Sequential Olefinations on 2-Arylmethylidene-2-phosphonoacetates: A One-Pot Highly Stereoselective Synthesis of 1,2,3-Trisubstituted 1,3-Butadienes

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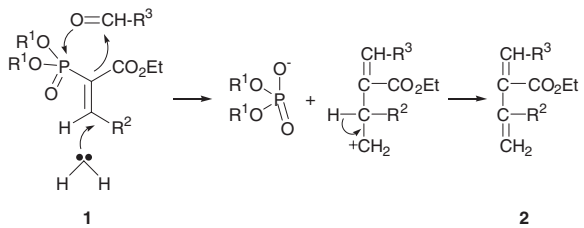
An efficient one-pot synthetic protocol for the preparation of 1,2,3-trisubstituted dienes by a sequential addition of 2-arylmethylidene-2-phosphonoacetates and various aldehydes to trimethylsulfonium iodide/sodium dimsylate in DMSO–THF has been developed. The dienes were produced with very high stereoselectivity preferring for the (*Z*)-isomer.

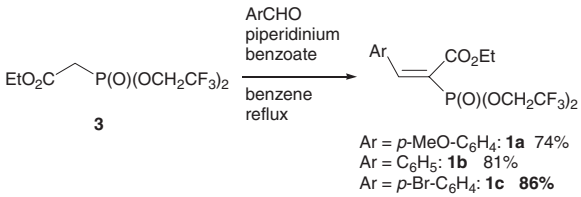
Substituted 1,3-butadienes enjoy widespread use in synthesis owing to their ready participation in the famous Diels–Alder (D–A) reaction for building the skeleton of complex molecules.[1] Electron-donating substituents on the dienes favor a normal-electron-demand D–A reaction, while electron-withdrawing groups on the same favor an inverse-electron-demand. Di- or tri-substituted butadienes containing electron donating and/or withdrawing groups at the 2,3- or 1,2,3-positions are very important, since they can be used for both classes of D–A reactions, depending upon the dienophiles and reaction conditions. Regio- and stereospecific methods to prepare highly substituted dienes having both electron-donating and electron-withdrawing substituents are limited. A convenient synthetic protocol is desired for quick access to these precursors. A multicomponent approach[2] to these highly and differentially substituted 1,3-dienes could be envisaged from simple building blocks, as shown in Scheme 1. The addition of a nucleophilic carbene equivalent to a Michael acceptor **1** containing a phosphonate group and its subsequent reaction with an aldehyde should provide the desired diene **2** via a Horner–Wadsworth–Emmons reaction.[3]

An excess of dimethylsulfonium methylide[4] or its combination with a base, like sodium dimsylate, can act as an equivalent of carbene. While the former protocol has been used for the preparation of allylic alcohols from epoxides[5] and one-carbon homologated terminal alkenes from alkyl halides or mesylates,[6] the later combination has been used in sequential one-pot olefination–methylation with various activated olefins for the preparation of 1-substituted vinyl silanes and styrenes.[7] We report herein on a successful one-pot synthetic protocol for the preparation of 1,2,3-trisubstituted dienes by a sequential addition of activated 2-arylmethylidene-2-phosphonoacetates and various aldehydes to trimethylsulfonium iodide–sodium dimsylate.

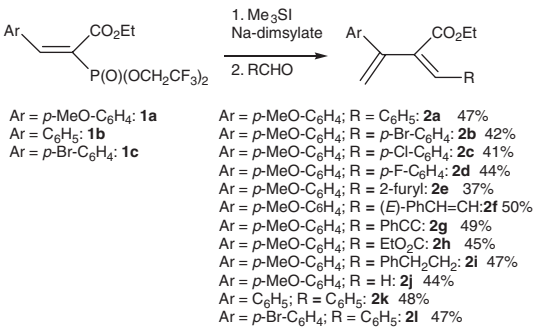


Scheme 1.

