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Hypophosphorous Acid Mediated Dehalogenation in Water

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Abstract: A new methodology has been developed to reduced the water soluble organohalides in aqueous solution in high yields using hypophosphorous acid. Copyright © 1996 Elsevier Science Ltd

Water as solvent is very interesting in organic synthesis because the toxic organic solvent can be avoided. During the last decades, a number of reactions using water as solvent have been reported.[1] However, water is rarely used in reductions because of the chemical incompatibility with most reducing agents.[2] A water soluble organotin hydride was made by Breslow[3] for the dehalogenation of water soluble organohalides. Most recently, it has been reported that tributyltin hydride with detergents can be used for the reduction in water.[4] However, organotin compounds are generally toxic and expensive, and difficult to remove completely from the desired products. Also, the solubility of organotin hydride has limited them to organic solvents. It has been reported that hypophosphorous acid is a good alternative to tri-*n*-butyltin hydride (compared with tri-*n*-butyltin hydride, hypophosphorous acid is less toxic, inexpensive and easy to remove from the products),[5] and it is available as water solution.[6] Therefore, it was thought that hypophosphorous acid is an ideal reagent for the reduction of water soluble compounds.[7]

Indeed, when 3-iodobenzoic acid was treated with hypophosphorous acid, AIBN, and $NaHCO_3$ in water, dehalogenated product was obtained in 95% isolated yield. $NaHCO_3$ was used to neutralize the acidity of hypophosphorous acid and buffer the reaction solution. In the blank experiment (without AIBN) the starting 3-iodobenzoic acid remained unchanged. The method was applicable to aryl iodides (table 1. entries 1-3 and 8). Aryl bromides were not reduced efficiently (entries 4 and 7). However, alkyl bromides were reduced effectively (entries 6 and 9). When the solubility of the product is too high, the yield was decreased due to the loss of the product during the work up process (entry 5). Water soluble aryl chlorides, alkyl chlorides and water insoluble substrates remained unchanged in the attempted radical dehalogenation. These findings indicate that the hypophosphorous acid is useful for the radical dehalogenation for the water soluble iodo- or bromo-compounds. Other H_3PO_2 mediated synthetic transformation in water is under investigation.

Table 1. Reduction of Organohalides with H_3PO_2 in Water [a]

Entry	Substrate	AIBN (eq)	Time (min)	Yield (%) [b]
1	3-$IC_6H_4CO_2H$	0.4	60	95
2	2-$IC_6H_4CO_2H$	0.4	60	94
3	5-Iodosalicylic acid	0.4	60	91
4	3-$BrC_6H_4CO_2H$	2.0	300	53 (40) [c, d]
5	3-Iodopropionic acid	0.4	60	45
6	(±)-2-Bromo-3-methyl butyric acid	0.6	90	98
7	5-Bromo uracil	1.0	150	50 (41) [c,d]
8	5-Iodo uracil	0.6	90	89
9	Methyl 6-bromo-6-deoxy-α-glucopyranoside	1.0	150	70

[a] 5 eq of H_3PO_2 was used. [b] Isolated yield. [c] The recovered yield of starting material is shown in parentheses. [d] Measured by NMR.

Typical procedure: A solution of 3-iodobenzoic acid (0.4 g, 1.6 mmol), hypophosphorous acid (0.8 mL, 8.0 mmol, 50 % solution in water) and $NaHCO_3$ (0.88 g, 10.56 mmol) in water (10 mL) under argon was treated with AIBN (0.052 g, 0.31 mmol) twice (30 min interval) during reflux. The solution was made alkaline with 1M NaOH and washed with $CHCl_3$. The aqueous layer was acidified with conc. HCl and extracted with $CHCl_3$, and the extract was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed and the residue was crystallized (CH_2Cl_2/hexanes) to give benzoic acid (0.19g, 95%).

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