Mechanism of the Grignard Addition Reaction. XV. The Reaction of Grignard Reagents with Benzylpyridinium Chloride

Torkil Holm

The Technical University of Denmark, Department of Organic Chemistry, Building 201, DK-2800 Lyngby, Denmark

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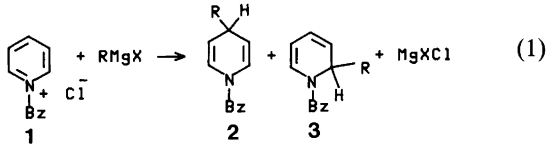
The reaction of Grignard reagents with benzylpyridinium chloride produces 2-alkyl-*N*-benzyl-1,2- and 4-alkyl-*N*-benzyl-1,4-dihydropyridines. The mechanism seems to be polar, concerted except for the t-butylmagnesium reagent. The adducts may reduce the starting material to the unreported, non-alkylated *N*-benzyl-1,4-dihydropyridine. If the Grignard-alkyl is secondary, crystalline 4-alkylidene-1,4-dihydropyridines may be produced. Thermal rearrangements of *N*-benzyl-1,4-dihydropyridines lead to migration of the benzyl group.

Grignard reagents do not react with pyridine under normal conditions. Pyridinium compounds resulting from oxidation or acylation of nitrogen are, however, highly reactive. *N*-Acyl[1] and *N*-oxide[2] derivatives of pyridine have been used as substrates for Grignard reagents since the activating group may be easily removed after the alkylation. *N*-Alkylpyridinium salts are known to be reactive toward Grignard reagents,[3] but no systematic work has been published concerning such reactions.

In the present work the reaction of *N*-benzylpyridinium chloride with Grignard reagents has been studied for a series of reagents with the objective of finding the product distributions and assessing the chemical properties of the reaction products.

Results and discussion

When a Grignard reagent was added to a suspension of benzylpyridinium chloride in THF, heat was evolved and the salt went into solution. After work-up the oily residue was investigated by NMR spectroscopy. The products were mainly 1-benzyl-2-alkyl-1,2-dihydropyridines and 1-benzyl-4-alkyl-1,4-dihydropyridines [eqn. (1)]. The overall yields were 50–70 %, and some polymeric material was usually found.



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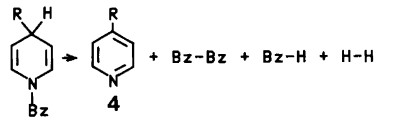
R = a, methyl; b, isopropyl; c, butyl; d, isobutyl; e, *tert*-butyl; f, benzyl; g, phenyl.

In Table 1 are given the relative yields of the 1,2- and the 1,4-adduct. It is seen that unhindered reagents such as methylmagnesium bromide and phenylmagnesium bromide yield 1,2-addition products, while a hindered reagent such as isopropylmagnesium bromide reacts mainly by 1,4-addition. Primary Grignard reagents (benzyl inclusive) yield both 1,2- and 1,4-addition. The ratio of 1,4:1,2 could be raised if catalytic amounts of a complex cuprous salt was added to the pyridinium salt before the addition of the Grignard reagent (Table 1).

The alkyl-1,4-dihydropyridines could be distilled under vacuum, but were sensitive to oxidation by air, while the 1,2-adducts were air-sensitive and tended to polymerise during attempted distillation.

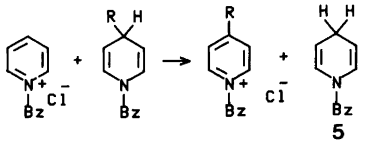
When 1-benzyl-4-*tert*-butyl-1,4-dihydropyridine was heated to 300 °C and exothermic reaction took place in which *tert*-butylpyridine was formed together with dibenzyl, toluene, and hydrogen(?) [eqn. (2)]. Through the



(2)

hydrochloride the 4-*tert*-butylpyridine could be isolated, albeit in low yield.

The 1,4-dihydropyridines are reducing agents. If less than the equivalent amount of *tert*-butyl Grignard reagent was used in the reaction and the reaction mixture was heated to 80 °C for a short period, the unused benzylpyridinium salt was reduced to the unknown 1-benzyl-1,4-dihydropyridine. This was the result of transfer of hydride ion from product to starting material in a reaction catalysed by the magnesium halide which is formed in the reaction [eqn. (3)]. Hydride-ion transfer from dihydropyridines to



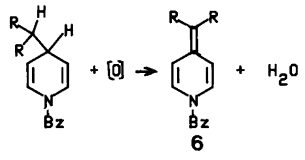
(3)

Table 1. Relative product distribution (%), resulting from the addition of Grignard reagents to benzylpyridinium chloride.

