Some Nucleophilic Addition Reactions of 2,5-Dihydropyridines: Synthesis of 2,3,6-Trialkyl(phenyl)-1,2,3,6-tetrahydropyridines and 2,3,6-Trialkyl(phenyl)pyridines

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A series of 2,5-dialkyl(phenyl)-2,5-dihydropyridines (2) was prepared by reacting 1-lithio-2-alkyl(phenyl)-1,2-dihydropyridines (1) with alkyl halides. The 2,5-dihydropyridines (2) are stable when maintained cold under a nitrogen atmosphere, and these compounds react with alkyl(phenyl)lithium compounds by nucleophilic addition to the C=N moiety. The resultant products are 2,3,6-trialkyl(phenyl)-1,2,3,6-tetrahydropyridines (4) which can be oxidized (selenium) to the corresponding 2,3,6-trialkylpyridines (5).

The reactions of pyridine–tetrakis(*N*-dihydropyridyl)-aluminate complexes and of pyridine–alkyllithium complexes with alkyl halides are sources of 3-alkyl-[1] and 2,5-dialkyl(phenyl)pyridines,[2-5] respectively. We recently reported[5] the synthesis of a series of 2,5-dialkyl(phenyl)-2,5-dihydropyridines (2) obtained in the reactions of 1-lithio-2-alkyl(phenyl)-1,2-dihydropyridines (1) with alkyl halides. Evidence presented in support of the 2,5-dihydropyridine structures included the fact that they undergo reduction with lithium aluminum hydride to the corresponding tetrahydropyridines (3), and the sequence of reactions **1** → **3** was proposed as a general synthesis of 2,5-dialkyl-1,2,5,6-tetrahydropyridines (3). These reactions are summarized in Scheme I.

The addition of hydride ion to the C=N moiety of the 2,5-dihydropyridines (2) suggested that other nucleophiles could be added. In this paper, we report the reactions of some 2,5-dihydropyridines with alkyllithium compounds. This reaction is the basis of a sequence of reactions capable of producing a variety of 2,3,6-trialkyl(phenyl)-1,2,3,6-tetrahydropyridines (4) and 2,3,6-trialkyl(phenyl)pyridines (5). Trisubstituted tetrahydropyridines[6] and pyridines[7] having this substitution pattern are relatively rare.

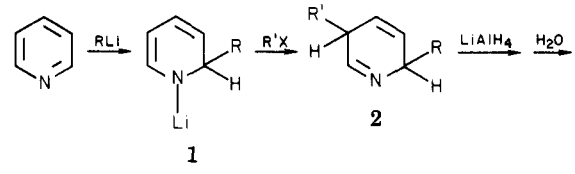
Results and Discussion

The general procedure used to convert pyridine–alkyl(phenyl)lithium complexes (1) to 2,3,6-trialkyl(phenyl)-1,2,3,6-tetrahydropyridines (4) and 2,3,6-trialkyl(phenyl)pyridines (5) is summarized in Scheme II.

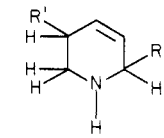
The pyridine–alkyl(phenyl)lithium complexes (1) used in this study were prepared by reacting pyridine with *n*-butyl-, *tert*-butyl-, or phenyllithium by the method previously described.[5] Each complex 1 was treated with methyl iodide in order to prepare several representative 2,5-dialkyl(phenyl)-2,5-dihydropyridines (2). These compounds decompose when they are heated or exposed to air, but most were found to be stable for several days when kept cold under a nitrogen atmosphere. Although no attempt was made in this study to identify these unstable compounds, most have been characterized previously by their NMR spectra.[5] The complexes 1 and 2,5-dihydropyridines 2 prepared are summarized in Table I.

In general, we have observed[5] high-yield conversions of 1-lithio-2-alkyl(phenyl)-1,2-dihydropyridines (1) to the corresponding 2,5-dialkyl(phenyl)-2,5-dihydropyridines (2)

Scheme I

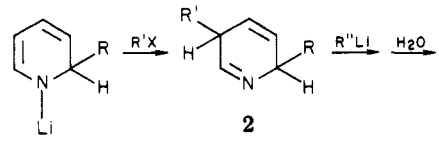


1 2

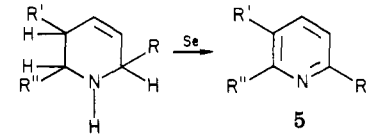


3a, R = *t*-Bu; R' = CH_3
b, R = *t*-Bu; R' = C_2H_5
c, R = *n*-Bu; R' = CH_3
d, R = Ph; R' = CH_3
e, R = Ph; R' = C_2H_5

