A Novel Double Olefination. Highly Stereoselective Synthesis of Trifluoromethylated 1,3-Butadienylphosphonates

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The bisphosphoryl-stabilized carbanion (**2**), generated from tetraethyl ethyl-1,1-bisphosphonate (**1**) and *n*-butyllithium in tetrahydrofuran (THF), was acylated by the addition of trifluoroacetic anhydride to give trifluoroacylated bisphosphonate (**3**). Without isolation, **3** was reacted with [(diethylphosphinoyl)methyl]lithium, and elimination of phosphonic acid anion afforded **4**. Treatment of **4** with LDA gave phosphoryl-stabilized carbanion **5**, which in the reaction medium was able to react with aldehyde to give substituted trifluromethylated 1,3-butadienylphosphonates in 66−88% yields with the 1*E*,3*E* isomer exclusively or predominately. Thus, the double-olefination methodology provides a simple and convenient synthesis of the title compounds. The first example of crystallization of diethyl 1-methyl-2-trifluoromethyl-4-(4′-nitrophenyl)-1,3-butadienylphosphonate with 1,4-dinitrobenzene was obtained by a cocrystallization method. Hence, the configuration of the products could be ascertained on the basis of the crystal structure. A possible mechanism for the explanation of stereochemical results is proposed.

Introduction

Recently, a double-olefination methodology has been found for the preparation of allenes in a one-pot reaction.[1] Vinylphosphonium salts are conveniently obtained from the reaction of carbonyl compounds with titanium-substituted ylide species and can be converted to allenes by deprotonation and condensation with aldehydes.[1a] Allenes can also be synthesized by condensation of a phosphorus methylide, Ti(IV) halide alkoxide and aromatic aldehydes in one-pot procedure.[1b] This methodology is simple and convenient. However, only aldehydes bearing an α-proton were able to afford 1,3-dienes rather than allenes.[1b]

Functionalized vinylphosphonates have attracted much interest in synthetic chemistry, and the synthetic applications have been widely investigated in the last two decades.[2] It has been reported in recent years that vinylphosphonates and 1,3-dienylphosphonates bearing an ene moiety are useful intermediates that have been used in the synthesis of bicyclic compounds and of cadalane and valerenic acid sesquiterpenoids.[3] However, the synthetic methodologies are the classic Knoevenagel condensation mediated by titanium compounds[3b] and the palladium-catalyzed coupling reaction.[4] Furthermore, the method for the preparation of fluorinated analogues is limited.[5] Therefore, to develop an effective method for their preparation would be valuable. Sequential transformations have emerged in recent years as a powerful methodology for their operational simplicity and efficient entry to complex compounds by including two or more transformations in a single operation to increase the complexity of substrate starting from commercially available relatively simple precusors.[6] In our laboratory, sequential transformations of phosphonates have been developed as a general synthetic approach for perfluoroalkylated α-fluoro-α,*β*-unsaturated esters,[7] perfluoroalkylated 4-cyanoalka-1,4-dienes,[8] perfluoroalkylated α,*β*-unsaturated nitriles,[9] and tetrasubstituted perfluoroalkylated (*Z*)-α,*β*-unsaturated esters,[10] which would be difficult to prepare otherwise.

Results and Discussion

In our continuing investigation of the synthetic application of seqential transformation of phosphonates in organic synthesis,[7−10] herein we report a novel double olefination via seqential transformation of phosphonates and its application to the synthesis of trifluoromethylated 1,3-butadienylphosphonates with 1*E*,3*E* isomers exclusively or predominately.

