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A facile one-pot synthesis of α-fluoro-α,β-unsaturated esters from alkoxycarbonylmethyltriphenylphosphonium bromides

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Abstract—A convenient one-pot synthesis of α-fluoro-α,β-unsaturated esters from ethoxy- and *tert*-butoxycarbonylmethyltriphenylphosphonium bromide was developed. The fluorinated phosphoranes, generated in situ from alkoxycarbonylmethyltriphenylphosphonium bromides and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®), undergo a Wittig reaction with aldehydes to yield α-fluoro-α,β-unsaturated esters with (*Z*)-selectivity.

Although the van der Waal radius of the fluorine atom is comparable to that of hydrogen, the replacement of a hydrogen atom in a molecule by a fluorine atom can significantly change the properties of a molecular system, as the fluorine substituent often enhances an organic compound's biological activities.[1] Thus, syntheses of fluorine-containing compounds are of special interest to organic chemists.[2]

α-Fluoro-α,β-unsaturated esters are versatile fluorinated building blocks for the preparation of biologically active compounds. Though other methods are available,[3–6] the main synthetic methods for the preparation of α-fluoro-α,β-unsaturated esters and related compounds are the Wittig and the Horner–Wadsworth–Emmons (HWE) reactions.[3] For the latter, Xu and DesMarteau[7] developed a convenient one-pot synthesis of α-fluoro-α,β-unsaturated nitriles using diethyl cyanofluoromethanephosphonate. The HWE reaction usually gives good (*E*)-selectivity at low temperatures (e.g., −78 °C). Nagao and co-workers recently reported a (*Z*)-selective HWE reaction for the preparation of (*Z*)-α-fluoro-α,β-unsaturated esters.[8] For the Wittig reaction, ethoxycarbonylfluorophosphoranes were synthesized by Thenappan and Burton.[9] They used ethyl α-bromo-α-fluoroacetate as the starting compound and studied alkylation of the ethoxylcarbonylfluoromethylenephosphoranes. However, there has been no paper concerning the reaction of the phosphorane with aldehydes.

In this context, we report the first example of the reaction of alkoxycarbonylfluoromethylenephosphoranes with aldehydes to give α-fluoro-α,β-unsaturated esters. We used ethyl bromoacetate as the starting compound, because the α-bromo-α-fluoroacetate is expensive. Thus, we studied the synthesis of alkoxycarbonylfluoromethylenephosphorane **4** by electrophilic fluorination of the parent phosphorane **2** readily prepared from inexpensive ethyl bromoacetate. We also studied the one-pot synthesis of α-fluoro-α,β-unsaturated esters from ethyl bromoacetate and stereoselectivity in this Wittig reaction.

Selectfluor® **6** (1.5 equiv) reacted with phosphorane **2**, generated in situ by the treatment of phosphonium bromide **1** with sodium hydride (1.5 equiv), in acetonitrile at room temperature for 48 h. Sodium hydride was then added, followed by the addition of 4-chlorobenzaldehyde **10a** (1 equiv). After stirring at room temperature for 20 h, 15% yield of α-fluoro-α,β-unsaturated ester **5a** (*E*/*Z* = 1:3) was obtained along with 23% yield of nonfluorinated ester **9** (*E*/*Z* = 12:1). Under the same conditions, *N*-fluorobenzenesulfonimide **7** was used instead of **1** to give **5a** (*E*/*Z* = 1:4) and **9** (*E*/*Z* = 11:3) in 5% and 11% yields, respectively. The reaction using 1-fluoropyridinium triflate **8** as a fluorinating agent afforded only **9** (*E*/*Z* = 10:1) in 55% yield. When 2 equiv of **6** were used, 42% yield of **5a** (*E*/*Z* = 1:3) was obtained without yielding **9**[10] (Scheme 1).

Keywords: Electrophilic fluorination; One-pot synthesis; Wittig reaction; Selectfluor®.
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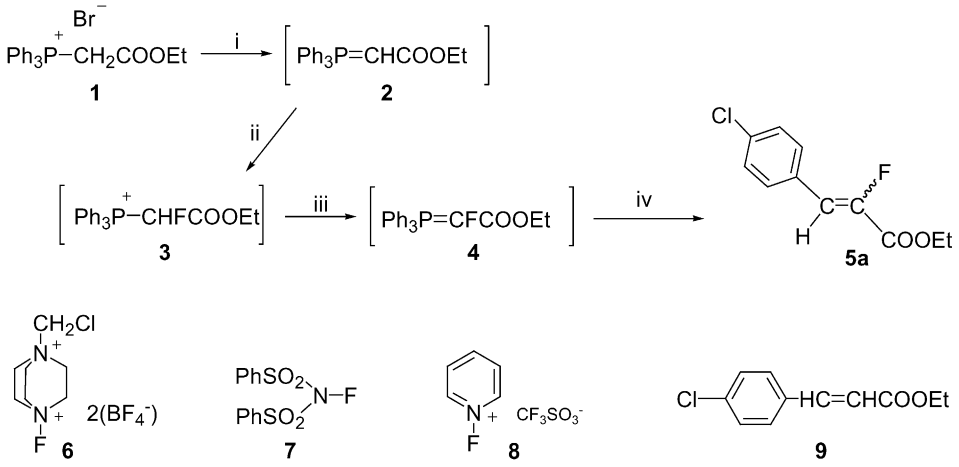
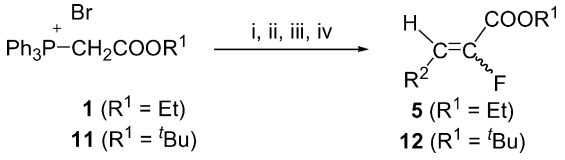


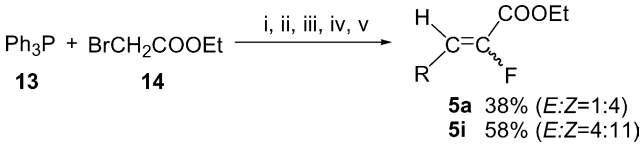
Scheme 1. Reagents and conditions: (i) NaH, CH_3CN, rt; (ii) **6**–**8**, rt; (iii) NaH, rt; (iv) 4-chlorobenzaldehyde (**10a**), rt.

