

A Facile Synthesis of Ethyl 2,4-Dimethoxy-6-perfluoroalkylbenzoates via Acyclic Precursors

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The acyclic precursors, methyl 3-perfluoroalkyl-4-carbethoxy-5-methoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoates (**4**) were obtained via the addition reaction of ethyl 3-methoxy-4-(triphenylphosphoranylidene)but-2-enoate (**2**) with equally molar methyl 2-perfluoroalkynoates (**3**). Ethyl 2,4-dimethoxy-6-perfluoroalkylbenzoates (**5**) were synthesized in high yield via an intramolecular elimination of Ph₃PO of **4** by heating in anhydrous benzene in a sealed tube. The structure of these compounds was confirmed by IR, ¹H, ¹³C, 2D C-H cosy NMR and mass spectra and elemental analyses. The possible reaction mechanisms were also proposed.

Keywords acyclic precursor, intramolecular Wittig reaction, fluorinated polysubstituted arene, ethyl 2,4-dimethoxy-6-perfluoroalkylbenzoate

Introduction

Polysubstituted arenes are important intermediates in synthetic medicines and dyestuffs, and the fluorinated analogues are more attractive as a result of their lipophilicity and the increment of activity.^{1,2} Therefore, to study the convenient and efficient synthesis of polysubstituted arenes is valuable in organic synthetic methodology. We have designed a simple synthesis of fluorinated polysubstituted arenes through the intramolecular Wittig reaction of a new phosphorous ylide.³⁻⁶ The ylide possessing a conjugated six-carbon main chain with a terminal carbonyl group is the product of the nucleophilic addition of a phosphorane to an electron-deficient alkyne.

In this paper, we report a simple synthesis of ethyl 2,4-dimethoxy-6-perfluoroalkylbenzoates (**5**) from the acyclic precursors methyl 3-perfluoroalkyl-4-carbethoxy-5-methoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoates (**4**).

Results and discussion

Reaction of ethyl 3-methoxy-4-(triphenylphosphoranylidene)but-2-enoate (**2**), which was derived from bromide **1**, with equally molar methyl 2-perfluoroalkynoates (**3**) at room temperature afforded the adduct products, methyl 3-perfluoroalkyl-4-carbethoxy-5-methoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoates (**4**), in good yields. Intramolecular elimination of Ph₃PO occurred when compounds **4** were heated in anhydrous

benzene in a sealed tube to 180—210 °C for 30—40 h to give ethyl 2,4-dimethoxy-6-perfluoroalkylbenzoates (**5**) (Scheme 1) in high yield. The reaction results are illustrated in Table 1. The structures of compounds **4** and **5** were confirmed by IR, ¹H, ¹³C NMR and mass spectra and elemental analyses (Tables 2 and 3).

Scheme 1

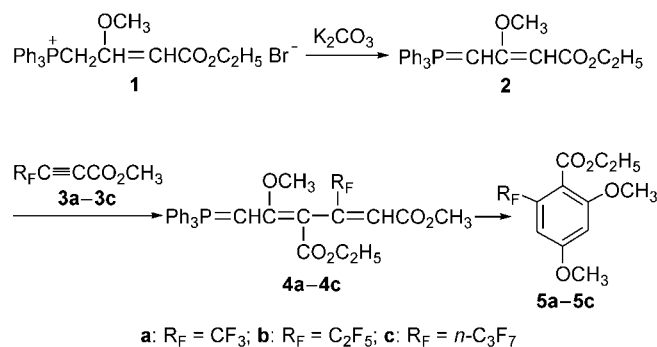


Table 1 Preparation of compounds **4** and **5**

Product	Reaction temperature/°C	Reaction time/h	m.p./°C	Yield/%
4a	25	7—8	187—188	87
4b	25	7—8	158—159	93
4c	25	7—8	141—142	83
5a	180—190	36—40	oil	84
5b	190—210	36—40	oil	81
5c	190—210	36—40	oil	83

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Table 2 IR, ^1H NMR and mass spectral data and microanalyses of products **4** and **5**

