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# A simple approach to the synthesis of ethyl 2-ethoxy-4-methoxy-6-perfluoroalkylbenzoates via acyclic precursors [1]

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## Abstract

The acyclic precursors, methyl 3-perfluoroalkyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoates **3a–c** were obtained through the addition reaction of ethyl 3-ethoxy-4-(triphenylphosphoranylidene)but-2-enoate **1** with equally molar of methyl 2-perfluoroalkynoates **2a–c**. Ethyl 2-ethoxy-4-methoxy-6-perfluoroalkylbenzoates **4a–c** were synthesized with high yields via an intramolecular elimination of $Ph_3PO$ of **3a–c** by heating in anhydrous benzene in a sealed tube. The structures of these compounds were confirmed by IR, MS, $^1H$, $^{13}C$ and $^{19}F$ NMR spectra, and elemental analyses. The reaction mechanisms were also proposed.

*Keywords:* Synthesis; Phosphoranes; Acyclic precursors; Intramolecular Wittig reaction; Ethyl 2-ethoxy-4-methoxy-6-perfluoroalkylbenzoates

## 1. Introduction

Polysubstituted arenes are important intermediates in industry of synthetic medicines and dyestuffs, the fluorinated analogues are more attractive as a result of their lipophilicity and the increment of activity [1,2]. However, their preparations using classical aromatic substitution reaction suffered from long synthetic procedures, the presence of complicated positional isomers, and the difficulty of introducing the fluoroalkyl group [3]. Therefore, to study the convenient and efficient syntheses of polysubstituted arenes with the perfluoroalkyl group is valuable in organic synthetic methodology. Recently, we had designed a synthetic process for fluorinated polysubstituted arenes through a nucleophilic addition of a phosphorane to an electrodeficient alkyne to produce a new phosphoric ylide which possesses a conjugated six-carbon main chain with a terminal carbonyl group. Under heating, this acyclic precursor gives rise to a polysubstituted arene via an intramolecular elimination of $Ph_3PO$. Several types of tri- or tetrasubstituted benzoates were synthesized via this method [4–8]. It is a preferable method, because of its simplicity, and a sole product with definite positional functional groups.

Alkylated polyfunctional phenolic derivatives were used as efficient disinfectants in the early days [9]; it is interesting to survey the abilities of the disinfecting and disinfesting of their fluoroanalogues. As a continuation of this study, a simple synthesis of ethyl 2-ethoxy-4-methoxy-6-perfluoroalkylbenzoates **4a–c** will be reported.

## 2. Results and discussion

Reaction of ethyl 3-ethoxy-4-(triphenylphosphoranylidene)but-2-enoate **1** with equally molar of methyl 2-perfluoroalkynoate **2** at room temperature afforded the adduct products methyl 3-perfluoroalkyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoate **3** instantaneously with high yield. When perfluoroalkynoate is used excessively, **3** can further react with **2** to give a byproduct, and the yield of **3** was decreased. Intramolecular elimination of $Ph_3PO$ occurred when compound **3** was heated in anhydrous benzene in a sealed tube at 160–210 °C for several hours to give ethyl 2-ethoxy-4-methoxy-6-perfluoroalkylbenzoate **4** in high yield (Scheme 1).

The structure of product **4** and its relative positions of substituted groups in the aromatic ring were established on the basis of spectra data; **4a** is used as an example to illustrate this. It is a benzenoid compound with four functional groups in the ring, in which two aromatic protons with chemical shifts 6.71 and 6.59 are located meta to each other, as they

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[1] This paper is the 21st report on our studies of the Chemistry and Application of Phosphonium and Arsonium Ylides. For Part XX, see *Chin. J. Chem., 13* (1995) 468.

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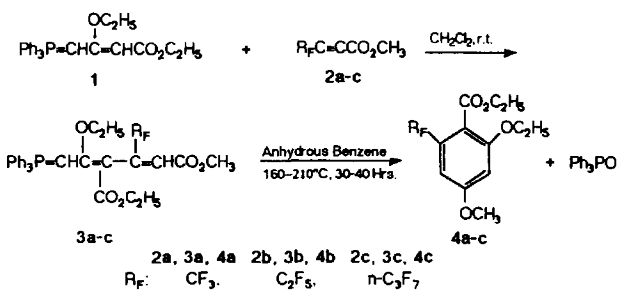


Scheme 1.

appear to be two doublets with $J=2$ Hz. In mass spectrum, the fragment with $m/z=219$ $[M–CO_2C_2H_5]^{+\cdot}$ exhibits **4a** to be a derivative of ethyl benzoate, in which two alkoxy groups are a methoxy and an ethoxy respectively. According to the splitting pattern and coupling constant of $^{13}C$ NMR spectrum, the trifluoromethyl group is situated between an aromatic proton and a carboethoxy group. The relative positions of methoxy and ethoxy groups were ascertained by $^1H$–$^{13}C$ shift correlation 2D-NMR experiment. In the light of the above facts, it follows that compound **4a** is believed to be ethyl 2-ethoxy-4-methoxy-6-trifluoromethylbenzoate.

