

## Radical Cyclization Reaction Using a Combination of Phosphinic Acid and a Base in Aqueous Ethanol

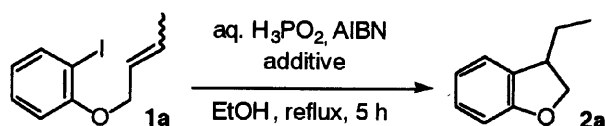
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Treatment of allylic ether of 2-iodophenol or 2-haloethanal allylic acetal with phosphinic acid, a base and a radical initiator (AIBN or triethylborane) in aqueous ethanol provided the corresponding radical cyclization product in excellent yield. An addition of a base is critical to employ phosphinic acid as a radical mediator.

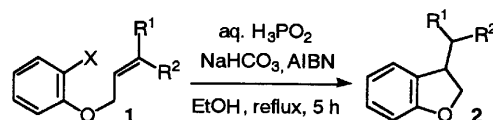
During the recent dramatic development of radical methodology in organic synthesis, tributyltin hydride has played a leading role<sup>1</sup> despite its toxicity and the difficulty incurred in residue removal. For this reason, new radical mediators to replace tin compounds have been actively investigated.<sup>2,3</sup> Among them, Barton's<sup>4</sup> and other<sup>5</sup> groups reported phosphinic acid ( $\text{H}_3\text{PO}_2$ ) as a cheap, much less toxic and easily removable chain carrier in various reduction reactions although toxic solvents such as dioxane and benzene were employed.<sup>6</sup> To reduce total toxicity in radical reaction, it is important to pay attention to the solvent employed where the radical reaction is carried out. Here, we wish to report the radical cyclization with phosphinic acid in aqueous ethanol. The indispensable addition of a base is also described.



None	3% (67% recovery)
10 mmol $\text{NaHCO}_3$	87%
10 mmol KOH	91%
10 mmol $\text{Et}_3\text{N}$	89%
5 mmol aq. HCl	0% (38% recovery)

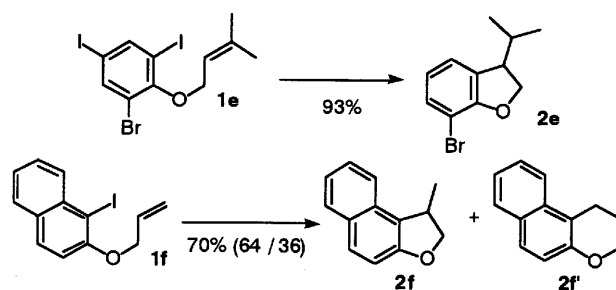
Scheme 1.

First, we chose **1a** as a substrate to examine radical cyclization by means of phosphinic acid in ethanol. A solution of **1a** (1 mmol), phosphinic acid (50% aqueous solution, 1.1 mL, 10 mmol), and AIBN (0.3 mmol) in ethanol (5 mL) was heated at reflux for 5 h. Contrary to our expectations, the desired product **2a** was obtained in only 3% yield and **1a** (67%) was recovered. Then, this reaction was performed in the presence of sodium hydrogencarbonate (10 mmol). Surprisingly, the yield improved sharply up to 87%. Potassium hydroxide or triethylamine was also highly effective to give **2a** in 91% or 89% yield, respectively. On the other hand, addition of hydrochloric acid suppressed the reaction completely.



X	R <sup>1</sup>	R <sup>2</sup>	Yield
<b>1a</b>	I	CH <sub>3</sub>	H 87% (60%*)
<b>1b</b>	I	H	H 48%
<b>1c</b>	I	CH <sub>3</sub>	CH <sub>3</sub> 83%
<b>1d</b>	Br	CH <sub>3</sub>	CH <sub>3</sub> 3% ( <b>1d</b> , 67%)

\*  $\text{Et}_3\text{B}$  (2 mmol) was used at room temperature.



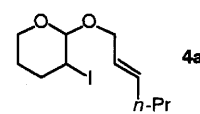
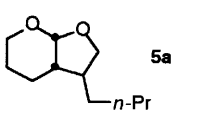
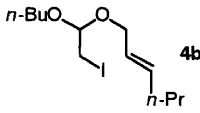
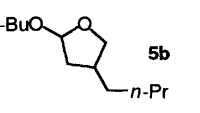
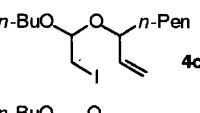
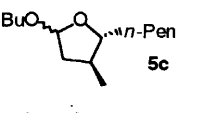
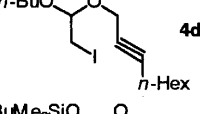
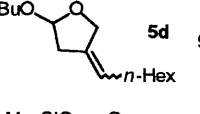
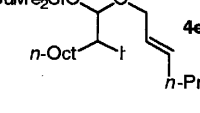
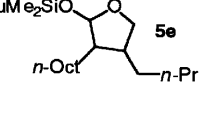
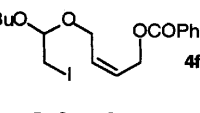
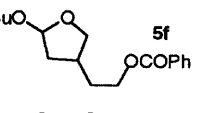
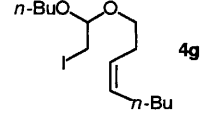
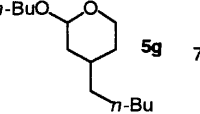
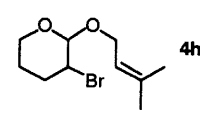
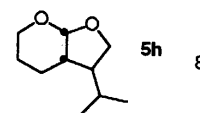
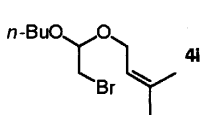
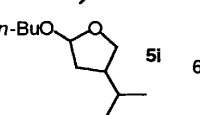
Scheme 2.