Three 2-arylmethylidene-2-phosphonoacetates **1a–c** were synthesized in very good yields using fluorinated phosphonoacetate **3**[8] and the corresponding aldehydes by a Knoevenagel-type reaction (Scheme 2). When **1a** was added to a reaction mixture containing 2.5 molar amounts of sodium dimsylate and 1 molar amount of Me_3SI, and quenched the reaction with benzaldehyde, it gave the desired diene **2a**, though in moderate yield, but exclusively as the (*Z*)-isomer. The corresponding ethylphosphonopropenoate derivative did not give the diene product under similar conditions. The electrophilicity of the diethylphosphonate group is less than that of the 2,2,2-trifluoroethylphosphonate group, which probably retards the formation of the betaine intermediate, and hence the diene product in a sterically congested system, like us. The higher electrophilicity of trifluoroethylphosphonate is also responsible for the formation of a kinetically controlled[3] (*Z*)-olefin product. To survey the generality of this one-pot sequential double olefination for the synthesis of substituted 1,3-dienes, we attempted the reaction with various aldehydes, as shown in Scheme 3. Reactions of 2-arylmethylidene-2-phosphonoacetates **1a–c** with benzaldehyde and substituted benzaldehydes exclusively gave the (*Z*)-isomers of the dienes. The product **2e**, obtained from 2-furaldehyde and **1a** was contaminated with 5% of its (*E*)-isomer. The diene products **2g** and **2h** contained 15% and 8% of the corresponding (*E*)-isomers, respectively. The (*E*)-isomers were formed with consistent and reproducible ratios, thus



Scheme 2.



Scheme 3.

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suggesting their direct formation in the H–W–E reaction. Base sensitive aldehydes, such as ethyl glyoxalate and 3-phenylpropanal, required the addition of a 0.5 molar amount of acetic acid prior to their addition into the reaction mixture.

In summary, this one-pot procedure offering high stereoselectivity and easy access to the starting materials makes this methodology of value for the synthesis of difficultly substituted dienes. Although the yields were moderate, it is worthwhile mentioning that the products were easily isolable by chromatography because the by-products were highly polar, or water soluble.

Experimental

Ethyl (*E*)-2-[Bis(2,2,2-trifluoroethyl)phosphonato]-3-(4-methoxyphenyl)-2-propenoate (1a). A General Procedure: A solution of *p*-anisaldehyde (1.83 mL, 15 mmol, 1.5 molar amount), **3**[8] (3.32 g, 10 mmol, 1 molar amount), and piperidinium benzoate (207 mg, 1 mmol) in benzene (23 mL) was heated under reflux fitted with a Dean–Starke apparatus for 3 days. The reaction mixture was cooled, washed with water and with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed to give **1a** ($E/Z = 95/5$) (3.31 g, 74%). Crystallization in EtOAc–hexanes provided pure (*E*)-**1a**. Data for (*E*)-**1a**: Mp 54 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, $J = 7.1$ Hz, 3H), 3.85 (s, 3H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.36–4.50 (m, 4H), 6.91 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 7.69 (d, $J = 28$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.63, 55.36, 62.02, 62.52 (dq, $J = 4.4$, 38.2 Hz, 2C), 114.12 (2C), 116.97 (d, $J = 190.4$ Hz), 122.45 (dq, $J = 9.8$, 277.5 Hz, 2C), 125.20 (d, $J = 22$ Hz), 132.53 (2C), 152.00 (d, $J = 7.6$ Hz), 162.35, 165.05 (d, $J = 14.1$ Hz). Anal. Calcd for $C_{16}F_6H_{17}O_6P$: C, 42.68; H, 3.81%. Found: C, 42.43; H, 4.10%.

One-Pot Synthesis of Ethyl (*Z*)-3-(4-Methoxyphenyl)-2-phenylmethylidene-3-butenoate (2a). A General Procedure: A solution of sodium dimsylate (1.25 mmol, 2.5 molar amounts) in DMSO (1.4 mL) was prepared, diluted with THF (1.5 mL), and cooled on an ice-salt bath (−8 °C). Solid Me_3SI (123 mg, 0.6 mmol, 1.2 molar amount) was introduced into the flask and the reaction mixture was stirred for 15 min. A solution of **1a** (0.225 mg, 0.5 mmol, 1 molar amount) in THF (2 mL) was rapidly added to the reaction mixture, slowly brought to room temperature, and stirred for 1 h. The reaction mixture was cooled (0 °C) and benzaldehyde (0.06 mL, 0.6 mmol, 1.2 molar amount) was added to it. The reaction mixture was stirred at room temperature overnight, diluted with water, and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed to give the diene **2a** (68 mg, 47%) as a thick oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (t, $J = 7.1$ Hz, 3H), 3.83 (s, 3H), 4.20 (q, $J = 7.1$ Hz, 2H), 5.32 (s, 1H), 5.36 (s, 1H), 6.69 (s, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.29–7.37 (m, broad, 7H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.75, 55.21, 61.09, 113.58 (2C), 115.74, 128.29 (5C), 129.52 (2C), 132.02, 133.48, 135.43, 136.23, 146.39, 159.33, 169.33. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.89; H, 6.55%. Found: C, 77.65; H, 6.81%.

The preparation and analytical data of **1b**, **1c**, and **2b**–**2l** are deposited as Document No. K04731 at the office of the Editor of Bull. Chem. Soc. Jpn.

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