Tetrahedron Letters No.59, pp. 5151-5154, 1969. Pergamon Press. Printed in Great Britain.

# SOME NOVEL PROPERTIES OF DIHYDRO-1,3-OXAZINES AND THEIR USE IN FORMYLATION OF ORGANOMETALLICS

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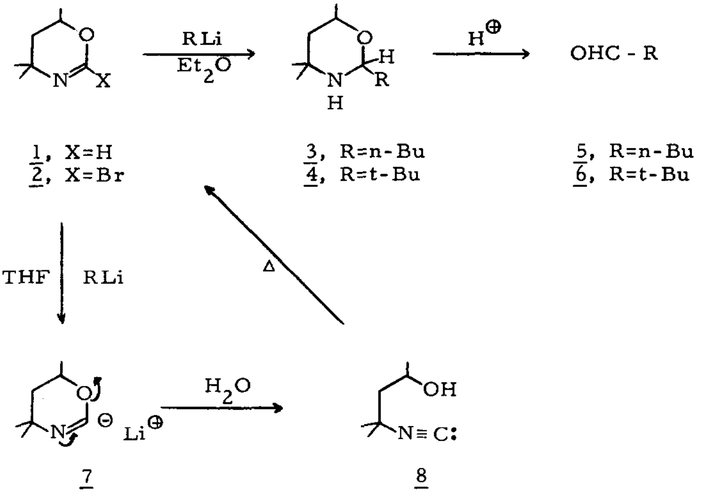
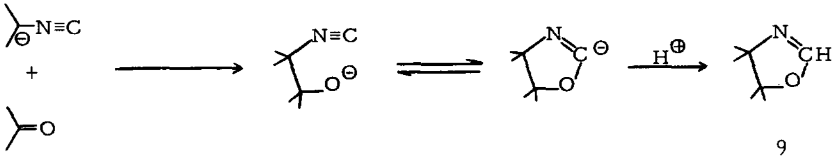
(Received in USA 14 November 1969; received in UK for publication 20 November 1969)

In our quest for a one-carbon homologation of organometallics leading to aldehydes, a goal with comparable significance to the carbonation of organometallics, we turned to the dihydro-1,3-oxazines, 1 and 2.[1] This ring system has already been shown to be of considerable value as a precursor for two[2] and three[3] carbon extended aldehydes, ketones[4] and acids.[5] We report here results which, with respect to our initial aim, were only partly successful yet revealed some unusual properties of the dihydro-1,3-oxazine ring.[6]



The trimethyldihydro-1,3-oxazine, 1 [ bp 37° (42 mm); ir (neat) 1665 $cm^{-1}$; nmr ($CCl_4$) δ6.75, (s, 1, N=CH ]was treated with 1.1 equiv of n-butyllithium at -78° in THF in an attempt to generate the anion, 7. After hydrolytic work-up, the isonitrile 8 (80%) was obtained as the only product [ bp 47° (0.4 mm); ir (neat) 3395 and 2115 $cm^{-1}$; nmr ($CCl_4$) δ3.95, (m, 1), 3.45, (b, 1, exchanged with $D_2O$), m/e 127 ]. The isonitrile was also obtained when 1 was treated with butyllithium at 25°. The dihydro-1,3-oxazine anion (7) is therefore not sufficiently long-lived under these conditions to be synthetically useful for reaction with electrophiles. The reversible nature of the hydroxyisonitrile and the dihydro-1,3-oxazine was confirmed by heating the former (tetradecane, 2hr, 250°) and completely converting it to the latter. These results support the presence of a similar equilibrium recently postulated[7] to precede the formation of 2-oxazolines (9) from metallated isonitriles and carbonyl compounds.