Compound	MS m/z	IR ν/cm^{-1}	Microanalysis, found (calcd)	^1H NMR (CDCl_3) δ
4a	556	1650 1715	C 64.32 (64.75) H 4.93 (5.07)	1.16 (t, $J=7.15$ Hz, 3H, CH_3)
				2.71 (s, 3H, O_2CH_3) 3.68 (s, 3H, OCH_3) 4.05 (q, $J=7.15$ Hz, 2H, OCH_2) 4.97—5.05 (m, 1H, $\text{P}=\text{CH}$) 6.08 (s, 1H, $=\text{CH}$) 7.42—7.84 (m, 15H, ArH)
4b	606	1650 1724	C 61.57 (61.39) H 4.81 (4.65)	1.13 (t, $J=6.59$ Hz, 3H, CH_3) 2.87 (s, 3H, O_2CH_3) 3.70 (s, 3H, OCH_3) 3.99 (q, $J=6.59$ Hz, 2H, OCH_2) 4.69—4.75 (m, 1H, $\text{P}=\text{CH}$) 6.23 (s, 1H, $=\text{CH}$) 7.36—7.62 (m, 15H, ArH)
				1.21 (t, $J=6.87$ Hz, 3H, CH_3) 2.88 (s, 3H, O_2CH_3) 3.69 (s, 3H, OCH_3) 4.02 (q, $J=6.87$ Hz, 2H, OCH_2) 4.73—4.84 (m, 1H, $\text{P}=\text{CH}$) 6.21 (s, 1H, $=\text{CH}$) 7.45—7.74 (m, 15H, ArH)
4c	656	1650 1727	C 58.71 (58.54) H 4.51 (4.30)	1.36 (t, $J=7.16$ Hz, 3H, CH_3) 3.85 (s, 3H, 4- OCH_3) 3.91 (s, 3H, 2- OCH_3) 4.38 (q, $J=7.16$ Hz, 2H, OCH_2) 6.64 (s, 1H, 3-ArH) 6.74 (s, 1H, 5-ArH)
				1.35 (t, $J=7.14$ Hz, 3H, CH_3) 3.85 (s, 3H, 4- OCH_3) 3.86 (s, 3H, 5- OCH_3) 4.37 (q, $J=7.14$ Hz, 2H, OCH_2) 6.63 (s, 1H, 3-ArH) 6.65 (s, 1H, 5-ArH)
5a	278	1736 1611	C 51.64 (51.80) H 4.59 (4.71)	1.33 (t, $J=6.99$ Hz, 3H, CH_3) 3.84 (s, 3H, 4- OCH_3) 3.85 (s, 3H, 2- OCH_3) 4.37 (q, $J=6.99$ Hz, 2H, OCH_2) 6.62 (s, 1H, 3-ArH) 6.66 (s, 1H, 5-ArH)
				14.4 (s, CH_3), 51.2 (s, O_2CH_3), 57.9 (s, OCH_3), 58.3 (s, O_2CH_2), 56.1 (d, $^1J_{\text{C-P}}=127$ Hz, $\text{P}=\text{CH}$), 117.9 (s, $\alpha\text{-C}$), 127.3 (m, CF_3), 125.8 (s, $\gamma\text{-C}$), 128.7—133.2 (m, Ph_3P), 144.4 (q, $^2J_{\text{C-F}}=30.1$ Hz, $\beta\text{-C}$), 165.7 (s, $\delta\text{-C}$), 167.9 (s, CO_2), 178.8 (s, CO_2)
5b	328	1739 1611	C 47.65 (47.57) H 4.14 (3.99)	14.5 (s, CH_3), 51.2 (s, O_2CH_3), 57.9 (s, OCH_3), 57.9 (s, O_2CH_2), 54.7 (d, $^1J_{\text{C-P}}=125$ Hz, $\text{P}=\text{CH}$), 119.4 (q-t, $^1J_{\text{C-F}}=245.1$, $^2J_{\text{C-F}}=37.1$ Hz, CF_2), 116.8 (m, CF_3), 124.1 (s, $\alpha\text{-C}$), 126.2 (s, $\gamma\text{-C}$), 128.8—133.9 (m, Ph_3P), 142.0 (q, $^2J_{\text{C-F}}=23.2$ Hz, $\beta\text{-C}$), 165.8 (s, $\delta\text{-C}$), 167.2 (s, CO_2), 178.8 (s, CO_2)
				14.1 (s, CH_3), 50.7 (s, O_2CH_3), 57.5 (s, OCH_3), 57.5 (s, O_2CH_2), 55.8 (d, $^1J_{\text{C-P}}=125$ Hz, $\text{P}=\text{CH}$), 115.6 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 117.1 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 113.3 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 123.8 (s, $\alpha\text{-C}$), 125.7 (s, $\gamma\text{-C}$), 128.1—132.9 (m, Ph_3P), 142.3 (q, $^2J_{\text{C-F}}=24.2$ Hz, $\beta\text{-C}$), 165.6 (s, $\delta\text{-C}$), 166.4 (s, CO_2), 178.7 (s, CO_2)
5c	378	1738 1610	C 44.59 (44.46) H 3.62 (3.46)	14.1 (s, CH_3), 50.7 (s, O_2CH_3), 57.5 (s, OCH_3), 57.5 (s, O_2CH_2), 55.8 (d, $^1J_{\text{C-P}}=125$ Hz, $\text{P}=\text{CH}$), 115.6 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 117.1 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 113.3 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 123.8 (s, $\alpha\text{-C}$), 125.7 (s, $\gamma\text{-C}$), 128.1—132.9 (m, Ph_3P), 142.3 (q, $^2J_{\text{C-F}}=24.2$ Hz, $\beta\text{-C}$), 165.6 (s, $\delta\text{-C}$), 166.4 (s, CO_2), 178.7 (s, CO_2)
				14.1 (s, CH_3), 50.7 (s, O_2CH_3), 57.5 (s, OCH_3), 57.5 (s, O_2CH_2), 55.8 (d, $^1J_{\text{C-P}}=125$ Hz, $\text{P}=\text{CH}$), 115.6 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 117.1 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 113.3 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 123.8 (s, $\alpha\text{-C}$), 125.7 (s, $\gamma\text{-C}$), 128.1—132.9 (m, Ph_3P), 142.3 (q, $^2J_{\text{C-F}}=24.2$ Hz, $\beta\text{-C}$), 165.6 (s, $\delta\text{-C}$), 166.4 (s, CO_2), 178.7 (s, CO_2)

