Tetrahedron Letters No. 4, pp 311 - 312, 1972. Pergamon Press. Printed in Great Britain.

GRIGNARD REACTION WITH PYRIDINE-N-OXIDE

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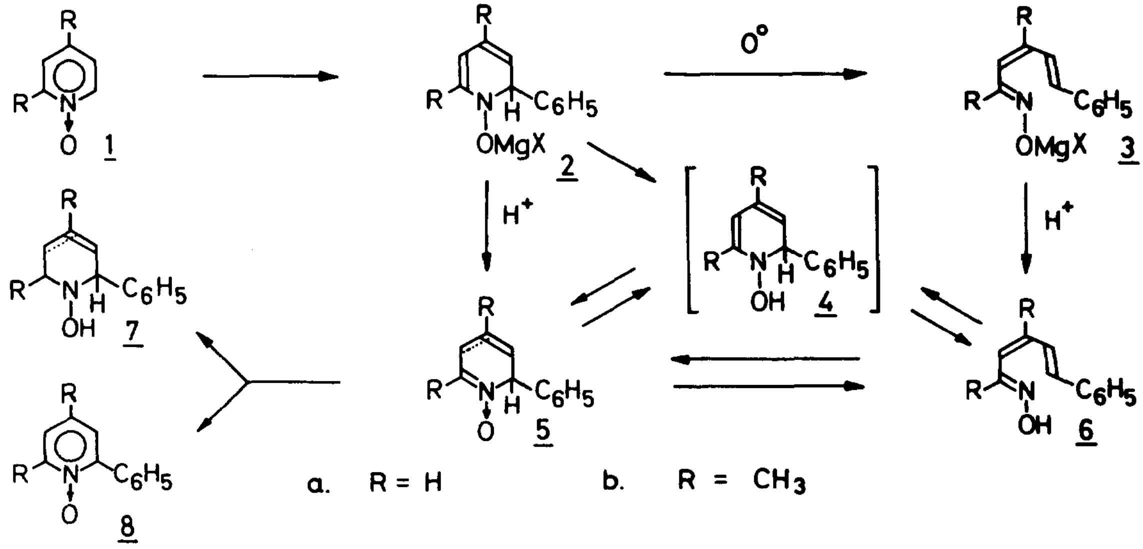
(Received in UK 21 December 1971; accepted for publication 28 December 1971)

Our interest in thermal rearrangement reactions of dienone oximes [1] has led us to reinvestigate the addition of phenyl magnesium bromide to pyridine-N-oxide 1a [2]. This reaction has recently been reported by Kellogg [3] to lead to 5-phenyl-2,4-pentadienaldoxime 6a and not to its cyclic valence isomer 4a as claimed previously [4]. While fully corroborating Kellogg's results our study has shown that the reaction takes a different course when carried out at low temperature.

When the addition of 1a to phenyl magnesium bromide in THF and the protonation of the adduct is carried out at -50° only traces of 6a are obtained. The main product (45 %) is 2-phenyl-1,2-dihydropyridine-N-oxide 5a, a water soluble oil. Its structure follows from its spectral properties [5] (no absorption in the IR at 3600-3000 cm^{-1} and in the UV above 280 nm) and from its chemical reactions. It yields a cycloadduct (mp. 106°) with phenylisocyanate involving its nitrone partial structure [6]. At 50° 5a disproportionates into 7a (mp. 105°) and 8a (mp. 158°) [7] (10-28 % each). In addition a substantial amount (15-45 %) of oxime 6a is formed. Disproportionation [8] and ring opening are competing reaction pathways for 5a, the latter being favored in dilute solution.



a. R = H b. R = CH_3

The reaction of lutidine-N-oxide 1b with phenyl magnesium bromide takes an analogous course as that of 1a. Above 0° oxime 6b (mp. 94°) is obtained (40 %). Structure and stereochemistry of 6b follow from its spectral properties 1) and from its preparation from 6-phenyl-3,5-hexadien-2-one of established configuration 9). At -25° however the main product (44 %) is an oil to which structure 5b (conjugated double bonds) can be assigned (IR: no band at 3600-3000 cm^{-1}; UV: 310 nm/ ε 8000). 5b which gives a picrate (mp. 118°) and a cycloadduct with phenylisocyanate (mp. 127°) is more stable than its non methylated homologue 5a. Disproportionation to 7b (mp. 97°) and 8b (oil, picrate mp. 147°) occurs only above 160° and no isomerization to oxime 6b can be observed. On the other hand oxime 6b is quantitatively converted into its cyclic isomer 5b upon reflux in ethanol or cyclohexane whereas the non methylated oxime 6a is recovered unchanged when heated up to 140° 1).

These results can best be explained through the reaction sequence depicted in the chart. Nitrones 5a and 5b are formed through protonation on carbon of primary Grignard adducts 2a and 2b. These adducts are stable only in the cold. At 0° they undergo an electrocyclic ring opening (2 → 3) yielding oximes 6a and 6b after protonation. The position of the ring-chain equilibrium $5 \rightleftharpoons 6$ depends on the substituents on the molecular skeleton. While 6a is favored over its cyclic isomer 5a, the relative stabilities are reversed in the methylated system: 5b being more stable than 6b. The shift of the equilibrium in the direction of the cyclic isomer upon replacement of hydrogens through methyl groups is not unexpected 10). In the described interconversions of open chain dienone oximes and cyclic nitrones the N-hydroxy-1,2-dihydropyridines 4a and 4b are possible intermediates 1).

We gratefully acknowledge support of this work by a contribution from CIBA-GEIGY company and by a grant from the "Schweizerischer Nationalfonds" (Nr. 5037-2).

Footnotes and References

1) See following communication.
2) Presented in part at the meeting of the Swiss Chemical Society, St. Gallen, Oct. 4, 1969 (rf. Chimia 24, 24 (1970) and at the IUPAC Symposium on Cycloaddition Reactions, Munich, Sept. 7 - 10, 1970.
3) T.J. Van Bergen and R.M. Kellogg, J. Org. Chem. 36, 1705 (1971).
4) T. Kato and H. Yamanaka, J. Org. Chem. 30, 910 (1965); T. Kato, H. Yamanaka, T. Adachi and H. Hirunama, J. Org. Chem. 32, 3788 (1967).
5) All stable, new compounds were characterized by their IR-, UV- (ethanol) and NMR- (CCl_4) spectra and gave satisfactory elemental analyses. Upper limits of 1-2° melting ranges are given as mp.
6) R. Huisgen, Angew. Chemie 75, 604 (1963).
7) H. Gilman and J.T. Edward, Can. J. Chem. 31, 457 (1953).
8) Disproportionation of structurally similar dihydropyridinium salts is reported to proceed under mild conditions: E.M. Fry, J. Org. Chem. 28, 1869 (1963).
9) A.F. Kluge and C.P. Lillya, J. Org. Chem. 36, 1977, 1988 (1971).
10) E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, New York 1962, p. 196.