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REGIOCONTROLLED METALATION OF DIETHYL β-DIALKYLAMINOVINYLPHOSPHONATES: A NEW SYNTHESIS OF SUBSTITUTED β-KETOPHOSPHONATES

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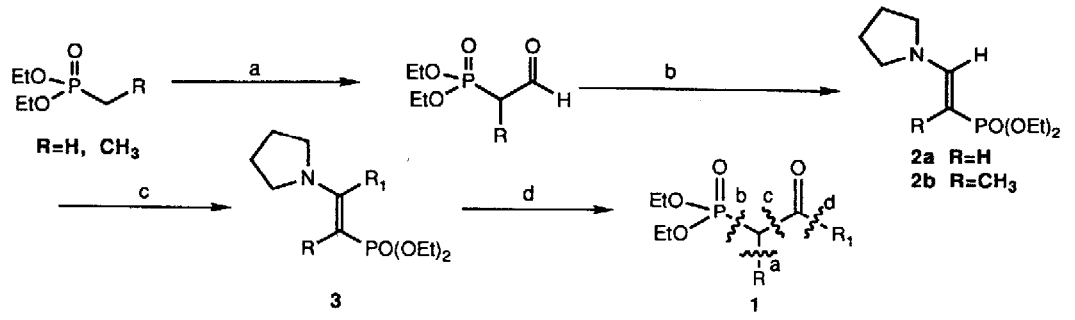
Summary: The metalation of diethyl β-dialkylaminovinylphosphonates (vinylogous phosphoramides (VPA)) and their reaction with a variety of electrophiles is described. Upon mild hydrolysis these derivatives provide good yields of β-ketophosphonates.

Traditional methods for preparation of substituted phosphonates are of limited value for the preparation of substituted β-ketophosphonates **1**, reagents useful for homologation of aldehydes and ketones to α,β-unsaturated ketones *via* the Wadsworth-Emmons/Horner reaction.[1,2] Recently, several new methods have been developed with the goal of providing a synthetic route to this class of compounds, however, as yet a general synthesis has not become available.[3,4] Previous approaches have focussed on construction of bonds **a** - **c** in **1**.[4,5] Herein we describe our studies of a fundamentally different bond construction (bonds **d** and/or **a** in **1**) which gives access directly to β-ketophosphonates of a broad range of structural types. Conceptually related to the metalation of acrylic acid derivatives described by Schmidt[6] and our work and that of others concerning heteroatom assisted vinyl anion formation,[7] this lynch-pin approach employs vinyl anions generated by regiocontrolled metalation of diethyl β-dialkylaminovinylphosphonates **2** (vinylogous phosphoramides (VPA)).

Suitable vinylogous phosphoramides such as **2a,b** are readily available in good overall yield (60-70%) as shown in Scheme 1.[8,9] Metalation of **2a** and **2b** under kinetic control occurs readily α to the pyrrolidino group upon treatment of **2a** or **2b** in THF at -78°C (or -40°C for 2b) with sBuLi for 40 min (2h for **2b**) as demonstrated by deuterium incorporation upon quenching with D_2O (100%).

The α-pyrrolidino lithium anions derived from **2a** and **2b** react quite readily with a variety of electrophiles as shown in Table 1.[10] Primary alkyl halides react smoothly although inverse addition of the anion at 0°C is required to maintain the regiochemical integrity of the initially formed anion in the case of EtI. Isopropyl bromide proved unreactive independant of addition mode or counterion (Li, Cu) . Acylation by both methyl and allyl chloroformate also proceeded uneventfully and in good yield providing access to pyruvyl phosphonates which may have considerable utility for the preparation of substituted vinyl pyruvates. The intermediate substituted vinylogous phosphoramides **3** can be readily isolated *via* workup at neutral pH and are quite stable to storage. Mild acidic hydrolysis with either oxalic acid on SiO_2 or aq EDTA led cleanly and in high yield to the derived β-ketophosphonates **1**.[11] However, attempted reaction with epoxides and aldehydes or ketones led to intractable materials possibly due to enolization or the instability of the products to workup. Use of chelating counterions which would reduce the basicity of the anion could conceivably obviate this limitation.

SCHEME 1[a]



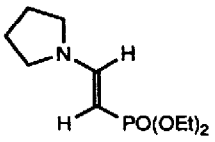
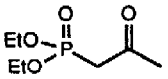
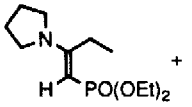
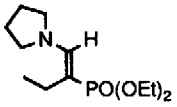
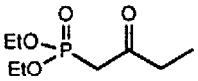
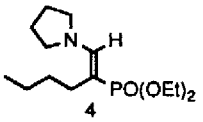
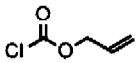
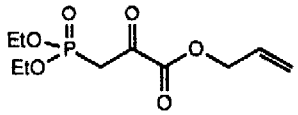
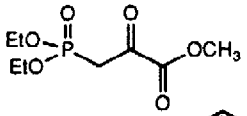
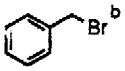
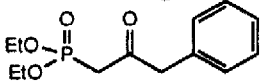
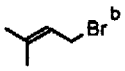
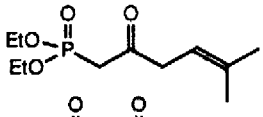
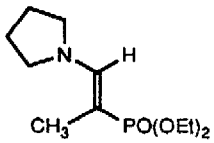
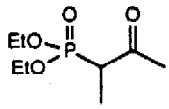
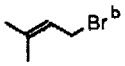
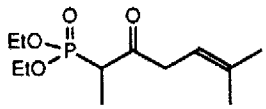
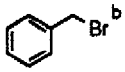
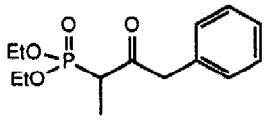
[a] **Reagents:** a) nBuLi (1.2 equiv, 1.6 M in hexanes), THF, -78°C, 0.5h then DMF (1.2 equiv), -78° → 25°C, 0.5h followed by 20% aq HCl (v/v), 25°C, 2h; b) pyrrolidine (1.2 equiv), PhH (-H_2O), Δ, 2h; c) sBuLi (1.2-1.5 equiv, 1.3M in C_6H_{12}), THF, -78° or -40°C, 40min to 2h then R_1X (1.5-4 equiv), -78° or -40° → 25°C, 1h; g) oxalic acid on wet SiO_2, 25°C, 1h or aq EDTA (0.08 M), Et_2O, 25°C, 1-5h.

