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A simple and efficient radical reduction using water-soluble radical initiator and hypophosphorous acid in aqueous alcohol

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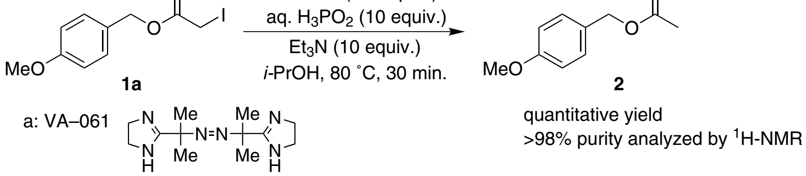
Abstract—A simple, mild, and high-yielding procedure for the reduction of various halogenated compounds using a combination of the water-soluble radical initiator, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), a water-soluble chain carrier, hypophosphorous acid, and the base, triethylamine, in aqueous alcohol is described. The reagents used in this method are all water soluble, and therefore, an almost pure desired product can be readily obtained using only an extraction procedure.

Radical reduction is one of the useful synthetic methodologies.[1] The reductive reagents (e.g., tributyltin hydride [*n*-Bu_3SnH],[1] tris(trimethylsilyl)silane [$(TMS)_3SiH$],[1,2] etc.) have often been used in many radical reactions. However, organotin compounds are toxic and expensive, and are difficult to be completely removed from the desired reaction products. Silanes are also very expensive and sometimes difficult to remove. On the other hand, hypophosphorous acid as a water-soluble chain carrier is cheap, much less toxic, and easily removable.[3,4] Recently, Barton and other groups have reported a radical reaction using hypophosphorous acid,[3] and we have recently reported the radical cyclization of hydrophobic substrates using the combination of the water-soluble radical initiator 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061),[4] the water-soluble chain carrier, 1-ethylpiperidinehypophosphite (EPHP), and the surfactant, the cetyltrimethylammonium bromide (CTAB), in water.[5] We now report a radical reduction in aqueous isopropyl alcohol using the combination of VA-061, hypophosphorous acid, and triethylamine. Since these reagents are all water soluble, they can be easily removed.

We examined the radical reduction of the iodide substrate **1a** using VA-061, aqueous H_3PO_2, and Et_3N in aqueous isopropyl alcohol at 80 °C (Scheme 1).[6] The reduction smoothly occurred (30 min) to give the reductive product **2**[7] in a quantitative yield and the almost pure desired product could be obtained only by extraction with ethyl acetate. The purity of this product was found to be >98% based on the ^{1}H NMR analysis.

We then investigated the generality of this reduction with various halogenated substrates under similar conditions. These compounds used in the reduction are shown



Scheme 1. Radical reduction of **1a** using water-soluble reagents.

Keywords: Radical reduction; Hypophosphorous acid; The water-soluble radical initiator; Aqueous alcohol.

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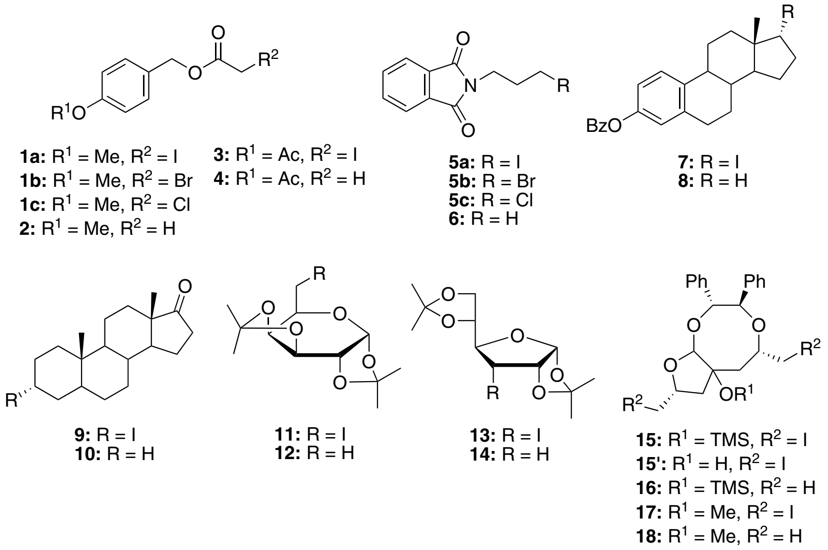

Scheme 2. Various substrates of radical reduction.

in Scheme 2. The results are summarized in Table 1. These iodide substrates **1a**, **3**, **5**, **7**, **9**, **11**, **13**, **15**, and **17** afforded the reductive product **2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, and **18**[8] in excellent yields (entries 1, 2, 4–11), respectively. This reductive method was also used for a large-scale reaction (10 mmol scale; **1a**: 3.06 g, entry 2), and the reproducibility of the reaction was confirmed. All these products purified by an extraction procedure were >98% purity based on the ^{1}H NMR analysis. The substrates bearing various functional groups (e.g., ester **1a**, **3**, **7**, imide **5**, ketone **9**, acetal **11**, **13**, **15**, **17**, silyl ether **15**, and cyclic ether **11**, **13**, **15**, **17**) could be used in our method.

