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RAPID AND EFFICIENT REDUCTION OF ALIPHATIC NITRO COMPOUNDS TO AMINES

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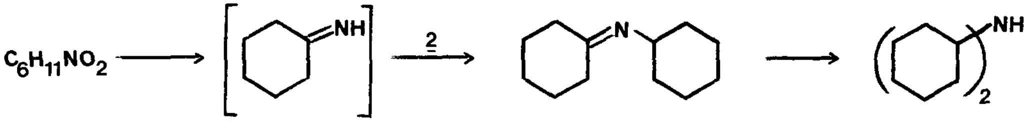
Summary: The combination of $NaBH_4$ with catalytic quantities of $NiCl_2$ smoothly reduces aliphatic nitro compounds to amines in methanol; Ni_2B formed in situ is the active catalyst.

Recent advances in the alkylation of nitroaliphatic compounds have led to several new carbon-carbon bond forming strategies in organic synthesis.[1] For this chemistry to gain more widespread use, improved methods must be developed to modify or remove nitro groups. While nitroarenes can be reduced to anilines by many different techniques,[2] far fewer reagents are known which successfully reduce aliphatic nitro groups to their corresponding amines. Nitroaliphatic compounds have traditionally been reduced by high-pressure hydrogenation,[3] lithium aluminum hydride[4] or aluminum amalgam.[5] Only in the last few years have alternative methods emerged,[6] including the use of transfer hydrogenation,[7] and titanium (II) reagents.[8,9]

Work in our laboratory on the mechanism of cobalt(II)-promoted $NaBH_4$ and $LiAlH_4$ reductions has shown that amorphous transition metal borides play an essential (and sometimes surprising) role as heterogeneous catalysts in the reduction of nitriles, alkenes and alkyl halides.[10] Although several diverse types of transition metal salt-hydride reagents are known to reduce nitroarenes,[11] we could find no published example of nitroalkane reductions by such systems. Nevertheless, it seemed worthwhile to ask whether one of the more highly reactive borides might catalyze the hydride reduction of aliphatic nitro groups. Here we report that the combination of nickel boride (Ni_2B) and $NaBH_4$ in CH_3OH smoothly reduces a variety of primary, secondary and tertiary nitroaliphatic compounds to amines within ca. 15 min at rt. The process is catalytic in boride, which is prepared in situ by the $NaBH_4$ reduction of $NiCl_2$ in CH_3OH.[12]

Preliminary experiments revealed that neither the boride alone nor boride under hydrogen could reduce nitrocyclohexane 1 to cyclohexylamine 2.[12,13] However mixtures of Ni_2B with $NaBH_4$ in CH_3OH rapidly reduced 1 to 2 in good yield, although the desired product was contaminated with variable amounts of dicyclohexylamine 4, depending on the quantity and preparation of catalyst. Compound 4 most likely arose from imine 3, generated *in situ* from 2 and transient amounts of cyclohexanone imine, a presumed reduction intermediate.



1 3 4

Dimer 3 seemed to be suppressed when freshly prepared, finely divided boride was used. Typically, a sonicated solution of $NiCl_2$ in CH_3OH was pre-reduced at rt using 1.0-1.5 equiv $NaBH_4$. After sonicating for 30 min, the first-formed clumps of Ni_2B were dispersed as a very finely divided precipitate. Best results (98:2 2:4) were obtained using 25 mole percent of catalyst prepared in this fashion, along with 3-3.5 equiv of $NaBH_4$ (see Table). Reductions of 1 using $NaBH_4$-$NiCl_2$ in 2-propanol/water or ethanol were considerably slower and gave several additional byproducts.[12] Methanolic $NaBH_4$-cobalt boride (Co_2B) failed to reduce nitroaliphatic compounds. The following preparation of 5-amino-5-methyl-2-hexanol is representative.

A 100 mL roundbottom flask containing $NiCl_2$-$6H_2O$ (.368g, 1.55 mmol) and CH_3OH (30 mL) was sonicated to effect complete solution, then solid $NaBH_4$ (.176g, 4.65 mmol) was added portionwise (**CAUTION: frothing**). After 30 min, 5-nitro-5-methyl-2-hexanol (.500g, 3.1 mmol) was added in CH_3OH (2 mL) followed by more solid $NaBH_4$ (.410g, 10.9 mmol) over a 5 min period. Five minutes later, when thin layer chromatography indicated all the nitro compound had disappeared, the reaction mixture was filtered through Celite and the boride rinsed with CH_3OH (10 mL). The combined filtrates were eluted onto a 20mm x 100mm Dowex 50(H+) column previously equilibrated with CH_3OH. After rinsing with more CH_3OH (150 mL), elution with 1.5 *M* NH_3 in CH_3OH (150 mL) afforded .309g (76%) of product aminoalcohol as a colorless, viscous oil.

In the case of less water-soluble amines, products could be isolated simply by evaporating the methanol filtrate and carrying out acid-base partition extraction.

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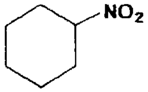
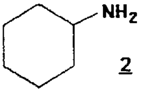
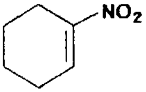
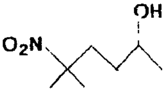
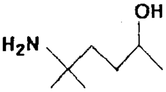
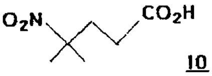
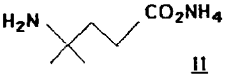
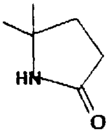
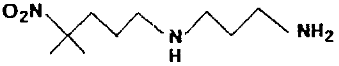
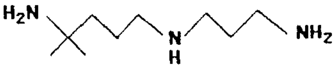
TABLE

$NaBH_4$ - Ni_2B Reductions of Nitroaliphatic Compounds

Reactant[a]		Product[b]		(Yield)[c]
	1		2	(68%)[d]
	5		2	(66%)[d]
$C_8H_{17}NO_2$	6	$C_8H_{17}NH_2$	7	(61%)
	8		9	(76%)
	10		11	(64%)
	12		13	(50%)[e]
	14		15	(69%)[f]

(a) All reductions were carried out according to the representative procedure on the previous page.
(b) Products were identified by comparison with authentic samples, where possible. Satisfactory IR, NMR and mass spectra were obtained for all new compounds.
(c) Yields reported are for isolated, pure compounds.
(d) Isolated as its HCl salt; lower yields are due to appreciable water solubility of this product.
(e) Product stirred 2d at rt in CH_3OH before workup.
(f) We thank Dr. S. Nagarajan for preparing and reducing 14.

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