Scheme II

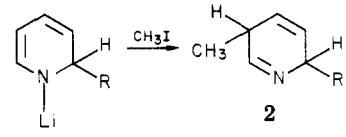


1 2



4 5

Table I. Pyridine–Alkyllithium Complexes (1) and 2,5-Dihydropyridines (2)



1 2

no.	R	no.	R
1a	Ph	2a	Ph
1b	*n*-Bu	2b	*n*-Bu
1c	*t*-Bu	2c	*t*-Bu

(1) Giam, C. S.; Abbott, S. D. *J. Am. Chem. Soc.* **1971**, *93*, 1294.
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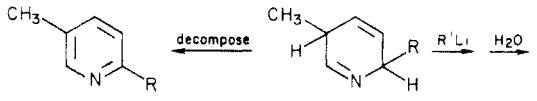
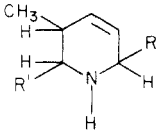
Table II. Ratios of 2,3,6-Trialkyl-1,2,3,6-tetrahydropyridines (4) and 2,5-Dialkylpyridines (6)



6 2



4

compd	R	R'	rel ratio of 4 to 6	vinyl proton abs of 4, ppm
4a	*t*-Bu	*t*-Bu	79:21	5.62 (pr, AB, d)
b	*t*-Bu	CH_3	70:30	5.55 (m), 5.68 (m)
c	*n*-Bu	Ph	46:54	5.62 (m)
d	*t*-Bu	*n*-Bu	95:5	5.60 (m), 5.68 (m)
e	Ph	*n*-Bu	52:48	5.63 (m)
f	*n*-Bu	*t*-Bu	54:46	5.58 (m)

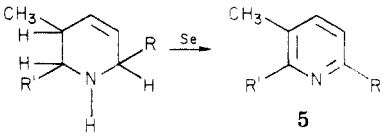
and of the latter to 2,5-dialkyl(phenyl)-1,2,5,6-tetrahydropyridines (3) by lithium aluminum hydride reduction.

Each of the 2,5-dihydropyridines 2 when treated with an alkyl(phenyl)lithium compound[8] and then hydrolyzed gave a 2,3,6-trialkyl(phenyl)-1,2,3,6-tetrahydropyridine (4). The success of the reaction between each 2,5-dihydropyridine (2) and an alkyllithium compound is apparently related to the stability of the 2,5-dihydropyridine 2 and to the size and strength of the nucleophile derived from the alkyllithium compound. Any of the 2,5-dihydropyridine 2 which decomposes before the alkyllithium compound is added or which fails to react with the alkyllithium compound and decomposes on workup will appear as the corresponding 2,5-dialkyl(phenyl)pyridine (6). Thus, the success of the reaction at this stage of the overall sequence was monitored by analyzing the crude mixture to determine the ratio of 2,5-dialkyl(phenyl)-pyridine (6) to 2,3,5-trialkyl(phenyl)-1,2,3,6-tetrahydropyridine (4). This was accomplished by obtaining (preparative GLC) samples of the products of each reaction and characterizing them by their NMR spectra. Generally, the tetrahydropyridines show a broad absorption near 5.6 ppm for the vinyl protons.[5] The relative percentages of 2,5-dialkyl(phenyl)pyridines (6) and of 2,3,5-trialkyl(phenyl)-1,2,3,6-tetrahydropyridines (4) are summarized in Table II.

The NMR analysis of each of the GLC-collected samples of tetrahydropyridines 4b and 4d showed more than one absorption near 5.6 ppm, suggesting the presence of stereoisomers. This was supported by the fact that oxidation (selenium) of each mixture assumed to contain stereoisomers gave a single 2,3,5-trialkyl(phenyl)pyridine (5). Since the purpose of this investigation was to establish the reactions necessary to provide a variety of substituted tetrahydropyridines (4) and pyridines (5), no attempt was made to isolate and characterize the isomers. The stereochemistry of tetrahydropyridines 4 and those formed by lithium aluminum hydride reduction of 2,5-dihydropyridines[5] is currently under investigation. The position of addition of the alkyl or phenyl group in the conversion of 2,5-dihydropyridine 2 to tetrahydropyridine 4 is clearly established by the prior[5] characterization of 2 and the NMR analysis of each trialkyl(phenyl)pyridine (5) produced by selenium oxidation of 4. The trialkyl(phenyl)-pyridines 5 synthesized in this study are summarized in Table III.

