Indium as a Reducing Agent: Deprotection of 4-Nitrobenzyl Ethers and Esters

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Abstract: Indium in aqueous ethanolic ammonium chloride is an effective method for the deprotection of 4-nitrobenzyl ethers and esters.

Key words: indium, nitro group reduction, deprotection

Indium metal has found a few uses in organic chemistry of late, most notably in the generation of synthetically useful allylindium species.^{1,2} However, the first ionisation potential of indium (5.8 eV),¹ which is lower than zinc (9.4 eV) or tin (7.3 eV) and close to that of alkali metals such as sodium (5.1 eV), suggests that the metal ought to be a potent reducing agent. In this context we have recently reported that indium is a useful reagent for the reduction of aromatic nitro groups,³ and for the reduction of the heterocyclic ring in quinolines, isoquinolines, and quinoxalines.⁴ We now report the use of indium metal in the deprotection of 4-nitrobenzyl ethers and esters.

The 4-nitrobenzyl protecting group has seen use in the protection of alcohols, thiols, amines (as the 4-nitrobenzyl carbamates), and carboxylic acids.^{5,6} For example, 4-nitrobenzyl esters are much more stable to acidic hydrolysis than other benzyl esters, and are recommended for glutamic acid and aspartic acid side chain protection in solid-phase peptide synthesis. Such protecting groups have also seen extensive use in the β -lactam field. Methods of deprotection include: Na_2S or $Na_2S_2O_4$ reduction, catalytic hydrogenolysis, TBAF, or oxidative cleavage with alkaline hydrogen peroxide. Electrochemical methods have also been used, especially for the unmasking of alcohols, either direct electrolytic reduction, or oxidative electrolysis following initial chemical reduction of the nitro group. Despite the undoubted usefulness of the 4-nitrobenzyl protecting group, many of the methods of deprotection have drawbacks in that they are not compatible with the presence of other functionalities or protecting groups. Therefore we investigated the use of indium metal as a mild method for nitro group reduction with concomitant cleavage of the benzylic C-O bond.

A range of alcohols, phenols and carboxylic acids were protected as their 4-nitrobenzyl ethers or esters using standard methodology. On treatment with indium metal, the nitro group is reduced, and the benzylic C-O bond is cleaved to liberate the deprotected compound and form 4toluidine as the by-product. The method is simple to effect: the substrate is simply heated in the presence of indium and ammonium chloride in aqueous ethanol. Work-up involves filtration, and acidification, before extraction into organic solvent.⁷ The acidification is usually to low pH, but neutralisation of the aqueous layer is sufficient for basic substrates or acid sensitive materials. The recovered substance requires little or no further purification, the 4toluidine by-product being washed out into the aqueous layer. The results are shown in Table 1.

 Table 1
 Deprotection of 4-nitrobenzyl ethers and esters

	R O In NH ₄ Cl, aq. EtOH	ROH
1	R	Yield / %
a	PhCH ₂ CH ₂	87
b	PhOCH ₂ CH ₂	98
c	PhCH ₂ OCH ₂ CH ₂	100
d	(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl	93
e	$4-MeO-C_6H_4$	81
f	$4-Ac-C_6H_4$	97
g	$3-OHC-C_6H_4$	61
h	2,3,5-Me ₃ -C ₆ H ₂	100
i	2,4,5-Cl ₃ -C ₆ H ₂	90
j	6-quinolinyl	97
k	4-Cl-C ₆ H ₄ -CO	90
1	(±)-CbzNHCHMeCO	96

All substrates were cleaved in good yield, and benzyl carbamates and benzyl ethers remained intact, demonstrating the selectivity of the reaction. Other functional groups were also unaffected by the conditions; thus carbonyl groups (in the form of aldehydes and ketones), and chlorides were not reduced, and in the case of 6-(4-nitrobenzyloxy)quinoline, the protecting group was removed faster than the reduction of the heterocyclic ring. These results further demonstrate the utility of metallic indium as a reducing agent in organic synthesis.

Acknowledgement

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References and Notes

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- (7) Indium powder (100 mesh, 1.0 g) was added to a solution of the substrate (1.0 mmol) in methanol (10 ml) and saturated ammonium chloride solution (3 ml) and the mixture heated at reflux. After 18 h the cooled reaction mixture was filtered through Celite, diluted with water (50 ml) and the pH adjusted to ~2 (7 for basic substrates) with 2 M hydrochloric acid then extracted with dichloromethane (or ethyl acetate) (3 x 15 ml). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to give the desired product with no need for further purification. Deprotected compounds were compared with the original unprotected substrate and literature data.

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