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INTRAMOLECULAR FORMATION OF OXAZOLIUM SALTS AND THEIR REACTION WITH N- AND C-NUCLEOPHILES.[1]

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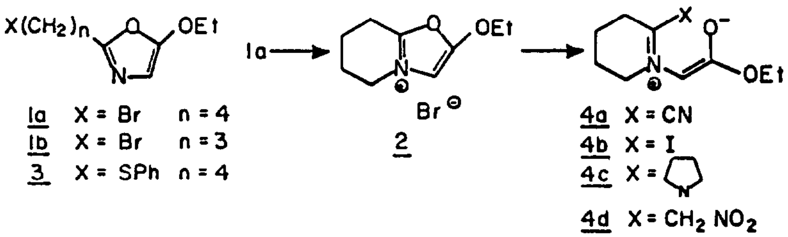
Summary. We report the first intramolecular formation of an oxazolium salt and its reaction with N- and C-nucleophiles, leading to isolation of piperidine derivatives via azomethine ylides. Trapping of the latter produced tetrahydroindolizines.

Azomethine ylides have been of considerable synthetic utility for generation of five-membered nitrogen rings.[2] Several routes are available for their formation,[3] of which the pyrolysis of suitably substituted aziridines[3c,d] have been of prime importance. Recently, Vedejs and coworkers[4] described a useful entry to azomethine ylides via hydride reduction of oxazolium salts or their reaction with cyanide ions. These azomethine ylides were trapped by dipolarophiles to produce pyrroline or pyrrolidine rings.

In connection with our studies of reactions of oxazoles[5], we became interested in intramolecular reactions leading to oxazolium salts. We report here the first examples of intramolecular alkylation of an oxazole and the reactivity of the resulting oxazolium salt as well as the fate of the azomethine ylides, produced in this manner, in the absence and presence of dipolarophiles.

The substrates 2-(ω-bromoalkyl)-5-ethoxy-oxazoles **1a,b** were readily prepared from the corresponding bromoalkyl cyanides by reaction with ethyl diazo acetate in the presence of BF_3-etherate.[6] NMR studies in $CDCl_3$ indicated a slow equilibration of **1a** with the cyclic oxazolium salt **2**.[7] Reaction of **1a** with phenylthiolate ion produced only the substitution product **3**. On the other hand, heating of **1a** with KCN in acetone in the presence of a catalytic amount of NaI for 13 h (or 3 days at 20°C) produced the tetrahydropyridine **5** in quantitative yield.[8a] Apparently, addition of cyanide ion to the oxazolium salt was followed by ring opening to an azomethine ylide **4a**, which underwent a proton shift to produce **5**. When an equivalent amount of NaI was used, the product isolated was 2-oxopiperidine-1-acetic acid **9a**, apparently a result of attack of trace amounts of water on **4b** and ester cleavage by iodide ion.[8b] The intermediacy of the ylide **4a** was shown by trapping with either an electron rich (acetone pyrrolidine enamine) or an electron poor dipolarphile (dimethyl acetylenedicarboxylate) to produce the indolizines **6**[8c] or **7**[8d] respectively. As expected the reaction is faster in the more polar MeCN than in acetone.

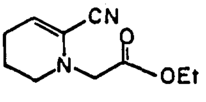


Among other carbon nucleophiles studied in the reaction with **1a**, nitromethane anion produced the nitro enamine **8**[8c] in 63% yield. This product **8** is the result of attack by a carbanion on the oxazolium salt **2**, followed by azomethine ylide formation 4d and proton transfer of the more acidic hydrogen.[9]

Reaction of **1a** with ethyl carbazate in THF or acetonitrile produced the substituted 2-oxo-piperidine-1- hydrazide **9**.[8b]

The lower homolog **1b** did not produce oxazolium salt products under conditions that **1a** had reacted. Apparently, fusion of a five membered ring to the oxazole produces too much strain.

The structure assignment of **5-9** is based on correlated ^{1}H- and ^{13}C NMR and mass spectra.[8] Further work is in progress to exploit the synthetic potential of these reactions.



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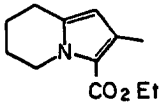

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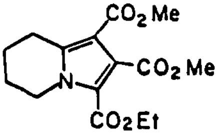

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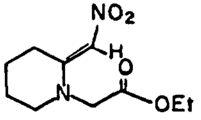

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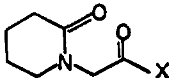

9a X = OH

9b X = NH NHE

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7. Formation of cyclic oxazolium salt **2** is indicated by a down field shift of all protons, e.g. H-4: 7.63 ppm *vs* 5.88 ppm in compound **1**.
8. The characteristic spectral data of compounds (**5-9**) are as follows: a. **5**: 2220 cm^{-1}, 115.56 ppm (CN), 1745 cm^{-1}, 169.88 ppm (CO$_2$Et), 5.42, 115.08 ppm (C=CH). b. **9a**: 171.10, 170.98 ppm (CO$_2$H, N(CO)). MS: 157 (MH$^+$), 140 (MH$^+$-H$_2$O). c. **6**: 135.71, 129.86, 118.08, 108.83 (pyrrole carbons), 5.74 ppm (pyrrole H-4, J=0.05 Hz). d. **7**: 3.89, 3.77 ppm (CO$_2$Me), 141.43, 125.69, 118.78, 109.49 (pyrrole carbons). e. **8**: m p 117°C, 6.60 ppm (vinylic H). f. **9b**: 3245 cm^{-1}, 8.73, 7.05 ppm (NH), 156.25 (NCO$_2$Et).
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