These facts clearly show that a base is essential to carry out the phosphinic-acid-mediated radical reaction smoothly and suggest the actual chain carrier would be a phosphinate anion.<sup>7</sup>

The results of radical cyclization using an aq  $\text{H}_3\text{PO}_2$  /  $\text{NaHCO}_3$  / EtOH system are summarized in Scheme 2. Allyl ether **1b** afforded dihydrobenzofuran derivative **2b** in moderate yield due to its volatility as well as the formation of by-product **3**<sup>8</sup> (15%). Triethylborane, instead of AIBN, could act as a radical initiator at room temperature.<sup>9</sup> Although aryl bromide **1d** resisted reduction, selective cyclization of **1e** could be achieved in excellent yield.<sup>10</sup> When allyl ether of iodonaphthol **1f** was employed as a substrate, 6-endo cyclization was observed<sup>11</sup> in addition to 5-exo cyclization.

Next, we focused on radical cyclization of haloacetals (Table 1). For example, to iodoacetal **4a** was added a solution of phosphinic acid, sodium hydrogencarbonate (1.5 eq to  $\text{H}_3\text{PO}_2$ ), and AIBN in ethanol<sup>12</sup> and the resulting mixture was heated at reflux. The reaction was completed within 30 min. Extraction (ethyl acetate/brine) and concentration followed by purification through short silica gel column cleanly gave bicyclic acetal **5a** in 98% yield. Some comments are worth noting. (1) *tert*-Butyldimethylsilyl ether **4e** and benzoate ester **4f** were tolerant under this basic condition. (2) Decreasing the amount of  $\text{H}_3\text{PO}_2$  and  $\text{NaHCO}_3$  led to slightly lower yet good yields (**4c** and **4f**). (3) Slow addition of a solution of  $\text{H}_3\text{PO}_2$ ,  $\text{NaHCO}_3$  and 4,4'-azobis(4-cyanopentanoic acid) in water to **4g** afforded six-membered **5g** in 79% yield. (4) Bromo analog

**Table 1.** Radical cyclization of haloacetals using  $\text{H}_3\text{PO}_2/\text{NaHCO}_3/\text{EtOH}$  system<sup>a</sup>

	<b>4a</b>		<b>5a</b>	98% (74/26) 82% (81/19) <sup>b</sup>
	<b>4b</b>		<b>5b</b>	97% (76/24)
	<b>4c</b>		<b>5c</b>	96% (51/49) 74% (50/50) <sup>c</sup>
	<b>4d</b>		<b>5d</b>	95% (55/45)
	<b>4e</b>		<b>5e</b>	100% (39/33/19/9) 96% (39/39/15/7) <sup>c</sup>
	<b>4f</b>		<b>5f</b>	100% (70/30) 80% (66/34) <sup>b</sup>
	<b>4g</b>		<b>5g</b>	79% (51/49) <sup>d</sup>
	<b>4h</b>		<b>5h</b>	83% (61/39) <sup>e</sup>
	<b>4i</b>		<b>5i</b>	64% (63/37) <sup>e</sup>

<sup>a</sup> **4** (1.0 mmol),  $\text{H}_3\text{PO}_2$  (10 mmol),  $\text{NaHCO}_3$  (15 mmol) and AIBN (0.1 mmol) in ethanol (5 mL) were heated at reflux for 30 min otherwise noted. <sup>b</sup>  $\text{Et}_3\text{B}$  (2 mmol), instead of AIBN, was used at room temperature (3 h). <sup>c</sup> **4** (1.0 mmol),  $\text{H}_3\text{PO}_2$  (5 mmol),  $\text{NaHCO}_3$  (7.5 mmol) and AIBN (0.2 mmol) in ethanol (5 mL) were heated at reflux for 3 h. <sup>d</sup> To a solution of **4g** in refluxing ethanol was added a solution of  $\text{H}_3\text{PO}_2$  (10 mmol),  $\text{NaHCO}_3$  (15 mmol) and 4,4'-azobis(4-cyanopentanoic acid) (0.1 mmol) in water for 5 h. <sup>e</sup> AIBN (0.3 mmol x 2) was used and the reaction completed within 10 h.

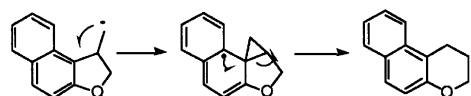
**4h** or **4i** could be used as a substrate although longer reaction time and a larger amount of AIBN were needed.

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## References and Notes

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- Reduction of restricted water-soluble substrates in water was reported. D. O. Jang, *Tetrahedron Lett.*, **37**, 5367 (1996).
- In the previous reports using phosphinic acid, reactions were carried out with a base necessarily to protect acid-sensitive functionalities (see Refs. 4 and 5) or to solve a substrate with a carboxylic group into water (see Ref. 6).
- Phosphorous-centered radical easily adds to terminal olefin (see Ref. 4).
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- We checked whether  $n\text{-Bu}_3\text{SnH}$  also has the ability to discriminate between aryl iodide and aryl bromide. Treatment of **1e** with exactly 2.0 equimolar amounts of  $n\text{-Bu}_3\text{SnH}$  and a catalytic amount of AIBN in refluxing benzene afforded **2e** in 66% yield exclusively after removal of the tin residue with aqueous KF.
- Slow addition of  $\text{H}_3\text{PO}_2$  and  $\text{NaHCO}_3$  to a solution of **1d** and AIBN gave **2d** and **2e** in the same ratio. This means direct 6-endo cyclization occurred, that is, the reaction path as below would be improbable.



- A basic phosphinate solution should be prepared in advance.