Oxidation of Alcohols *via* Alkoxymagnesium Halides by an NAD$^+$ Model Compound[1)]

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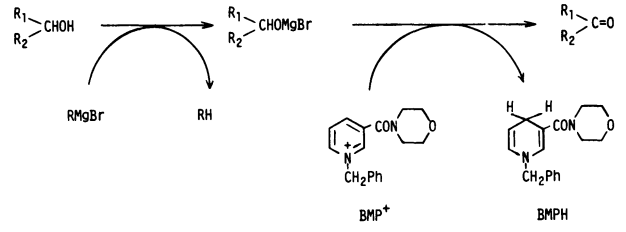
Synopsis. Alkoxymagnesium bromides prepared from phenylmagnesium bromide and alcohols are capable of reducing an NAD$^+$ model compound to the 1,4-dihydronicotinamide in good yields. The carbonyl products were detected in quantitative yields from diphenylmethanol and 1-phenylethanol but in low yields from benzyl alcohol and aliphatic alcohols. This is a new route to 1,4-dihydronicotinamides with alcohols although it remains uncertainty whether or not the route has relevance as a model process for NAD$^+$ oxidaiton of alcohols.

In alcohol dehydrogenases, the interconversion of aldehydes (or ketones) and alcohols occurs in conjunction with that of NADH and NAD$^+$ coenzymes. In contrast to a number of investigations on the NADH model reduction of carbonyl substrates, there are only a few examples for the NAD$^+$ model oxidation of alcoholic substrates.[2-5)] The contrast suggests the difficulty to mimick the NAD$^+$-dependent oxidations in model systems. Interestingly, it is well established that 5-deazaflavin and its analogs which have the isoelectronic structure to NAD$^+$ can oxidize alcohols,[6-8)] but the mechanistic difference between 5-deazaflavin and NAD$^+$ is not well understood. One important information to exploit NAD$^+$ model oxidation would be the fact that protic or acidic media are very favorable to reduction of carbonyls by NADH,[9,10)] whereas oxidation of alcohols by 5-deazaflavin proceeds favorably in basic media.[11)] The findings are quite understandable from a viewpoint of the principle of the microscopic reversibility. Meanwhile, some metal ions such as Mg^{2+} and Zn^{2+} play a crucial role not only in the dehydrogenase reduction but also in the NADH model reduction.[12)] The principle suggests, therefore, that alcohols would be oxidized by an NAD$^+$ model compound through the metal (Mg^{2+} or Zn^{2+}) alkoxide intermediates. We here report that alkoxymagnesium halides prepared from a Grignard reagent and alcohols are capable of reducing an NAD$^+$ model compound to the 1,4-dihydronicotinamide in good yields, although the yields of the carbonyl products are in some cases unstatisfactory.



We used 1-benzyl-3-morpholinocarbonylpyridinium bromie (BMP$^+$) as an NAD$^+$ model compound. BMP$^+$ was prepared by the reaction of 3-morpholinocarbonylpyridine[2)] and benzyl bromide in benzene at reflux temperature for 4 h; mp 117—120 °C, yield 80.8%. Found: C, 55.63; H, 5.33; N, 7.49%. Calcd for $C_{17}H_{19}N_2O_2Br$: C, 56.21; H, 5.27; N, 7.71%.

1-Benzyl-3-morpholinocarbonyl-1,4-dihydropyridine (BMPH) was prepared from BMP$^+$ and $Na_2S_2O_4$ according to the method of Kim and Chaykin[13)]; oil, one spot on TLC, yield 64%. NMR (Me_2SO-d_6): 4-CH_2, δ= 3.00, 2H; morpholine protons, 3.35 (4H) an 3.52 (4H); 5- and 6-H, 4.2—4.4, 2H; N-CH_2, 5.97, 2H; 2-H and benzene protons, 7.3—7.4, 6H. The mixture of BMPH and 1-benzyl-3-morpholinocarbonyl-1,6-dihydropyridine was prepared by the reduction of BMP$^+$ by $NaBH_4$ in methanol. The ratio of 1,4- *vs.* 1,6-isomer determined on the basis of NMR[14)] was 57/43.

A typical experimental procedure is as follows: phenylmagnesium bromide (3.5 mmol) was prepared in 10 ml of anhydrous tetrahydrofuran (THF). Alcohol (3.5 mmol) was added and the reaction mixture was stirred for 3 h at room temperature under a nitrogen stream. Then, BMP$^+$ (2.8 mmol) in a mixed solvent of 20 ml THF and 20 ml *N,N*-dimethylformamide was added. The progress of the reaction (25 °C) was monitored analyzing the aliquot withdrawn from the reaction mixture. The yield of the dihydronicotinamide was directly determined by HPLC analysis: Shimadzu LC-3, Lichroprep RP-18, acetonitrile: water=8:2 v/v. To determine the yields of the oxidized carbonyl products the sample was once mixed with aqueous solution (pH 4) and extracted with chloroform. The chloroform solution was analyzed on GLC. Both methods had been certified by making the calibration curves using the authentic samples.