Grignard reagent	Uncatalysed reaction		CuI catalysis	
	1,2-Adduct	1,4-Adduct	1,2-Adduct	1,4-Adduct
CH_3MgBr	99	1	66	34
$(CH_3)_2CHMgBr$	5	95		
C_4H_9MgBr	60	40		
$(CH_3)_2CHCH_2MgBr$	67	33		
$(CH_3)_3CMgCl$	36	64	20	80
C_6H_5MgBr	91	9	65	35
$C_6H_5CH_2MgBr$	45	55	30	70

ketones is known to be catalysed by the ions of zinc and magnesium.[4]

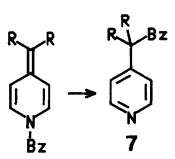
Certain 1,4-dihydropyridines underwent an interesting oxidation with oxygen. When isopropylmagnesium bromide or other secondary Grignard reagents were added to benzylpyridinium chloride and the reaction mixture, after evaporation of the solvent, was heated to 80 °C for 2 h in air, limited oxidation took place and after work-up 1-benzyl-4-isopropylidene-1,4-dihydropyridine could be isolated by crystallisation from hexane. This reaction seemed to be fairly general and was performed using isopropyl, *sec*-butyl, cyclopentyl, and cyclohexyl Grignard reagents [eqn. (4)].



6 (4)

During their preparation at 80 °C in air these alkylidenedihydropyridines resisted attack by oxygen because of complex formation with magnesium halide, but as the free compounds they were extremely labile. The fast reaction with atmospheric oxygen precluded the use of microanalysis, and the compounds were identified solely by means of NMR spectroscopy.

When the isopropylidenedihydropyridine was heated above 120 °C a rearrangement took place in which the benzyl group migrated from nitrogen to the benzylic carbon of the side chain with the formation of an aromatic pyridine ring [eqn. (5)]. Very few 4-alkylidene-1,4-dihydropyridines



7 (5)

have been reported in the literature.[5,6]

Reaction mechanism. Clues to the mechanism of reactions of Grignard reagents are usually found from the study of the product distribution and from reactivity measurements.[7-9] Although a complete account of the reaction products was not obtainable no definite 'radical type' products were identified in the present investigation, and no transient coloration was observed during the addition reactions.

The reactivity of the various Grignard reagents toward benzylpyridinium chloride was studied by competition experiments since regular kinetic measurements were not possible using the insoluble salt. NMR analysis of the product from the reaction of a small amount of the salt with a large excess of a mixture of two Grignard reagents clearly showed the following reactivity series for alkylmagnesium reagents: benzyl > isopropyl >> phenyl >> *tert*-butyl > ethyl > butyl > methyl.

This series bears little resemblance to the series obtained with typical 'homolysis type' substrates such as benzophenone, pyridazine, azobenzene, or di-*tert*-butyl peroxide, which react by homolytic mechanisms.[8] While the homolysis series: *tert*-butyl > isopropyl > benzyl > ethyl > methyl > phenyl is almost invariant since it is related to the increasing carbon–magnesium bond strength going from left to right, the reactivity series for polar reactions results from the interplay between the steric requirements of the substrates and the thermodynamic properties of the reagents. For the polar addition to an unconjugated carbonyl compound such as acetone the steric factor dominates and the series is: benzyl > phenyl > ethyl > methyl > butyl > isopropyl > *tert*-butyl. The 'acetone series' bears some resemblance to that obtained with the pyridine salt, and it is important to note that phenyl > butyl > *tert*-butyl. Phenyl has low steric requirements and allows very effective concerted reaction mechanisms. The *tert*-butyl reagent is extremely bulky and although highly unstable is always a poor nucleophile.

Considering the product distribution it seems possible that *tert*-butylmagnesium bromide reacts with pyridinium salt by homolysis. The reason why isopropylmagnesium bromide reacts to form almost exclusively the 1,4-adduct (Table 1), while methylmagnesium bromide yields the 1,2-adduct is that the larger bulk of isopropyl prevents the direct attack at the 2-position. That the even more bulky *tert*-butyl produces a relatively large ratio of 1,2:1,4 might be an indication of a homolytic mechanism being more

effective in this case. The ratio 1,2:1,4 in a homolytic mechanism is determined in a fast recombination step and the steric requirements of the radicals may be smaller than those of the ions.