The reaction sequence is shown in Scheme 1. The bisphosphoryl-stabilized carbanion **2**, generated from the corresponding bisphosphonate and *n*-butyllithium in tetrahydrofuran (THF), was acylated by the addition of trifluoroacetic anhydride to give trifluoroacylated phosphonate **3.** Without isolation, **3** was attacked by [(diethylphosphinoyl)methyl]lithium, and elimination of phosphonic acid anion afforded **4**. Treatment of **4** with LDA gave phosphoryl-stabilized carbanion **5**, which in the reaction medium was reacted with aldehydes to give substituted trifluoromethylated 1,3-butadienylphosphonates in 66−88% yields with 1*E*,3*E* isomers exclusively or predominately. The results are summarized in Table 1.

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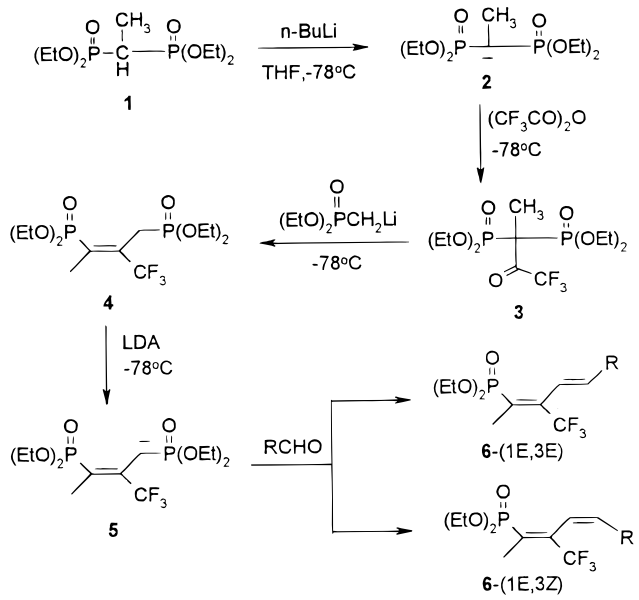
Scheme 1



Scheme 2

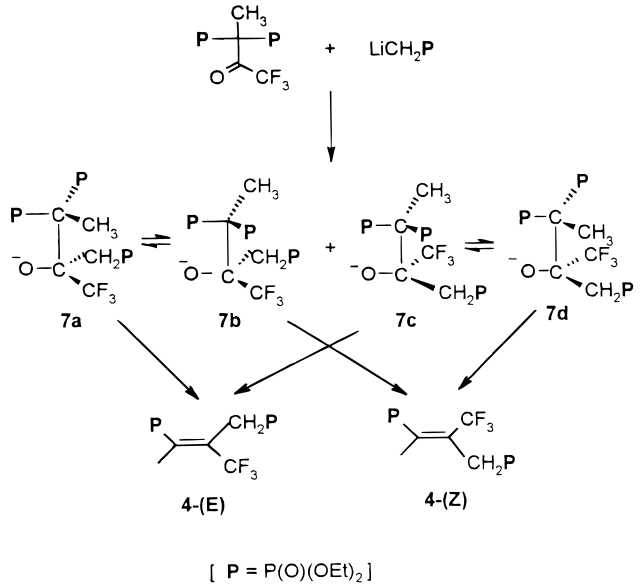


Table 1. Preparation of Substituted Trifluoromethylated 1,3-Dienylphosphonates

compd	R	yields[a] (%)	1*E*,3*E*:1*E*,3*Z*[b]
6a	c-C_3H_5	73	100:0
6b	2-furyl	81	100:0
6c	4-$NO_2C_6H_4$	72	100:0
6d	2-$CF_3C_6H_4$	83	100:0
6e	(*E*)-$C_6H_4CH{=}CH$	67	100:0
6f	4-$CH_3OC_6H_4$	80	98:2
6g	4-$CH_3C_6H_4$	88	95:5
6h	4-ClC_6H_4	66	95:5
6i	4-FC_6H_4	77	90:10
6j	C_6H_5	71	90:10

[a] Isolated yields. [b] The ratios of 1*E*,3*E* and 1*E*,3*Z* isomers were estimated on the basis of NMR data.

