Published in final edited form as:
Tetrahedron Lett. 2014 November 19; 55(47): 6467–6469. doi:10.1016/j.tetlet.2014.10.006.

A New Method for the Cleavage of Nitrobenzyl Amides and Ethers

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Abstract

A mild and efficient *o*- and *p*-nitrobenzyl cleavage protocol was developed. *o*- and *p*-Nitrobenzyl groups were easily removed from a variety of substrates using 20% aqueous NaOH in methanol at 75 °C, presumably via oxidation at the benzylic position by oxygen dissolved in the solution. These easily introducible and removable nitrobenzyl groups can serve as valuable protecting groups for the synthesis of multifunctional, complex molecules.

Keywords

Protecting group; *o*-Nitrobenzyl group; *p*-Nitrobenzyl group; Amide protection; Deprotection

The selection of protection groups is critical to the synthesis of multifunctional complex molecules. Over the past decades, a wide variety of protecting groups have been developed to mask specific functional groups selectively.[1,2] However, despite considerable effort, relatively few protecting groups have been developed for the amide *N-H* (e.g., PMB, TBS, Benzyl, SEM, allyl, etc.).[3] Consequently, limitations associated with cleavage of amide protecting groups often arise.[4] Herein, we report *o*- and *p*-nitrobenzyl groups as easily introducible and removable protecting groups for both R_2N-*H* (including amides) and *RO-H* groups.

In the course of our efforts toward the synthesis of the polycyclic, complex alkaloid perophoramidine, we serendipitously found that the *o*-nitrobenzyl group was easily removed by using 20% aqueous NaOH in methanol at 75 °C (Scheme 1).[5] *o*-Nitrobenzyl groups have been used as photocleavable protecting groups for amides and heterocycles such as indoles, benzimidazole, and 6-chlorouracil as well as the more common hydroxyl group.[6,7] In addition, a method for removing *p*-nitrobenzyl groups on hydroxyl groups in two steps by

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Supplementary Material: Supplementary data associated with this article can be found, in the online version, at XXXXXXXXXXXX.

reduction to a *p*-aminobenzyl group followed by electrochemical oxidation was disclosed by the Kusumoto group.[8] To the best of our knowledge, ours was the first example of using simple aqueous NaOH to remove a nitrobenzyl group from a lactam.

To explore the general reactivity of nitrobenzyl group cleavage reactions by using simple aqueous NaOH, we initially chose 3,3-dimethyl oxindole as a test substrate (Table 1). We found that both *ortho*- and *para*-nitrobenzyl groups on oxindoles **3a** and **3c** were smoothly cleaved under our standard conditions (entries 1 and 3). However, a *meta*-nitrobenzyl group as well as a simple benzyl group on the oxindole nitrogen (**3b** and **3d**) were both unreactive (entries 2 and 4). Notably, the *o*-nitrobenzyl group was also successfully removed even in the absence of light (entry 5). Interestingly, only trace amounts of product were observed when degassed water and methanol were used (entry 6). Furthermore, we discovered that cleavage of the *o*-nitrobenzyl group was successful when the degassed water and methanol were purged with oxygen gas (entry 7). We therefore concluded that oxygen was necessary for the reaction, but light was not.