Not surprisingly, the lithium anions derived from **2a** and **2b** failed to react cleanly with activated electrophiles such as allylic and benzylic bromides, although these classes of halides could be coupled effectively *via* the homocuprate, obtained by treatment of CuBr-DMS complex with 2 equivalents of lithio **2a** or **2b**, to give good yields (based on halide) of the expected δ,ε olefinic or aryl β-ketophosphonates upon mild acidic hydrolysis. In these cases, to avoid formation of undesirable byproducts during workup, the crude reaction mixture was directly subjected to hydrolysis with aq EDTA (0.08 M)/ Et_2O (2 phase system) which afforded the δ,ε-unsaturated β-ketophosphonates **1** (R = $CH_2CH{=}C(CH_3)_2$ or CH_2Ph).[12]

The α-pyrrolidino anion derived from **2a** undergoes isomerization to the thermodynamically favored α-phosphono anion on warming to room temperature, in a manner similar to the acrylates studied by Schmidt (Table 1).[6,13] However, for **2a**, the apparent mixture at equilibrium (~3-4:1 α-phosphono/α-pyrrolidino) as judged by deuterium quenching is less enriched in the more stable anion presumably reflecting the smaller difference in pKa of the two protons in the vinylogous phosphoramides when compared to the related acrylates, as the result of poorer anion stabilization by the phosphono group. Quenching with reactive halides (eg. EtI) affords mixtures of vinylogous phosphoramides **3** whose ratio roughly reflects the equilibrium ratio of anions. However, when a less reactive halide (eg. nBuBr) was employed with the equilibrated anion mixture derived from **2a**, alkylation was observed only α to phosphorus but conversion was incomplete. The residual starting material is approximately that corresponding to the α-pyrrolidino anion present in the mixture and may arise *via* elimination due to the relatively high basicity of the α-pyrrolidino anion. Altering the electronegativity of the phosphorus moiety by adjustment of the substitution at phosphorus may overcome this difficulty.

These results indicate that the anions derived from vinylogous phosphoramides represent a new and potentially useful approach to the preparation of β-ketophosphonates which are difficult to obtain by more conventional methods. Further investigations are in progress to explore the scope of the methodology and solutions to current limitations.

Acknowledgment - We gratefully acknowledge a grant from the National Cancer Institute of the NIH (CA-29108) in support of these studies and for an NRSA fellowship to M.A.W (GM-10641).

VPA	Electrophile	Hydrolysis	Product	Yield
	CH_3I	A		80[c]
	EtI		SM +  + 	
			1 : 3 : 1[g]	
	EtI [a]	A		76
	nBuBr		 + SM	
			4 : 1[g,h]	
		A		74
	$ClCO_2CH_3$	A		48
	 [b]	A		58[d]
	 [b]	B		85[d]
	CH_3I	A		74[e]
	 [b]	B		59[f]
	 [b]	A		22[d]

Hydrolysis conditions: (A) oxalic acid/SiO_2/CH_2Cl_2 (B) 0.08 M EDTA/Et_2O

(a) inverse addition of anion to electrophile (b) homocuprate of anion employed

(c) yield varied from 40-60% on 1g scale (d) based on homocuprate (e) 2 equiv sBuLi and 4 equiv MeI

(f) based on electrophile, 2.5 equiv of homocuprate employed (g) ratio based on integration of proton NMR

(h) 1 equiv DMPU added

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9. All new substances exhibited satisfactory spectroscopic (IR, NMR) and combustion or high resolution mass spectral analytical data.

10. Typical Experimental Procedure: A solution of **2a** (46.24mg, 0.18 mmol) in 0.73 mL of dry THF (~ 0.25 M) was cooled to -78°C and treated with 0.19 mL of 1.2 M sBuLi in cyclohexane (0.23 mmoles, 1.3 equiv). After stirring at -78°C for 40 min, the slightly yellowish solution was treated with CH_3I (17 μL, 0.27 mmol, 1.5 equiv) and allowed to warm to room temperature. After an additional 45 min, the reaction was quenched with sat NaCl and the mixture partitioned with Et_2O. The Et_2O extracts were dried with $MgSO_4$, and concentrated *in vacuo*. A slurry of 0.34g SiO_2 (60-200 mesh) in 1 mL methylene chloride was treated with 34 μL of 10% aq oxalic acid and stirred until homogeneous (approx. 2-3 minutes). A solution of crude **3** in 1 mL of CH_2Cl_2 was added and the reaction stirred at room temperature for 1 h. The reaction mixture was filtered through celite and glasswool and then concentrated *in vacuo* to give 0.025g (70% yield from **2a**) of the known β-ketophosphonate **1** (R_1= CH_3). Comparable yields have been obtained on 1-10g scale.

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12. For an alternate preparation of this class see: Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc.* **1984**, *106*, 3875.

13. The mechanism of this isomerization has not been determined, however, a process involving bimolecular proton transfer seems to be a plausible pathway.

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