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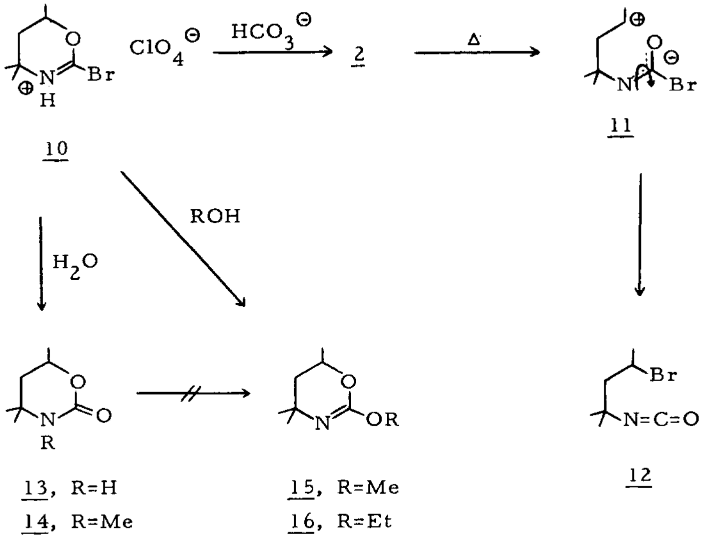
When the oxazine 1, in ether, was treated with n-butyl- or t-butyllithium at -78°, addition to the C=N link occurred and the tetrahydro-1,3-oxazines 3 and 4 were obtained in 66 and 55% yields respectively. Hydrolysis in aqueous oxalic acid afforded valeraldehyde 5 (2,4-DNP 107-108°) and pivaldehyde 6 (2,4-DNP 208-209°). The formylation of organolithium reagents was, therefore, shown to be feasible and the potential value of this method for preparing labelled aldehydes ($1\text{-}C^{14}$, $O^{18}$) from ready sources ($^{14}CN^{\ominus}$ and $H_2O^{18}$) is obvious.

The 2-bromodihydro-1,3-oxazine 2 (unstable oil, conveniently stored as its perchlorate salt 10 at -20°) was treated with n-butyllithium and likewise found to yield the hydroxyisonitrile 8. This is undoubtedly due to formation of the anion 7 via halogen-metal exchange. Unexpectedly, the reaction of 2 with Grignard reagents resulted in complete recovery of starting material.[9] Heating ( ~125°) converted 2 to the bromoisocyanate 12 [m/e 206; ir (neat) 2255 $cm^{-1}$; nmr ($CCl_4$) δ4.25 (m, 1), 2.18 (m, 2), 1.80 (d, 3) 1.40 (d, 6)].

This unusual thermal rearrangement presumably occurs through an intermediate approaching the dipolar species 11 which involves bond rotation and recombination forming 12. On the other hand, the perchlorate salt 10 was quite susceptible to nucleophilic addition being easily transformed by water into the cyclic carbamate 13 (mp $124^{\circ}$) and by alcohols to the 2-alkoxy derivatives 15 and 16, after neutralization. Alkylation of 13 with methyl iodide-sodium hydride resulted only in N-methylation 14 (mp $84^{\circ}$) and no O-methyl product 15 was observed. Studies are in progress in an attempt to capitalize on the unusual properties of 1 and 2 toward useful one-carbon homologation processes.[10]



ACKNOWLEDGEMENTS: Financial assistance from the National Science Foundation (GP-9592), Petroleum Research Fund, Hoffman La Roche, CIBA, Warner-Lambert, and Merck is deeply appreciated.

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4. A.I. Meyers and A.C. Kovelesky, J. Am. Chem. Soc., 91, 5887 (1969).

5. A.I. Meyers, I.R. Politzer, B.K. Bandlish, and G.R. Malone, ibid., 91, 5886 (1969).

6. Little is known regarding the chemistry of this relatively ancient ring system other than its formation and hydrolysis (Z. Eckstein and T. Urbanski in Advances in Heterocyclic Chemistry, Vol. 2, Academic, New York, p. 311.

7. F. Gerhart and U. Schollkopf, Tetrahedron Letters, No. 59, 6231 (1968).

8. Current difficulty with this synthetic method centers around the poor yields (10-15%) encountered in the preparation of 1 using the scheme described in ref. 1 above. Studies are in progress to increase the efficiency of preparing 1. On the other hand, the yields of 2 are much more respectable (50-60%) and based upon its facile conversion to the isonitrile 8 and thermal cyclization to 1, may provide sufficient quantities for synthetic purposes.

9. The stability of 2-alkyl (and 2-aryl) dihydro-1,3-oxazine toward the Grignard reagent has recently been utilized as the basis for a unique protecting group; ref. 5 and work currently underway.

10. The existing methods for formylating organometallics have been discussed (J. Carnduff, Quart. Reviews, 20, 179 (1966).