With the standard conditions in hand, we explored the scope of the *o*- and *p*-nitrobenzyl group cleavage reactions with various substrates (Table 2). *o*- and *p*-Nitrobenzyl protected substrates were easily prepared by a variety of methods, including reductive amination, simple alkylation, EDCI coupling, and acylation. The *o*-nitrobenzyl group on a highly functionalized communesin F intermediate **5** was smoothly cleaved under our standard conditions in good yield (entry 1).[5] *p*-Nitrobenzyl groups on amide 7 and lactam **9** were also cleaved in moderate yields (entries 2 and 3). The *p*-nitrobenzyl group on urea **11** was also successfully cleaved and methyl 4-nitrobenzoate was isolated as a by-product (entry 4). An attempt to remove the *p*-nitrobenzyl group on secondary carbamate **13** proved unsuccessful (entry 5). Additionally, removal of the *p*-nitrobenzyl group on amine **15** was facile, furnishing aniline **16** in 65% yield (entry 6). Interestingly, 4-nitrobenzaldehyde was isolated as a by-product in this reaction, presumably resulting from the oxidation reaction at the benzylic position by oxygen dissolved in the solution. Furthermore, we successfully removed the *p*-nitrobenzyl groups from ethers **17** and **19** in moderate yields (entries 7 and 8). This work offers a one-step alternative to previous work by the Kusumoto group.[8] In the cases of deprotection reactions from urea **11** and ether **17**, the corresponding hemiaminal ether and acetal intermediates were observed (see ref. 9). It is important to note that these deprotection conditions are compatible with free hydroxyl groups, aminals, aryl bromides, methyl carbamates, silyl ethers, and Boc groups present on the substrates.

A representative procedure is as follows: To a 20 mL scintillation vial with a magnetic stir bar were added *p*-nitrobenzyl protected oxindole **3c** (30 mg, 0.10 mmol, 1.0 equiv), MeOH (1.0 mL), and 20% aq NaOH (1.0 mL). The reaction mixture was stirred for 1.5 h at 75 °C. The reaction mixture was then cooled to 23 °C, and extracted with EtOAc (3×2 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to afford 3,3-dimethyloxindole **4** (10.3 mg, 63% yield).

In summary, a mild and efficient deprotection protocol was discovered for the cleavage of *o*- and *p*-nitrobenzyl ethers, amides, ureas, and anilines. Since relatively few options for

protection of the amide *N-H* functionality exist, easily introducible and removable *o*- and *p*-nitrobenzyl groups could prove useful in the synthesis of alkaloids and biologically active molecules, which possess amide functionalities. In our laboratory, this has already proven to be the case in our formal syntheses of communesin F and perophoramidine. In addition, *p*-nitrobenzyl protected anilines, ureas, and alcohols were also competent substrates for this transformation, which may further its utility as a mild deprotection method in cases where other conditions fail.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank NIH-NIGMS (R01GM080269-01), Amgen, and Caltech for financial support. S.-J.H thanks Fulbright (Foreign Student Program, No. 15111120) and the Ilju Foundation of Education & Culture (Pre-doctoral Research Fellowship) for financial support.

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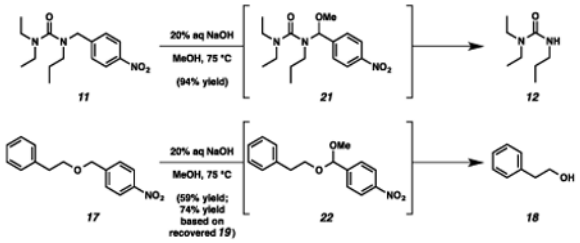
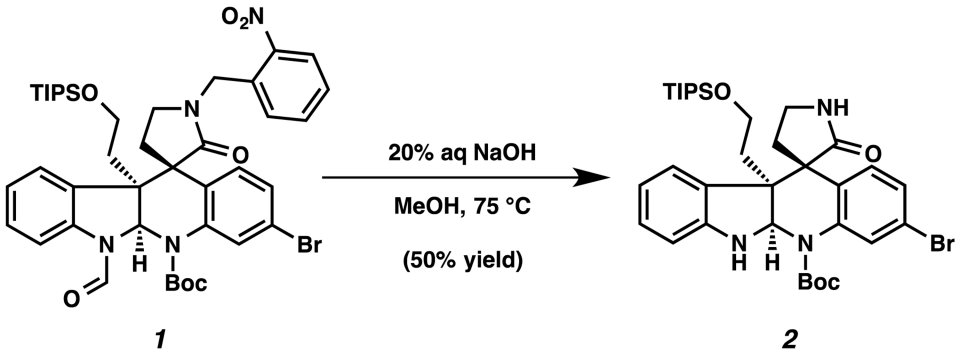
9. From the deprotection reaction of urea **11**, hemiaminal ether intermediate **21** was observed in 1 hour under the Standard reaction conditions and intermediate **21** was converted to propyl urea **12** after 10.5 hours. In addition, acetal **22** was observed in 2 hours during the deprotection reaction of ether **17**, and the desired phenylethyl alcohol **18** was isolated after 32 hours.





