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## A CONVENIENT PREPARATION OF $\alpha$ -PHOSPHONO ESTERS AND LACTONES VIA C-P BOND FORMATION

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**Abstract:** The reaction of ester and lactone enolates with diethyl phosphorochloridite, followed by air oxidation of the immediate reaction products, has proven to be a general alternative to the traditional Arbuzov synthesis of  $\alpha$ -phosphono esters and lactones.

Traditional methods<sup>1</sup> for the preparation of  $\beta$ -keto phosphonates and  $\alpha$ -phosphono lactones, methods such as the Arbuzov reaction<sup>2</sup> and the Michaelis-Becker reaction,<sup>3</sup> employ phosphorus nucleophiles for displacement of halogen from an  $\alpha$ -halo carbonyl compound. To broaden the variety of readily accessible phosphonates, both in terms of the carbonyl component and with respect to the phosphonate esters, we have initiated a program to develop new methods for C-P bond formation based on enolate chemistry and phosphorus electrophiles. These studies have resulted in several new methods for preparation of phosphonates, including a base induced rearrangement of vinyl phosphates<sup>4-7</sup> that provides phosphonate derivatives of cyclic ketones, esters, and lactones, and an application of Kowalski's method<sup>8</sup> for oxyvinyl lithium formation in reactions with dialkyl phosphorochloridates.<sup>9</sup> Our success in preparation of  $\alpha$ -phosphono ketones and some esters via reaction of the enolates with diethyl phosphorochloridite,<sup>10</sup> along with a report by Boeckman *et al.*<sup>11</sup> on C-P bond formation in dioxinones, prompts this report of our most recent efforts to prepare  $\alpha$ -phosphono esters and  $\alpha$ -phosphono lactones from their respective enolates.

The fundamental reaction sequence is given in equation 1. After treatment of the ester or lactone with LDA to form the lithium enolate, addition of a solution of diethyl phosphorochloridite and in situ air oxidation of the immediate products gives the expected phosphono ester or lactone.<sup>12</sup> As shown in Table 1, most of these

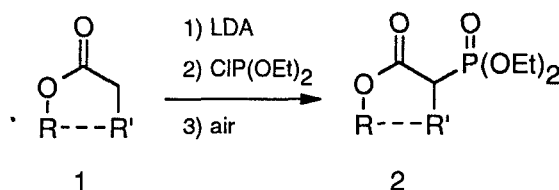
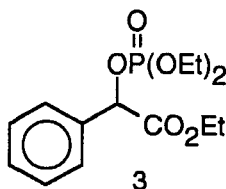


Table 1: Synthesis of Phosphonates from Ester and Lactone Enolates

Entry	Ester/Lactone	Phosphonate	n	% Yield	Solvent
1				57	ether
2				73	ether
3				60	ether
4				44	ether
5			1	66	ether/HMPA
6			2	62	ether/HMPA
7			1	69	ether
8			2	64	ether/HMPA
9			3	68	ether
10			9	51	ether

reactions could be conducted in diethyl ether. In some cases (entries 5, 6, and 8), addition of one equivalent of HMPA decreased by-product formation considerably.<sup>13</sup>

As summarized in Table 1, the results were generally favorable even though all of these esters are somewhat hindered by substituents at the  $\beta$ -carbon. Ethyl cyclohexylacetate gave the desired phosphonate in 57% yield, which is consistent with earlier results obtained from ethyl isovalerate.<sup>10</sup> The comparably hindered ester methyl citronellate was converted to its phosphonate in 73% yield. Phosphonylation of an  $\alpha,\beta$ -unsaturated ester, ethyl 3,3-dimethylacrylate, gave only the  $\alpha$ -phosphono ester, with no trace of the *gamma* product detectable by  $^1\text{H}$  or  $^{31}\text{P}$  NMR. The only surprising result was found with ethyl phenylacetate (entry 4). In this one case, the typical reaction sequence resulted in formation of a second major product (ca. 25%) along with the desired phosphonate<sup>5</sup> (44%). The unexpected product was identified as the diethyl phosphate derivative of ethyl mandelate (**3**) based on its spectral data. However, despite formation of this mandelate derivative, the yield of the desired phosphonate is improved over that obtained through vinyl phosphate rearrangement.<sup>5</sup>



This procedure also can be applied to some short chain diesters. Both diethyl succinate and diethyl glutarate gave the desired phosphonates<sup>14,15</sup> in good yields. However, no phosphonates were detected (by  $^{31}\text{P}$  NMR or GC-MS) with the longer chain diesters diethyl adipate or diethyl pimelate. Presumably the anions of these diesters undergo competitive Claisen condensations instead of the desired reaction.

Finally, we have examined use of this sequence to prepare  $\alpha$ -phosphono lactones directly from lactones of different ring-sizes. Five-, six-, and seven-membered ring lactones (entries 7, 8, and 9) gave the known phosphonates<sup>5</sup> in an average yield of approximately 67%. This success prompted investigation of a macrocyclic lactone. The 13-membered-ring lactone (entry 10) was converted to the target phosphonate in 51%, representing a dramatic improvement over the previous synthesis.<sup>5</sup>

While many phosphono esters and lactones can be prepared by the Arbuzov synthesis, that reaction is sensitive to steric hindrance.<sup>16</sup> Furthermore, an Arbuzov synthesis generally requires initial preparation of the  $\alpha$ -halo ester or lactone. The phosphorochloridite/oxidation approach appears to be less sensitive to steric factors, and proceeds directly from the ester or lactone to the phosphonate without preparation

of the  $\alpha$ -halo compound. Based on the examples reported here, this method appears to be general and more convenient than a traditional Arbuzov synthesis of phosphono esters and lactones.

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