On the basis of the structure of **4**, the structure of **3** can be drawn as methyl 3-perfluoroalkyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoate. Also, all the spectra of compound **3** can explain the above structure perfectly.

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

## 3. Experimental

M.p.s are uncorrected. M.p.s were measured with WRS-1 Digital Melting Point Apparatus made by Shanghai Physical Optical Instrument Factory (SPOIF), China. IR spectra were recorded on a 7400 spectrometer (Shanghai Analytical Instrument Factory, China) for samples as KBr discs. NMR spectra were determined with an AC-100SC spectrometer for solutions in $CDCl_3$ with tetramethylsilane as internal standard for $^1H$ NMR, and trifluoroacetic acid as external reference for $^{19}F$ NMR. $J$ values are given in hertz. Mass spectra were run on an HP 5989A spectrometer.

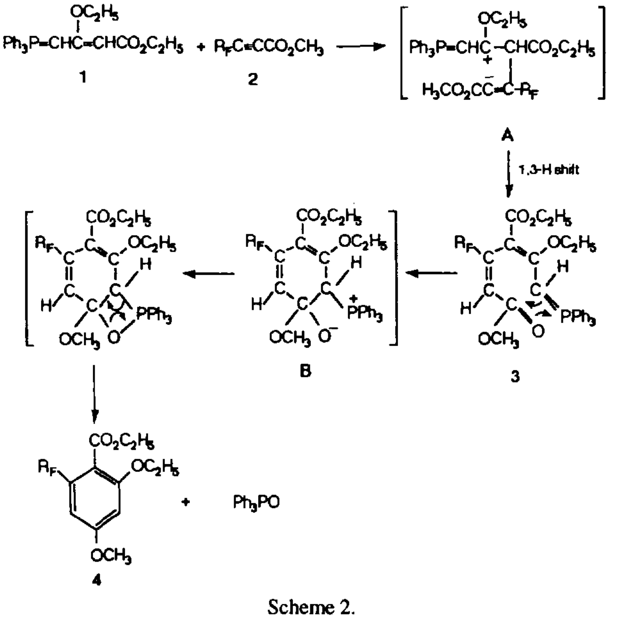
Ethyl 3-ethoxy-4-(triphenylphosphoranylidene)but-2-enoate **1** [10], methyl 2-perfluoroalkynoates **2a–c** [11,12] were prepared according to the respective literature method. Light petroleum refers to the fraction boiling in the range 60–90 °C.

## 4. Preparation of methyl 3-perfluoroalkyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoates 3a–c

A solution of **2** (1 mmol) in 2 mL methylene chloride was added to a solution of **1** (0.418 g, 1 mmol) in 10 mL methylene chloride. The reaction mixture was stirred at room temperature for 5 min. The solvent was evaporated and the residue was purified on a siliga gel G column with EtOAc-light petroleum (2:1) as eluent to give compound **3**. Further purification was by recrystallization from n-hexane-benzene.

Methyl 3-trifluoromethyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoate **3a** (85.8%) had an m.p. 164.5–165.9 °C (Found: C, 65.75; H, 5.2. $C_{31}H_{30}O_5PF_3$ requires C, 65.26; H, 5.30%); $\upsilon_{max}$ cm$^{-1}$ 1715, 1650, 1600, 1490, 1435 and 1395; $\delta_H$ 7.63 (15 H, m, ArH), 6.39 (1 H, s, =CH), 5.09 (1 H, d, $^2J_{PH}$ 23.0, P=CH), 4.07 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 3.69 (3 H, s, $OCH_3$), 3.17 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 1.18 (3 H, t, $^3J_{HH}$ 7.5, $CH_3$) and 0.36 (3 H, t, $^3J_{HH}$ 7.5, $CH_3$); $\delta_C$ 176.10 (C=O), 166.23 (C=O), 166.12 [C(OR)=], 144.83 (m, $CF_3$), 133.51–126.29 (m, Ar), 124.63 [$C(R_F)$=], 118.83 (=CH), 117.17 (=C), 82.40 (m, P=CH), 66.42 ($OCH_2$), 58.36 ($OCH_2$), 51.03 ($OCH_3$), 14.37 ($CH_3$) and 14.11 ($CH_3$); $\delta_P$ 14.56 (s, $Ph_3P$); $\delta_F$ 15.44 (s, $CF_3$); $m/z$ 570 ($M^{+\cdot}$, 6.23%), 511 (6.94), 501 (7.57), 497 (14.32), 303 (90.43), 262 (100), 183 (32.99) and 108 (12.60).