Experimental

Grignard reagents were prepared from reagent-grade magnesium using commercially available alkyl halides and solvents. Benzylpyridinium chloride (**1**) was prepared in quantitative yield from an equimolar mixture of benzyl chloride and pyridine. The initial reaction was fast, but complete reaction required 3–4 weeks at room temperature. The solid product was pulverised in a dry atmosphere. M.p. of the pure product 131–132 °C. Alternatively, the salt may be formed in an overnight reaction at room temperature between 1 mol of benzyl chloride and 3 mol of pyridine. The crystalline mass is freed of excess pyridine by being heated at 100 °C for 3 h at 0.5 mmHg.

N-*Benzyl(alkyl)dihydropyridines* (**2**) and (**3**). *N*-Benzylpyridinium chloride (2.05 g, 10 mmol) was suspended in 20 ml of THF. 10 ml of 1 M Grignard reagent in ether were added over 2 min from a syringe, with cooling under tap water. The mixture was stirred magnetically for 10 min in the absence of air. With continued stirring 5 ml of 30 % sodium hydroxide solution were added, precipitating the magnesium salts and leaving a clear organic phase, which was concentrated under vacuum at 80 °C leaving the product as a dark oil, which was analysed by NMR spectroscopy. NMR spectra (250 MHz, $CDCl_3$) of the 1-benzyl-4-alkyl-1,4-dihydropyridines were essentially identical except for signals pertaining to the alkyl group with signals at δ 7.3 (m, 5 H, phenylic), δ 5.85 (app. d, 2 H, *J* 8.3 Hz, vinylic, α to N), δ 4.40 (m, 2 H, vinylic, β to N), δ 4.17 (s, 2 H, benzylic), δ ca. 3 (m, 1 H, allylic).

The above procedure when using *tert*-butylmagnesium chloride yielded 1.9 g (84 %) of an oil consisting of 64 % 1,4- and 36 % 1,2-addition product. distillation at 117–120 °C at 0.5 mmHg gave 1.1 g (48 %) of almost pure *N*-benzyl-*tert*-butyl-1,4-dihydropyridines and 0.8 g of tar. Yields and product distributions in Table 1 are based on the crude undistilled oils. The second column in Table 1 shows the product distributions obtained if 200 mg of $CuI–Bu_3P$ are added to the pyridinium salt before the addition of the Grignard reagent.

4-tert-*Butylpyridine* (**4**). 1 g of 1-benzyl-4-*tert*-butyl-1,4-dihydropyridine was heated to 325 °C. A sudden exothermic reaction caused the mixture to boil and reflux. After 3 min at 200 °C 0.5 g of a distillate b.p. 190–195 °C were collected which consisted of bibenzyl and 4-*tert*-butylpyridine. The mixture was extracted with dilute hydrochloric acid. From the aqueous phase 4-*tert*-butylpyridine was liberated with base. yield 0.25 g. When the crude 4-*tert*-butyl-1,4-dihydropyridine was heated without preceding distillation under vacuum the yield was 0.36 g (26 % overall).

N-*Benzyl-1,4-dihydropyridine* (**5**). To benzylpyridinium chloride (20.5 g, 0.1 M) suspended in 50 ml of THF were added with magnetic stirring and water-cooling, 75 mmol of *tert*-butylmagnesium chloride in ether (1.8 M). After 10 min the solvents were removed on a rotary evaporator at 45 °C. The remaining oil was placed in a flask at 80 °C for 2 h. The contents were cooled and triturated with 60 ml of ether and 40 ml of 30 % sodium hydroxide solution until all of the magnesium salts had been converted into the hydroxide. The ether was separated and evaporated. Fractional distillation yielded a fraction (3 g) b.p. 78 °C at 0.3 mmHg, which according to NMR spectroscopy contained 55 % **5** and 34 % **2a** b.p. 110 °C (0.3 mmHg). A small forerun was, according to NMR spectroscopy, >90 % **5**.

