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A New Bisphosphonate Reagent for the Synthesis of (*Z*)-Olefins and Bis(trifluoroethyl) Phosphonates

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Abstract

A new Wadsworth-Emmons reagent, tetrakis(2,2,2-trifluoroethyl) methylenediphosphonate, was prepared and its reaction with aldehydes to yield (*Z*)-vinyl phosphonates is described. Additionally, an example of a base catalyzed isomerization of a (*Z*)-vinyl phosphonate to the corresponding (*E*)-allylic phosphonate is also discussed.

Keywords: Wadsworth-Emmons Reaction; Olefins; Phosphonic acids and derivatives; Ylides

The past decade has seen a renewed interest in the synthesis of retinoids and carotenoids due in part to their diverse biological activity [1,2]. The major thrust of such synthetic efforts has been directed toward development of reliable methods for the stereoselective synthesis of carbon-carbon double bonds.

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 [3]. Among the various types of precursors to phosphorus ylides, phosphonates have emerged as valuable synthetic intermediates in the preparation of alkenes, dienes [4] and polyenes [5]. However, the Wadsworth-Emmons reaction of the phosphonate reagents 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, high (*Z*)-selectivity in the synthesis of α,β-unsaturated esters has been obtained by employing bis(trifluoroethyl) phosphono [7] or diarylphosphono acetates [8] as reagents for the synthesis of (*Z*)-α,β-unsaturated esters. Unfortunately, the utility of 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 [9]. Therefore, it would be synthetically useful to develop a reliable method for the preparation of bis(trifluoroethyl) phosphonate reagents, which would allow the selective synthesis

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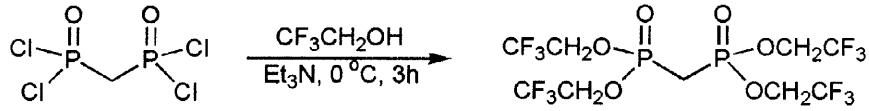
of compounds containing (*Z*)-olefins.

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 Wadsworth-Emmons reaction conditions affords the (*E*)-vinyl phosphonates [10]. Additionally, the tetrakis(2,2,2-trifluoroethyl) methylenediphosphonate provides a synthetic route to allylic bis(trifluoroethyl) phosphonates via the base catalyzed isomerization of the corresponding vinyl bis(trifluoroethyl) phosphonates [11].

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.[1]

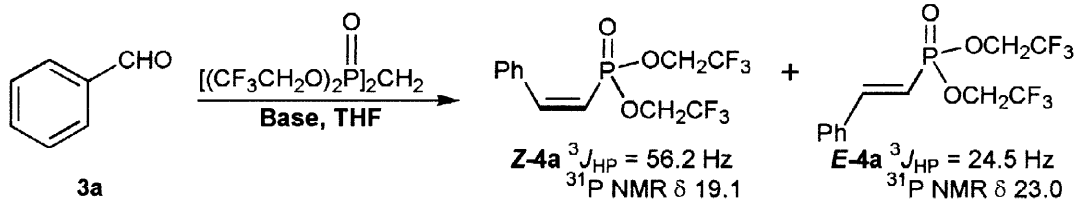


1 **2**

The reagent **2** was first allowed to react with benzaldehyde to identify the best conditions for the Wadsworth-Emmons reaction. Among the bases examined, potassium hexamethyldisilazide/18-Crown-6 was found to provide the highest yield of product with the greatest stereoselectivity (Table 1). These data are consistent with the work of Still who showed high (*Z*)-selectivity in the synthesis of unsaturated esters using a bis(trifluoroethyl) phosphono ester under similar reaction conditions [7].

Table 1

Wadsworth-Emmons Reaction of **2** with Benzaldehyde[2,3]



3a

***Z*-4a** $^3J_{HP}$ = 56.2 Hz, ^{31}P NMR δ 19.1

***E*-4a** $^3J_{HP}$ = 24.5 Hz, ^{31}P NMR δ 23.0

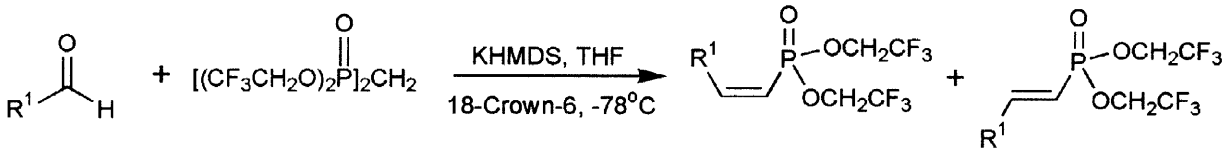
Base/Conditions	Yield	*Z*/*E* Ratio[a]
KHMDS, 18-Crown-6, -78 °C	99%	93/7
KHMDS, -78 °C	97%	67/33
KH, 18-Crown-6, -78 °C	31%	50/50
NaH, 18-Crown-6, -78 °C	67%	64/36
NaH, 15-Crown-5, -78 °C	73%	69/31
NaH, 15-Crown-5, 0 °C	58%	71/29
NaH, -78 °C	65%	59/41
NaH, 0 °C	40%	24/76

[a] *Z*/*E* ratios were determined from crude reaction mixtures by integration of both GC/MS peaks and ^{31}P NMR

Next, the Wadsworth-Emmons reaction of **2** with several representative aldehydes was studied. Reaction of **2** with a variety of aldehydes using potassium hexamethyldisilazide as a base and 18-Crown-6 afforded the vinyl phosphonates in good yield with reasonable (*Z*)-selectivity (Table 2).

