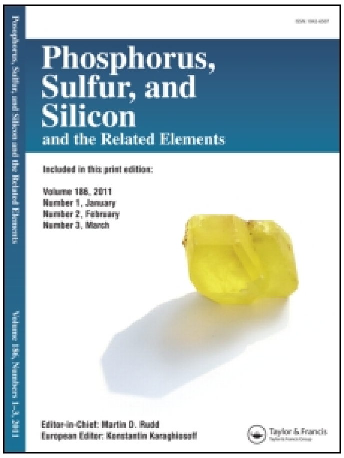

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A Facile Synthesis of Vinyl and Allylic 2,2,2-Trifluoroethyl Phosphonates

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Condensation of several representative aldehydes with the anion derived from tetrakis(2,2,2-trifluoroethyl) methylenediphosphonate, a new Wadsworth-Emmons reagent, afforded (Z)-vinyl phosphonates in good yields. The latter, when treated with a catalytic amount of potassium *tert*-butoxide in DMSO isomerized to the corresponding (*E*)-allylic phosphonates, which produce *E,Z*-dienes when reacted with a second aldehyde.

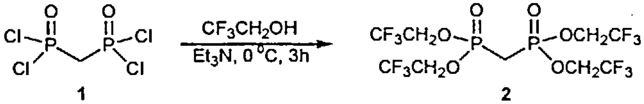
Keywords: vinyl phosphonate; allylic phosphonate; (Z)-alkene; diene

The past decade has seen a renewed interest in the synthesis of retinoids and carotenoids due in part to their diverse biological activity.[1] The major thrust of such synthetic efforts has been directed toward development of reliable methods for the stereoselective synthesis of conjugated polyenes.

Phosphorus ylides are important reagents for the construction of carbon-carbon double bonds, most notably because their use affords control of the olefin regio- and stereoselectivity.[2] Among the various types of precursors to phosphorus ylides, allylic phosphonates have emerged as valuable synthetic intermediates in the preparation of dienes[3] and polyenes[4], essential pivots in retinoid chemistry.[5] However, the Wadsworth-Emmons (W-E) reaction commonly employed in these syntheses shows a strong preference for the formation of the (*E*)-isomer. While attempts to increase the amount of (*Z*)-isomer have had limited success, it may be obtained under certain conditions.[6] For example, Still has developed a widely recognized method to selectively synthesize (*Z*)-α,β-unsaturated esters by employing a bis(trifluoroethyl) phosphonate moiety in the reagent.[7] Unfortunately, the utility of allylic bis(trifluoroethyl) phosphonate reagents to synthesize (*Z*)-olefins is limited because of the low nucleophilicity of the phosphite necessary to prepare them by classical routes.[8] Therefore, it would be synthetically useful to develop a reliable method for the preparation of allylic phosphonate reagents, which would allow (*Z*)-olefin selectivity in the preparation of polyenes.

This paper describes the synthesis of a new reagent, tetrakis(2,2,2-trifluoroethyl) methylene diphosphonate (**2**), and its utility in the preparation of (*Z*)-vinyl phosphonates. This reagent complements tetraethyl methylenediphosphonate, which under W-E reaction conditions affords the (*E*)-vinyl phosphonates.[9] Additionally, the tetrakis(2,2,2-trifluoroethyl) methylenediphosphonate provides a facile synthetic route to allylic bis(trifluoroethyl) phosphonates via the base catalyzed isomerization of the corresponding vinyl bis(trifluoroethyl) phosphonates.[10]

The new reagent, tetrakis(2,2,2-trifluoroethyl) methylenediphosphonate, was easily synthesized by reaction of methylenebis(phosphonic dichloride) (**1**) in 2,2,2-trifluoroethanol with triethylamine as base to furnish the bisphosphonate **2** in 90% yield.



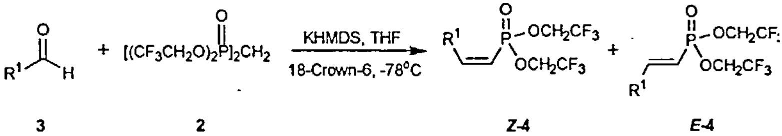
The reagent **2** was first allowed to react with benzaldehyde to identify the best conditions for the W-E reaction. Among the eight bases examined, potassium hexamethyldisilazide (KHMDS)/18-Crown-6/-78 °C was found to provide the highest yield of product with the greatest stereoselectivity. These data are consistent with the work of Still who showed high (*Z*)-selectivity in the synthesis of unsaturated esters using a bis(trifluoroethyl) phosphonoester under similar reaction conditions.[7]