1-benzyl-4-isopropylidene-1,4-dihydropyridine (**6**). Addition of 12 ml of 1 M isopropylmagnesium bromide in ether to 2.05 g benzylpyridinium chloride was carried out as above. After the addition the solvents were removed under vacuum at 40 °C and the resulting clear oil was heated in an open, 100 ml conical flask at 80 °C for 16 h. After cooling, ether and 30 % sodium hydroxide were added and the magnesium salts were converted into a smear of magnesium hydroxide. The ether was evaporated to leave 1.3 g of an oil, which was dissolved in ether. Addition of pentane, cooling, and scratching yielded 0.6 g of material m.p. 58–62 °C. Recrystallisation gave m.p. 70–71 °C. M.p. for the analogous cyclohexylidene-, cyclopentylidene- and methylpropylidene-derivatives were 90–92, 70–73 and 35–37 °C, respectively.

4-(1,1-Dimethyl-2-phenylethyl)pyridine. When heated to 150 °C the *N*-benzyl-4-isopropylidene-1,4-dihydropyridine rearranged exothermally within 1 min to form the crude 4-alkylpyridine (**7**).

Kinetics. To benzylpyridinium chloride (0.5 g, 2.43 mM) suspended in 10 ml of THF was added, with stirring at room temperature, a mixture of 7 ml each of two 1 M ethereal solutions of Grignard reagents. Work-up was as above. The amounts of the various addition products were evaluated by NMR spectroscopy, and the predominant product was assumed to arise from the most reactive Grignard reagent. The following observations were made: *tert*-butyl > methyl, isopropyl >> *tert*-butyl, *tert*-butyl > butyl, benzyl > isopropyl.

NMR spectra. $CDCl_3$ at 250 MHz, chemical shift in ppm.

1-Benzyl-2-methyl-1,2-dihydropyridine (**3a**). δ 7.3 (m, 5 H), 6.05 (app. d, 1 H, *J* 7.2 Hz), 5.87 (dd, 1 H, *J* 7.2, 9.5 Hz), 4.95 (dd, 1 H, *J* 9.5, 5.5 Hz), 4.67 (ddd, *J* 5.5, 7.0, 1.5 Hz), 4.30 and 4.14 (AB system, *J* 15.5 Hz), 4.01 (br quintet, *J* 5.5 Hz), 1.08 (d, 3 H, *J* 6.3 Hz).

1-Benzyl-2-butyl-1,2-dihydropyridine (**3c**). δ 7.3 (m, 5 H), 6.09 (app. d, 1 H, *J* 7.0 Hz), 5.91 (dd, 1 H, *J* 9.6 Hz), 4.97

(dd, 1 H, *J* 9.4, 5.5 Hz), 4.65 (ddd, 1 H, *J* 5.5, 7.0, 1.5 Hz), 4.29 and 4.17 (AB system, *J* 15.5 Hz), 3.92 (m, 2 H), 1.33 (m, 6 H), 0.88 (m, 3 H).

1-Benzyl-2-isobutyl-1,2-dihydropyridine (**3d**). δ 7.3 (m, 5 H), 6.09 (app. d, 1 H, *J* 7.0 Hz), 5.91 (ddd, 1 H, *J* 9.5, 5.4, 0.9 Hz), 5.01 (ddd, 1 H, *J* 9.6, 5.6, 1.2 Hz), 4.71 (ddd, *J* 5.5, 7.1, 1.5 Hz), 4.27 and 4.18 (AB system, *J* 15.5 Hz), 3.88 (m, 2 H), 1.7 (m, 1 H), 0.90 (d, 3 H, *J* 6.5 Hz), 0.82 (d, 3 H, *J* 6.5 Hz).

*1-Benzyl-2-*tert*-butyl-1,2-dihydropyridine* (**3e**). δ 7.3 (m, 5 H), 6.16 (app. d, 1 H, *J* 6.7 Hz), 6.06 (dd, 1 H, *J* 5.5, 9.5 Hz), 4.94 (ddt, 1 H, *J* 5.7, 7.0, 5.5 Hz), 4.77 (ddd, 1 H, *J* 5.7, 7.0, 1.3 Hz), 4.39 and 4.25 (AB system, 2 H, *J* 16.0 Hz), 0.925 (s, 9 H).

1,2-Dibenzyl-1,2-dihydropyridine (**3f**). δ 7.3 (m, 10 H), 6.14 (app. d, 1 H, *J* 7.0 Hz), 5.98 (ddd, 1 H, *J* 9.3, 5.5, 0.9 Hz), 4.84 (ddd, 1 H, *J* 4.5, 5.8, 1.1 Hz), 4.16 (s, 2 H), 4.01 (d, *J* 13.0 Hz), 3.93 (d, *J* 13.0 Hz), 2.86 (dd, 1 H, *J* 6.5, 13.0 Hz), 2.72 (dd, 1 H, *J* 6.5, 13.0 Hz).

