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# REDUCTION WITH N-BENZYL-1,4 DIHYDRONICOTINAMIDE. A REINVESTIGATION.

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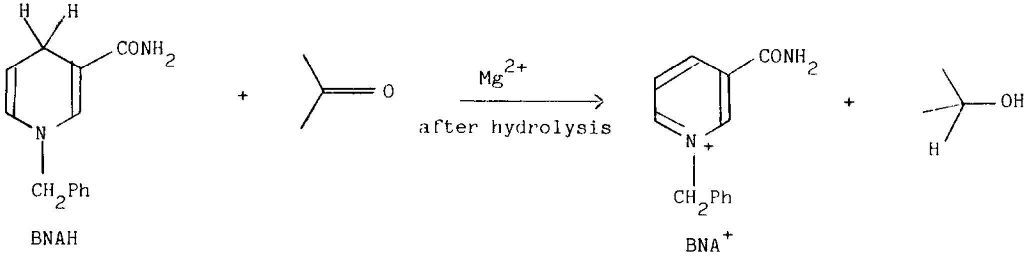
Summary: 3- or 4-Formylpyridines, cyclohexen -2 one and $\beta$-nitrostyrene can be reduced with BNAH: these substrates were previously reported to be inert or very unreactive toward this reagent.

1-Benzyl-1,4 dihydronicotinamide (BNAH) is of interest as a model of the biochemistry important reduced coenzyme nicotinamide-adenine-dinucleotide (NADH). It has been shown to reduce a very wide variety of organic substrates (1).



With NADH models immobilized on a Merrifield resin, we have obtained excellent yields in the reduction of numerous substrates (2). In some cases, compounds which were inert or not very reactive toward free NADH models were successfully reduced under these conditions. The most significant observations are reported in the third and fourth columns of table 1.

The important divergencies between some of the results prompted us to re-examine reactions of these substrates with BNAH in the conditions we applied to the grafted model (1 equivalent of each reagent: BNAH, substrate, magnesium perchlorate, dry acetonitrile as solvent, in a sealed tube flushed with nitrogen at 80°C). Results are given in the fifth column of table 1.

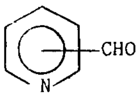
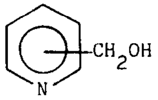
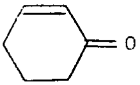
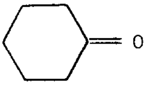
| 1<br>Substrate | 2<br>Product | 3<br>Previous yields | 4 | 5<br>Re-examined yields with BNAH |
|---|---|---|---|---|
| | | With BNAH | With the grafted model | |
|  2 1a |  2 | "good" (3) | 100 (2) | 100 |
| 3 1b | 3 | 0 (3) | 94 (2) | 70 |
| 4 1c | 4 | ε (3) | 100 (2) | 70 |
|  2 |  | 0 (4) | 80 (2) | 100 |
| $PhCH{=}CH{-}NO_2$ 3 | $PhCH_2CH_2NO_2$ | 22 (2) | 100 (2) | 100 |

Table I

Some previously reported non-reactive substrates are in fact reduced in good to quantitative yields. The most noteworthy results are those reported for compounds 1b and 2 .

Our success appears to be a consequence of the practice acquired with immobilised models: use of pure reagents in hyper-dry solvents.

A study of the reduction of p-nitrobenzaldehyde (pNBA) shows the influence of increasing amounts of water.

| $H_2O$ % in reactional medium | $H_2O$/pNBA mole ratio | Yields of alcohol with BNAH | with the grafted model |
|---|---|---|---|
| ≃ 0 | $< 10^{-2}$ | 100 | 100 |
| 0,1 | 0,5 | 84 | 40 |
| 0,2 | 1 | 76 | 27 |
| 0,4 | 2 | 66 | 18 |

Table II

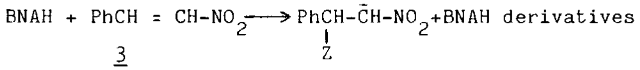
It is well known that in biological systems reactions of NADH occur in a hydrophobic microenvironment (6) In our experiments, we worked in similar conditions i.e. absence of water. So the results described in table 1 can be easily explained(NADH models are often water sensitive (7) ).

Concerning formyl-pyridines, the difference in behaviour of 1a was previously explained by an enhancement of reactivity due to the participation of the adjacent nitrogen in magnesium complexation (8). The results with 1b and 1c lead us to suppose that the role of this phenomenon is overestimated.