In the HPLC analysis we could detect BMPH, but

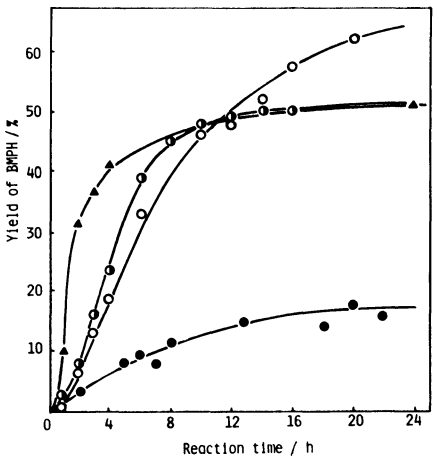


Fig. 1. Time-dependence of the yield of BMPH (1,4-isomer). ▲: Diphenylmethanol, ●: benzyl alcohol, ◑: 1-octanol, ○: cyclohexanol. The plot for 1-phenylethanol is essentially identical to that for diphenylmethanol.

Table 1. Product analysis for the reaction of BMP^+ and alkoxymagnesium bromides

Alcohol	Reaction time / h	Yield/%[a] BMPH	Yield/%[a] Carbonyl compound
Diphenylmethanol	24	51.2	100
1-Phenylethanol	24	52.0	100
Benzyl alcohol	5	8.8	0.2
	22	15.8	0.2
1-Octanol	4	24.1	0.9
	16	50.8	0.8
Cyclohexanol	8	40.3	trace ($\approx$0.1)
	20	61.9	trace ($\approx$0.1)

a) Yield based on BMP^+.

neither the 1,6-isomer nor the 4,4′-dimer[15] was detected. Speculating from the accuracy of the HPLC analysis, the yield of the 1,6-isomer (even if it was produced) would be less than 3%. The time-dependence of the BMPH yield is illustrated in Fig. 1 and the typical results are summarized in Table 1.

The oxidation of alcohols by 5-deazaflavin and its analogs affords the oxidized carbonyl products in good yields and in some cases the yields under aerobic conditions exceed 100% because of the autorecycling nature.[6–8] In the previous experiments of NAD^+ model oxidation, however, the analysis of the oxidized products was rather incomplete or unsuccessful: For example, the analysis of acetaldehyde was not carried out in the reaction with lithium ethoxide[3] and the oxidized product could not be detected in spite of the authors' best efforts in the reaction with glyceraldehyde.[4] We found that the reaction with diphenylmethanol and 1-phenyethanol affords the corresponding ketones in quantitative yields, whereas benzaldehyde expected for the oxidation of benzyl alcohol could be detected only in 0.2% yield. We first considered that the difference might be attributed to the steric difference between primary and secondary alcohols, because the unfavorable adduct formation between alkoxides and BMP^+ would be relatively suppressed in sterically crowded secondary alcohols. In fact, it was suggested in the oxidation by 5-deazaflavin analogs that to suppress the adduct formation leads to the efficient oxidation of alcohols.[8] This may be true for aromatic alcohols but is not the case for aliphatic alcohols, because the oxidation of cyclohexanol, as well as that of 1-octanol, gave only a trace amount of cyclohexanone. Two possibilities come to mind as a general scheme to explain the reaction. First, these reaction products may undergo further reaction in the strongly basic reaction solution. In relation to this, we observed that the yields increase up to 3—4% in the initial stage and then decrease. The second possibility is associated with the adduct formation proposed by Ohno *et al.*[4] In the HPLC analysis we sometimes detected a few unknown peaks (absorbing at around 350 nm) other than the 4,4′-dimer, but these peaks were not found for the oxidation of diphenylmethanol and 1-phenylethanol. Hence, the whole story of this reaction may be more complex than described by a single scheme. Further extensive studies are thus necessitated to answer this question.

It is known that 1,4-dihydronicotinamides result selectively from the oxidation of lithium ethoxide or glyceraldehyde.[3,4] Also in our reaction with alkoxymagnesium bromides, the 1,4-isomer of BMPH was produced selectively. As seen in Fig. 1, the reactions with diphenylmethanol and 1-phenylethanol ($t_{1/2}$ 1,4-2 h) was much faster than those with benzyl alcohol (6 h), 1-octanol (4 h), and cycloloxanol (7 h). It may be of some significance that the reactions yielding the corresponding carbonyl products are faster than others.

In the previous examples the yields of 1,4-dihydronicotinamides obtained from the 1:1 molar ratio reaction are not high (21—28%).[2,3] On the other hands, the yields of BMPH in the present system are much higher (50.8—61.9%) except benzyl alcohol. In particular, one can expect not only the high yield of BMPH but also the quantitative production of the ketones for the oxidation of diphenylmethanol and 1-phenethyl alcohol. We believe, therefore, that although it is still equivocal mechanistically whether or not the present reaction has direct relevance to NAD^+-dependent oxidations, the method is undoubtedly useful as a convenient route to 1,4-dihydronicotinamides with "alcohols."

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