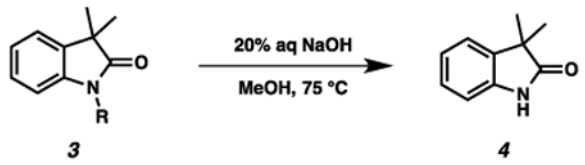
1 2

Scheme 1.

o-Nitrobenzyl group cleavage on perophoramidine intermediate (**1**).

Table 1

Cleavage of nitrobenzyl groups on 3,3-dimethyloxindole.



3 *4*

Entry	Substrate	R	Time (h)	Yield (%)
1	***3a***	-*o*-nitrobenzyl	5	69
2	***3b***	-*m*-nitrobenzyl	24	0
3	***3c***	-p-nitrobenzyl	1.5	63
4	***3d***	-benzyl	24	0
5[a]	***3a***	-*o*-nitrobenzyl	6.5	72
6[b]	***3a***	-*o*-nitrobenzyl	12	trace
7[b,c]	***3a***	-*o*-nitrobenzyl	6.5	66

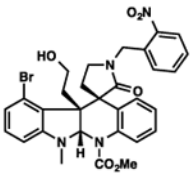
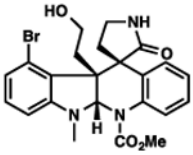
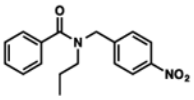
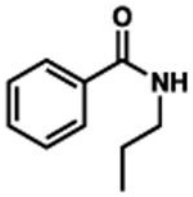
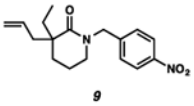
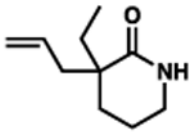
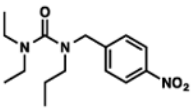
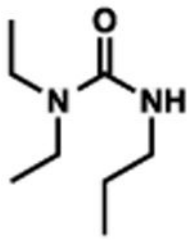
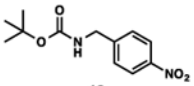
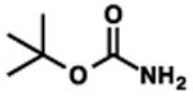
[a] The reaction was performed in the dark.

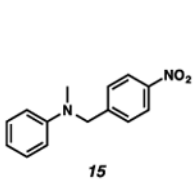
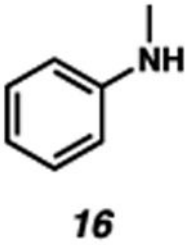
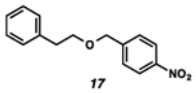
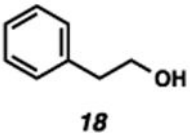
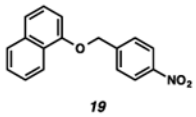
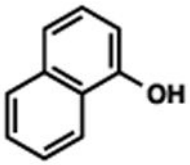
[b] Degassed water and methanol were used.

[c] Purged wlth O_2.

Table 2

Scope of the *o*- and *p*-nitrobenzyl deprotecion reactions.

Entry	Substrate	Product	Time (h)	Yield (%)
1	 5	 6	4	70
2	 7	 8	12	42
3	 9	 10	1	55
4	 11	 12	10.5	94[a,b]
5	 13	 14	6	0

Entry	Substrate	Product	Time (h)	Yield (%)
6	 15	 16	2	65[c]
7	 17	 18	32	59[b] (74)[d]
8	 19	 20	48	48

[a] Methyl 4-nitrobenzoate was isolated as a by-product.

[b] See Ref. 9 for detail.

[c] 4-Nitrobenzaldehyde was isolated as a by-product.

[d] Yield based on recovered starting material.