N-Ethylpiperidine Hypophosphite Mediated Intermolecular Radical Carbon-Carbon Bond Forming Reaction in Water

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Abstract: *N*-Ethylpiperidine hypophosphite mediated radical addition reactions to electron deficient alkenes in aqueous media have been developed. The reactions afford high isolated yields of addition products without using a large excess of alkenes.

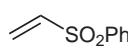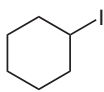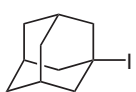**Key words:** radical reactions, addition reactions, alkenes, alkyl halides, water

Among a number of radical reactions in organic synthesis, the carbon-carbon bond forming reactions is one of the most important application of radical reactions.[1] Although organotin hydrides, especially *n*-Bu$_3$SnH, have been widely used as radical chain carriers for the carbon-carbon bond forming reactions, they have several drawbacks such as toxicity, high cost, and difficulty to eliminate toxic tin byproducts from the desired products. Due to these reasons, they are not suitable for a large-scale work in pharmaceutical industry. Various research efforts have been made to search ideal alternatives to organotin hydrides.[2] Among them, *N*-ethylpiperidine hypophosphite (EPHP) has been proven to be the most promising substitute for organotin hydrides in radical reactions such as dehalogenation, deoxygenation and carbon-carbon bond forming reactions.[3–5] EPHP has several advantages over organotin hydrides including cost-effectiveness, non-toxicity and easy work-up process.

Water is an attractive solvent in organic reactions from economical and environmental points of view. The use of water as a solvent in radical reactions is relatively rare[4,6] whereas various ionic and pericyclic reactions in water have been reported frequently.[7] It has been thought that EPHP would be a suitable radical chain carrier in aqueous media because of its high solubility in water. As part of our ongoing research to expand the application of EPHP in organic synthesis, we herein report the scope and limitations of EPHP as a radical chain carrier for intermolecular carbon-carbon bond forming reactions in water.[8]

First, we examined the possibility of radical intermolecular carbon-carbon bond forming reactions in water with cyclododecyl iodide and phenyl vinyl sulfone. The reaction of cylcohexyl iodide (1 equiv) with phenyl vinyl sulfone (1 equiv) in degassed water in the presence of EPHP (3 equiv) and azo*bis*isobutyronitrile (AIBN) under argon

at 100 °C produced the desired addition product in 83% yield without forming significant by-products such as hydrolyzed or reduced products (Table 1, entry 1). The reaction also proceeded smoothly at 80 °C with *i*-PrI (Table 1, entry 2). It is worth noting that the reaction accomplished in water without using a phase transfer agent (PTA). A water-soluble primary alkyl iodide could be a radical precursor while a hydrophobic alkyl iodide gave no addition product (Table 1, entries 3 and 4). The reaction with the hydrophobic primary alkyl iodide in H$_2$O–THF (1:1, v/v) proceeded to give the reduced product in 40% yield with a trace amount of the addition adduct (Table 1, entry 5). A tertiary alkyl halide was converted readily into the corresponding alcohol under the conditions (Table 1, entry 6).

Table 1 Radical Addition Reactions of Alkyl Halides (1 equiv) to Phenyl Vinyl Sulfone (1 equiv) with EPHP in H$_2$O

Entry	Substrate	EPHP (equiv)	AIBN (equiv)	Time (h)	Yield (%)
1		3	0.25	1	83
2[a]	*i*Pr–I	3	0.25	0.5	77
3	I(CH$_2$)$_2$CO$_2$H	3	0.25	0.6	71
4	CH$_3$(CH$_2$)$_{11}$–I	3	0.25	0.6	0 (77)[b]
5[c]	CH$_3$(CH$_2$)$_{11}$–I	3	0.5	2	4 (41)[b] (40)[d]
6		3	0.25	0.5	0 (72)[e]

[a] The reaction was carried out at 80 °C.
[b] Recovered starting material.
[c] In water/THF (1:1, v/v).
[d] *n*-Dodecane.
[e] 1-Adamantanol.

Next, we investigated the effect of phase transfer reagent on the reaction using cetyltrimethylammonium bromide (CTAB). The reaction of cyclohexyl iodide (1 equiv) with 2-cyclohexenone (1 equiv) in the presence of EPHP (3 equiv) and AIBN in water at 100 °C did not proceed efficiently giving 12% yield of the addition product (Table 2,

entry 1). A very similar result was obtained with a large excess of the radical acceptor using a water soluble radical initiator, 4,4′-azobis(4-cyanovaleric acid) (ACVA) (Table 2, entry 2). However, the reaction proceeded smoothly in the presence of a phase transfer agent (CTAB) (Table 2, entry 3). It implies that the solubility of substrates is a key factor for the efficiency of the reaction, and the solubility of substrates in H_2O enhanced by a phase transfer agent. The cationic phase transfer agent, CTAB, was found to be the most efficient phase transfer agent among the phase transfer agents used (Table 2, entries 3–5). The reaction with a hydrophobic primary alkyl halide produced a trace amount of the addition product without a phase transfer agent whereas in the presence of CTAB, a moderate yield of the addition product was obtained (Table 2, entries 6 and 7).

