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Mild and Selective Sodium Azide Mediated Cleavage of *p*-Nitrobenzoic Esters

José A. Gómez-Vidal, Michael T. Forrester, and Richard B. Silverman*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60201-3113

agman@chem.northwestern.edu

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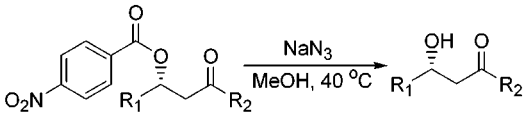
ABSTRACT



A mild and selective cleavage of *p*-nitrobenzoic esters by sodium azide in methanol is reported. This new methodology is mild enough for use with acid- or base-sensitive compounds. No elimination byproducts are formed. Fmoc- and trifluoroacetyl-amino protecting groups, benzyl esters, and ethyl esters remain unaffected. Less reactive compounds are discussed in terms of steric factors, and yields are increased by altering the azide solvation.

The Mitsunobu reaction has been extensively reported for the inversion of hydroxy-bearing stereocenters.[1] The use of *p*-nitrobenzoic acid was reported to increase the efficiency of this methodology in hindered secondary alcohols,[2] and this acid has become a standard when inverting the configuration of chiral alcohols.[3] A potential drawback of this methodology occurs when the formed ester is β to a carbonyl group: hydrolysis of this intermediate under basic conditions proceeds with elimination, affording the conjugated enone as the major product (Scheme 1).

Different conditions have been described to cleave esters under mild conditions.[4] For example, Bi(III)-mandelate was reported as a catalyst for the hydrolysis of aryl acetates.[5] Scandium trifluoromethanesulfonate was developed for the selective cleavage of acetates in the presence of a coordinative group.[6] Nucleophilic dealkylation or nucleophilic attack on the ester carbonyl group using alkali metal salts were described at high temperature to obtain the free acid under neutral conditions.[7] Alkali azide and alkali iodine in DMF at 100 °C were used for cleavage of phosphonic acid diesters to monoesters.[8] Potassium cyanide was reported as a catalyst for ester exchange in refluxing ethanol[9] or the *O*-deacylation of polyacylated sugars.[10]

Scheme 1

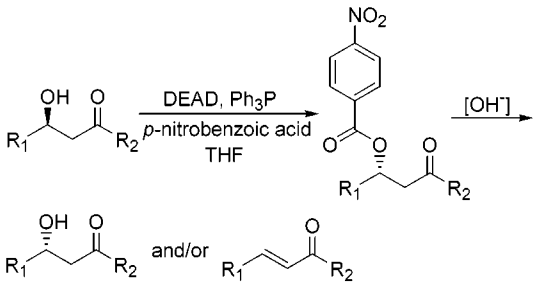


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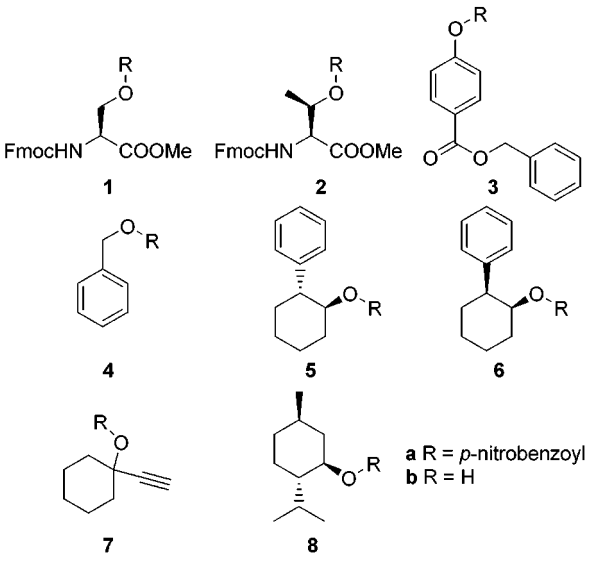
Table 1. Conditions and Results for *p*-Nitrobenzoic Ester Cleavage



ester	NaN_3 (equiv)	solvent[a]	temp (°C)	reaction time (h)	yield[b] (%)
1a	5	MeOH	35	14	95
2a	5	MeOH	35	24	100
3a	3	MeOH	40	6	100
3a	0.1	A	40	5 days	80
4a	3	B	40	6	94
5a	3	MeOH	40	24	54
5a	3	C	50	24	74
5a	3	C	75	24	74
5a	6	C	50	24	96
6a	6	C	50	24	52
6a	6	C	50	60	81
7a	3	MeOH	40	6	79
8a	1.1	MeOH	40	24	49

[a] A, MeOH/DMF (3/1); B, MeOH/DME (1/3); C, MeOH/ACN (6/1); DMF, *N*,*N*-dimethylformamide; DME, 1,2-dimethoxyethane; ACN, acetonitrile. [b] Isolated hydroxy compounds (R = H).