Methyl 3-pentafluoroethyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoate **3b** (86.3%) had an m.p. of 131.2–132.7 °C (Found: C, 62.35; H, 4.8. $C_{32}H_{30}O_5PF_5$ requires C, 61.94; H, 4.84%); $\upsilon_{max}$ cm$^{-1}$ 1735, 1650, 1600, 1580, 1480, 1438 and 1372; $\delta_H$ 7.63 (15 H, m, ArH), 6.20 (1 H, s, =CH), 4.70 (1 H, d, $^2J_{PH}$ 24.0, P=CH), 3.97 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 3.69 (3 H, s, $OCH_3$), 3.51 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 1.10 (3 H, t, $^3J_{HH}$ 7.5, $CH_3$) and



Scheme 2.

0.38 (3 H, t, $^3J_{HH}$ 7.5, $CH_3$); $\delta_C$ 178.13 (C=O), 166.95 (C=O), 166.20 [C(OR)=], 143.60 (m, $C_2F_5$), 134.62 [C($R_F$)=], 133.42–128.27 (m, Ar), 125.28 (=CH), 81.50 (m, P=CH), 66.39 ($OCH_2$), 57.93 ($OCH_2$), 51.24 ($OCH_3$), 14.49 ($CH_3$) and 14.22 ($CH_3$); $\delta_P$ 14.10 (s, $Ph_3P$); $\delta_F$ −6.67 (3 F, s, $CF_3$) and −36.17 (2 F, m, $CF_2$); *m/z* 620 ($M^{+\cdot}$, 4.12%), 561 (4.61), 547 (8.09), 501 (14.13), 303 (72.66), 262 (100), 183 (43.13) and 108 (18.68).

Methyl 3-heptafluoropropyl-4-carboethoxy-5-ethoxy-6-(triphenylphosphoranylidene)hexa-2,4-dienoate **3c** (90.4%) had an m.p. of 124.2–125.1 °C (Found: C, 60.24; H, 4.6. $C_{33}H_{30}O_5PF_7$ requires C, 59.11; H, 4.51%); $\upsilon_{max}$ $cm^{-1}$ 1725, 1650, 1590, 1485, 1439 and 1370; $\delta_H$ 7.57 (15 H, m, ArH), 6.17 (1 H, s, =CH), 4.76 (1 H, d, $^2J_{PH}$ 24.0, P=CH), 3.97 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 3.70 (3 H, s, $OCH_3$), 3.47 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 1.10 (3 H, t, $^3J_{HH}$ 7.5, $CH_3$) and 0.38 (3 H, t, $^3J_{HH}$ 7.5, $CH_3$); $\delta_C$ 178.36 (C=O), 166.99 (C=O), 166.29 [C(OR)=], 143.80 (m, $C_3F_7$), 133.43–128.33 (m, Ar), 125.15 [C($R_F$)=], 123.72 (2× =C), 81.50 (m, P=CH), 66.31 ($OCH_2$), 57.95 ($OCH_2$), 51.22 ($OCH_3$), 14.47 ($CH_3$) and 14.18 ($CH_3$); $\delta_P$ 13.99 (s, $Ph_3P$); $\delta_F$ −3.62 (3 F, s, $CF_3$), −32.85 (2 F, m, $CF_2$) and −48.86 (2 F, d, *J*21.0 $CF_2$); *m/z* 670 ($M^{+\cdot}$, 3.24%), 611 (3.60), 597 (18.14), 501 (18.14), 303 (87.16), 262 (100), 183 (34.48) and 108 (14.99).

## 5. Preparation of ethyl 2-ethoxy-4-methoxy-6-perfluoroalkylbenzoates 4a–c

The solution of **3** (1 mmol) in 10 mL anhydrous benzene was heated in a sealed tube at 160–210 °C for 30–40 h. The solvent was removed and the residue was separated on a siliga gel G column with light petroleum as eluent to give compound **4**. Further purification was by recrystallization from petroleum ether. Triphenylphosphine oxide was obtained by using EtOAc-light petroleum (1:1) as eluent.