To examine the scope and limitations of this method, we applied it to adding alkyl radicals to various alkenes. The results are summarized in Table 3. The reactions with electron-deficient terminal alkenes proceeded with high efficiency and good yields (Table 3, entries 1,2 and 5–7). It is important to note that the addition reactions are quite efficient without using a large excess of alkenes. The reaction showed low reactivity when no CTAB (Table 3, entry 3) or a stoichiometric amount of EPHP (Table 3, entry 4) was used. In the case of an acyclic β-substituted alkene such as crotononitrile, there was no detection of the addition product (Table 3, entry 8). The reaction could also be carried out at room temperature. The reaction of cyclohexyl iodide with phenyl vinyl sulfone in the pres-

ence of Et_3B at room temperature gave 85% yield of the addition product (Table 3, entry 9). With 2-cyclohexenone, 63% of the addition product was obtained along with the addition product of an ethyl radical to the alkene in 13% yield (Table 3, entry 10).[9]

In summary, we have been developed an EPHP-mediated new process for 1,4-addition of alkyl radicals to electron deficient alkenes in water. It is noteworthy that high yields of the addition products were obtained without using a large excess of radical. For hydrophobic substrates, the efficiency of the reaction was enhanced dramatically by adding a phase transfer reagent.
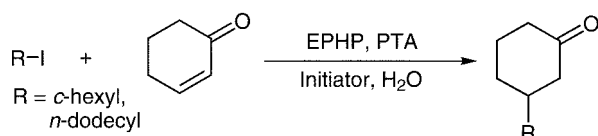
Typical procedure was as follows unless noted otherwise:

A mixture of cyclohexyl iodide (0.062 mL, 0.48 mmol), phenyl vinyl sulfone (80 mg, 0.48 mmol), CTAB (173 mg, 0.48 mmol), EPHP (0.68 mL, 2.09 M solution in 1,4-dioxane, 1.43 mmol), and ABCVA (42 mg, 0.12 mmol) in degassed H_2O (10 mL) under argon was heated to 80 °C for 1.5 h. The solution was diluted with EtOAc, and then washed with distilled water and brine consequently. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10:1, hexane/EtOAc) to give ethyl-(2-cyclohexyl) phenyl sulfone (98 mg, 82%).

Acknowledgement

Table 2   Radical Addition Reactions of Alkyl Iodides (1 equiv) to 2-Cyclohexenone (10 equiv) with EPHP in H_2O under Various Reaction Conditions

R—I   +   [2-cyclohexenone] $\xrightarrow[\text{Initiator, } H_2O]{\text{EPHP, PTA}}$ [3-substituted cyclohexanone]

R = c-hexyl, n-dodecyl

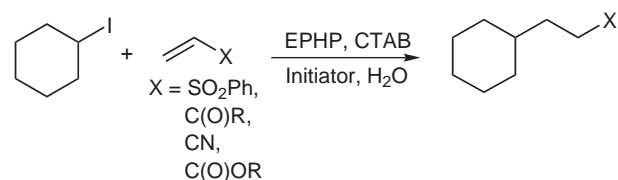| Entry	Alkyl Iodide	PTA (equiv)	Initiator (equiv)	Temp. (°C)	Time (h)	Yield (%)
1[a]	c-hexyl—I	–	AIBN (1.0)	100	10	12
2	c-hexyl—I	–	ABCVA (1.0)	80	7	17
3	c-hexyl—I	CTAB (1.0)	ABCVA (0.5)	80	3	82
4	c-hexyl—I	Triton-X-100[b] (1.0)	ABCVA (0.5)	80	3	58
5	c-hexyl—I	SDS[c] (1.0)	ABCVA (0.5)	80	3	41
6	n-dodecyl—I	–	ABCVA (0.5)	100	4	3 (30)[d]
7	n-dodecyl—I	CTAB (1.0)	ABCVA (0.5)	100	4	54 (30)[e]

[a] 1 Equiv of 2-cyclohexenone was used.
[b] Triton X-100: polyoxyethylene(10)isooctylphenyl ether.
[c] SDS: sodium dodecyl sulfate.
[d] n-Dodecane. Starting material was recovered in 62% yield.
[e] n-Dodecane.

Table 3 Radical Addition Reactions of Cyclohexyl Iodide to Various Alkenes with EPHP (3 equiv) in the Presence of CTAB (1 equiv) in H_2O

Entry	Alkene	Equiv of Alkene	Initiator (equiv)	Temp. (°C)	Time (h)	Yield (%)
1	SO_2Ph	1	ABCVA (0.25)	80	1.5	81
2	SO_2Ph	1	ABCVA (0.25)	100	0.5	94
3[a]	SO_2Ph	1	ABCVA (0.25)	80	1.5	43
4[b]	SO_2Ph	1	ABCVA (0.25)	100	2	53
5	$C(O)OCH_3$	1	ABCVA (0.25)	75	1.5	70
6	CN	3	ABCVA (0.25)	70	1.5	81
7	$C(O)CH_3$	3	ABCVA (0.5)	80	2.5	81
8	CN	3	ABCVA (1.0)	80	10	0
9	SO_2Ph	1	Et_3B (1.0)	25	4	85
10	O	10	Et_3B (1.0)	25	4	63 (13)[c]

[a] Without using CTAB.
[b] 1 Equiv of EPHP was used.
[c] 3-Ethylcyclohexanone.

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