Table 2

Reaction of **2** with Representative Aldehydes[2,3]



3 **2** ***Z*-4** ***E*-4**

Entry	Aldehyde	R^1	Yield	*Z/E* Ratio[a]	^{31}P NMR δ (*Z*, *E*)
a	Benzaldehyde	C_6H_5	99%	93/7	19.1, 23.0
b	Phenylacetaldehyde	$C_6H_5CH_2$	84%	77/23	19.9, 21.7
c	(*E*)-Cinnamaldehyde	$C_6H_5CH{=}CH$	88%	91/9	20.4, 22.8
d	Heptanal	$CH_3(CH_2)_5$	66%	61/39	20.4, 22.2
e	Isobutyraldehyde	$(CH_3)_2CH$	54%	56/44	20.4, 23.0
f	Cyclohexane-carboxaldehyde	C_6H_{11}	76%	74/36	19.6, 22.7

[a] *Z/E* ratios were determined from crude reaction mixtures by integration of both GC/MS peaks and ^{31}P NMR

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-f** showed lower yields, control experiments with compound ***Z*-4b** indicated the reduced (*Z*)-selectivity appears to result from equilibration of the resulting olefins 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 5%, ^{31}P NMR δ 30.3) which has been demonstrated to result from the base catalyzed isomerization of the corresponding vinyl

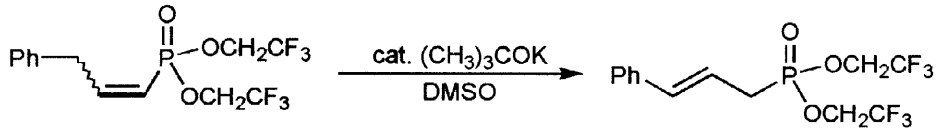
[1] **Tetrakis(2,2,2-trifluoroethyl) methylenediphosphonate (2)**: mp 37-39 °C; ^{1}H NMR δ 4.48 [m, 8H], 2.83 [t, 2H, J = 22.0 Hz]; ^{13}C NMR δ 122.2 [dq, J_{CCOP} = 8.4 Hz, J_{CF} = 277.5 Hz], 62.9 [dq, J_{COP} = 5.6 Hz, J_{CCF} = 38.4 Hz], 26.1 [t, J_{CP} = 141.0 Hz]; ^{31}P NMR δ 21.3.

[2] All compounds gave satisfactory ^{1}H, ^{13}C, ^{31}P NMR and GC/MS data. Stereochemical assignments of all compounds were determined from ^{1}H NMR $^3J_{HP}$ coupling constants and ^{31}P NMR data. In general, the (*Z*)-vinyl phosphonates exhibit upfield signals compared to the (*E*)-vinyl phosphonates in ^{31}P NMR. These data are consistent with previously reported ^{31}P NMR data on (*Z*)- and (*E*)-vinyl phosphonates [12].

[3] **Typical Wadsworth-Emmons Procedure**. The ylide was generated under an inert atmosphere by dropwise addition of potassium hexamethyldisilazide (0.50 mmol) to a stirred solution of **2** (0.50 mmol) and 18-crown-6 (2.50 mmol) in 10 mL of anhydrous THF, maintained at a temperature of -78 °C. After 20 minutes, addition of a solution of the desired aldehyde (0.45 mmol) in 2 mL of THF was followed by stirring of this reaction mixture for an additional 2 hours while warming to room temperature. Saturated NH_4Cl was added and the product was extracted with ether (2x). The ether extracts were then washed with water (2x) and brine. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo to afford the vinyl phosphonate isomers as colorless oils that were separable by flash chromatography.

phosphonate [11].

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 both vinyl phosphonates ***Z*-4b** or ***E*-4b** isomerized exclusively to the allylic phosphonate **5** when treated with a catalytic amount of potassium *tert*-butoxide in DMSO [11].



***Z*-4a** or ***E*-4a** **5**

The stereochemical outcome of this reaction is also worth noting. Reaction of either ***Z*-4b** or ***E*-4b** 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 of the base catalyzed isomerization, as well as stereochemical control of both vinyl and allylic phosphonate formation, are currently underway.

In conclusion, a new approach to the synthesis of (*Z*)-vinyl phosphonates utilizing a new bisphosphonate reagent has been developed. The reagent also allows an original approach to the synthesis of bis(trifluoroethyl) phosphonates, which are not readily available by other methods. In addition the synthesis of an allylic bis(trifluoroethyl) phosphonate via the base catalyzed isomerization of the corresponding vinyl bis(trifluoroethyl) phosphonate has also been demonstrated.

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