Ethyl 2-ethoxy-4-methoxy-6-trifluoromethylbenzoate **4a** (84.5%) had an m.p. of 26.3–27.2 °C (Found: C, 53.40; H, 5.1. $C_{13}H_{12}O_4F_3$ requires C, 53.43; H, 5.17%); $\upsilon_{max}$ $cm^{-1}$ 1732, 1610, 1590, 1445, 1375, 1345, 1270 and 1220; $\delta_H$ 6.71 (1 H, d, $^4J_{HH}$ 2, ArH), 6.59 (1 H, d, $^4J_{HH}$ 2, ArH), 4.37 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 4.03 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 3.81 (3 H, s, $OCH_3$) and 1.35 (6 H, m, 2×$CH_3$); $\delta_C$ 166.04 (C=O), 161.54 (Ar), 157.89 (Ar), 129.29 (q, $^2J_{CF}$ 127.7, Ar), 115.79 (d, $^3J_{CF}$ 10.0, Ar), 102.19 (d, $^3J_{CF}$ 18.8, Ar), 102.52 (Ar), 65.05 ($OCH_2$), 61.74 ($OCH_2$), 55.72 ($OCH_3$), 14.51 ($CH_3$) and 14.10 ($CH_3$); $\delta_F$ 16.25 (s, $CF_3$); *m/z* 292 ($M^{+\cdot}$, 31.31%), 247 (100), 219 (58.55), 218 (86.30), 190 (51.23), 171 (17.92), 159 (6.10) and 69 (13.03).

Ethyl 2-ethoxy-4-methoxy-6-pentafluoroethylbenzoate **4b** (83.8%) had an m.p. of 31.7–32.5 °C (Found: C, 49.03; H, 4.4. $C_{14}H_{12}O_4F_5$ requires C, 49.12; H, 4.48%); $\upsilon_{max}$ $cm^{-1}$ 1745, 1610, 1585, 1445, 1370, 1345, 1270 and 1210; $\delta_H$ 6.61 (2 H, m, 2×ArH), 4.36 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 4.01 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 3.83 (3 H, s, $OCH_3$) and 1.36 (6 H, m, 2×$CH_3$); $\delta_C$ 166.06 (C=O), 161.12 (Ar), 157.59 (Ar), 126.94 (Ar), 103.73 (Ar), 103.74 (Ar), 102.66 (Ar), 64.91 ($OCH_2$), 61.67 ($OCH_2$), 55.72 ($OCH_3$), 14.48 ($CH_3$) and 14.00 ($CH_3$); $\delta_F$ −7.37 (3 F, s, $CF_3$) and −34.46 (2 F, s, $CF_2$); *m/z* 342 ($M^{+\cdot}$, 32.98%), 297 (100), 269 (61.20), 268 (57.49), 240 (27.26), 221 (13.35), 209 (1.44), 171 (17.61), 119 (0.63) and 69 (13.03).

Ethyl 2-ethoxy-4-methoxy-6-heptafluoropropylbenzoate **4c** (88.7%) had an m.p. of 24.1–25.5 °C (Found: C, 46.11; H, 3.9. $C_{15}H_{12}O_4F_7$ requires C, 45.92; H, 3.83%); $\upsilon_{max}$ $cm^{-1}$ 1745, 1610, 1590, 1450, 1375, 1350, 1268 and 1210; $\delta_H$ 6.62 (2 H, m, 2×ArH), 4.44 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 4.05 (2 H, q, $^3J_{HH}$ 7.5, $OCH_2$), 3.83 (3 H, s, $OCH_3$) and 1.38 (6 H, m, 2×$CH_3$); $\delta_C$ 166.04 (C=O), 161.12 (Ar), 157.68 (Ar), 126.99 (Ar), 104.16 (Ar), 104.16 (Ar), 102.83 (Ar), 65.01 ($OCH_2$), 61.70 ($OCH_2$), 55.73 ($OCH_3$), 14.51 ($CH_3$) and 13.96 ($CH_3$); $\delta_F$ −3.85 (3 F, m, $CF_3$), −31.28 (2 F, m, $CF_2$) and −48.41 (2 F, t, *J*20, $CF_2$); *m/z* 392 ($M^{+\cdot}$, 34.20%), 347 (100), 319 (61.09), 318 (56.57), 290 (15.74), 271 (11.17), 259 (1.47), 171 (40.82), 169 (1.67) and 69 (4.80).

## 6. Acknowledgement

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