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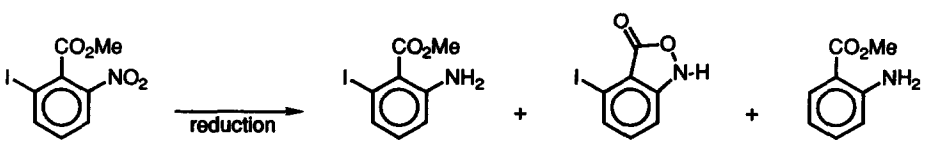
Nickel Boride Reduction of Aryl Nitro Compounds

Herbert H. Seltzman* and Bertold D. Berrang
Research Triangle Institute, Research Triangle Park, NC 27709

Summary: Nickel boride smoothly reduces aryl nitro compounds to the corresponding anilines in the presence of iodo and ortho carboalkoxy groups in contrast to the problematic reductions by other methods.

The reduction of aromatic nitro compounds has been conducted with a wide variety of reducing agents, some of which are incompatible with other substituents on the aromatic ring. Iodo groups are often cleaved by catalytic hydrogenation and metal-acid reductions. The presence of an ortho carboalkoxy group often yields, instead of anilines, 2,1-benzisoxazole-3-ones[1] (eg **3**) from an intermediate reduction stage of the nitro group. In an effort to prepare methyl 2-amino-6-iodobenzoate (**2**) by reduction of the corresponding nitro compound, as an intermediate to modified iodosobenzoic acids as enzyme mimics, the above complications were experienced. Reduction of **1** with $FeSO_4/NH_4OH$, Sn^o/HCl, $SnCl_2$ or sulfide-modified $Pt/C/H_2$ gave predominantly the benzisoxazolone **3** with lesser amounts of the deiodinated **4**. A minor amount of the desired **2** formed from reaction with Sn^o.



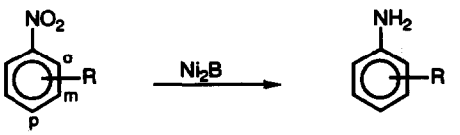
1 **2** **3** **4**

The reported[2] reduction of aryl nitro compounds with $NaBH_4$-$NiCl_2$ was applied to **1** and the corresponding acid. In neither reduction was **3** observed, but both suffered substantial deiodination affording exclusively or mostly anthranilic acid. Only the carboxylic acid reaction gave an iodoanthranilic acid. In this procedure a black precipitate was produced. When the precipitate was preformed from $Ni(OAc)_2 \cdot 4\ H_2O/NaBH_4$ and isolated for use in the subsequent reduction, quantitative conversion to **2** and its corresponding carboxylic acid was achieved. This reagent, a form of nickel boride[3], had been shown to reduce aryl nitro compounds but had not been used with the unusually sensitive moieties as above.[4] We extended the examination to the reduction of labile iodonitrobenzenes and methyl o-nitrobenzoate and obtained clean selective reduction suggesting the wider scope of the nickel boride reductions in these sensitive cases.

The nickel boride was readily prepared by treatment of $Ni(OAc)_2 \cdot 4\ H_2O$ (10.0 g, 40 mmol) in 150 mL of water with $NaBH_4$ (6.05 g, 160 mmol in 80 mL water) dropwise with stirring at 10-15 °C over 30 min. The black granular precipitate which separated was filtered, washed with water (3 x 25 mL), ethanol (50 mL) and dried in vacuo to give 3.0 g of the free flowing black granular solid. The exact identity of the easily handled nickel boride is not known but approximates Ni_2B.[3,5]

A typical reduction is demonstrated with methyl 2-iodo-6-nitrobenzoate (**1**) (0.5 g, 1.6 mmol) which was treated with Ni_2B (500 mg) in MeOH (28 mL) and 7 mL 1 M HCl and warmed to 60 °C for 30 min. Dilution with water and addition of NH_4OH until basic afforded a suspension which was extracted into ether and dried over Na_2SO_4. Removal of solvent in vacuo afforded methyl 2-amino-6-iodobenzoate as a yellow oil in 85% yield and 98% purity.[6] Acidification of the aqueous layer and extraction with ethyl acetate afforded 2-amino-6-iodobenzoic acid (14%). The iodonitrobenzenes were warmed for 1.5 h.

The Table includes the results for the clean formation of the unstable iodoanilines **9-12** which were single component products (gc) that were identified by their mass spectra and the comparison of their ^1H NMR spectra[7] to those of the known iodoanilines. Similarly, methyl nitrobenzoate was converted to methyl anthranilate in good yield and purity.



