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Hypophosphite Mediated Carbon-Carbon Bond Formation[1]: A Clean Approach to Radical Methodology

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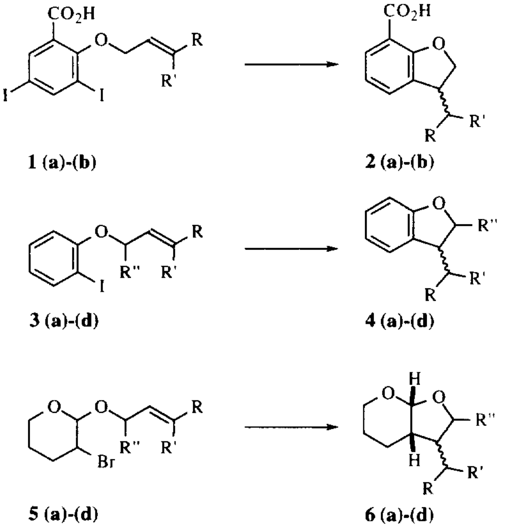
Abstract: Hypophosphorous acid (H_3PO_2) and its corresponding 1-ethylpiperidine salt have been used to mediate carbon-carbon bond forming radical reactions in both aqueous and organic media.The methods used avoid many of the problems associated with tributyltin hydride based methodology.

In recent years there has been great emphasis on finding alternative reagents to tributyltin hydride (Bu_3SnH).[2] Although widely used in synthetic studies as a radical chain carrier, the neurotoxicity of tin has limited the use of Bu_3SnH in industrial applications. This toxicity is a particular problem since tin residues are difficult to remove and often contaminate products. Water-soluble tin reagents developed by the teams of Breslow[3] and Collum,[4] as well as the polymer-supported tin reagents of Neumann *et al.*[5] have gone some way to improve matters although the use of these methods is limited. Silicon-based radical chain carriers such as tristrimethylsilylsilane[6] (TTMSS) provide an effective alternative to tin reagents although these compounds are often costly. The development of a "green", cost-effective alternative to Bu_3SnH would allow many more industrial applications of radical methodology. Recent publications[7] have described the use of phosphorus-centred radicals derived from H_3PO_2 and its salts to effect functional group interconversions such as de-oxygenations and de-halogenations. The methodology developed in these papers however has not, to date, been applied to radical C-C bond-forming reactions. We now report the successful use of H_3PO_2 and 1-ethylpiperidine hypophosphite in radical cyclisations[§] onto various alkene side-chain units of both aryl iodide and alkyl bromide substrates as shown in Figure 1.



1 (a)-(b) → **2 (a)-(b)**

3 (a)-(d) → **4 (a)-(d)**

5 (a)-(d) → **6 (a)-(d)**

No.	R	R'	R''	yield (%)
2(a)	H	H	-	68
2(b)	CH_3	H	-	74
4(a)	H	H	H	64
4(b)	CH_3	H	H	63
4(c)	CH_3	CH_3	H	66
4(d)	H	cyclohexyl		64
6(a)	H	H	H	85
6(b)	CH_3	H	H	94
6(c)	CH_3	CH_3	H	81
6(d)	H	cyclohexyl		76

Figure 1

Reaction substrates **1(a)-(b)** were treated at reflux with H_3PO_2 in the presence of sodium hydrogen carbonate. Initiation of the reaction was carried out using AIBN. On completion of the reaction, aqueous

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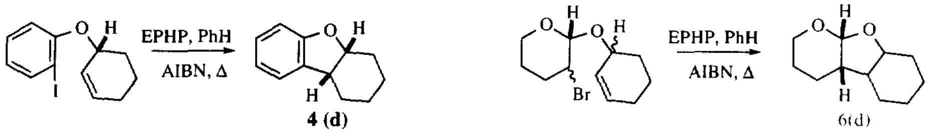
work-up allowed the 5-*exo*-trig cyclised, water-soluble products **2 (a)**-**(b)** to be isolated in good yield. The success of these cyclisations prompted investigation into the use of hypophosphite salts in organic media. Compounds **3(a)**-**(d)** were treated with 1-ethylpiperidine hypophosphite (EPHP) in refluxing benzene followed by aqueous work-up to yield the expected 5-*exo*-trig cyclisation products **4(a)**-**(d)**. In order to complement these aryl radical reactions, attention was focussed on alkyl radical cyclisations. Reaction substrates **5(a)**-**(d)** were prepared using a literature procedure[8] and treated under similar conditions to those used for the aryl radical substrates. The cyclisation reactions were again successful and gave rise to high yields of compounds **6(a)**-**(d)**.

In conclusion, the use of hypophosphite salts for the mediation of carbon-carbon bond forming reactions has been reported. Both aryl and alkyl radicals have been generated and cyclisation products have been isolated in good to excellent yield. An added advantage lies in the fact that hypophosphite residues are easily removed by aqueous work-up. The synthetic potential of this methodology has been demonstrated in the preparation of [6.5.6] tricyclic compounds **4(d)** and **6(d)**. Further applications of this chemistry to the total synthesis of natural products are under investigation.



4 (d)

6(d)

Figure 2

Example Preparation:

A stirred solution of 1-ethylpiperidine hypophosphite (3.58 g, 20 mmol) and 3-bromo-2-crotyloxytetrahydropyran **5(b)** (0.468 g, 2 mmol) in benzene (20 ml)was heated at reflux for 1h. AIBN (0.134 g, 0.8 mmol) was added in two portions over 30 min and reflux continued for 72 h. On cooling, the reaction was diluted with distilled petroleum ether (20 ml) and washed successively with sodium hydrogen carbonate (10 ml), aqueous hydrochloric acid (2M, 2 x 10 ml), sodium hydrogen carbonate (10 ml) and brine (10 ml). The organic layer was then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography on silica using petroleum ether : diethyl ether (5:1) afforded the product *7-ethyl-2,9-dioxabicyclo[4.3.0]nonane* **6(b)** as a colourless oil (0.293 g, 94%).

§ *Note added in proof.* After submission of this paper, we note the publication of related cyclisations onto alkynes.[9,10]

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