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DIHYDRO-1,3-OXAZINES. XII. THE OXAZINE α-CARBANION-KETENIMINE REARRANGEMENT.

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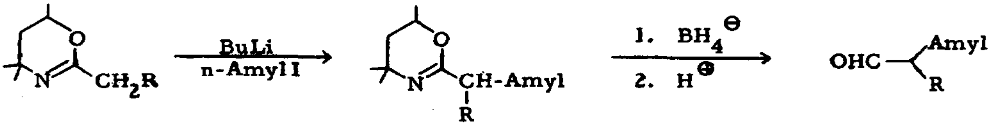
The reaction of metallated 2-methyl (1) and 2-benzyl (2) dihydro-1,3-oxazines with electrophilic reagents (e.g. n-amyl iodide) producing alkylated derivatives (4 and 5) which ultimately lead to aldehydes (7 and 8) has been recently reported.[2] However, when the 2-substituent is of the alkyl type, (3) little or no reaction occurs with electrophiles (e.g. n-amyl iodide), yet addition of D_2O to 3 after treatment with butyllithium does afford the α-deuterio derivative, 4 (R=D).[3] The lack of alkylation on the dihydro-1,3-oxazine carrying 2-substituents other than methyl or benzyl would detract somewhat from the synthetic utility of this method. For this reason a detailed investigation was undertaken using the 2-(1-phenylhexyl) dihydro-1,3-oxazine, 5, as a model system and the unusual results obtained prompts this report.