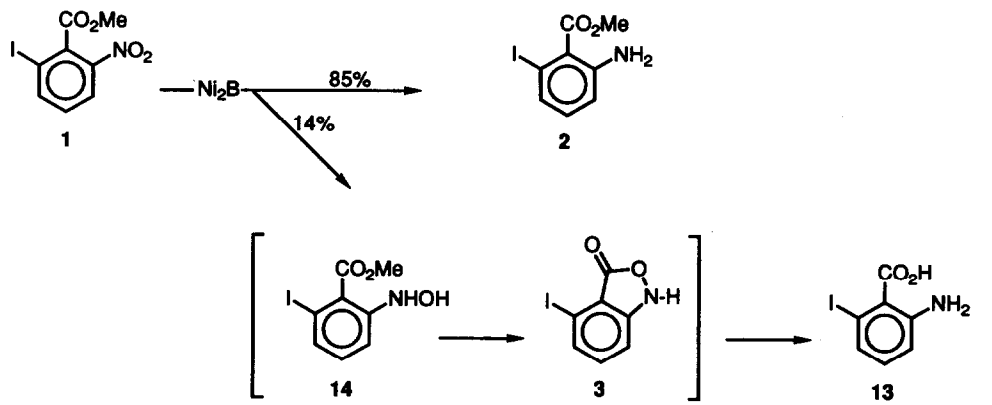
1, 5-8 **2, 9-12**

Compound	R	Product	Yield
1	o-CO_2Me, m-I	2	85%*
5	o-I	9	72%
6	m-I	10	83%
7	p-I	11	76%
8	o-CO_2Me	12	80%

*An additional 14% was obtained as the corresponding carboxylic acid

Since the non-nickel mediated reductions of **1** described above did not reduce the benzisoxazolone **3**, it was of interest to see if Ni_2B could effect this reduction. Indeed, similar treatment of **3**[8] as for **1** gave 2-amino-6-iodobenzoic acid (**13**)[9] in 90% yield. This compound has evaded preparation by diverse reduction methods[10] requiring circuitous routes for its synthesis.[11] Its facile preparation with Ni_2B further highlights the important selectivity and scope of Ni_2B reductions.

A modest amount of anthranilic acids were obtained as a by product from the reduction of the nitro esters. The acid can be accounted for by a partial reaction pathway that proceeds via formation and reduction of an intermediate benzisoxazolone. This pathway is supported by the reported[12] rapid intramolecular cyclization of aryl hydroxylamines (eg. **14**), derived from intermediate reduction of the nitro group, with o-carboalkoxy groups to give the corresponding benzisoxazolone, and the observed facile reduction of the latter to the anthranilic acid with Ni_2B.



The easy preparation of nickel boride and the facile high yield reduction of nitroaromatics containing the often incompatible o-carboalkoxy and/or iodo moieties suggest this reagent as a method of choice for sensitive reductions of aryl nitro compounds.

Acknowledgment

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References and Notes

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2. Nose, A.; Kudo, T. *Chem. Pharm. Bull.*, **1981**, *29*, 1159-1161.
3. Brown, C. A. *J. Org. Chem.*, **1970**, *35*, 1900-1904.
4. Nose, A.; Kudo, T. *Chem. Pharm. Bull.*, **1989**, *37*, 816-818.
5. Stringent drying (0.01 mmHg/P_2O_5) is to be avoided as it yields a pyrophoric material.
6. Compound **2**: TLC (SiO_2; 10% EtOAc in hexane; UV) R_f 0.28. GC (2% OV-17, 200 °C) R_t 3.98 min (> 98% purity). ^1H NMR 250 MHz ($CDCl_3$) δ 7.22 (dd, 1 H, J = 7.5 H, 2.5 Hz, 3-H), 6.80 (t, 1 H, J = 7.5 Hz, 4-H), 6.62 (dd, 1 H, J = 7.5 Hz, 2.5 Hz, 5-H), 4.7 (bs, 2 H, -NH_2, exchangeable with D_2O), 3.9 (s, 3 H, -COOMe).
7. Pouchert, C. J., *The Aldrich Library of NMR Spectra*, Ed. II, Aldrich Chemical Compnay, Inc., Milwaukee, WI, **1983**, *1*, 996-1012.
8. Compound **3**: ^1H NMR 250 mHz (DMSO d_6/D_2O) δ 11.91 (in DMSO d_6, bs, 1 H, NH, D_2O exchangeable), 7.72 (dd, 1 H, J = 7.3, 0.75 Hz, 5-H), 7.43 (dd, 1 H, J = 8.2, 7.3 Hz, 4-H), 7.33 (dd, 1 H, J = 8.2, 0.75 Hz, 3-H); MS (EI) m/e 261 (M^+, base), m.p. 175-177 °C.
9. Compound **13**: ^1H NMR 500 mHz (DMSO d_6/D_2O) δ 8.2 (in DMSO d_6, bs, 1 H, acidic H, D_2O exchangeable), 7.03 (dd, 1 H, J = 7.6, 1.1 Hz, 5-H), 6.77 (dd, 1 H, J = 8.2, 7.6 Hz, 4-H), 6.69 (dd, 1 H, J = 8.2, 1.1 Hz, 3-H); MS (EI) m/e 263 (M^+), 245 (M-H_2O), 218 (M-CO_2H), 127 (I); m.p. 145-6 °C (lit.[10] 147-8 °C).
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