(8) The 2,5-dihydropyridines (2) appear to be unreactive with Grignard reagents as shown by the fact that 2,5-dihydropyridine 2c did not give detectable amounts of either tetrahydropyridine 4c or 4d when stirred for 12 h at room temperature with an excess of *n*-butylmagnesium bromide or phenylmagnesium bromide, respectively.

Table III. 2,3,6-Trialkyl(phenyl)-1,2,3,6-tetrahydropyridines (4) and 2,3,6-Trialkyl(phenyl)pyridines (5)



4 5

compd 4 and 5	R	R'
a	*t*-Bu	*t*-Bu
b	*t*-Bu	CH_3
c	*n*-Bu	Ph
d	*t*-Bu	*n*-Bu
e	Ph	*n*-Bu
f	*n*-Bu	*t*-Bu

Experimental Section

General Methods. Elemental analyses were performed by Galbraith Laboratories, Inc. Nuclear magnetic resonance spectra were obtained on Varian T-60 and HA-100 instruments. Analyses of reaction product mixtures and relative percentage yields of products were obtained on a Varian Aerograph 90-P3 gas chromatograph equipped with a 20 ft × $^3/_8$ in. column composed of 30% SE-30 on Chromosorb W (60/80 mesh). Infrared spectra were recorded on a Perkin-Elmer 621 instrument. Alkyllithium compounds were obtained as solutions in varying concentrations from Aldrich Chemical Co.

General Procedure for Preparing 2-Alkyl(phenyl)-1-lithio-1,2-dihydropyridines (1). The pyridine–alkyllithium complexes 1 were prepared by adding a pyridine–solvent mixture to a cooled solution containing the desired alkyllithium compound (−70 °C for *tert*-butyllithium–pentane solution and 0 °C for *n*-butyllithium–hexane and phenyllithium–ether solutions). The details of this procedure have been described previously[5]. The complexes prepared in this study are summarized in Table I.

General Procedure for Preparing 2,5-Dialkyl(phenyl)-2,5-Dihydropyridines (2). The pyridine–alkyllithium complexes 1 described above in Table I were reacted with methyl iodide at 0 °C to prepare the 2,5-dialkyl-2,5-dihydropyridine (2). The detailed procedures for preparing and the properties of the 2,5-dihydropyridines used in this study have been previously described.[1] These are summarized in Table I.

General Procedure for Reacting 2,5-Dialkyl(phenyl)-2,5-dihydropyridines (2) with Alkyl(phenyl)lithium Compounds. Preparation of 2,3,6-Trialkyl(phenyl)-1,2,3,6-Tetrahydropyridines (4). In a nitrogen-flushed drybox, 0.04 mol of a solution of the desired alkyl(phenyl)lithium compound was added to a three-necked, round-bottomed flask containing a magnetic stirring bar. The flask was fitted with a serum cap and two glass stoppers and removed from the drybox. One stopper was replaced by a condenser fitted with a mineral oil bubbler, and the flask was flushed with nitrogen. A positive nitrogen atmosphere was maintained as the alkyl(phenyl)lithium compound was cooled to −70 °C (dry ice–isopropyl alcohol mixture) for *tert*-butyllithium and to 0 °C (ice–water mixture) for other alkyllithium compounds.

A solution containing 0.04 mol of the desired 2,5-dihydropyridine 2 was added in small portions via a syringe to a stirred solution containing 0.04 mol of the alkyl(phenyl)lithium compound. The mixture was stirred at room temperature overnight.

The mixture was cooled to 0 °C, and 30 mL of water was added slowly. The layers were separated, and the aqueous layer was extracted with two 20-mL portions of ethyl ether. The combined

organic layers were washed with 20 mL of water, the layers were separated, and the organic layer was dried (K_2CO_3). Removal of the solvent by rotary evaporation generally gave a light yellow oil. Samples of any 2,5-dialkyl(phenyl)pyridine (**6**) formed on decomposition of a 2,5-dialkyl(phenyl)-2,5-dihydropyridine (**2**) and of tetrahydropyridine **4** were collected by preparative GLC. The NMR spectrum of each compound **6** was compared to that of a sample prepared from the reaction of complex **1** and methyl iodide followed by decomposition of the resultant 2,5-dialkyl-(phenyl)-2,5-dihydropyridine (**2**). Each sample of tetrahydropyridine **4** was analyzed for a narrow multiplet near 5.6 ppm which is characteristic of the vinyl protons of these compounds. The NMR spectra of tetrahydropyridines **4b** and **4d** showed more than one absorption in the region near 5.6 ppm, suggesting the presence of stereoisomeric tetrahydropyridines.