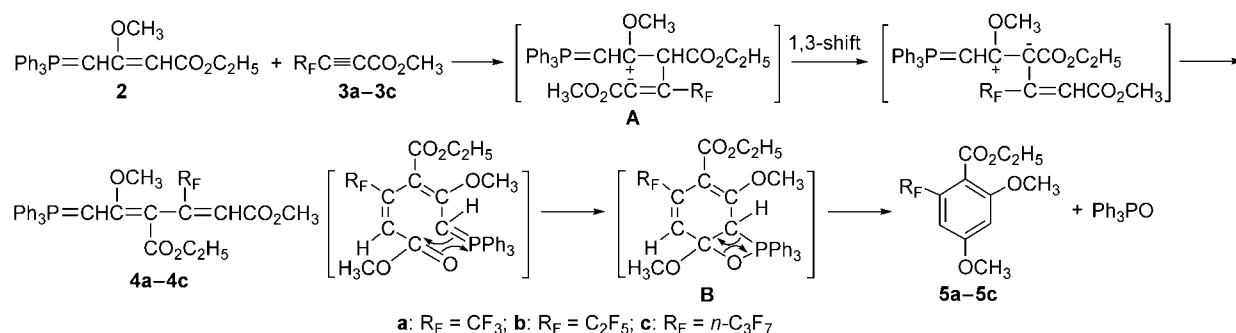
Table 3 ^{13}C NMR spectral data of products **4** and **5**

Compound	^{13}C NMR (CDCl_3) δ
4a	14.4 (s, CH_3), 51.2 (s, O_2CH_3), 57.9 (s, OCH_3), 58.3 (s, O_2CH_2), 56.1 (d, $^1J_{\text{C-P}}=127$ Hz, $\text{P}=\text{CH}$), 117.9 (s, $\alpha\text{-C}$), 127.3 (m, CF_3), 125.8 (s, $\gamma\text{-C}$), 128.7—133.2 (m, Ph_3P), 144.4 (q, $^2J_{\text{C-F}}=30.1$ Hz, $\beta\text{-C}$), 165.7 (s, $\delta\text{-C}$), 167.9 (s, CO_2), 178.8 (s, CO_2)
4b	14.5 (s, CH_3), 51.2 (s, O_2CH_3), 57.9 (s, OCH_3), 57.9 (s, O_2CH_2), 54.7 (d, $^1J_{\text{C-P}}=125$ Hz, $\text{P}=\text{CH}$), 119.4 (q-t, $^1J_{\text{C-F}}=245.1$, $^2J_{\text{C-F}}=37.1$ Hz, CF_2), 116.8 (m, CF_3), 124.1 (s, $\alpha\text{-C}$), 126.2 (s, $\gamma\text{-C}$), 128.8—133.9 (m, Ph_3P), 142.0 (q, $^2J_{\text{C-F}}=23.2$ Hz, $\beta\text{-C}$), 165.8 (s, $\delta\text{-C}$), 167.2 (s, CO_2), 178.8 (s, CO_2)
4c	14.1 (s, CH_3), 50.7 (s, O_2CH_3), 57.5 (s, OCH_3), 57.5 (s, O_2CH_2), 55.8 (d, $^1J_{\text{C-P}}=125$ Hz, $\text{P}=\text{CH}$), 115.6 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 117.1 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 113.3 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 123.8 (s, $\alpha\text{-C}$), 125.7 (s, $\gamma\text{-C}$), 128.1—132.9 (m, Ph_3P), 142.3 (q, $^2J_{\text{C-F}}=24.2$ Hz, $\beta\text{-C}$), 165.6 (s, $\delta\text{-C}$), 166.4 (s, CO_2), 178.7 (s, CO_2)

