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SYNTHESIS AND REACTIONS OF 3-SUBSTITUTED-2-PHOSPHOMETHYL ACRYLATES

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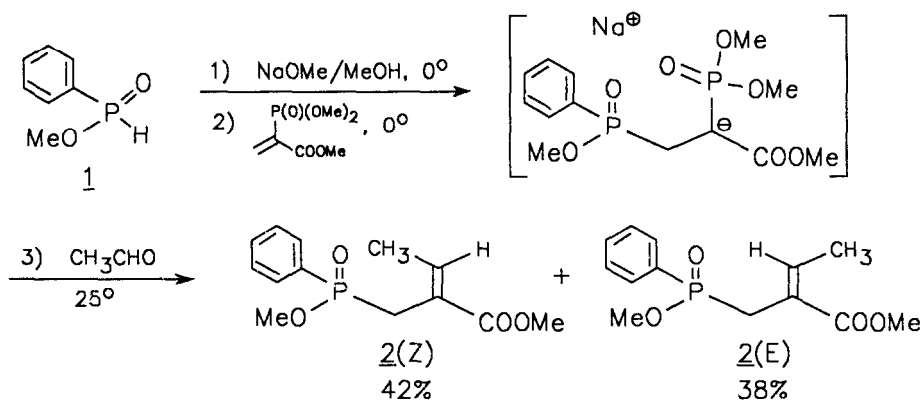
Abstract: 3-Substituted-2-phosphomethyl acrylates can be prepared from a variety of phophorous nucleophiles and aliphatic or aromatic aldehydes *via* a sequential Michael reaction followed by a Wittig-Horner-type olefination.

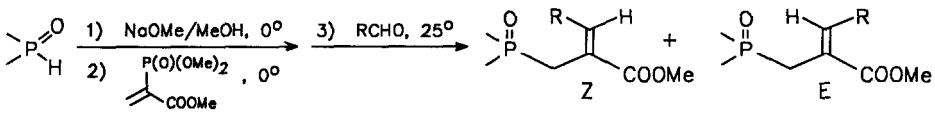
In recent years, interest in design of enzyme inhibitors has contributed to a renaissance in organophosphorous chemistry. For example, the similarity of phosphonic acids to carboxylic acids has made the former a logical replacement for the carboxyl group in several inhibitor designs.[1a,b,c] Phosphonic acids have also been employed in transition state inhibitors to mimic acylphosphate intermediates. Similarly, the tetrahedral configuration of pentavalent phosphorous species has made them appropriate choices for incorporation into inhibitors wherein a presumed reactive tetrahedral intermediate can be replaced by a covalently stable phosphorous moiety.[1b,d,e]

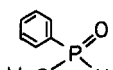
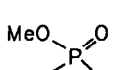
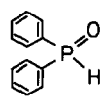
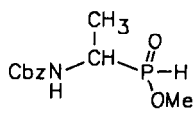
In connection with our interest in phosphinic acid enzyme inhibitors,[1d,e] we became interested in 3-substituted-2-phosphomethyl acrylates, both as an inhibitor design as well as an attractive synthetic intermediate. Existing methods of synthesis[2] are limited by lack of generality or by low yields. We wish to describe a convenient and efficient preparation of these compounds which will tolerate a multitude of functionality. The sequence utilizes readily available phosphorous nucleophiles in combination with simple aldehydes in a three-step, one-pot Wittig-Horner-type olefination[3], illustrated for the reaction of methyl phenylphosphinate and acetaldehyde[4] (Table 1; entry 4).



The reaction proceeds smoothly under mild conditions to afford the products in good to high yield; several examples are presented in Table I. In general, the phosphorous component, dissolved in methanol (0.3-0.5M), is treated with a slight excess of 2.0M methanolic sodium methoxide, and the resulting solution treated with 1.5 equivalents of 2-trimethylphosphonoacrylate[5] at 0°C. After 30 minutes, 2 equivalents of the aldehyde are added and the mixture stirred at ambient temperature for 3 hours. After extractive isolation, the products, obtained as a mixture of **Z** and **E** isomers, are purified and separated by routine silica gel chromatography.[6] Under these conditions, the **Z** isomer predominates slightly. Spectral identification of the isomers is based on the chemical shifts of the olefinic protons.[7] In the **E** isomers, this resonance generally appears at δ 6.0-6.5 ppm, while in the **Z** configuration, this signal is shifted downfield, and appears at about δ 7.0 ppm.

