Tetrahedron Letters, No. 8, pp.1-3, 1959. Pergamon Press Ltd. Printed in Great Britain.

ORIENTATION IN THE REACTION OF PHENYLLITHIUM WITH 3-SUBSTITUTED PYRIDINES

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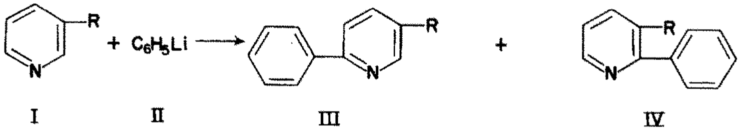
(Received 4 June 1959)

A STUDY of the addition of phenyllithium to 3-substituted pyridines was undertaken to determine the orientation of the entering phenyl group. While this work was in progress Wiley _et al._[1] reported that the reaction of 3-phenylpyridine I(R = C_6H_5) with phenyllithium II was selective in giving 2,5-diphenylpyridine III(R = C_6H_5) exclusively. The formation of 2,3-diphenylpyridine IV(R = C_6H_5), which Wiley _et al._ regard as less probable, was not observed.



The addition of other nucleophilic reagents such as sodamide[2,3] and butyl-

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[1] R. H. Wiley, C. H. Jarboe, P. X. Callahan and J. T. Nielsen, J. Org. Chem. 23, 780 (1958).

[2] E. Plazek, A. Marcinikov and Ch. Stammer, Roczn. Chem. 15, 365 (1935); Chem. Abstr. 30, 1377 (1936).

[3] E. Hardegger and E. Nikles, Helv. Chim. Acta 39, 505 (1956).

lithium[4] to 3-substituted pyridines indicated the preferential formation of the 2,3-isomer in such reactions. Since our results with phenyllithium also show this trend we report some of our observations.

With 3-picoline, II gave 2-phenyl-3-picoline IV($R = CH_3$), b.p. 154-156°/18 mm, (picrate, m.p. 165-166°), and 6-phenyl-3-picoline III($R = CH_3$), b.p. 162-164°/20 mm, (picrate, m.p. 181-183°), the relative yields of IV and III being in the ratio of 8:1 respectively. The structure of the main product was proved by permanganate oxidation to 2-phenylpyridine-3-carboxylic acid IV(R = COOH), m.p. 168-169° (lit.[5] m.p. 168-169°) which was converted *via* the acid chloride into 4-azafluorenone,[6] m.p. 139.5-141.5°, by $AlCl_3$ in light petroleum. When the acid chloride was treated with $AlCl_3$ in benzene 3-benzoyl-2-phenylpyridine IV($R = C_6H_5CO$), b.p. 155-160°/15 mm, picrate, m.p. 137.5-138.5°, was obtained. The structure of 2-phenyl-3-picoline was confirmed by direct comparison with a specimen obtained unambiguously by Ishiguro *et al.*,[5] the IR spectra of the products and their picrates being identical and a mixed melting point of the picrates being undepressed. The NMR spectrum of the product was also consistent with its formulation as 2-phenyl-3-picoline. The structure of III($R = CH_3$) was similarly proved by oxidation to 2-phenylpyridine-5-carboxylic acid, m.p. 232-233° (lit.[7] m.p. 233°). A dimethyldipyridyl, characterized as the dipicrate, m.p. 204-206° (decomp.), was isolated as a byproduct of the reaction and shown to

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[4] N. J. Leonard and B. L. Ryder, *J. Org. Chem.* **18**, 596 (1953).

[5] T. Ishiguro, Y. Morita and K. Ikushima, *Yakugaku Zasshi* **78**, 220 (1958); *Chem. Abstr.* **52**, 11846g (1958).

[6] Z. Skraup and A. Cobenzl, *Monatsh.* **4**, 436 (1883), report m.p. 140-141° for 4-azafluorenone.

[7] N. Nienburg, *Chem. Ber.* **67**, 874 (1934).

be different from 3,3'-dimethyl- and 5,5'-dimethyl-2,2'-dipyridyl by a comparison of the picrates. The structure of this byproduct was not investigated further at this stage.

In view of the results of Wiley et al.[1] the possible steric effect of the 3-substituent upon the orientation of the entering phenyl groups was investigated in the reaction of II with nicotine. The product was shown to be a 1:1 mixture of 2-phenyl- IV(R = $-\alpha-C_4H_7NCH_3$) and 6-phenylnicotine III(R = $-\alpha-C_4H_7NCH_3$) by vapour phase chromatography. The two isomers were separated by preparative vapour phase chromatography giving 2-phenylnicotine, b.p. 145°/0.7 mm, picrate, m.p. 211-213° and 6-phenylnicotine, b.p. 165°/0.6mm, picrate, m.p. 170-171°. The structures of the isomers were assigned on the basis of their infrared spectra (characteristic bands at 1610-1570 cm^{-1}) and by oxidation of the second fraction to 2-phenylpyridine-5-carboxylic acid.

Addition of II and of other nucleophilic reagents seems to occur preferentially at the 2-position but the 3-substituent, if sufficiently bulky, may exert a steric effect resulting in appreciable addition at the 6-position also. The exclusive formation of 2,5-diphenylpyridine[1] might be attributed to steric inhibition of coplanarity in the transition state in the formation of the 2,3-isomer.

Acknowledgements - The authors wish to thank Dr. Ishiguro for samples of 2-phenyl-3-picoline and its picrate, and Varian Associates for the NMR spectrum of 2-phenyl-3-picoline and its interpretation. This work was supported by a National Research Council of Canada grant.