# The hydrogenolysis of N-benzyl groups with magnesium and ammonium formate

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The selective deprotection of several *N*-Bn amino derivatives to the corresponding amines and the removal of *S*-Bn and *O*-Bn groups from the protected amino acids with ammonium formate and magnesium is reported.

**Keywords:** catalytic transfer hydrogenation, ammonium formate, magnesium, deprotection

Benzyl (Bn) groups are very popular for protecting amines, alcohols and thiols.[1,2] The facile removal of protecting groups from labile or reactive organic functionalities is an important objective. Although a number of methods have been reported for debenzylation, catalytic transfer hydrogenolysis,[3,4] which involves a catalyst and hydrogen donor is one of the most commonly used methods. The application of Pd/C with ammonium formate for the rapid debenzylation of *N*-Bn amino derivatives[3,5] has been reported. Although, catalytic transfer hydrogenation is a more effective deprotection procedure than catalytic hydrogenation, it suffers from the disadvantage that the reaction must be carried out for relatively long times at reflux temperature with potential damage to other functional groups[6] particularly those susceptible to hydrogenolysis. The major disadvantage of this method is the use of palladium as catalyst, which is highly expensive and its pyrophoric nature makes it to difficult to handle.

The use of low-cost metals such as magnesium,[7] zinc[8] and lead[9] as catalysts for transfer reduction reactions has been reported from our laboratory. The utility of magnesium as a low-cost metal for the selective hydrogenolysis of some commonly used protecting groups in peptide synthesis has also been reported.[10] However, there are no reports on the use of this low-cost metal as a catalyst for the transfer hydrogenolysis of *N*-Bn derivatives. In this context we now report the conventional hydrogenolysis of *N*-Bn derivatives using magnesium and ammonium formate in methanol followed by the successful deprotection of *S*-Bn and *O*-Bn derivatives. The deprotection proceeds selectively and smoothly but requires longer reaction time to give moderate to good yields. In view of reports of microwave-induced organic reaction enhancement (MORE) chemical techniques[11] enhancing reaction rate and yield we have also tested the feasibility of carrying out debenzylation under microwave irradiation (MWI).

Following a recent report on the microwave-assisted deprotection of *N*-Cbz and *N*-Bn derivatives,[12] we now report a rapid, efficient and simple microwave-assisted deprotection of protected *N*-Bn and *O*-Bn derivatives to give the corresponding amines and alcohols respectively, using magnesium and ammonium formate in ethylene glycol. We prefer to conduct the deprotection in an open vessel in an inexpensive unmodified domestic microwave oven, which produces 2450 MHz radiation controlled by an "on–off" cycle. To regulate the microwave energy input into the small-scale reaction mixtures we used a "heat sink" namely, a beaker of water placed next to the reaction vessel inside the oven. This method gives the desired debenzylated products in good to excellent yields (85–95%). The deprotection can be accomplished within two to three minutes. The results are summarised in Table 1.

The progress of the hydrogenolysis was followed by TLC on silica gel plates and by change in the IR spectrum. In the IR spectrum the deprotection of *S*-Bn derivatives was accompanied by the appearance of a weak absorption band at 2600–2550cm$^{-1}$ which confirms the presence of a free –SH group.

**Table 1** Catalytic transfer hydrogenolysis of *S*-Bn, *O*-Bn and *N*-Bn derivatives using magnesium and ammonium formate

| Substrate | Product | Reaction time | | | | Yield/%[a] M.p./°C | | Specific rotation $[\alpha]_D^{25}$ | |
|---|---|---|---|---|---|---|---|---|---|
| | | C/ min | MWI/ min | C | MWI | Found | Reported | Found | Reported[13] |
| Boc-Cysteine(Bn) | Boc-Cysteine | 90 | – | 90 | – | 75–78 | 76–78[13] | +8.0 ° (c1, $C_2H_5OH$) | +8.1 ° (c1, $C_2H_5OH$) |
| Boc-Cysteine(4-Me-Bn) | Boc-Cysteine | 120 | – | 90 | – | 75–78 | 76–78[13] | +8.0 ° (c1, $C_2H_5OH$) | +8.1 ° (c1, $C_2H_5OH$) |
| Boc-Thr (OBn) | Boc-Thr | 180 | 3.0 | 80 | 95 | 152–154 | 154–155[13] | +11.3° (c 1, $CH_3OH$) | +11.37° (c 0.99, $CH_3OH$) |
| Boc-Ser (OBn) | Boc-Ser | 180 | 2.5 | 82 | 95 | 141–142 | 140–142[13] | +13.2° (c 3, $CH_3OH$) | +13.3° (c 3.06, $CH_3OH$) |
| Boc-Tyr (OBn) | Boc-Tyr | 180 | 3.0 | 79 | 92 | 135–136 | 136–138[13] | +3.6° (c 2, $CH_3OH$) | +3.9° (c 2.04, AcOH) |
| $C_6H_5NHBn$ | $C_6H_5NH_2$[b] | 90 | 1.5 | 75 | 90 | 182–184 | 184–186[15] | – | – |
| *o*-$ClC_6H_4NHBn$ | *o*-$ClC_6H_4NH_2$[c] | 100 | 2.0 | 80 | 92 | 205–206 | 208[15] | – | – |
| *p*-$ClC_6H_4NHBn$ | *p*-$ClC_6H_4NH_2$ | 120 | 2.0 | 80 | 93 | 70–71 | 72[15] | – | – |
| *p*-$CH_3OC_6H_4NHBn$ | *p*-$CH_3OC_6H_4NH_2$ | 120 | 2.0 | 80 | 89 | 56–58 | 57[15] | – | – |
| *o*-$CH_3OC_6H_4NHBn$ | *o*-$CH_3OC_6H_4NH_2$ | 150 | 3.0 | 75 | 92 | 58–60 | 60[14] | – | – |
| *p*-$H_3CC_6H_4NHBn$ | *p*-$H_3CC_6H_4NH_2$ | 120 | 3.0 | 75 | 95 | 46 | 45[14] | – | – |
| *m*-$HOOCC_6H_4NHBn$ | *m*-$HOOCC_6H_4NH_2$ | 150 | 2.5 | 75 | 80 | 173–174 | 174[14] | – | – |
| *p*-$HOC_6H_4NHBn$ | *p*-$HOC_6H_4NH_2$ | 120 | 3.0 | 80 | 90 | 186–188 | 186[15] | – | – |
| α-$C_{10}H_8NHBn$ | α-$C_{10}H_8NH_2$ | 80 | 2.5 | 85 | 92 | 49-50 | 50[15] | – | – |
| β-$C_{10}H_8NHBn$ | β-$C_{10}H_8NH_2$ | 90 | 3.0 | 78 | 90 | 110–112 | 111–113[15] | – | – |
| *4*-$C_5H_4NNHBn$ | *4*-$C_5H_4NNH_2$ | 100 | 1.5 | 80 | 95 | 157–159 | 158–160[14] | – | – |
| *p*-$CH_3COOC_6H_4NHBn$ | *p*-$CH_3COOC_6H_4NH_2$[d] | 90 | 2.0 | 80 | 93 | 148–151 | 150[15] | – | – |
| o-$BrC_6H_4NHBn$ | o-$BrC_6H_4NH_2$ | 90 | 2.5 | 80 | 85 | 115–118 | 116[15] | – | – |