Table I

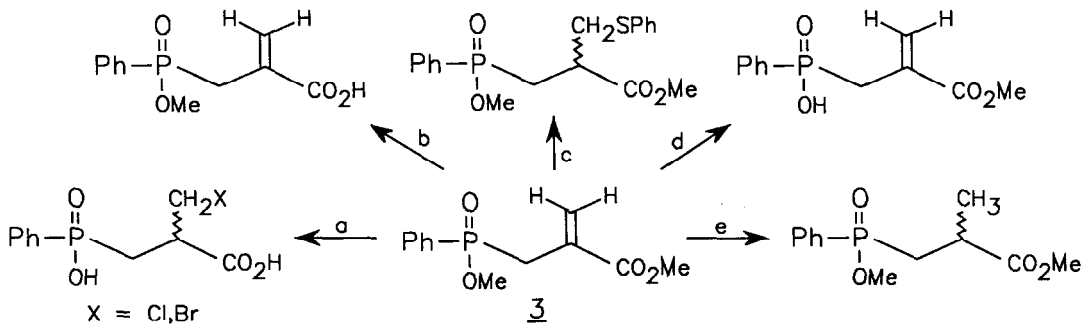


Phosphorous Nucleophile	Entry	RCHO	Yield[a] Z isomer	E isomer
	1	HCHO[b]	72%	
	2	CH_3CHO	42%	38%
	3	$PhCH_2CH_2CHO$	48%	36%
	4	$(CH_3)_2CHCHO$	38%	28%
	5	HCHO[b]	65%	
	6	$PhCH_2CH_2CHO$	44%	37%
	7	PhCHO	49%	35%
	8	$n-C_5H_{11}CHO$	44%	31%
	9	HCHO[b]	78%	
	10	$n-C_5H_{11}CHO$	50%	42%
	11	$cyclo-C_6H_{11}CHO$	32%	30%
	12	HCHO[b]	76%	

[a]Satisfactory spectral and microanalytical data were obtained for all compounds
[b]37% aqueous formaldehyde.

As demonstrated in the Table, the scope of this reaction is quite broad. Aliphatic and aromatic aldehydes, as well as formaldehyde, can be converted to the corresponding acrylate derivatives. Total yields of products are generally good; slightly lower yields are obtained from reactions employing α,α-disubstituted aldehydes (Table I; entries 4,11). Similarly, a variety of phosphorous nucleophiles can be employed, leading to a series of structurally diverse compounds.

The 3-substituted-2-phosphomethyl acrylates undergo a variety of simple transformations that increase their value as synthetic intermediates. As illustrated below for the adduct of methyl phenylphosphinate and formaldehyde, **3**, the molecule has several sites for potential elaboration.



a: HX, 100° b: 1) aq. LiOH/MeOH 2) 3N HCl c: PhSH/NaOMe/MeOH

d: 1) LiI/THF/25° 2) 3N HCl e: H_2, Pd/C, MeOH

Mineral acids add to the double bond (reaction **a**) in an anti-Markovnikov manner which takes place with concommitant hydrolysis of both esters. Sulfur nucleophiles and some nitrogen nucleophiles add to the acrylate unit (reaction **c**). Selective reaction of either the carboxylic or phosphinic acid ester can also readily be accomplished (reactions **b** and **d**). Hydrogenation of the acrylate double bond (reaction **e**) offers an alternate route[8] to 2-substituted-3-phosphopropanoate esters.

With several simple routes available for the synthesis of phophonous acids,[9] the methodology described here is particularly useful in the construction of phosphinic acid derivatives. Of special interest in this class are the aminoalkyl phosphonous acids, phosphorous analogs of naturally occuring amino acids.[9a] Use of these compounds in the sequence described here leads to a novel class of compounds, the dehydrophosphinodipeptides, illustrated by entry 12 in Table I. While several members of this class possess interesting biological properties in their own right[10], the compound shown is a key intermediate for further elaboration into an inhibitor of the enzyme D-alanyl-D-alanine ligase.[1e]

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4. ^{1}H NMR (300MHz, $CDCl_3$, ppm relative to internal $CHCl_3$ set at δ 7.25);
2(**Z**): δ 7.7 (m, 2H), 7.5 (m, 3H), 7.00 (m, 1H), 3.65 (d, 11Hz, 3H), 3.51 (s, 3H), 3.16 (d, 18Hz, 2H), 1.72 (dd, 5Hz, 7Hz, 3H).
2(**E**): δ 7.7 (m, 2H), 7.5 (m, 3H), 6.15 (m, 1H), 3.64 (d, 11Hz, 3H), 3.52 (s, 3H), 3.03 (m, 2H), 2.00 (dd, 5Hz, 7Hz, 3H).

5. Obtained from Fluka Chemical Corporation.

6. Preparative medium pressure chromatography was carried out with Lobar LiChroprep Si60 (E. Merck, 40-63μm) prepacked columns, eluting with EtOAc/MeCN (9:1) or EtOAc/MeOH (19:1). Under these conditions, the **Z** isomer elutes first.

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