Table 1. Radical reduction using VA-061, aq H_3PO_2, and Et_3N in *i*-PrOH at 80 °C

Entry	Substrate	VA-061 (equiv)	Time (h)	Product	Yield (purity)[a]
1	**1a**	0.5	0.5	**2**	Quant. (>98%)
2[b]	**1a**	0.5	0.5	**2**	Quant. (>98%)
3	**1b**	0.5	0.5	**2**	Quant. (>98%)
4	**3**	0.5	0.5	**4**	Quant. (>98%)
5	**5**	0.5	0.5	**6**	Quant. (>98%)
6	**7**	0.5	0.5	**8**	Quant. (>98%)
7	**9**	0.5	0.5	**10**	Quant. (>98%)
8	**11**	0.5	0.5	**12**	Quant. (>98%)
9	**13**	0.5	0.5	**14**	Quant. (>98%)
10[c]	**15**	1	0.5	**16**[8]	Quant. (>98%)
11[c]	**17**	1	0.5	**18**[8]	95% (>99%)[d]

[a] The yields are after purification by extraction procedure. The purity was analyzed by ^{1}H NMR.

[b] Large-scale reaction (10 mmol, 3.06 g).

[c] Hypophosphorous acid (20 equiv) and triethylamine (30 equiv) were used.

[d] The yield is after purification on PLC plate.

We found that this condition was most effective for the unstable substrate **15** compared with other known conditions (Table 2).[3] Under the condition using AIBN, aq H_3PO_2 and Et_3N in benzene, the corresponding reduced product **16** was obtained in 34% yield and the desilylated product was contaminated (entry 3). When the reduction was carried out in water, the reductive product was not obtained at all, and the starting material **15** was recovered accompanied with the desilylated substrate **15′**. Furthermore, our condition was more effective than the standard reductive condition, AIBN and n-Bu_3SnH in benzene (entry 5). Next, we tried to apply the bromides **1b**, **5b**, and chlorides **1c**, **5c** to our method. When we used the α-bromocarbonyl substrate **1b**, the reductive product **2** was produced in quantitative yield (Table 1, entry 3). However, the reductions of the bro-

Table 2. Radical reduction of **15** under the various reaction conditions

Entry	Reductive reagent (equiv)	Initiator (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	H_3PO_2 (20)	VA-061 (0.5)	Et_3N (30)	*i*-PrOH	80	0.5	Quant. (>98%)[b]
2	H_3PO_2 (20)	AIBN (0.5)	Et_3N (30)	*i*-PrOH	80	0.5	83[c]
3	H_3PO_2 (20)	AIBN (0.5)	Et_3N (30)	Benzene	Reflux	3	34[c]
4	H_3PO_2 (20)	AIBN (0.5)	$NaHCO_3$ (30)	H_2O	90	3	0[d]
5	H_3PO_2 (20)	Et_3B (0.5)	$NaHCO_3$ (30)	H_2O	Rt	12	0[d]
6	n-Bu_4SnH (5)	AIBN (0.1)	—	Benzene	Reflux	3	73[c]

[a] Yield of isolated **16**.

[b] This yield is after purification by extraction procedure. The purity was analyzed by ^{1}H NMR.

[c] The yields are after purification by column chromatography.

[d] Starting material and the desilylated substrate were recovered.

mide **5b** and chloride **1c** were not completed and afforded the corresponding products **2**, **6** in low yields accompanied by the corresponding alcohol compounds as a side product. With other chloride **5c**, the reduction did not proceed at all.

In summary, we have discovered that the combination of a water-soluble azo-type radical initiator (VA-061), a water-soluble chain carrier (hypophosphorous acid) and a base (triethylamine) is a simple and efficient reaction system to accomplish radical reductions in aqueous alcohol. This method makes it easy to purify the desired product and various substituted substrates can be used for this method; therefore, we believe that this procedure may find widespread use in organic synthesis.

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6. General procedure for the preparation of reductive compounds (**2**): VA-061 (50.1 mg, 0.20 mmol) was added to a solution of the iodide substrate (**1a**) (122 mg, 0.40 mmol), hypophosphorous acid in water (0.44 mL, 4.0 mmol, 50% solution in water), and Et_3N (0.56 mL, 4.0 mmol) in *i*-PrOH (4 mL) at room temperature. The reaction mixture was then stirred and heated to 80 °C for 0.5 h. The organic solvent in the reaction mixture was evaporated and then water was added. The crude mixture was extracted with EtOAc, and the organic layer was washed with saturated NH_4Cl, water and brine, dried with Na_2SO_4, and concentrated to afford the pure reductive compound **2**[7] (72 mg, 0.40 mmol, quantitative yield, purity >98% by ^1H NMR) as a yellowish oil, which was used without further purification.
   IR: $\tilde{\nu}$ 3000 cm^{-1}, 2960, 2912, 2837, 1732 (C=O), 1614, 1585, 1444, 1359, 1242, 1176, 1032, 963, 821. ^1H NMR (300 MHz/$CDCl_3$/TMS): δ 2.06 (s, 3H, $CH_3C{=}O$), 3.80 (s, 3H, CH_3O), 5.03 (s, 2H, CH_2O), 6.87 (d, 2H, Ar-*H*, $J = 8.7$ Hz), 7.28 (d, 2H, Ar-*H*, $J = 8.7$ Hz). ^{13}C NMR (75 MHz/$CDCl_3$/TMS): δ 170.84 (C=O), 159.55 (C), 130.02 (CH), 127.98 (C), 113.85C (CH), 66.01 (CH_2O), 55.16 (CH_3O), 20.94 (CH_3).
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