

## Preferential Hydrogenolysis of NAP Esters Provides a New Orthogonal Protecting Group Strategy for Carboxylic Acids

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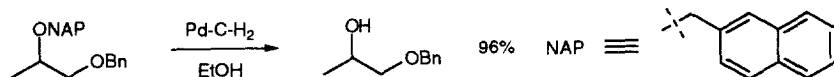
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**Abstract.** Selective hydrogenolysis of 2-naphthylmethyl (NAP) esters in the presence of a benzyl ester has been observed with a wide range of dicarboxylic acids. Orthogonal deprotection of NAP esters with challenging substrates can be achieved if the other carboxylic acids in the molecule are protected with 4-trifluoromethyl benzyl group instead of benzyl groups. © 1999 Elsevier Science Ltd. All rights reserved.

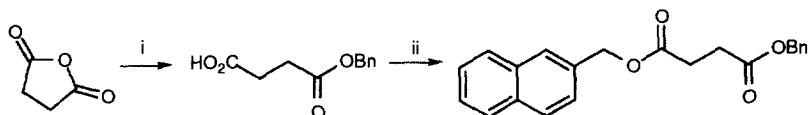
The protection of reactive functional groups with a benzyl group is one of the most frequently adopted protecting group strategies in organic synthesis [1-2]. Its mild removal by catalytic hydrogenolysis constitutes a distinct advantage in molecules that are sensitive to harsh conditions. We recently reported the 2-naphthylmethyl (NAP) group (Scheme 1), as a new benzyl type protecting group for hydroxy groups [3]. It was proposed that the extended aromatic system of the NAP group increases its binding affinity to the metal surface compared to benzyl which leads to the selective cleavage of the NAP group.

### Scheme 1



We now report the application of the NAP group for the orthogonal protection of carboxylic acids [4-8]. Differentially protected dicarboxylic acids, **1a-e** [9], were prepared by a two step synthesis involving anhydride ring opening using benzyl alcohol to give the corresponding monobenzyl ester which is coupled with 2-naphthylmethanol using DCC [10] to form the diesters in good overall yield (Scheme 2).

### Scheme 2



Reaction Conditions: i BnOH, 90 °C, 3hrs; ii DCC, DMAP, NAP-OH, CH<sub>2</sub>Cl<sub>2</sub>, 1hr (86% 2 steps)

Hydrogenolysis of the diesters **1a-f** proceeded smoothly to afford the monobenzyl diacids in excellent yield **2a-f** (Table 1). Of particular interest is the deprotection of the dipeptide **1f** in almost quantitative isolated yield. This example highlights a possible application of this protecting group strategy in peptide synthesis.

Table 1

	Substrate 1-	Reaction Time / mins	Pd/C mgmmol <sup>-1</sup>	Product 2-	Isolated Yield %
a		75	25		92
b		70	25		90
c		80	25		90
d		60	14		89
e		240	20		93
f		75	20		97

A representative procedure for the diesters was as follows: a solution of diester **1a** (353 mg, 1.01 mmol) in ethyl acetate (5 ml) was added to a stirred suspension of palladium on carbon (25 mg, 10%) in ethanol (10 ml) and ethyl acetate (5 ml) that had been purged with hydrogen gas. The reaction was stirred for 75 minutes under 1 atmosphere of hydrogen gas until complete by tlc. The reaction mixture was filtered through a short column of Florisil and eluted with ethyl acetate. Evaporation and purification by flash column chromatography (dichloromethane  $R_f = 0$  to methanol/dichloromethane 1:9  $R_f = 0.65$ ) afforded the monobenzyl ester **2a** as a colourless oil (194 mg, 92 %).

When we investigated substrates bearing an  $\alpha$ -heteroatom, such as **1g-j**, it is found that orthogonal deprotection was only achieved when the NAP group is on the carboxyl group next to the substituent (Table 2). The results seem to suggest that the heteroatom can promote hydrogenolysis of the adjacent ester. The electron withdrawing effect of these substituents could make the carboxy moiety a better leaving group or they could facilitate preferential binding to the adjacent ester. To achieve clean removal of the NAP group whilst preventing cleavage of a benzyl group that has an adjacent heteroatom, it is necessary to reduce the reactivity of the benzyl group.

Table 2

	Substrate 1-	Reaction Time / mins	Pd/C mgmmol <sup>-1</sup>	Product 2-	Isolated Yield %
<b>g</b>		45	12		91
<b>h</b>		80	10		70*
<b>i</b>		120	20		91
<b>j</b>		120	20		63*

\* The side product was the fully deprotected dicarboxylic acid.

In our previous investigations we identified that the benzylic carbon bears a partial positive charge in the transition state and that electron donating substituents on the benzyl group increase the rate of debenzylation while electron withdrawing substituents retard the cleavage [3]. We anticipated that the introduction of the 4-trifluoromethyl substituent onto the benzyl group would reduce its activity which should help prevent its cleavage during the deprotection of the NAP group. The hydrogenolysis of **1k** afforded the desired monoester **2k** in high isolated yield and illustrates how the combination of NAP with a deactivated benzyl group can achieve orthogonal protection of carboxylic acids with challenging substrates (Table 3).

Table 3

	Substrate 1-	Reaction Time / mins	Pd/C mgmmol <sup>-1</sup>	Product 2-	Isolated Yield %
<b>h</b>		80	10		70
<b>k</b>		100	12		91

In summary, we have demonstrated the utility of the NAP group as a carboxylic acid protecting group that can be removed in the presence of other benzyl esters. By manipulating the electronics of the aromatic ring to deactivate the benzyl group, the NAP group may still be cleaved selectively even with challenging substrates.

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