For the assignment of the configuration of products, we did the X-ray crystallographic analysis of **6c**. As is known, the derivatives of phosphonates usually are oils and hard to crystallize. Fortunately, to the best of our knowledge, the first example of crystallization of phosphonate (**6c**) was successfully obtained by a cocrystallization method. The crystal of diethyl 1-methyl-2-(trifluoromethyl)-4-(4′-nitrophenyl)-1,3-butadien-ylphosphonate was grown with 1,4-dinitrobenzene from *n*-pentane. The crystal structure of **6c** shows that the methyl group is cis with respect to the trifluoromethyl group (1*E*) and the H group is trans with respect to the H group (3*E*). Hence, the configuration of products could be ascertained on the basis of the crystal structure.

The stereochemical results may be rationalized as follows: The mechanism of first olefination for the formation of trifluoromethylated α,β-unsaturated bisphosphonate is analoguous to that of bisphosphonate reported in the literature[11,12] and is outlined in Scheme 2.

The stereoselectivity of the reaction is determined by the condensation step. The reaction is initiated by nucleophilic attack of nucleophile on the carbon−oxygen double bond of the carbonyl group, and the C−C bond making step results in a racemic adduct, for which two pairs of enantiomeric conformers are possible for the olefination step to occur (Scheme 2). The reactive size of groups is $PO_3Et_2 > CF_3 > CH_3 > CH_2PO_3Et_2$.[11] Since the **7a/7c** pair involves syn-periplanar (eclipsed) orientation of two pairs of "small"/"large" substituents ($CH_2PO_3Et_2/PO_3Et_2$, CF_3/CH_3), those conformers should be favored relative to the **7b/7d** pair, which contains unfavorable "large"/"large" (CF_3/PO_3Et_2) nonbond interactions. Therefore, the stereoselectivity of olefination in our case is a function of the conformational equilibrium of the adduct. Each of those intermediates decomposes via a syn elimination, affording **4-(*E*)** or **4-(*Z*)**. In our case, formation of **7a/7c** will be favored over **7b/7d**, and the *E* isomer was obtained exclusively.

The mechanism of the second olefination for the fomation of the title compounds is analoguous to that of the Horner−Waldsworth−Emmons reaction[13] and is outlined in Scheme 3.

Each of those intermediates decomposes via a syn elimination, affording **6-(1*E*,3*E*)** or **6-(1*E*,3*Z*)**. Like the former explanation, **8a** will be favored over **8b**, and the *E* isomer was obtained exclusively or predominately (see Table 1).

In conclusion, the double-olefination methodology has been applied to the synthesis of substituted trifluoromethylated 1,3-butadienylphosphonate, giving 1*E*,3*E* isomers exclusively or predominately in a one-pot reaction. This methodology provides a simple and convenient synthesis of the title compounds from readily available starting materials. The crystal of diethyl 1-methyl-2-(trifluoromethyl)-4-(4′-nitrophenyl)-1,3-butadienylphosphonate with 1,4-dinitrobenzene was obtained by a cocrystallization method for the assignment of the configuration of the products. The title compounds would be expected to be useful intermediates for the synthesis of fluorine containing biologically active compounds. This double-olefination methodology can also be extended to

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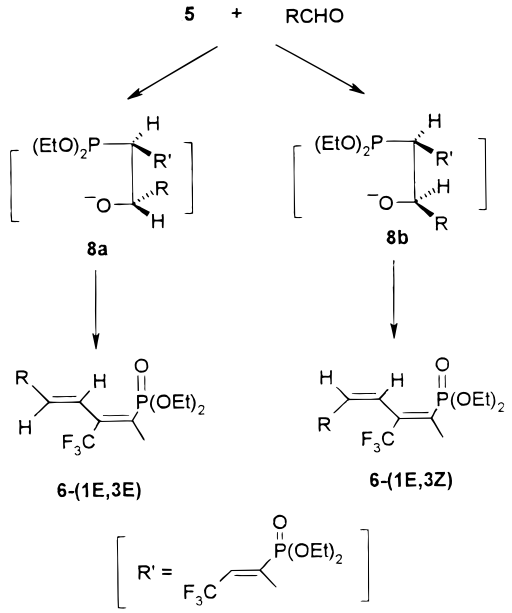
(13) Tasi, H.-J.; Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1994**, *59*, 7085.