General Procedure for Oxidation of Tetrahydropyridines 4a-f. Preparation of 2,3,6-Trialkyl(phenyl)pyridines (5). The crude tetrahydropyridine **4** (~0.4 mol) was refluxed with 0.08 mol (6.5 g) of selenium powder in 35 mL of mesitylene for 36 h. The unreacted selenium was removed by filtration, and the dark brown solution was extracted with four 20-mL portions of 6 M HCl. The combined extracts were cooled to 0 °C, made basic by slow addition of saturated NaOH solution, and extracted with three 30-mL portions of ethyl ether. The combined extracts were dried (K_2CO_3), and the ether was removed by rotary evaporation, leaving a yellow oil which was distilled and analyzed by GLC. Pure samples of trialkyl(phenyl)pyridines were obtained by preparative GLC.

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Registry No. 1a, 77070-58-7; **1b**, 77070-59-8; **1c**, 77070-60-1; **2a**, 66562-51-4; **2b**, 77070-61-2; **2c**, 66562-50-3; **4a**, 77070-62-3; **4b**, 77070-63-4; **4c**, 77070-64-5; **4d**, 77070-65-6; **4e**, 77070-66-7; **4f**, 77070-67-8; **5a**, 38222-84-3; **5b**, 77070-68-9; **5c**, 77070-69-0; **5d**, 77070-70-3; **5e**, 77070-71-4; **5f**, 77070-72-5; **6a**, 56029-43-7; **6c**, 27012-26-6; **6e**, 27012-22-2.

Palladium-Assisted N-Alkylation of Indoles: Attempted Application to Polycyclization

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The palladium(II) complexes of the olefins ethene, propene, and 1-hexene reacted with 1-lithioindole to produce N-alkylated indoles exclusively. Attempts to perform this N-alkylation intramolecularly (to form tricyclic material from 2-allylskatole) failed. Anilines with dienic side chains in the 2-position were subjected to Pd(II)-assisted cyclization conditions in attempts to induce polycyclization. However, only monocyclization was observed.

A variety of heterocyclic systems can be synthesized by using palladium-catalyzed intramolecular functionalization of olefins as the ring-forming step. In this way, *o*-allylphenols were converted to benzofurans,[1] α,β-unsaturated ketoximes to isoxazoles[2] or pyridines,[3] γ,δ-unsaturated alcohols to 2-vinyltetrahydrofurans,[4] 2'-hydroxychalcones to flavones,[5] and penta-2,4-dienoic acids to 2-pyrones.[6] We have recently synthesized isocoumarins from *o*-allylbenzoic acids[7] and indoles from *o*-allylanilines[8] using similar procedures. We have also developed polycyclization processes using sequential, palladium-promoted, cyclization–insertion reactions.[9] A different potential approach to tricyclic systems, particularly to pyrroloindoles, would involve multiple cyclizations of anilines having dienic side chains in the ortho position (eq 1). Since closure of the second ring would necessarily involve the indole nitrogen as the nucleophile, palladium-assisted N-alkylation of indoles was studied concurrently with polycyclization studies.

Indole has been allylated at the 1- or 3-position by allyl acetate, with $Pd(acac)_2$ as a catalyst in refluxing acetic acid.[10] This chemistry probably involves the amination

Table I. Pd(II)-Assisted N-Alkylation of Indole (Eq 2)

R	M	isolation	product	yield, %[a]
H	Li	H_2	1	62
H	Na	H_2	1	9
H	K	H_2	1	trace
H	MgBr	H_2	1	0
H	NBu_4^+	H_2	1	trace
H	Li	β elimination	3	77
H	Li	CO/MeOH	4	40
Me	Li	H_2	1	28
			2	68
n-Bu	Li	H_2	1	66
			2	25
NHAc	Li	H_2		0

[a] Reported yields are based on palladium and are for isolated, purified products.

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(2) K. Maeda, T. Hosokawa, S.-I. Murahashi, and I. Moritani, *Tetrahedron Lett.*, 5075 (1973).
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