PHENYLLITHIUM–PYRIDINE ADDUCT AS A REDUCING AGENT FOR KETONES

R. A. Abramovitch and B. Vig
Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan
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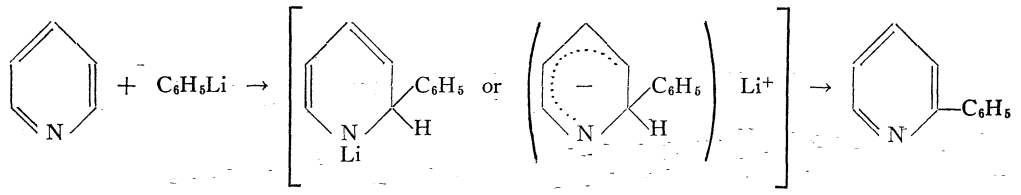
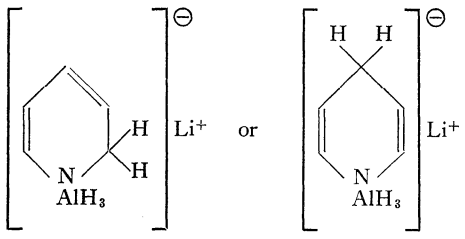
ABSTRACT

The reduction of ketones to the corresponding alcohols using 1,2-dihydro-2-phenylpyridyllithium has been studied. Benzophenone is reduced more readily than is acetophenone, which in turn is more readily reduced than cyclohexanone. It is suggested that the by-product formed in the reduction of benzophenone is 4-diphenylhydroxymethyl-2-phenylpyridine.

The reaction of phenyllithium with pyridine and substituted pyridines has been studied extensively in these laboratories (1–4). The reaction is thought to proceed in two stages: the first is the addition leading to the formation of 1,2-dihydro-2-phenylpyridyllithium, which has been formulated either as I*a* or I*b*; this, on heating, splits off lithium hydride to give 2-phenylpyridine (II). Alternatively, it may be treated with water and the 1,2-dihydro-2-phenylpyridine formed oxidized *in situ* to II. It occurred to us that the adduct I might well behave as a selective reducing agent and it was proposed to examine the possibility of reducing a number of ketones making use of this intermediate. While this work was in progress Lansbury and Peterson (5) reported the results of their interesting work carried out using the adduct III formed between pyridine and lithium aluminum hydride, a reagent similar in many ways to the one used in the present work.



I*a* I*b* II



III

Dihydropyridines play an important role in biological oxidation–reduction systems and many dihydropyridine derivatives have been reported to reduce a variety of substances non-enzymically: nitro groups (6, 7), olefinic double bonds (7, 8), ketones (9), keto acids (10), quinones (7, 11), and other functional groups. The reduction of hexachloroacetone proceeds readily to give a reasonably good yield (53–60%) of the alcohol (9), but chloral only gives a 3% yield of 2,2,2-trichloroethanol with 1-benzyl-1,4-dihydronicotinamide.

Acetone is not reduced by this reagent (9) whereas alloxan is reduced rapidly by 1-methyl or 1-*n*-propyl-1,4-dihydronicotinamide (12).

The reduction of benzophenone by the intermediate I in pyridine–ether solution was investigated in detail. A solution of phenyllithium was prepared in the usual manner and added to a solution of a large excess of pyridine in ether. To this was added the benzophenone and the products worked up by column chromatography. The yield of benzhydrol varied according to the amount of phenyllithium used relative to that of benzophenone, maximal yields being obtained when the molar ratio of I to benzophenone was 2 (Table I). Yields were lowered appreciably if pyridine was not used in excess. A

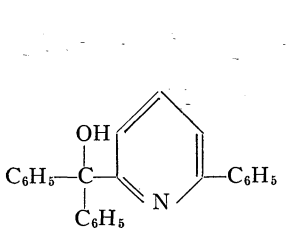
TABLE I

Reduction of benzophenone with I

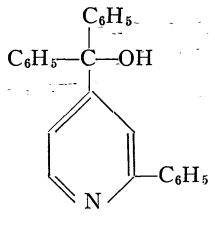
Molar proportion benzophenone/I*	1:1	2:1	3:1
Yield of benzhydrol (%)	20	64	23
Yield of by-product A (%)	Not determined	10	12.5

*Assuming that one equivalent of I is present for every equivalent of phenyllithium used. This is undoubtedly not the case since I undergoes polymerization quite readily (13).