Recently, picolinic acid has been reported as a new partner for the Mitsunobu reaction.[11] Hydrolysis of the picolinic esters with copper acetate in methanol affords the alcohol with no elimination byproduct. However, these conditions do not cleave a *p*-nitrobenzoic ester.

Herein we report a new procedure for the methanolysis of *p*-nitrobenzoic esters in the presence of sodium azide under very mild conditions.[12]

N-Fmoc-*O*-(*p*-nitrobenzoyl)-L-serine methyl ester was chosen to investigate the best conditions for the *p*-nitrobenzoate cleavage in the presence of two protecting groups sensitive to nucleophiles or basic conditions. These conditions were applied to a number of substrates to determine the scope and limitations of this reaction (Table 1).

The two amino acids **1a** and **2a** were cleaved in high yield using an excess of sodium azide (Table 1). This clearly shows that these conditions do not affect base- or nucleophile-labile functionalities such as an Fmoc protecting group. No elimination products were observed under these conditions.

These conditions also are selective for *p*-nitrobenzoic esters. Other esters were less prone to hydrolysis, as shown for compound **3a**.[13] Methyl 4-hydroxybenzoate was not detected. Compounds that had bulky substituents or that were highly substituted in the α position showed less reactivity (**6a**, **7a**, and **8a** in Table 1) or no reactivity (compare **4** in Table 1 with **9** in Figure 1), presumably because of steric hindrance.

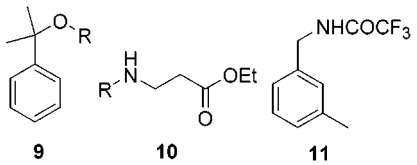


Figure 1. Compounds that were stable toward sodium azide in methanol under various temperature and time conditions. R = *p*-nitrobenzoyl.

It was necessary to carry out the reaction using a cosolvent when the reactivity of the compound was compromised using methanol as solvent. It has been reported that solvation has a role in the manifestation of the α effect in nucleophiles such as sodium azide.[14]

Ethyl esters such as **10** were not transesterified (Figure 1). This accounts for the necessity of an activated carbonyl group for cleavage under these conditions. Activated amides such as **10** and **11** were stable under these conditions. Trifluoroacetyl is an amino protecting group that has been reported as one of the more easily cleaved amides.[4] Lactones[13] and good leaving groups, however, are functional groups that are affected under these conditions.

An intermediate in this reaction (**12**) is proposed in Scheme 2. Nucleophilic attack of azide on the activated carbonyl group gives tetrahedral intermediate **12**, which presumably collapses to acyl azide **13** and gives methyl *p*-nitrobenzoate **14** and the free alcohol in the presence of methanol.

The proper balance of the carbonyl reactivity and the special reactivity of sodium azide that exhibits the α effect explains the selectivity already shown. Byproduct **14** was isolated and is formed in a 1:1 ratio with the free alcohol. This reaction is catalytic, as shown when it was carried out with only 0.1 equiv of sodium azide (Table 1). The use of

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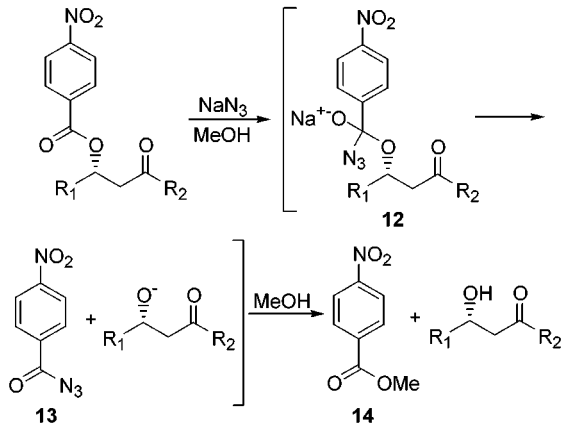
Scheme 2



an excess of sodium azide to reduce the reaction time was not inconvenient because it was easily separated from the reaction by aqueous workup. Moreover, the unreacted compound was recovered unaffected, when the reaction was not carried out to completion.

In summary, a new method for the cleavage of *p*-nitrobenzoates under mild conditions has been developed. The use of sodium azide in methanol with or without a cosolvent to cleave these esters will further extend the applicability of *p*-nitrobenzoic acid in the Mitsunobu reaction. Furthermore, these conditions open the scope of *p*-nitrobenzoyl as a selective protecting group for alcohols.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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