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C-PHOSPHORYLATION OF ENOLATES: AN ALTERNATE ROUTE TO COMPLEX CARBONYL-ACTIVATED PHOSPHONATES

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Summary: *A one-pot two-step phosphorylation procedure is described which is suitable for the preparation of thermally labile or highly substituted dialkyl phosphonates for use in Horner-Emmons olefinations. Such systems are not readily available using the traditional methods such as the Arbuzov reaction or acylation of dialkyl phosphonate carbanions. Reaction of dioxinone lithium enolates with diethyl chlorophosphite followed by oxidation provide the desired phosphonates in good to excellent yields and conversions.*

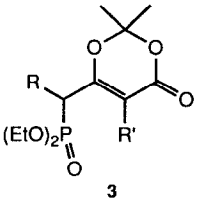
The utility of carbonyl-activated dialkyl phosphonates as reagents to effect olefination in complex substrates *via* the Horner-Emmons reaction is clearcut, and this methodology enjoys broad applications in contemporary synthetic chemistry.[1,2] However, far less effort has been expended in attempts to broaden the range of methods to prepare structurally complex and/or sensitive carbonyl-activated dialkyl phosphonates. The principle methods employed are based upon the Arbuzov reaction or upon C-acylation of α-phosphono carbanions.[1,2] These methods have significant limitations on their scope due to the lack of availability of the required starting materials (α-halo carbonyl compounds, acyl halides, or substituted dialkyl phosphonates), inherent limitations due to substitution (steric factors), and thermal and/or base sensitivity of the product phosphonates.[3] Accordingly, a number of new methods have been developed over the past several years which obviate some of the problems, but a truly general synthesis has yet to emerge.[3–5]

$(EtO)_2P(O)Cl$

1

$(EtO)_2PCl$

2



3

One potentially very general solution would involve direct C-phosphorylation of the appropriate carbonyl compound *via* the derived enolate. However, this process is not normally viable for aldehyde, ketone and ester enolates, since these species react principally or exclusively at oxygen with chlorophosphates such as **1**.[6] Since it had been previously established that substitution of carbanions at phosphorus is possible with lower oxidation state phosphorus (III) compounds,[7] we reasoned that under appropriate conditions (choice of counterion, solvent, temperature), a less

electrophilic phosphorus (III) derivative such as diethyl chlorophosphite (**2**) might react smoothly with enolates principally at carbon rather than oxygen, and be readily oxidized during workup to the desired phosphonate (Eq **1**). Furthermore, the required carbonyl compounds are generally more readily accessible, and a multitude of methods can be employed to generate an appropriate enolate. This method seemed particularly attractive for the preparation of thermally labile highly substituted dioxinone phosphonates of general structure **3** which we required for construction of substrates for our studies of ketene-mediated macrolactonization.[8] Thus, we examined the feasibility and generality of this method as decribed below.

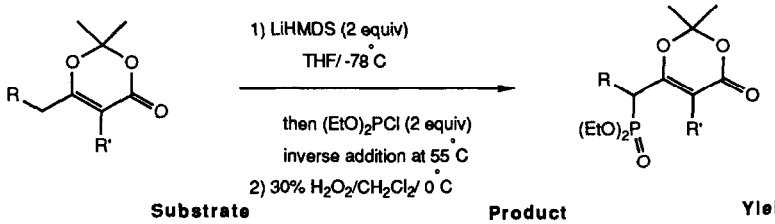
The required substituted dioxinones **4-7** (50-90%) were obtained by variations of literature procedures generally involving preparation of the appropriate β-keto acid *via* carboxylation of the enolate, and formation of the dioxinone by treatment with acetone in the presence of H_2SO_4/Ac_2O (Table 1).[9,10] In the case of **8-10**, alkylation of the dioxinone lithium enolate with the appropriate halide (iodide or bromide) afforded a mixture of α and γ alkylated dioxinones (1-3:1 (γ:α)) in 80-90% yield from which the desired γ-alkylated isomer was isolated by chromatography.[11]

The required dioxinone enolates could be generated with a variety of strong bases, however, control experiments showed that secondary amine bases, such as LDA, were not useful since the byproduct amines reacted readily with **2** necessitating use of a larger excess of phosphorylating agent. The best conditions were found to be use of $LiN(TMS)_2$ (2 equiv) in THF at -78°C which afforded the derived enolates quantitatively as judged by deuterium encorporation. Preliminary experiments involving slow addition of **2** (2 equiv) to a solution of the enolate at -78°C followed by warming to room temperature, workup, and brief treatment with 30% aq H_2O_2 in CH_2Cl_2 at 0°C afforded disappointingly low yields and conversions to the desired phosphonates. Since the air sensitivity of the intermediate phosphites precluded their isolation and purification, we routinely oxidized the crude products directly to the phosphonate prior to isolation and purification.

