

Cleavage of *N,N'*-Dialkylhydrazides with PhI(OH)OTs

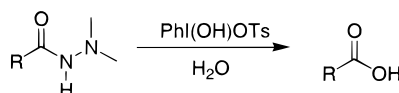
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ABSTRACT



N,N'-Dimethylhydrazides are efficiently cleaved to give the carboxylic acid upon treatment with PhI(OH)OTs in water or water/CH₂Cl₂ mixtures. The reaction occurs with the evolution of a gas.

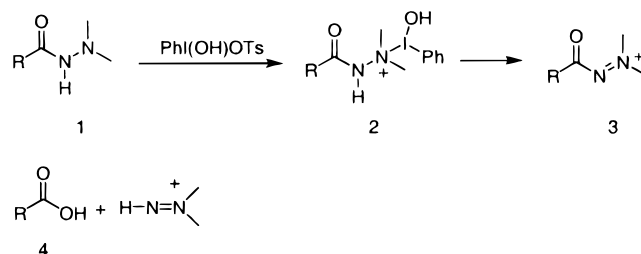
We have recently been investigating the use of *N,N'*-dialkylhydrazide for directed orthometalations¹ and found that there are few methods to cleave these derivatives. The available methods to achieve cleavage were developed by Barton² and Ho.³ Barton showed, in the context of the protection of penicillic acids, that *N,N'*-dialkylhydrazides could be cleaved with Pb(OAc)₄ or MnO₂, and Ho showed that dimethylhydrazides could be cleaved in low yield using NaOCl. We have recently shown that periodic acid or CuCl₂ can also be used to cleave dimethylhydrazides.^{1a} The cupric chloride method has the advantage that it is compatible with the presence of sulfur.

We now describe a new and mild method for the cleavage of *N,N'*-dialkylhydrazides that should greatly extend the utility of this group both in its use as a protective group⁴ and as a directing group in the orthometalation reaction. As illustrated in Scheme 1, treatment of a hydrazide with PhI(OH)OTs in an aqueous/organic medium at temperatures between -50 °C and rt very cleanly releases the acid from the hydrazide. During the course of this work, we noticed that the reaction occurs with the evolution of gas. Attempts to identify the gas by capturing it in an IR cell and recording

its infrared spectrum were unsuccessful because of high background levels of water and CO₂. We surmise that the gas is probably nitrogen and methane resulting from the decomposition of **4** through the diimide. The heat of reaction was measured in a CRC-90 calorimeter and found to be -88 kcal/mol (-372.3 kJ/mol) with the evolution of gas confirmed. On a 100 mg scale, this produced an adiabatic temperature rise of 18 °C, indicating that scale-up of this chemistry will require careful temperature control.

The use of alcoholic solvents results in the formation of mixtures of the acid and ester presumably because of competition in the hydrolysis of intermediate **2**. The reaction also works well in 10% aqueous NaOH and 10% HCl, acetonitrile, methylene chloride, or mixtures of water and methylene chloride. The reaction is fastest in water, with CH₂Cl₂ being the slowest (9% starting material remaining

Scheme 1



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after 10 min of reaction). Reaction times for the individual substrates were not optimized.

Table 1. Cleavage of Dialkylhydrazides with PhI(OH)OTs

hydrazide ^{a,e}	equiv of PhI(OH)OTs	solvent	% yield of acid
benzoic	2	water	91
benzoic ^b	1	water	59
benzoic ^c	1.3	water	80
octanoic	1.3	water	80
4-methoxybenzoic	1.3	water	73
4-nitrobenzoic	2	water	91
cyclohexene carboxylic	2	water	64
octanoic	1.3	water	80
3-TMS-furoic	1.3	CH ₂ Cl ₂	80
2- ⁱ PrS-benzoic		water	<i>d</i>
hydrocinnamic	2	CH ₂ Cl ₂	55
Naproxen	2	CH ₂ Cl ₂	71
		water	

^a All hydrazides were the dimethylhydrazide unless otherwise noted. ^b *N*-Phenyl hydrazide was used. ^c The morpholino hydrazide was used. ^d Oxidation of the sulfur to the sulfoxide occurs. ^e Satisfactory spectroscopic data was obtained for all new compounds.

Table 1 give the results for a series of hydrazides. The efficiency of the reaction is quite good with few limitations.

A testament to the mildness of the reaction is illustrated with the 3-trimethylsilylfuroic acid derivative, which cleanly gives the acid without the intervention of furan oxidation. The cleavage of the cyclohexene derivative is also noteworthy because of the well-known ability of hypervalent iodine derivatives to react with alkenes.⁵ In this case, the lower yield may be attributed to some overoxidation of the alkene. Sulfur derivatives are not compatible with this chemistry because they are oxidized to the sulfoxide.^{6,7}

The reaction can also be used to hydrolyze the *N*-phenylhydrazide and the morpholino derivative. No other hydrazides were examined, but others should work equally well.

Acknowledgment. We thank Sean Lapikas for running the CRC-90 calorimetry experiment.

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(7) **Sample experimental:** To a solution of *N,N*-dimethylbenzoic hydrazide (0.500 g, 3.04 mmol) in 5 mL of water was added [hydroxy-(tosyloxy)]iodobenzene (2.38 g, 6.08 mmol) at once. The reaction was stirred for 3 h (not optimized), and then 25 mL of CH₂Cl₂ and 20 mL water were added. The layers were separated, and the aqueous was extracted with 3 × 10 mL of CH₂Cl₂. The organic layer was concentrated to 10 mL and extracted with 3 × 10 mL of 10% NaOH. The aqueous was acidified to a pH of 2 and extracted with 3 × 20 mL of CH₂Cl₂. The organic was then dried with sodium sulfate. The solids were removed by filtration, and the solvent was removed by rotary evaporation to yield 338 mg (91%) of benzoic acid.