1-Ethylpiperidium Hypophosphite: A Practical Mediator for Radical Carbon-Carbon Bond Formation

Doo Ok Jang,* Dae Hyan Cho, Chan-Moon Chung

Department of Chemistry, Yonsei University, Wonju 220-710, Korea
Fax +82(33)7602182; E-mail: dojang@dragon.yonsei.ac.kr

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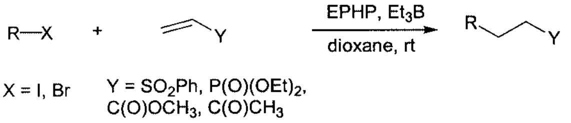
Abstract: 1-Ethylpiperidium hypophosphite could be used efficiently as radical chain carrier in the intermolecular carbon-carbon bond formation without using excess of alkenes under mild reaction conditions.

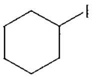
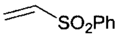
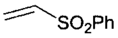
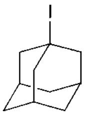
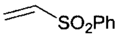
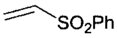
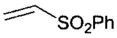
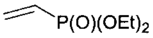
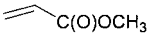
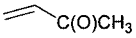
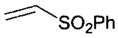
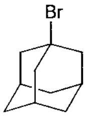
Key words: radical reactions, addition reactions, alkenes, alkyl halides

During last two decades, the number of application of radical reactions in organic synthesis has increased enormously. One of the important application of radical reactions is the formation of carbon-carbon bonds, either inter- or intramolecularly.[1] Especially ^{n}Bu$_3$SnH, organotin hydrides have been widely used as radical chain carriers for the carbon-carbon bond formation. However, they have several drawbacks including toxicity, high cost, instability to moisture, and difficulty to remove by-product from desired products. Therefore, they are not suitable for large-scale work and unacceptable for the pharmaceutical industry. There have been several research efforts to solve the problems. One approach is usage of modified tin reagents such as water-soluble,[2] polymer-supported,[3] or flurous tin hydrides.[4] Another is to find alternatives other than organotin reagents such as silanes,[5] phosphine-boranes,[6] hypophosphorous acid and amine salts of hypophosphorous acid.[7] 1-Ethylpiperidium hypophosphite (EPHP) is the most promising substitute among them for organotin hydrides in the radical reduction reactions such as dehalogenation and deoxygenation based on the criteria of cost-effectiveness, non-toxicity and easy work-up process. It has been applied for the construction of carbon-carbon bonds intramolecuarly.[8] However, there is no report that EPHP is used as a radical chain carrier in the intermolecular radical carbon-carbon bond formation that is more difficult than intramolecular carbon-carbon bond forming reactions.[9] In this paper, we wish to report the scopes and limitations of EPHP as a radical chain carrier in the intermolecular carbon-carbon bond formations.

When a mixture of cyclohexyl iodide (1 equiv), phenyl vinyl sulfone (1 equiv), 1-ethylpiperidium hypophosphite (3 equiv) and Et$_3$B (0.25 equiv) in dioxane under argon was treated with a catalytic amount of oxygen at room temperature followed by aqueous work-up, the addition product was obtained in 98% isolated yield. The reaction also proceeded without injection of oxygen, but longer reaction time was required. It was notable that 1-ethylpiperidium hypophosphite mediated radical addition reaction could be accomplished without using large excess of alkenes. Large excess of alkenes should be used to avoid the reduction of radical precursors in the organotin hydrides mediated carbon-carbon bond forming reactions. Another advantage of this process is that by-product are readily removed from desired products by aqueous work-up process.

Table Ethylpiperidium Hyphophosphite Mediated Radical Addition Reactions of Alkyl Halides to Alkenes.



Substrate	Alkene	O$_2$ (equiv)	Time (h)	Yield (%)
		0.015	1	98
		0	3	90
		0.015	1	94
		0.18	12[a]	84
		0.18	12[b]	29
		0.015	1	97
		0.015	1	80
		0.03	2	64
C$_{12}$H$_{23}$I		0.045	3	86
		0.015	1	0 (89)[c]

[a] At –20 °C, in toluene.
[b] At –40 °C, in toluene.
[c] Recovered substrate.

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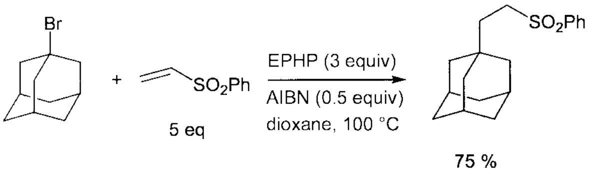
We chose 1-adamantyl iodide as a model compound to examine the reactivity of various alkenes under the conditions. The results are summarised in the Table. Vinyl sulfone produced the addition product in 94% yield. The reaction could be carried out even at –20 °C to produce the addition product in 84% yield. At –40 °C, the reaction could not proceed efficiently. Various electron-deficient alkenes could be utilised as good radical acceptors under the conditions. However, alkenes such as 1-octene and α,β-unsaturated cyclohexenone afforded 25% and 30% of addition products, respectively along with reduced products. The reaction could be accomplished with primary alkyl iodide as a radical precursor to give the corresponding addition product in 86% yield. When alkyl bromide was used as a radical precursor, the starting bromide was recovered without obtaining the addition product. However, the moderate yield of the addition product could be obtained when the reaction was carried out in boiling dioxane with excess of alkene (Scheme).



Scheme

In summary, we demonstrated that 1-ethylpiperidium hypophosphite could be used as radical chain carrier in the carbon-carbon bond formation without using excess of alkenes. The reaction could be carried out efficiently at room temperature and offered an easy work-up process.

Typical procedure was as follows unless noted otherwise:
To a solution of alkyl halide (1.0 equiv), alkene (1.0 equiv), 1-ethylpiperidium hypophosphite (3.0 equiv) and Et_3B (0.25 equiv, 1 M solution in hexanes) in dioxane was added air (1 mL/h, 0.015 equiv of O_2/h) at room temperature with a syringe pump until the reaction was completed by TLC. The reaction mixture was washed with water and then the product was purified by flash chromatography on silica gel.

Acknowledgement

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