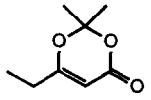
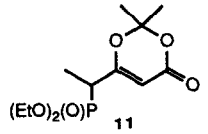
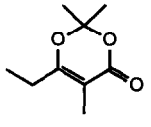
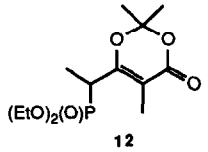
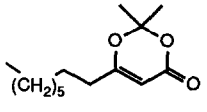
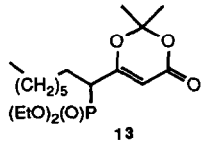
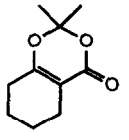
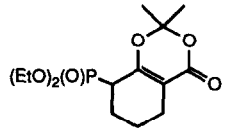
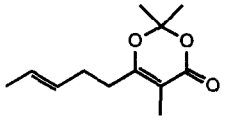
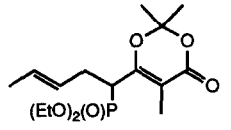
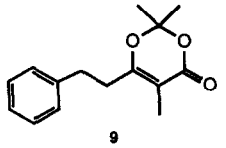
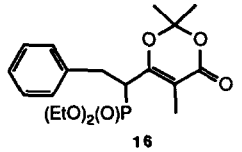
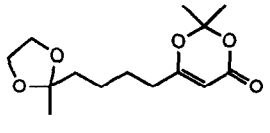
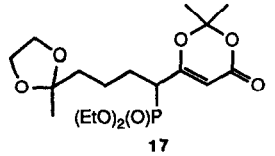
Control experiments were performed to identify the source of the problem. We were able to rule out acidic contaminants in **2**, as well as consumption of **2** by the hexamethyldisilazane. Furthermore, deuterium oxide quenching of the reaction mixtures prior to workup showed that enolate was still present ruling out proton transfer from the C-phosphorylated product and possibly competitive O-phosphorylation as well. Remarkably, the problem appeared to be an unexpectedly low reactivity of **2** with the enolate. We, therefore, employed much more vigorous conditions for the phosphorylation, and were rewarded with significant improvements both in yields and conversions.

The optimized reaction conditions, which were general for the group of substrates listed in Table 1, required the addition of a room temperature solution of the lithium enolate of the dioxinone, generated as described above, to a solution of **2** (2 equiv) in THF at 55°C and stirring at that temperature for 8 hr. Aqueous workup, and oxidation of the crude phosphite as described above followed by chromatographic purification afforded the desired phosphonates **11-17** in 59-83% yield for conversions of 51-100% (see Table 1).[10,12] The reaction conditions appear compatible with protected carbonyl groups and olefins, although we have not been, as yet, able to define conditions to achieve complete conversion. This difficulty may be the result of significant amounts of O-phosphorylation, although we never isolated products of that type due, undoubtedly, to their lability either to the oxidation conditions or to purification. Attempts to improve the conversion by the use of additives such as DMPU or HMPA, or the use of the more reactive potassium enolate were fruitless, resulting generally in increased yield but decreased conversion, results which are consistant with the hypothesis that O-phosphorylation is the competing process which limits the conversion.

Table 1



(1)

Substrate	Product	Yield(%)[a]
 4	 11	74(86)
 5	 12	59(100)
 6	 13	83(71)
 7	 14	75(56)
 8	 15	79(51)
 9	 16	65(70)
 10	 17	68(64)

a) Yields refer to isolated products after chromatographic purification and are corrected for conversion. Conversions are shown in parentheses.

This procedure should find use in cases where the carbonyl compounds are much more readily accessible than the corresponding halides or substituted alkyl phosphonates and in cases where the sensitivity of the substrate precludes the use of vigorous reaction conditions as are often required for the Arbuzov reaction. We will now examine simple ester and ketone enolates, although available precedent from acylation reactions of these species would suggest that the latter may be too unreactive and unselective to be of preparative use.

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(12) Typical experimental procedure: A solution of dioxinone **6** (50.4 mg; 0.21 mmol) in 1.7 mL of anh THF was cooled to -78°C and treated with 0.441 mL of a 1.0 M solution of LiHMDS in THF. After stirring for 40 min, the solution was warmed to room temperature, and transferred *via* syringe to a solution of chloro phosphite **1** (66mg, 0.42 mmol) in 2 mL of THF at 50°C. After 8hr at ~50°C, the mixture was quenched with 1 mL of sat NH_4Cl, diluted with 10 mL of ether, and the layers separated. After drying and concentration, the residue was redissolved in 2 mL of CH_2Cl_2, the solution cooled to 0°C and treated with 0.1 mL of 30% H_2O_2 for 3 min. The reaction was quenched with aq. $NaHSO_3$, the layers separated, and the organic phase dried and concentrated to afford, after chromatography on SiO_2 with elution by 50% EtOAc/hexanes, 45 mg (83%) of phosphonate **13** as a colorless oil along with 15 mg of recovered **6** (71% conversion).

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