the corresponding lithium amides 2a, 2b, 2c, 2d, and 2e respectively by treatment with butyllithium at -78°C (Scheme 1). Typically, the electrolysis of 0.06M 2a in a 30:1 mixture of THF-HMPA containing 0.25M lithium perchlorate

at a constant current of 25 mA/cm² with platinum anode by the use of a divided cell at -10°C generated the aminyl radical 3a which underwent a cyclization to give cis-1-methyl-2,5-disubstituted pyrrolidine 4a as the exclusive product in a 52% yield (Scheme 1). The results for the formation of the pyrrolidines from five alkenylamines 1a-1e by electrolysis under the same conditions are summarized in Table 1. The table indicates that cis-1-methyl-2,5-disubstituted pyrrolidines 4a-4e are formed in moderate yields by the electrolysis. GLC analysis was unable to detect any of the corresponding trans-2,5-disubstituted pyrrolidines as a product of the electrolysis. The cyclization appears therefore to be highly stereoselective. The yield of 4a was slightly decreased when electrolysis was conducted at -50°C, although the formation of by-products was suppressed at the temperature.



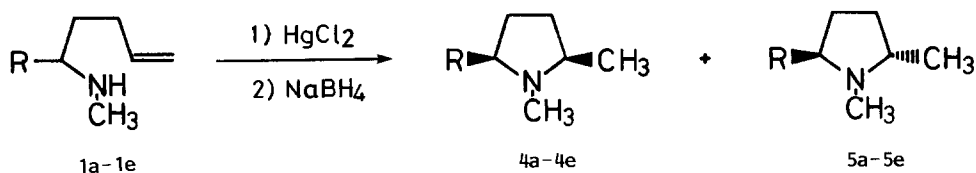
Scheme 1.

Table 1. Cyclization of 1a-1e by anodic oxidation of 2a-2e^a

| Amine | Temp. (°C) | Product ^b | Yield of <u>4</u> (%) ^c | Recovered <u>1</u> (%) ^c |
|-----------|------------|----------------------|------------------------------------|-------------------------------------|
| <u>1a</u> | -10 | <u>4a</u> | 52 | 29 |
| <u>1a</u> | -50 | <u>4a</u> | 41 | 52 |
| <u>1b</u> | -10 | <u>4b</u> | 48 | 44 |
| <u>1c</u> | -10 | <u>4c</u> | 46 | 50 |
| <u>1d</u> | -10 | <u>4d</u> | 31 | 9 |
| <u>1e</u> | -10 | <u>4e</u> | 34 | 4 |

a) Electricity passed was 1.2 Faradays per mol of 1a-1e. b) All the products in this Table gave satisfactory analytical and spectroscopic results. c) Determined by GLC using an internal standard.

The stereochemistry of pyrrolidines 4a-4e⁷ was established as follows. A catalytic hydrogenation of 2,5-dimethylpyrrole over platinum catalyst followed by N-methylation gave a single 1,2,5-trimethylpyrrolidine; this was identical to pyrrolidine 4d obtained by electrolysis. This result can be taken as an evidence that the 2,5-dimethyl groups of 4d are cis-oriented. On the other hand, it has been reported that the intramolecular aminomercuration of δ -alkenylamines followed by NaBH_4 reduction gives a mixture of 2,5-disubstituted pyrrolidines and piperidines.⁸ We therefore subjected alkenylamine 1d to this intramolecular amination in order to prepare pyrrolidine 4d and its trans isomer 5d and to compare it with the pyrrolidine formed by electrolysis. Treatment of 1d with mercury(II) chloride in $\text{THF-H}_2\text{O}$ followed by the reduction with NaBH_4 gave two isomeric pyrrolidines in 10% and 49% yields and the pyrrolidine formed in a lower yield with a shorter retention time in GLC was identical with 4d obtained by the electrolysis. The two substituents in pyrrolidine 5d obtained in a higher yield must therefore be trans-oriented (Scheme 2). This assignment is also in agreement with their ^1H NMR spectra.



Scheme 2.

Similarly, the intramolecular amination of 1a, 1b, 1c, and 1e gave pairs of two isomeric pyrrolidines.⁷ All the pyrrolidines obtained in the smaller amounts were identical to the 2,5-disubstituted pyrrolidines 4a, 4b, 4c, 4d, and 4e obtained by the electrolysis; this suggests a cis configuration of 2,5-disubstituents in these pyrrolidines.

The configuration of the phenyl and methyl groups of 5a was finally established by an X-ray crystallographic analysis of its quarternary ammonium bromide 6, m.p. 174-176°C, obtained by a treatment of 5a with methyl bromide. The crystal data for 6 were as follows: $\text{C}_{13}\text{H}_{20}\text{NBr}$, monoclinic, space group $\text{P2}_1/\text{c}$, $a=13.105(4)$, $b=10.111(4)$, $c=10.769(4)$ Å, $\beta=112.72(2)^\circ$, $z=4$, $D_c=1.364$ g cm^{-3} . The intensity data for 1884 independent reflections were collected on a Rigaku four-circle diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation.⁹ The structure was solved by the Monte Carlo direct method,¹⁰ and refined by the full-matrix least-squares method. The final R value was 0.045. The molecular structure of 6 having trans-oriented 2,5-disubstituents is shown in Figure 1. On the basis of this result the relationship of the two substituents attached to the C-2 and C-5 of 4a was established to be a cis one.

The neutral aminyl radicals generated by the anodic oxidation of lithium

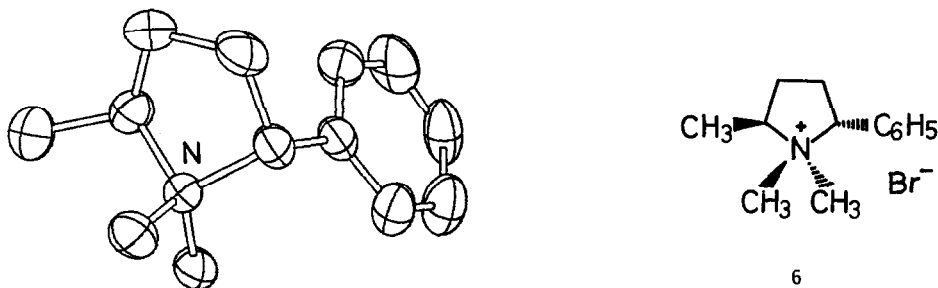


Fig. 1. Perspective view of trans-1,1,2-trimethyl-5-phenylpyrrolidinium bromide 6

alkenylamides were thus shown to cyclize in a highly stereoselective manner to give cis-1-methyl-2,5-disubstituted pyrrolidines. The present stereoselective electroorganic reaction may be useful in organic synthesis.

REFERENCES AND NOTES

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- These alkenylamines were prepared by the Grignard reaction of 4-bromo-1-butene with the appropriate aldehydes, followed by the oxidation of the resulting alcohols with pyridinium chlorochromate to the corresponding ketones, the transformation of the ketones into the N-methylimines, and the reduction of the imines with sodium borohydride. A commercially available 5-hexen-2-one was used for the preparation of **1d**. **1a**: b.p. 123-126°C (16 mm Hg); **1b**: b.p. 77-78°C (0.7 mm Hg); **1c**: b.p. 99-100°C (0.15 mm Hg); **1d**: b.p. 130-131°C; **1e**: b.p. 78-80°C (50 mm Hg).
- All the pyrrolidines obtained gave satisfactory analytical and spectroscopic (¹H NMR, IR, and Mass) results.
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