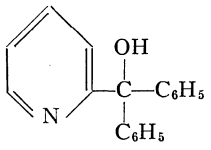
by-product (A) was also obtained in these reactions. The by-product A had the molecular formula $C_{24}H_{19}ON$. It formed a hydrochloride only with difficulty (it was not extracted easily from ether solution with dilute acid), but readily gave a picrate. The infrared spectrum of A indicated the presence of a hydroxyl group, but no —NH— group. Bands characteristic of a monosubstituted phenyl group were also present. Attempts to prepare an acetyl derivative were unsuccessful, suggesting that the hydroxyl group may be tertiary. The compound could not be reduced catalytically at room temperature and pressure. On the basis of these observations, and taking into account the nature of the reactants, two plausible structures for A are 2-diphenylhydroxymethyl-6-phenylpyridine (IV) and 4-diphenylhydroxymethyl-2-phenylpyridine (V). An attempt was made to synthesize IV by



IV



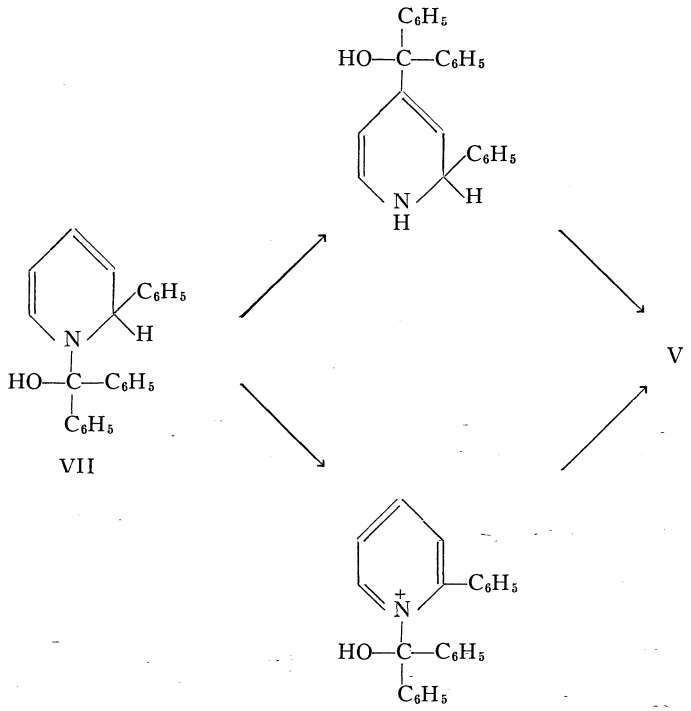
V



VI

the action of phenyllithium on diphenyl-2-pyridylmethanol (VI) (prepared by the action of 2-pyridyllithium on benzophenone): only starting material was recovered. 2-Bromo-6-phenylpyridine was obtained from 2-phenylpyridine via 2-amino-6-phenylpyridine (14). Reaction of 2-lithio-6-phenylpyridine with benzophenone gave the required tertiary alcohol (IV), which was different from the by-product A. That A probably has structure V was confirmed by the comparison of its n.m.r. spectrum (measured on a solution of the compound in carbon tetrachloride, at an oscillator frequency of 60 Mc/s and with tetramethylsilane as an internal standard) with that of authentic IV. The latter exhibited no peaks characteristic of a pyridine α-proton; instead, a multiplet centered at 484 c.p.s. was observed and is attributed to H_γ of the pyridine ring (1, 15). On the other hand, A exhibited a single-proton doublet centered at 524 c.p.s., which is characteristic of an H_α

proton in a pyridine ring (1, 15) and is consistent with the proposed structure (V). This by-product could arise in one of two ways: (i) by direct nucleophilic attack of benzophenone by intermediate I*b*, or (ii) by the reaction of I*a* with benzophenone to give an unstable dihydropyridine derivative (VII), which can then undergo a molecular rearrangement followed by dehydrogenation, or dehydrogenation followed by rearrangement, the



latter being similar in character to the Ladenburg rearrangement of 1-alkylpyridinium salts (16). It is not possible at this stage to distinguish between these two alternatives.

The reduction of acetophenone was investigated next. Using a 2:1 molar ratio of phenyllithium to acetophenone a low yield (14.5%) of α-phenylethanol was obtained, which could not be improved upon by varying the reaction conditions. Though a number of by-products could be isolated in a crude state by column chromatography of the reaction products none could be purified sufficiently for analysis. The reduction of cyclohexanone was also investigated: gas-chromatographic analysis of the reaction products indicated the formation of cyclohexanol in 6.5% yield. It would, therefore, appear that diaryl ketones are more readily reduced by I than are either arylalkyl or dialkyl ketones. The same conclusion was reached when the reducing agent used was III (5).

In a preliminary run in which I was used to reduce nitrobenzene no aniline could be detected gas chromatographically. An orange product was formed whose retention time was identical with that of azobenzene. A small amount of this product was collected but its infrared spectrum was different from that of azobenzene. It was not investigated further at this time.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured on a Perkin–Elmer Model 21 spectrometer equipped with sodium chloride optics, and n.m.r. spectra on a Varian A60 instrument.

Reduction of Benzophenone

The general procedure used to carry out this reaction will be described for the case in which the phenyllithium:benzophenone ratio is 2.