Scheme 3



the synthesis of other functionalized fluorinated dienes and now is being pursued.

Experimental Section

General Methods. Analytical samples were purified by Kugelrohr distillation with the oven temperature (ot) given. The published ^{19}F NMR spectra were recalculated using a standard chemical shift of reference δ(F) (CF_3COOH) −76.5 ppm with respect to δ(F) ($CFCl_3$) 0.00 ppm. MS were obtained using ionization and are reported as *m/e* (relative intensity). All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column.

Materials. All solvents were purified before use. THF was purified by distillation from sodium benzophenone ketyl. Tetraethyl ethyl-1,1-bisphosphonates (**1**) were prepared according to the known procedure.[14] [(Diethylphosphinoyl)-methyl]lithium was prepared by the reaction of *n*-butyllithium (3 mmol) and diethyl methylphosphonate (3 mmol) in tetrahydrofuran (20 mL) for 30 min at −78 °C.

General Procedure for the Preparation of Trifluoromethylated 1,3-Butadienylphosphonates 6. *n*-Butyllithium (3.3 mmol in 2.5 mL hexane) was added dropwise over 10 min to a stirred solution of tetraethyl ethyl-1,1-bisphosphonate(3 mmol) in absolute THF (20 mL) at −78° C under nitrogen. The mixture was stirred at −78 °C for 0.5 h, and trifluoroacetic anhydride (3 mmol) was added to it in one portion. Stirring was continued at −78 °C for 1 h, after which time [(diethylphosphinoyl)methyl]lithium (3 mmol) was added dropwise to the mixture, which was stirred for another 1 h. Then LDA and aldehyde were added in turn to the mixture, which was stirred for 1 h and allowed to warm to room temperature. After the mixture was stirred for 3 h and the aldehyde disappeared (showed by TLC), the reaction mixture was poured into water (10 mL), and the water layer was extracted with dichloromethane (4 × 20 mL). The combined organic layer was washed with water (2 × 10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography, eluting with petroleum ether (60−90 °C)−ethyl acetate (9:1) to give the product **6**.

Diethyl 1-methyl-2-(trifluoromethyl)-4-cyclopropyl-1,3-butadienyl phosphonate (6a): yield 73%; bp 130 °C/0.8 mmHg; 1*E*,3*E*:1*E*,3*Z* = 100:0; IR (neat) 1630, 1250, 1130, 950 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 6.68(d, 1H, J = 15.8 Hz), 5.49 (dd, 1H, J =15.6, 6.7 Hz), 4.13−4.00 (m, 4H), 2.06 (dq, 3H, J = 15.4, 2.2 Hz), 1.52−1.42 (m, 1H), 1.31 (t, 6H, J = 7.1 Hz), 0.79 (dt, 2H, J = 8.1, 4.5 Hz), 0.49 (dt, 2H, J = 9, 4.5 Hz); ^{19}F NMR($CDCl_3$/$CFCl_3$) δ −56.2 (s, 3F); MS 313 (M^+ + 1, 9), 312 (M^+, 40), 283 (40), 256 (100), 241 (41), 215 (51). Anal. Calcd for $C_{13}H_{20}F_3O_3P$: C, 50.00; H, 6.46. Found: C, 50.05; H, 6.49.

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Supporting Information Available: Characterization and analytical data of compounds **6b**−**j** and X-ray structure report including ORTEP diagram and tables of crystallographic data, atomic coordinates and thermal parameters, and bond length and angles for **6c** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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