Again, more surprising is the result obtained in the difficult reaction of 3 with BNAH without the assistance of magnesium ions.

$$\underset{\underline{3}}{PhCH{=}CH\text{-}NO_2} \xrightarrow[\text{no } Mg^{2+}]{BNAH} \underset{1\ \%}{PhCH_2CH_2NO_2} + \underset{5\ \%}{\text{"trimer"}} + \text{recovered } \underline{3}$$

The trimeric compound was identified by IR, $^1H$ RMN, mass spectra and elementary analysis as 1,3,5-triphenylbenzene (9); we postulate the following mechanism to explain its formation:

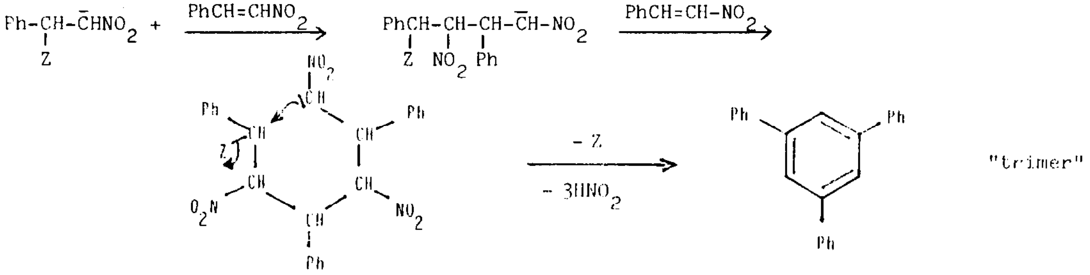


$$BNAH + \underset{\underline{3}}{PhCH = CH\text{-}NO_2} \longrightarrow \underset{\phantom{x}}{PhCH\text{-}\bar{C}H\text{-}NO_2} + BNAH \text{ derivatives}$$

with Z attached below the first CH.

intermediate

This intermediate (probably an anionic compound formed after hydrogen transfer) undergoes a double successive reaction with 3 leading to a cyclic product. Aromatisation occurs by the elimination of $HNO_2$.



BNAH is implicated in trimer formation since this product can not be detected without BNAH. Moreover, a very little amount of the starting BNAH is recovered, though its derivatives could not be identified.

The same reaction applied to (thienyl-2)-2 nitroethene gave a similar result: a small quantity of the trimeric compound 1,3,5-(thienyl-2)benzene was isolated (10).

## References and notes

1. Various unsaturated compounds such as C=O, C=S or C=N- are reduced by BNAH or related compounds. See for ex. D.M. STOUT and A.T. MEYERS, Chem. Rev., 82 , 223 (1982).

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c) R.A. HOOD and R.H. PRINCE, J. Chem. Soc. Chem. Commun, 163 (1979).

4.a) Cyclohexen-2 one has been reduced in moderate yields by N-propyl-1,4-dihydronicotinamide with the aid of a rhodium I catalyst.
K. NAKAMURA, M. FUJII, A. OHNO and S. OKA, Chemistry Letters, 925 (1984).

b) The same substrate gives cyclohexanone in good yields in reduction with Hantzsch ester on silica gel. An attempt to use BNAH was unsuccessful. K. NAKAMURA, M. FUJII, A. OHNO and S. OKA, Tetrahedron Letters, 25, 3983 (1984).

c) Cyclohexanone is obtained in good yield in the reduction of cyclohexen-2 one by 1,5-dihydro-3,7-dimethyl-10-p-tolyl-5 deazaflavin in formic acid, an autorecycling system which can be regarded as an NADH model. F. YONEDA, K. KURODA and K. TANAKA, J. Chem. Soc., Chem. Commun, 1194 (1984).

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b) β-nitrostyrene has been reduced by Hantzsch ester on silica gel (see 4b) and K. NAKAMURA, M. FUJII, S. OKA and A. OHNO, Chem. Lett., 523 (1985).

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7. D.J. NORRIS and R. STEWART, Can. J. Chem., 55 , 1687 (1977).

8.a) See ref 3b) and 3c) and also.

b) R.A. GASE, G. BOXHOORN and U.K. PANDIT, Tetrahedron Letters, 2889 (1976).

9. 1,3,5-Triphenylbenzene was isolated as by-product in the reaction of β-nitrostyrene with NaN$_3$ leading to 4-aryl-1,2,3 triazoles. N.S. ZEFIROV, Zh. Org. Khim. (Engl. translation), 12, 138 (1976)(C.A., 84, 104688).

10. 1,3,5-Tri(thienyl-2)benzene: m.p. 160°C. IR(KBr), 3095, 3060, 1592, 697 cm$^{-1}$. $^1$H NMR (CDCl$_3$) δ 7,68 (3H, s), 7.20-7.40 (2H, m), 7.06 (1H, q).

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