A solution of phenyllithium in dry ether was prepared from bromobenzene and lithium under nitrogen according to a standard procedure (3). The normality of the phenyllithium solution was determined by titration with standard hydrochloric acid solution. An ethereal solution of phenyllithium (0.018 mole, 50 ml) was added to a cooled solution of pyridine (18 g) in dry ether (20 ml) under dry, oxygen-free nitrogen at such a rate that the temperature of the mixture did not rise. A solution of benzophenone (1.6 g, 0.009 mole) in dry ether (12 ml) was now added dropwise and stirring continued at room temperature under nitrogen for another 12 hours. The reaction mixture was decomposed with dilute hydrochloric acid (which removed unchanged pyridine and the 2-phenylpyridine which was formed), the ether layer washed repeatedly with water and evaporated. The residue was chromatographed on a column of alumina. Elution with benzene – light petroleum (b.p. 40–60°) (1:1 v/v) and then with benzene gave benzhydrol (1.02 g), m.p. 63°, undepressed on admixture with an authentic sample (the infrared spectra of product and authentic sample were identical). Elution with ether:benzene (1:1 v/v) gave *4-diphenylhydroxymethyl-2-phenylpyridine* (0.300 g), m.p. 156–157° (after recrystallization from dilute ethanol). (Calc. for $C_{24}H_{19}ON$: C, 85.43; H, 5.68; N, 4.15; M.W., 337. Found: C, 85.60; H, 5.95; N, 4.32; M.W. (osmometer), 343.) The *picrate* was recrystallized from benzene and had m.p. 190–191°. (Calc. for $C_{24}H_{19}ON,C_6H_3O_7N_3$: C, 63.60; H, 3.91. Found: C, 63.43; H, 3.91.)

Reduction of Acetophenone

An ethereal solution (80 ml) of phenyllithium (0.049 mole) was added to a solution of pyridine (30 g) in dry ether as described above. A solution of acetophenone (2.95 g, 0.024 mole) in dry ether was then added and the mixture worked up as for benzophenone. Evaporation of the ether extract gave a mixture of products, which was distilled up to 150° at 20 mm to give a mixture of unreacted acetophenone and of α-phenylethanol (1.54 g). This was analyzed by gas chromatography on a 6-ft×1/4-in. column packed with silicone nitrile (17%) on Chromosorb W (80–100 mesh). The column temperature was 80° and the helium inlet pressure 40 p.s.i. Two peaks corresponding to acetophenone and α-phenylethanol were observed. The yield of α-phenylethanol was 14.5% based on the amount of acetophenone used (not taking into account the recovered acetophenone).

Reduction of Cyclohexanone

This was carried out as for the reduction of acetophenone using phenyllithium (0.030 mole) and cyclocyclohexanone (0.015 mole), and the gas-chromatographic analysis performed as above. The yield of cyclohexanol (not taking into account recovered cyclohexanone) was 6.5%.

Diphenyl-2-pyridylmethanol

2-Bromopyridine (3.16 g) in dry ether (20 ml) was added dropwise with stirring to a solution of *n*-butyllithium (0.03 mole) in dry ether (30 ml) under nitrogen at −62° over a period of 1 hour and the mixture stirred for another 30 minutes. A solution of benzophenone (3.64 g) in dry ether (15 ml) was added during 10 minutes while the temperature was kept at −62°. Stirring at this temperature was continued for a further hour after which the temperature was allowed to rise to room temperature. The mixture was treated with dilute hydrochloric acid, the ether layer removed, and the aqueous acid layer extracted with ether. The acid layer was neutralized with sodium bicarbonate, extracted with ether, the ether dried (Na_2SO_4) and evaporated to give *diphenyl-2-pyridylmethanol* (3.0 g), m.p. 105° after recrystallization from methanol. (Calc. for $C_{18}H_{15}ON$: C, 82.73; H, 5.79. Found: C, 82.57; H, 5.68.)

A number of attempts were made to phenylate this alcohol with phenyllithium in various molar proportions (including a large excess of phenyllithium). In all cases, unchanged carbinol was recovered. The failure of this reaction to occur might be due to the formation of an insoluble O-Li salt with the starting material.

2-Diphenylhydroxymethyl-6-phenylpyridine

A solution of 2-lithio-6-phenylpyridine was prepared as described above for 2-pyridyllithium using 2-bromo-6-phenylpyridine (1 g, 0.0043 mole) in dry ether (15 ml) and *n*-butyllithium (0.005 mole) in dry ether (30 ml). To this solution was added benzophenone (0.80 g) in dry ether (10 ml) and the reaction mixture worked up as above to give a crude product (2.58 g) which was purified by chromatography on a column of alumina (70 g). Elution with benzene – light petroleum (b.p. 40–60°) (1:4 v/v) gave *2-diphenylhydroxymethyl-6-phenylpyridine* (0.535 g), m.p. 135–136° after recrystallization from ethanol. (Calc. for $C_{24}H_{19}ON$: C, 85.43; H, 5.60. Found: C, 84.97; H, 5.68.) The infrared spectrum of this compound was different from that of by-product A.

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