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β-Alkoxyacrylate radical cyclization mediated by hypophosphite and triethylborane in ethanol

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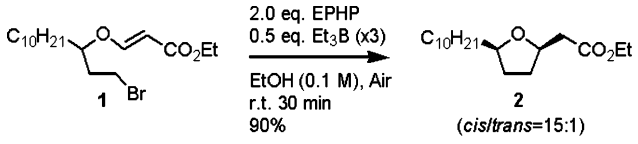
Abstract—Oxacycles were obtained in excellent yields via radical cyclization of β-alkoxyacrylates in the presence of 1-ethylpiperidinium hypophosphite and triethylborane in ethanol at room temperature.

Use of dialkyl phosphites and hypophosphite in radical-mediated deoxygenation and dehalogenation was pioneered by Barton. The reactions proceeded in the presence of benzoyl peroxide or AIBN in hot dioxane.[1] Similar reactions were carried out in the presence of AIBN in hot water or in hot DME.[2,3] 1-Ethylpiperidinium hypophosphite (EPHP)-mediated radical cyclization reactions proceeded in the presence of AIBN either in hot benzene, in hot water, or in hot toluene.[4–6] Radical cyclization reactions of allylic ethers of 2-iodophenol or 2-haloethanal allylic acetals were carried out using hypophosphite and AIBN in hot ethanol.[7] Use of VA-061, EPHP, and the surfactant CTAB in hot water was reported for radical cyclization of the usual iodo substrates.[8]

Stereoselective synthesis of oxacycles may be achieved via radical cyclization reactions of β-alkoxyacrylates.[9] Typical procedures utilize organotin hydrides and AIBN in hot benzene and we were keen to find alternative reaction conditions which avoid toxicity and work-up problems associated with organotin compounds. We examined efficacy of reactions using EPHP and found that the radical cyclization reaction of the β-alkoxyacrylate **1** proceeded efficiently in the presence of EPHP and triethylborane in ethanol at room temperature. An excellent yield of the tetrahydrofuran derivative **2** was obtained with 2 equiv. of EPHP when three half equivalent portions of triethylborane were added to the homogeneous ethanol solution at room temperature (Scheme 1). The reaction was complete in 30 min and proceeded with a good stereoselectivity favoring the *cis*-2,5-disubstituted product.



Scheme 1.

Tetrahydropyran formation was also efficient: the reaction mixture containing the substrate **3** was allowed to stand at room temperature for 1 hour to yield **4** in 85% yield. As expected, the cyclization reaction of **7** proceeded in a stereorandom manner to yield a 1:1 mixture **8**. The bromide **9** (an intermediate in the ambruticin synthesis[10]) was also a viable substrate, as the tetrahydropyran product **10** was obtained in 74% yield in 1 hour (Table 1). The aryl bromide **11** was a relatively poor substrate as the product **12** was obtained in lower yield. Generally, reaction conditions employed here were superior to the more common EPHP (5.0 equiv.)–AIBN (1.6 equiv.)–hot benzene (4 h) conditions as **10** was obtained in 55% yield under the latter conditions. In summary, efficient and clean radical cyclization reactions for many substrates should be possible employing EPHP (2.0 equiv.)–Et_3B (1.5 equiv.)–EtOH (rt).

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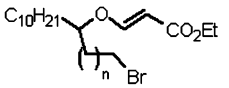
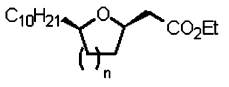
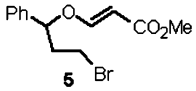
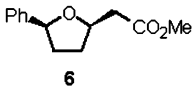
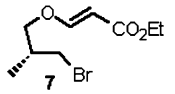
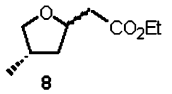
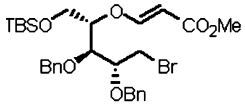
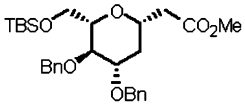
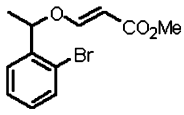
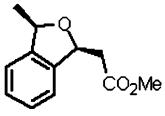
Table 1.

Substrates	Products		Time	Yield (%)
 **1** (n=1) **3** (n=2)	 **2** (n=1) **4** (n=2)	n=1 n=2	30 min 1 h	90 (15:1) 85 (>20:1)
 **5**	 **6**		30 min	87 (20:1)
 **7**	 **8**		30 min	93 (1:1)
 **9**	 **10**		1 h	74 (8:1)
 **11**	 **12**		30 min	35 (4:1)

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