The generality of this one-pot reaction is demonstrated by the reactions of **1** or the *tert*-butyl analogue **11** with aldehydes **10a**–**j**. The results are shown in Table 1. The reactions of **1** and **11** with **10a**–**j** afforded the corresponding ester **5a**–**j** and **12a**,**i** with (*Z*)-selectivity. The reaction time of fluorination was shortened to 1–3 h (conditions B and C). Triethylamine was used for the reaction of fluorinated phosphorane with aliphatic aldehyde **10i** to avoid the considerable side reaction, the aldol reaction. Although the yields are moderate, the reagents are easy to access and to handle. The ease of the tandem four-step procedure is advantageous (Scheme 2, Table 1).

With triphenylphosphine **13** and ethyl bromoacetate **14** as the starting materials, the one-pot synthesis of **5** was carried out (Scheme 3). Phosphonium bromide **1** was prepared from **13** and **14** in refluxing acetonitrile. Without isolation, the routine fluorination–Wittig



Scheme 2. Reagents and conditions: (i) NaH, CH_3CN, rt; (ii) **6**, rt; (iii) NaH, rt; (iv) R^2CHO **10a**–**j**, rt.



Scheme 3. Reagents and conditions: (i) CH_3CN, reflux, 2–4 h; (ii) NaH (1.5 equiv), rt, 1 h; (iii) **6** (2 equiv), rt, 1 h; (iv) NaH (2 equiv), rt; (v) RCHO **10a**,**i** (1 equiv), rt, overnight.

Table 1. One-pot synthesis of α-fluoro-α,β-unsaturated esters **5a**–**j** and **12a**,**i**

Entry	R^2	Phosphonium bromide	R^2	Aldehyde	Conditions	Product	Yield (%)	Ratio *E*/*Z*[d]
1	Et	**1**	4-Chlorophenyl	**10a**	A[a]	**5a**	42	1:3
2	Et	**1**	4-Chlorophenyl	**10a**	B[b]	**5a**	53	1:3
3	Et	**1**	2-Chlorophenyl	**10b**	B[b]	**5b**	31	1:4
4	Et	**1**	Phenyl	**10c**	B[b]	**5c**	40	1:11
5	Et	**1**	4-Anisyl	**10d**	B[b]	**5d**	29	1:3
6	Et	**1**	3-Anisyl	**10e**	B[b]	**5e**	29	1:2.6
7	Et	**1**	2-Furyl	**10f**	B[b]	**5f**	38	
8	Et	**1**	1-Naphthyl	**10g**	B[b]	**5g**	33	1:3
9	Et	**1**	Styryl	**10h**	B[b]	**5h**	30	1:6
10	Et	**1**	Nonyl	**10i**	C[c]	**5i**	42	8:25
11	Et	**1**	Cyclohexyl	**10j**	B[b]	**5j**	26	9:20
12	*t*-Bu	**11**	4-Chlorophenyl	**10a**	B[b]	**12a**	57	2:5
13	*t*-Bu	**11**	Nonyl	**10i**	C[c]	**12i**	50	2:5

[a] (i) NaH (1.5 equiv), rt, 4 h; (ii) **6** (2 equiv), rt, 48 h; (iii) NaH (2 equiv), rt; (iv) **10a** (1 equiv), rt, 15 h.
[b] (i) NaH (1.5 equiv), rt, 1–3 h; (ii) **6** (2 equiv), rt, 1–3 h; (iii) NaH (2 equiv), rt; (iv) **10** (1 equiv), rt, 12–15 h.
[c] (i) NaH (1.5 equiv), rt, 1–3 h; (ii) **6** (2 equiv), rt, 1–3 h; (iii) triethylamine (2 equiv), rt; (iv) **10** (1 equiv), rt, 12–15 h.
[d] Determined by ^1H NMR (500 MHz, $CDCl_3$) spectroscopy. Vinylic hydrogen–fluorine coupling constants, $J_{H-F} = 21.5$ Hz for *E*-**5a**, $J_{H-F} = 34$ Hz for *Z*-**5a**.

reaction procedure gave **5a**,**i** in satisfactory overall yields from **14**.

In conclusion, we have succeeded in developing a facile one-pot synthesis of α-fluoro-α,β-unsaturated esters **5a**–**j** and **12a**,**i** by the reaction of fluorinated phosphoranes, generated in situ from phosphonium salts and Selectfluor®, with aldehydes. The (*Z*)-isomers were the major products. This one-pot synthesis is a convenient method for the preparation of α-fluoro-α,β-unsaturated esters. It is not necessary to use expensive bromofluoroacetates as the starting materials for the synthesis of fluorinated phosphoranes. This method can be applied to synthesizing various fluorinated vinyl compounds having electron withdrawing group.

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