The W-E reaction of **2** with other aldehydes was also studied. Reaction of **2** with several representative aldehydes using KHMDS as a base with 18-Crown-6 afforded the vinyl phosphonates in good yield with reasonable (*Z*)-selectivity (Table 1).[11]

The reaction of **2** with the representative aldehydes was sensitive to the structure of the aldehyde showing a reduced yield and (*Z*)-selectivity when the aldehyde contained acidic α-protons. Although it is not clear why compounds **4b** and **4d-e** showed lower yields, the reduced (*Z*)-selectivity may be caused by equilibration of the resulting olefins during the reaction in the presence of the 1,1,1,3,3,3-hexamethyldisilazane. This conclusion seems reasonable in light of the fact that **3b** under the reaction conditions showed not only the presence of the vinyl phosphonate (**4b**), but also the (*E*)-allylic phosphonate (approximately 10%, ^{31}P NMR δ 30.3) which has been demonstrated to result from the base catalyzed isomerization of the corresponding vinyl phosphonate.[10]

In view of the tendency of vinyl phosphonate **4b** to isomerize under the Wadsworth-Emmons reaction conditions for its synthesis, it was not surprising to find that

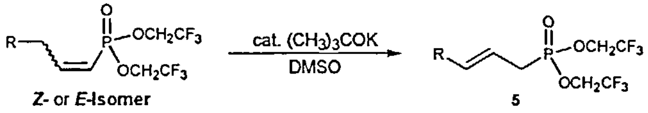
TABLE 1. Reaction of **2** with Representative Aldehydes

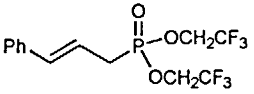
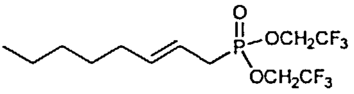
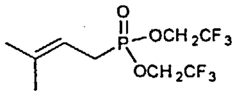


Entry	Carbonyl Compound	R^1	Yield	*Z*/*E* Ratio
a	Benzaldehyde	C_6H_5	99%	93/7
b	Phenylacetaldehyde	$C_6H_5CH_2$	84%	77/23
c	(*E*)-Cinnamaldehyde	$C_6H_5CH{=}CH$	88%	91/9
d	Heptanal	$CH_3(CH_2)_5$	66%	61/39
e	Isobutyraldehyde	$(CH_3)_2CH$	54%	56/44

either the (*Z*)- or (*E*)-isomer of the vinyl phosphonates **4b**, **4d** and **4e** isomerized exclusively to the (*E*)-allylic phosphonates when treated with a catalytic amount of potassium *tert*-butoxide in DMSO (Table 2).[10]

TABLE 2. Isomerization of Vinyl Phosphonates to Allylic Phosphonates



Allylic Phosphonate (5)	Yield	^{31}P NMR δ*E*-Isomer[a]
	94%	30.3 (28.7)[b]
	88%	31.6
	73%	30.7

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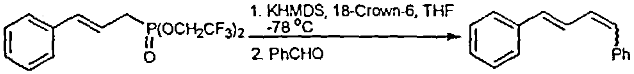
[a] Stereochemistry determined from ^1H NMR coupling constants and ^{31}P NMR data

[b] 20/1 mixture of *E*/*Z* stereoisomers after 1 hour

The stereochemical outcome of these reactions is also worth noting. Reaction of either the (*Z*)- or (*E*)-isomer afforded only the (*E*)-isomer of allylic phosphonate **5** as indicated by ^{1}H and ^{31}P NMR after 24 hours. However, ^{1}H and ^{31}P NMR analysis of the crude reaction mixture at 30 minute intervals revealed the presence of a small amount of (*Z*)-isomer (^{31}P NMR δ 28.7) during the first hour of the isomerization reaction. Further investigations in the stereocontrol of this reaction are currently underway.

To illustrate the utility of the allylic phosphonate reagents in the synthesis of dienes, the W-E condensation of **5b** with benzaldehyde was examined. Reaction of **5b** with benzaldehyde (KHMDS/18-Crown-6/-78 °C) afforded a 9:1 mixture of the *E,Z*- and *E,E*-isomers of 1,4-diphenyl-1,3-butadiene **6** in 76% overall yield (below).



5b **6**

In conclusion, a new approach to the synthesis of (*Z*)-vinyl phosphonates utilizing a new bisphosphonate reagent has been developed. In addition the vinyl bis(trifluoroethyl) phosphonates can be isomerized to the allylic bis(trifluoroethyl) phosphonates which may be of use as versatile intermediates in the stereoselective synthesis of polyenes containing (*Z*)-olefins.

Acknowledgments

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[11]] All compounds showed satisfactory ^{1}H, ^{13}C, ^{31}P NMR data and GC/MS data.