Continued

Compound	^{13}C NMR (CDCl_3) δ
5a	13.9 (s, CH_3), 55.6 (s, OCH_3), 56.2 (s, OCH_3), 61.7 (s, OCH_2), 101.5 (s, 3-C), 102.3 (s, 5-C), 101.5 (s, 1-C), 123.1 (q, $^1J_{\text{C-F}}=271.6$ Hz, CF_3), 129.1 (q, $^2J_{\text{C-F}}=30.2$ Hz, 6-C), 158.1 (s, 4-C), 160.2 (s, 2-C), 165.6 (s, $\text{C}=\text{O}$)
5b	13.7 (s, CH_3), 55.5 (s, OCH_3), 56.1 (s, OCH_3), 61.6 (s, OCH_2), 101.5 (s, 3-C), 103.7 (s, 5-C), 101.5 (s, 1-C), 113.3 (t-q, $^1J_{\text{C-F}}=245.2$, $^2J=38.0$ Hz, CF_2), 118.7 (q-t, $^1J_{\text{C-F}}=286.7$, $^2J=38.0$ Hz, CF_3), 129.1 (t, $^2J_{\text{C-F}}=30.2$ Hz, 6-C), 157.9 (s, 4-C), 161.1 (s, 2-C), 165.7 (s, $\text{C}=\text{O}$)
5c	13.7 (s, CH_3), 55.6 (s, OCH_3), 56.2 (s, OCH_3), 61.6 (s, OCH_2), 101.7 (s, 3-C), 104.7 (s, 5-C), 101.7 (s, 1-C), 108.5 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 110.2 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 118.1 (m, $\text{CF}_2\text{CF}_2\text{CF}_3$), 127.1 (t, 6-C), 158.0 (s, 4-C), 160.9 (s, 2-C), 165.7 (s, $\text{C}=\text{O}$)

Scheme 2



The possible mechanism for the formation of compound **5** is proposed as follows: first, C-2 of phosphorane **2** attacks β -C of ester **3** to give betain **A**, which then undergoes 1,3-H shift to form a new phosphorane **4**. At higher temperature, C-6 of new phosphorane **4** attacks the carbonyl carbon intramolecularly to form a six membered cyclic intermediate **B**, which then eliminates Ph_3PO to yield the title compound **5** (Scheme 2).

Experimental

Melting and boiling points were uncorrected. IR spectra were recorded on a 1600 series spectrophotometer (Perkin Elmer, USA). Solid samples were examined as KBr discs and oil samples as liquid films. NMR spectra were determined with a Gemini-2000 spectrometer, using solutions in CDCl_3 with tetramethylsilane and CDCl_3 as the internal standard for ^1H and ^{13}C NMR, respectively. J values are given in Hz. Mass spectra were run on an HP 5989A spectrometer. Microanalyses were performed with a Foss Heraeus CHN-O-RAPID elemental analysis instrument. Petroleum ether refers to the fraction boiling in the range 60–90 $^\circ\text{C}$.

Methyl 3-perfluoroalkyl-4-carbomethoxy-5-methoxy-6-(triphenylphosphoranylidene)-hexa-2,4-dienoates (**4**)

General procedure: To a suspension of **1**^{7,8} (1 mmol) in CH_2Cl_2 (10 mL) was added methyl 2-perfluoroalkynoates (**3a–3c**)⁹ (1 mmol) and K_2CO_3 (3 mmol), and the mixture was stirred at room temperature for the time indicated in Table 1. After the mixture was filtered to remove insoluble material, the solvent was removed under reduced pressure and the residue was separated on a silica gel column with EtOAc/petroleum ether (1 : 10,

V/V) as eluent to give red solids **4a–4c**. Further purification of **4** was carried out by recrystallization from EtOAc/petroleum ether to give analytically pure samples of **4a–4c**.

Ethyl 2,4-dimethoxy-6-perfluoroalkylbenzoates (**5**)

General procedure: A solution of **4a–4c** (1.0 mmol) in anhydrous benzene (5 mL) was heated in a sealed glass tube at 180–210 $^\circ\text{C}$ for 36–40 h. After the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was passed through a silica gel column and eluted with EtOAc/petroleum ether (1 : 100, V/V) to separate the products **5a–5c** from triphenylphosphine oxide.

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