1-Benzyl-2-phenyl-1,2-dihydropyridine (**3g**). δ 7.3 (m, 10 H), 5.78 (m, 1 H), 5.53 (app. d, 1 H, *J* 10.0 Hz), 3.96 (br s, 1 H), 3.79 (d, 1 H, *J* 13.5 Hz), 3.12 (d, 1 H, *J* 13.5 Hz), 2.92 (m, 1 H), 2.37 and 2.30 (AB system, *J* 11.0 Hz), 2.03 (m, 1 H).

1-Benzyl-1,4-dihydropyridine (**5**) δ 7.3 (m, 5 H), 5.78 (m, 2 H), 4.37 (m, 2 H), 4.16 (s, 1 H), 2.88 (m, 2 H).

1-Benzyl-4-isopropyl-1,4-dihydropyridine (**2b**). δ 7.3 (m, 5 H), 5.89 (d, 2 H, *J* 8.0 Hz), 4.34 (m, 2 H), 4.16 (s, 2 H), 4.17 (s, 2 H), 2.95 (q, 1 H, *J* 4.0 Hz), 1.43 (m, 1 H), 0.88 (d, 6 H, *J* 7.0 Hz).

1-Benzyl-4-butyl-1,4-dihydropyridine (**2c**). δ 7.3 (m, 5 H), 5.83 (d, 2 H, *J* 8.3 Hz), 4.38 (m, 2 H), 4.17 (s, 2 H), 3.05 (m, 1 H), 1.32 (m, 6 H), 0.88 (m, 3 H).

1-Benzyl-4-isobutyl-1,4-dihydropyridine (**2d**). δ 7.3 (m, 5 H), 5.82 (d, 2 H, *J* 8.0 Hz), 4.40 (m, 2 H), 4.17 (s, 2 H), 3.07 (m, 1 H), 1.7 (m, 2 H), 1.25 (m, 1 H), 0.87 (d, 6 H, *J* 6.5 Hz).

*1-Benzyl-4-*tert*-butyl-1,4-dihydropyridine* (**2e**). δ 7.3 (m, 5 H), 5.93 (d, 2 H, *J* 8.5 Hz), 4.46 (m, 2 H), 4.19 (s, 2 H), 2.73 (t, 1 H, *J* 4.15 Hz), 0.83 (s, 9 H).

1-Benzyl-4-isopropylidene-1,4-dihydropyridine (**7**, R = CH_3). δ 7.38–7.15 (m, 5 H), 5.93 (d, 2 H, *J* 7.9 Hz), 5.54 (d, 2 H, *J* 7.9 Hz), 4.29 (s, 2 H), 1.58 (s, 6 H).

1-Benzyl-4-cyclopentylidene-1,4-dihydropyridine. δ 7.36–7.15 (m, 5 H), 5.92 (d, 2 H, *J* 7.9 Hz), 5.36 (d, 2 H, *J* 7.9 Hz), 4.26 (s, 2 H), 1.8–1.4 (m, 8 H).

1-Benzyl-4-(1-methylpropylidene)-1,4-dihydropyridine. δ 7.38–7.16 (m, 5 H), 5.92 (ddd, 2 H, *J* 9.8, 7.0, 2.0 Hz), 5.55 (ddd, 2 H, *J* 17.0, 7.9, 2.9 Hz), 4.28 (s, 2 H), 1.97 (q, 2 H, *J* 7.5 Hz), 1.56 (s, 3 H), 0.92 (t, 3 H, *J* 7.5 Hz).

1-Benzyl-4-cyclohexylidene-1,4-dihydropyridine. δ 7.37–7.15 (m, 5 H), 5.90 (d, 2 H, *J* 8.0 Hz), 5.58 (d, 2 H, *J* 8.0 Hz), 4.24 (s, 2 H), 2.1–1.1 (m, 10 H).

4-(1,1-Dimethyl-2-phenylethyl)pyridine. δ 8.50 (dd, 2 H, *J* 6.3, 1.6 Hz), 7.15 (m, 5 H), 6.80 (m, 2 H), 2.86 (s, 2 H), 1.32 (s, 6 H).

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