Bn, $CH_2C_6H_5$; C, conventional method; MWI, microwave irradiation method; [a]yields of isolated pure products; [b]boiling point; [c]isolated as benzoyl derivative; [d]isolated as acetyl derivative.

$^1$H NMR spectra were obtained on an AMX-400 MHz spectrometer in $CDCl_3$ as the solvent using TMS as the internal standard. All of the products are known and the isolated products gave IR and $^1$H NMR spectra in agreement with their structures.

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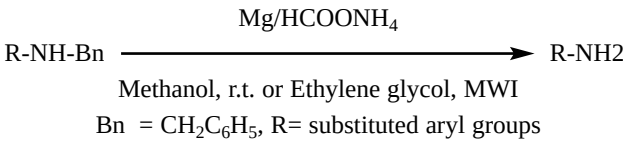


**Scheme 1**

The deprotection of *O*-Bn derivatives was confirmed by the appearance of a broad absorption band at 3600cm$^{-1}$ due to the free –OH group. The disappearance of a single strong absorption band between 3500–3200cm$^{-1}$, due to secondary –NH stretching, and the appearance of two strong symmetrical and unsymmetrical stretching absorption bands between 3500 and 3300 cm$^{-1}$ of free –$NH_2$ in the IR spectra clearly shows the successful hydrogenolysis of *N*-Bn amino derivatives. All the products were characterised by comparison of their TLC, melting points, IR spectra, $^1$H NMR spectra and specific rotation wherever necessary with authentic samples. Studies were also carried out to determine the optimum conditions for deprotection. These included the excess of donor required and the catalyst, solvent, concentration and reaction conditions. An excess of 2–4 equivalents of ammonium formate (per protecting group) proved to be ideal. We observed the optimal ratio of catalyst to substrate to be 1:5 moles for each protecting group to be removed. Methanol was the preferred solvent for the conventional method although it is better to use ethylene glycol as the solvent in the microwave-assisted deprotection, since other low boiling solvents were hazardardous during operation. As there is no modification in the domestic microwave oven for inert reaction conditions the deprotection of *S*-Bn derivatives of protected cysteine was not carried in microwave oven.

In summary we report a new catalytic transfer hydrogenolysis method using simple equipment for the deprotection of *N*-Bn, *O*-Bn and *S*-Bn derivatives using the low-cost metal, magnesium with ammonium formate. During this process many other reducible or hydrogenolysable substituents such as halogens, methoxy, phenol, ester, acid, ethene and Boc groups were unaffected. The yields of all products obtained were virtually quantitative and the products were analytically pure. Our method offers an economical and environmentally benign alternative to available procedures.

## Experimental

*(a) Conventional deprotection. general procedure:* A suspension of substrate (10 mmol), ammonium formate (20 mmol) and magnesium powder (2 mmol; particle size about 0.06–0.3 mm) in methanol (15 ml) was stirred at room temperature, under nitrogen. After completion of the reaction as monitored by TLC, the reaction mixture was filtered through a celite pad, washed with methanol (15 ml) and then the combined filtrate and washings were evaporated under vacuum. The residue was taken into chloroform or ether (30 ml), washed twice with saturated brine solution (30 ml) and finally with water (30 ml). The organic layer was dried over anhydrous sodium sulfate and evaporation of the organic layer followed by purification either by preparative TLC or by column chromatography provided the debenzylated product.

*(b) Microwave-assisted deprotection. general procedure:* A suspension of substrate (10 mmol), ammonium formate (20 mmol) and magnesium powder (2 mmol) in ethylene glycol (15 ml) in an Erlenmeyer flask was exposed to microwave irradiation at 160 power. A "heat sink" was maintained to control the microwave energy input in to the small-scale reaction mixture. After the reaction the reaction mixture was cooled and then filtered. The filtrate was diluted with water and extracted with ether or ethyl acetate (30 ml) and the organic layer was washed twice with saturated brine solution (30 ml) and finally with water (30 ml). The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated and the product purified either by preparative TLC or by column chromatography provided the debenzylated product.

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