Tetrahedron Letters No. 1, pp 59 - 62, 1974. Pergamon Press. Printed in Great Britain.

THE PREPARATION OF 1,2,4-TRI-ALKYL OR ARYL SUBSTITUTED 1,2-DIHYDROPYRIDINES BY GRIGNARD REAGENTS.

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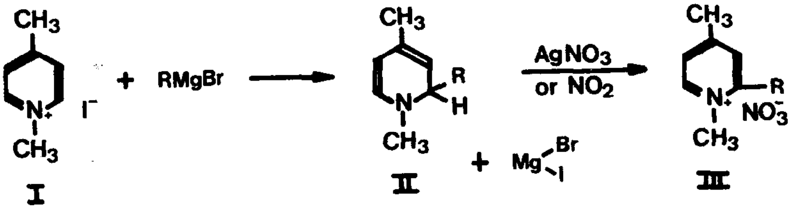
(Received in UK 29 October 1973; accepted for publication 23 November 1973)

A number of dihydropyridines have been prepared by the action of organometallic reagents on pyridines or pyridiniumsalts. A review of the literature up to 1971 has been published (1). The dihydroderivatives substituted only with non electronwithdrawing groups are very unstable and are usually intermediates in the synthesis of pyridine derivatives (2-5). Consequently the structures of these compounds are proved in a limited number of cases (6-8). Only the products N-phenyl-1,2-dihydropyridine and N-phenyl-1,4-dihydropyridine have been isolated in a pure state (9).

In the present paper we wish to report the preparation of 1,2,4-tri-alkyl or aryl substituted 1,2-dihydropyridines, obtained by the action of Grignard reagents on 4-alkyl substituted quaternary pyridiniumsalts. This type of reaction has been used before in a synthesis of an analgesic but the presence of an 1,2-dihydroderivative was only presumed (10).

Reaction scheme:



(a) R=Et (b) R= Phenyl

In order to isolate the air sensitive product II all operations are carried out in Schlenk-type glassware (11). No excess of Grignard reagents may be used. By the addition of 1,4-dioxane to the ethereal solution the magnesiumhalides are precipitated. The product IIa or IIb, obtained from the evaporated solution, is further purified by vacuumdistillation (yield > 70%). Oxidation by NO_2 (for IIb) or $AgNO_3$ (for IIa) yields the pure compounds IIIa or IIIb. Oxidation by iodine or air is less specific as is deduced from the PMR-spectra of the reaction mixtures.

Obviously this method of synthesis allows some freedom of choice for the substituents on the 1,2 and 4 positions, within a series of alkyl and aryl groups. A conclusive proof of structure is further given by the PMR-, IR- and UV-spectra. The PMR-spectra of IIa and IIb are in good agreement with the scarcely found spectra in the literature: see table I.

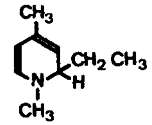
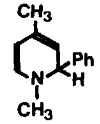
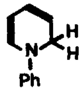
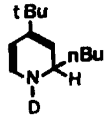
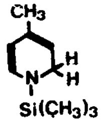
The signal assignment is established by double resonance on the (C_2)-H signal in the structure IIa and on the (C_6)-H signal in the structure IIb. Because of the small chemical shift differences for the signals of the protons (C_2)-H and (C_3)-H in structure IIb the assignment for both signals remains interchangeable. It is worth mentioning that the diffuse pattern of the (C_2)-H and the (C_3)-H signals in structure IIa and IIb is also found in the two 4-substituted reference compounds given in table I.

From the IR-spectra in the pure liquid state, the following peaks can be mentioned, for the structure confirmation:

Compound IIa: 3040 (sh), 2800 (m), 1657 (s), 1645 (s), and 1575 cm^{-1} (s).

Compound IIb: 3060 (m), 3030 (m), 2800 (m), 1660 (s), 1652 (sh), and 1575cm^{-1}(s).

TABLE 1 : P.M.R.-spectra of 1,2 dihydropyridines

	IIa		IIb		ref.9		ref.6		ref.7
									
	$\delta^{CDCl_3}_{TMS}$	J(Hz)	$\delta^{CDCl_3}_{TMS}$	J(Hz)	$\delta^{CCl_4}_{TMS}$	J(Hz)	δ^{b}_{TMS}		$\delta^{C_6H_6}_{TMS}$
(C_2)-H	3.86	(br.)	4.80^a	(br.)	4.26	$J_{2,3}$=3,.6	too broad to assign		3,72 d of d
(C_3)-H	4.68	(br.)	4.96^a	$J_{2,3}$=4	5.21	$J_{3,4}$=7.7 $J_{2,3}$=3.6	3,87	(br.)	4,73 (br.)
(C_5)-H	4.41	$J_{3,5}$=2 $J_{5,6}$=7	4.47	$J_{3,5}$=2 $J_{5,6}$=7	4,94	$J_{5,6}$=6.9 $J_{4,5}$=4,5	4,62	$J_{5,6}$=8,3	4,98
(C_6)-H	5.91	$J_{5,6}$=7	5.82	$J_{5,6}$=7	6,41	$J_{5,6}$=6,9	6,01	$J_{5,6}$=8,3	6,00
N-CH_3	2.76	s	2.55	s					
(C_4)-CH_3	1.78	s	1.69	s					1,72
$(C_2)CH_2$	1.5	m	-						
$(CH_2)CH_3$	0.88	t; J=8							
(C_2)-Ph			7.30						

a= both signals are interchangeable b= measured in the reaction mixture
s= singulet; t= triplet; m= multiplet; d of d: doublet of doublets
(br.)= broad

The UV-spectra taken in methanol solution, show supprisingly different absorption maxima for both compounds: 306nm in IIa; 348nm (and 270nm) in IIb. For the comparable compound 1-methyl-1,2-dihydropyridine an absorbtion maximum of 325nm is reported (12).

Experimental:

A solution of 90 mmole RMgBr in diethylether is added to a stirred suspension of 110 mmole 1,4-dimethylpyridiniumiodide in boiling ether. Refluxing is maintained for one hour, after which 250 mmole of 1,4-dioxane is added to the reaction mixture and the refluxing is continued for an additional hour. The cooled reaction mixture is filtered under nitrogen in a Schlenk-apparatus. From the filtrate the diethylether and the remaining 1,4-dioxane are boiled off. The residue is distilled in vacuum and the fraction with boiling point 37-38° at 2.5mm Hg is stored under nitrogen (yield $>$ 70%).

Acknowledgement:

The authors whish to thank the Fonds voor Kollektief Fundamenteel Onderzoek for financial help in this research program.

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