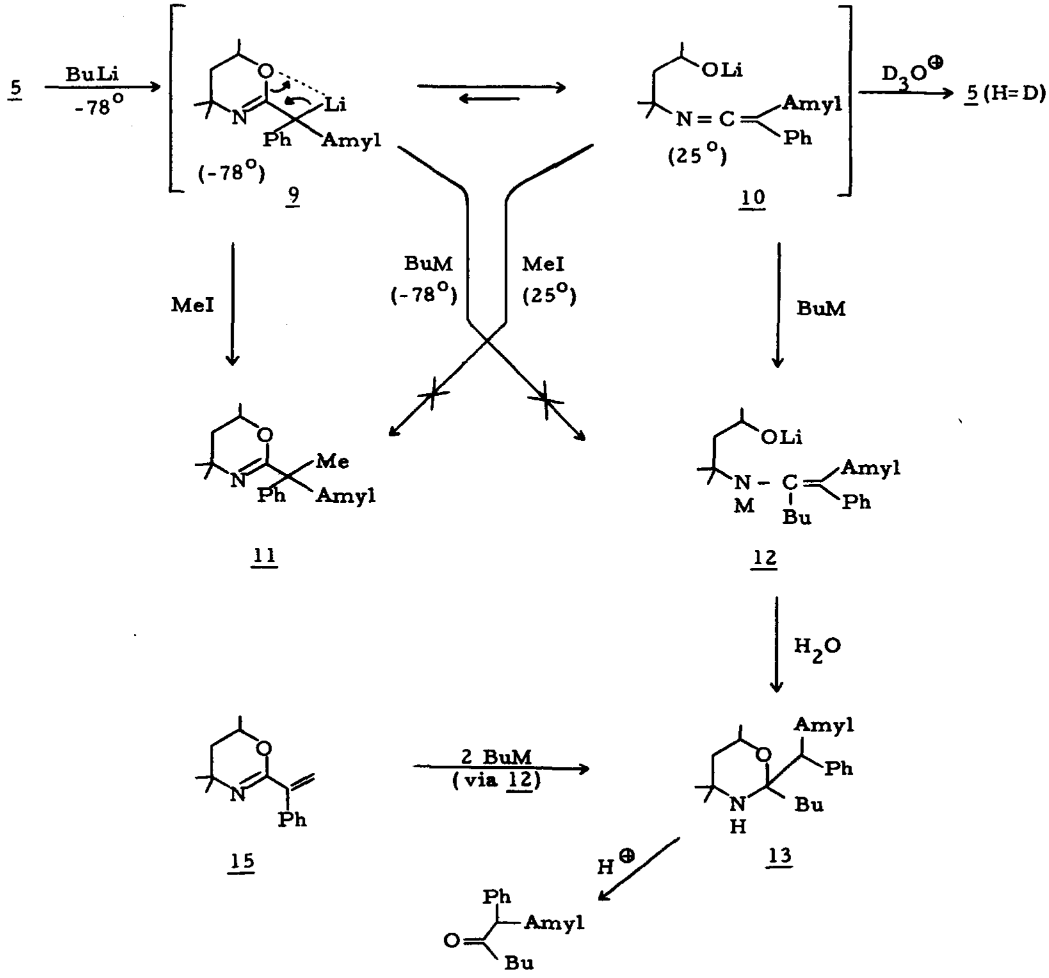
1, R=H
2, R=Ph
3, R=n-Amyl

4, R=H
5, R=Ph
6, R≠n-Amyl

7, R=H
8, R=Ph

When 5 was treated with n-butyllithium (THF, -78°) to form the lithio salt, 9, and then methyl iodide added at -78°, there was obtained, in 96% yield, the expected methylated derivative, 11 (oil, 1660 cm^{-1}). In sharp contrast to this, allowing the lithio salt solution to warm to room temperature before addition of methyl iodide, returned only the starting oxazine 5 after work-up in dilute acid.[4] If the lithio salt solution, after warming to room temperature is poured into water, the resulting oil extracted (ether), concentrated, and its infrared spectrum examined, there appeared an intense band at 2010 cm^{-1} and a strong broad band at 3400-3500 cm^{-1} suggesting the hydroxy-ketenimine[5] 10 (Li=H). Addition of aqueous acid ($DCl-D_2O$) to 10 caused a rapid cyclization to the starting oxazine, 5 (H=D). It, therefore, appears that the oxazine carbanion 9 is stable at low temperatures and is completely converted to the ketenimine, 10, as the temperature rises to ambient. *This behavior indicates that the lithio oxazine may serve as a nucleophile or an electrophile depending upon the temperature of the experiment*. To demonstrate the electrophilic properties of the metallated dihydro-1,3-oxazine, the THF solution of 9 was once again allowed to warm to room temperature and then treated with n-butylmagnesium bromide or n-butyllithium. After stirring at 25° for 18 hr, the reaction was diluted with water and the 2,2-disubstituted tetrahydro-1,3-oxazine 13 was isolated (>90%). The latter undoubtedly arose *via* spontaneous ring closure of the adduct 12 after hydrolysis.[6] Mild acidic cleavage (oxalic acid) of 13 afforded 6-phenyl-5-undecanone, 14 (ir 1710 cm^{-1}, m/e 232) in 78% yield. When butyllithium (or Grignard) was added to the lithio salt of 5 at -78° and the temperature maintained at -78° for 3 hr followed by addition of dilute acid, no tetrahydro-1,3-oxazine was obtained and the starting dihydro-1,3-oxazine, 5, was completely recovered. Thus, little or no ketenimine had formed (or reaction was too slow) at the lower temperature, yet addition of methyl iodide under these conditions gave excellent yields of 11.

From a previous study[7] involving the 2-(α-styryl)dihydro-1,3-oxazine, 15, it was possible to prepare the tetrahydro-1,3-oxazine 13 by addition of two equivalents of n-butyl lithium (or Grignard). Acidic cleavage also produced 6-phenyl-5-undecanone, 14, in 68% yield. Thus, the ketenimine 10 can be produced either by proton abstraction (from 5) or by nucleophilic addition (to 15). To ascertain whether or not an equilibrium exists between 9 and 10, methyl iodide was added at room temperature to the lithio salt of 5 (presumably now existing as the ketenimine). After 0.25, 3, and 18 hr there was indeed a progressive increase (~0, ~7, and ~40%) in the extent of methylation to 11, clearly demonstrating the tautomeric interconversion of 9 and 10. The position of the equilibrium has been found to be sensitive to the nature of the 2-substituent and this aspect is currently under investigation. These results also help to clarify the lack of alkylation of the α-carbanions of 2-alkyl dihydro-1,3-oxazines since in the absence of a stabilizing phenyl group, the rearrangement to ketenimines is undoubtedly quite rapid.[8] This dramatic temperature effect upon the nucleophilic vs. electrophilic behavior of the tautomers has formed the basis for a further useful ketone synthesis from dihydro-1,3-oxazines.[9]



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2. H.W. Adickes, I.R. Politzer, and A.I. Meyers, J. Am. Chem. Soc., 91, 2155 (1969) and references cited therein.
3. A.I. Meyers and H.W. Adickes, unpublished results. The reaction of the anion of 3 with alkyl halides has been found to give 1-10% of alkylated material and yields as high as 40% have been realized by carrying out the metallation (BuLi) in the presence of alkyl halides. The intramolecular alkylation to form 2-cycloalkyl dihydro-1,3-oxazines, however, proceeds normally [J. Am. Chem. Soc., 91, 765 (1969)].
4. The lithio salt 10 does not alkylate due to the total inertness of the OLi bond. This behavior has previously been observed in this series (see ref. 2 above).
5. C. L. Stevens and J. C. French, J. Am. Chem. Soc., 76, 4401 (1954).
6. Hydrolysis of 12 gives the hydroxy enamine which is tautomeric with its Schiff base form [M. Pfau and C. Ribiere, Chem. Comm., 66 (1970)] and also with 13. Current experiments have shown that 12 can be alkylated further in situ and specifically on the carbon bearing the amyl and phenyl group. This is, therefore, another example of Stork's metallated enamines [J. Am. Chem. Soc., 85, 2178 (1963)] and Wittig's modification [Angew. Chem. Int. Ed. 7, 7 (1968)] and provides additional latitude in preparing unsymmetrical ketones.
7. A. I. Meyers and A. C Kovelesky, Tetrahedron Letters, 4809 (1969).
8. When the oxazine contains a completely aliphatic 2-substituent, i.e. 2-cyclopentyl or 2-(sec-butyl) the ketenimine forms immediately upon proton abstraction even at -78°. Therefore, 5 provided an example where both species (carbanion and ketenimine) could be studied.
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