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REDUCTION OF AROYL AZIDES WITH SODIUM BOROHYDRIDE / NICKEL (II) CHLORIDE

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ABSTRACT: Aroyl azides (cf. 1) generally are reduced to the corresponding amides 2 in very high yield and under mild conditions using the sodium borohydride / nickel (II) chloride system.

Acyl azides are important synthetic intermediates in organic chemistry.¹ While many acyl azides derived from alkyl carboxylic acids are unstable and decompose at room temperature, aroyl azides are stable compounds which can be handled safely. We have recently reported that aroyl azides are reduced predominantly to the corresponding benzyl alcohols with sodium borohydride in methanol.² In continuation, we now disclose that aroyl azides (*cf.* 1) form exclusively³ the corresponding benzamides (*cf.* 2) upon treatment with the sodium borohydride / nickel (II) chloride system (scheme). The latter has been employed previously for the reduction of alkyl azides to amines.⁴

Thus, treatment of benzoyl azide (1a) with excess sodium borohydride in dry methanol at 0°C in the presence of nickel (II) chloride \bullet 6H₂O resulted in exclusive formation of benzamide (2b) [100% yield] within five minutes. The results of

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Scheme

$$4-X-C_6H_4CON_3 \qquad \xrightarrow{\text{NaBH}_4 / \text{NiCl}_2 \cdot 6H_2O}_{\text{MeOH, 0-10°C, 5 min}} \qquad 4-X-C_6H_4CONH_2$$

1 & 2	Х	Yield [%] ^{a,b}	1 & 2	x	Yield [%] ^{a,b}
a	Н	100	d	NO ₂	20 ^c
b	Cl	95	e	CH ₃	96
c	Br	80	f	СН ₃ О	98

Table. Reduction of Aroyl Azides (1) with NaBH₄ / NiCl₂•6H₂O

^a Reaction was conducted at 0-10°C and monitored by TLC for absence of azide ^bYields are of isolated and purified products

^c 6% of 4-aminobenzamide (2, X=NH₂) also was isolated

similar reductions of several other aroyl azides with electron-withdrawing groups (4-Cl [1b], 4-Br [1c], 4-NO₂ [1d]) or electron-donating groups (4-Me [1e], 4-MeO [1f]) are gathered in the table. The results indicate that substitution of groups with +I or -I effects in the *para* position of the aryl ring does not have much effect upon the rate of reduction. This result is in contrast to our earlier observations with the sodium borohydride reduction of aroyl azides to benzyl alcohols.² Therein, we found that while electron-donating groups (*e.g.* 4-Me and 4-MeO) retarded the rate of reaction, electron-withdrawing groups (*e.g.* 4-NO₂ and 4-Cl) enhanced it, supporting a mechanism wherein attack of hydride ion upon the electron-deficient carbonyl carbon of the acyl azide was the rate limiting step. Reduction with sodium borohydride / nickel (II) chloride is more like catalytic hydrogenation, possibly involving radical intermediates.⁵ Thus, in the present case it was not surprising to find little effect upon the course or speed of the reaction upon changing substituents.

The reaction of 4-nitrobenzoyl azide under the present conditions was of interest since the substrate has two reducible groups, *viz.* -CON₃ and -NO₂. Reduction of the nitro group to the corresponding amine using sodium borohydride / nickel (II) chloride is known⁶ and, indeed, on treatment of 1d with this system a mixture of 4-nitrobenzamide 2d (20%) and 4-aminobenzamide 2 (X=NH₂) [6%] was obtained.

In an attempt to effect as complete reduction as possible, the nitroazide 1d was subjected to more vigorous conditions involving the use of excess sodium borohydride (pellets), nickel (II) chloride and ultrasonication for two hours. The sole product (72%) proved to be methyl 4-aminobenzoate (4-NH₂C₆H₄CO₂Me), presumably obtained by ultrasonically stimulated azide replacement by methanol and subsequent nitro group reduction. Support for this conjecture came when the reaction was repeated using less sodium borohydride. Work-up afforded methyl 4-nitrobenzoate (4-NO₂C₆H₄CO₂Me) in 52.5% yield. It is curious that under strongly reductive conditions substitution precedes reduction.

Extension of the methodology to the use of sodium borohydride / cobalt (II) chloride hexahydrate was examined briefly. Thus, using this latter system, 4-chlorobenzoyl azide (1b) was reduced quantitatively to 4-chlorobenzamide (2b) and further studies of this approach are underway.

In conclusion, the present method offers a convenient, mild, high yield route for the reduction of many aroyl azides to the corresponding amides, complementary to the sodium borohydride reduction of aroyl azides to benzyl alcohols.

EXPERIMENTAL

General Methods: Aroyl azides were prepared from the corresponding redistilled aroyl chlorides and sodium azide in acetone. No further purification was carried out before reduction. Benzamide products were identified by m.p., co-TLC and comparison of IR and NMR spectra with those of authentic samples.

General Procedure for Reduction of Aroyl Azides: Reduction of benzoyl azide (1a) is representative of the procedures employed. A mixture of benzoyl azide (1.47g, 10mmol) and nickel (II) chloride hexahydrate (4.74g, 20mmol) in methanol (100mL) was cooled to 0-10°C. With stirring, sodium borohydride (0.74g, 20mmol)

was added in one portion. Reaction progress was monitored by TLC using a hexane / ethyl acetate mixture (9:1) as eluant and complete conversion usually occurred within 5-10 minutes. The mixture was quenched by the addition of saturated brine (20mL) and extracted with dichloromethane (5 x 20mL). The combined organic layers were washed with brine (10mL), dried (Na₂SO₄) and evaporated *in vacuo* to yield benzamide, 1.23g (100%), identical (m.p., IR, TLC) to an authentic sample.

Reduction of 4-Nitrobenzoyl azide (1d) with NaBH₄ / NiCl₂.

i) without ultrasonication

Using 4-nitrobenzoyl azide (1d) in the general procedure gave an impure product which was subjected to column chromatography on silica gel. Gradation elution starting with dichloromethane / acetone (4:1) gave 4-nitrobenzamide (2d), 0.33g (20%), identical (m.p., IR, TLC) to an authentic sample, followed by 4-aminobenzamide 2 (X=NH₂), 0.08g (6%), identical (m.p., IR, TLC) to an authentic sample. The low yield overall may be due to the poor solubility of the products in the extraction solvent but no attempt was made to optimize this procedure.

ii) with ultrasonication

a) with limited sodium borohydride

To a solution of nickel chloride hexahydrate (0.50g, 2.15 mmol) in methanol (50mL) was added sodium borohydride (0.43g, 11.47mmol; pellet) under ultrasonication. After a few minutes, 4-nitrobenzoyl azide (0.20g, 1.04mmol) was added. After 1.5h the mixture was filtered through filter aid and evaporated to yield a light yellow solid which after recrystallization from ethanol gave 0.099g (52.5%) identical (m.p., IR, mass) to an authentic sample of methyl 4-nitrobenzoate.

b) with excess sodium borohydride

To a solution of nickel chloride hexahydrate (0.50g, 2.15 mmol) in methanol (50mL) was added sodium borohydride (0.42g, 11.2mmol; pellet) under ultrasonication. After a few minutes, 4-nitrobenzoyl azide (0.20g, 1.04mmol) was

added. Every 0.5h for 2h a further half pellet of sodium borohydride (approx. 0.8g in total) was added whereupon the mixture was filtered through filter aid and evaporated to yield a tan solid which after recrystallization from aqueous methanol gave 0.12g (72%) identical (m.p., IR, mass) to an authentic sample of methyl 4-aminobenzoate.

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