New Reaction Mode of the Horner-Wadsworth-Emmons Reaction for the Preparation of α-Fluoro-α,β-unsaturated Esters

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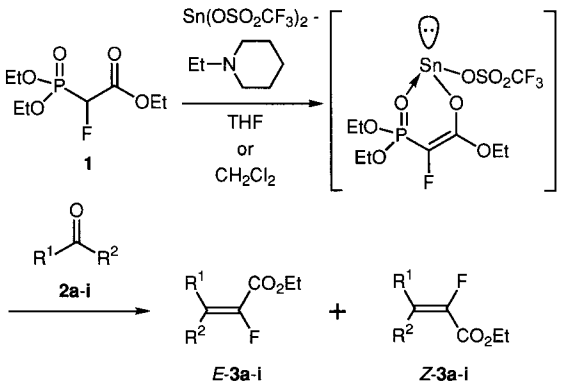
Abstract: Excellent *E*-selectivity was observed in the Horner-Wadsworth-Emmons (HWE) reactions of ethyl 2-fluoro-2-diethylphosphonoacetate **1** with alkyl aryl ketones **2a-f** using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine. Mg(II)-promoted HWE reactions of **1** with aldehydes **2h,i** afforded α-fluoro-α,β-unsaturated esters **3h,i** in a *Z*-selective manner depending on the reaction temperatures.

α-Fluoro-α,β-unsaturated esters play an important role in the preparation of biologically active fluorine compounds, and various synthetic methods have been developed.[1] Most of the construction methods for the α-fluoro-α,β-unsaturated esters have shown *Z*-selectivity.[2] However, Horner-Wadsworth-Emmons (HWE) reactions of aldehydes with ethyl 2-fluoro-2-diethylphosphonoacetate **1** can preferentially furnish *E*-α-fluoro-α,β-unsaturated esters.[3-5] There have been a few reports on the HWE reactions with ketones in the presence of some base but the stereoselectivity is not clear or poor.[6] Recently, we have developed a new reaction mode of the HWE reaction using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine to obtain excellent *Z*-selectivity in the reactions of methyl bis(trifluoroethyl)phosphonoacetate with l alkyl aryl ketones.[7] We now wish to report highly *E*-selective HWE reactions of ethyl 2-fluoro-2-diethylphosphonoacetate **1** with alkyl aryl ketones **2a-f** using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine as shown in Scheme 1. A tendency to afford *Z*-alkenes in the Mg(II)-mediated HWE reactions of fluorophosphonate **1** with aldehydes is also described. All reaction conditions and results are summarized in Tables 1-3.



a: R^1 = Ph, R^2 = Me
b: R^1 = Ph, R^2 = Et
c: R^1 = Ph, R^2 = *i*-Pr
d: R^1 = Ph, R^2 = *t*-Bu
e: R^1 = 2-naphthyl, R^2 = Et
f: R^1 = Ph, R^2 = C_5H_{11}
g: R^1 = CH_2CH_2Ph, R^2 = Et
h: R^1 = Ph, R^2 = H
i: R^1 = CH_2CH_2Ph, R^2 = H

Scheme 1

The HWE reactions of alkyl aryl ketones **2a-f** with **1** in the presence of sodium hydride in THF 0 °C gave the corresponding α-fluoro-α,β-unsaturated esters **3a-f** with modest *E*-selectivity (Table 1, entries 1-6). On the other hand, treatment of **2a-f** with **1** in the presence of $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in CH_2Cl_2 at 0 °C afforded alkenes **3a-f** in a highly *E*-selective manner, respectively (Table 2,

Table 1. NaH / THF mediated Horner-Wadsworth-Emmons reactions of **1** with ketones **2a-g** and aldehydes **2h,i**[a]

Entry	Ketone or Aldehyde	*t* / h	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**2a**	1	78	**3a** (85 : 15)
2	**2b**	2	93	**3b** (87 : 13)
3	**2c**	18	49	**3c** (78 : 22)
4	**2d**[d]	43	40	**3d** (72 : 28)
5	**2e**	1	97	**3e** (86 : 14)
6	**2f**	1	84	**3f** (90 : 10)
7	**2g**	1	86	**3g** (49 : 51)[e]
8	**2h**	1	82	**3h** (83 : 17)
9	**2i**	1	82	**3i** (83 : 17)

[a] Conditions: THF, 0 °C, **1** / NaH / **2** (1.7 : 1.5 :1)
[b] Isolated yield
[c] ^{1}H NMR (400 MHz, $CDCl_3$) analysis
[d] Reflux
[e] HPLC (TSK-GEL Silica 60, hexane - propan-2-ol) analysis

Table 2. $Sn(OSO_2CF_3)_2$ / *N*-ethylpiperidine / THF or CH_2Cl_2 mediated Horner-Wadsworth-Emmons reactions of **1** with ketones **2a-g** and aldehydes **2h,i**[a]

Entry	Ketone or Aldehyde	Solvent	*t* / h	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**2a**	CH_2Cl_2	23	91	**3a** (97 : 3)
2	**2b**	CH_2Cl_2	21	92	**3b** (99 : 1)
3	**2b**	THF	18	97	**3b** (93 : 7)
4	**2c**	CH_2Cl_2	20	95	**3c** (97 : 3)
5	**2d**	CH_2Cl_2	20	97	**3d** (98 : 2)
6	**2e**	CH_2Cl_2	19	94	**3e** (98 : 2)
7	**2f**	CH_2Cl_2	22	73	**3f** (99 : 1)
8	**2g**	CH_2Cl_2	22	86	**3g** (54 : 46)[d]
9	**2h**	THF	14	92	**3h** (84 : 16)
10	**2i**	THF	16	86	**3i** (95 : 5)

[a] Conditions: THF or CH_2Cl_2, 0 °C, **1** / $Sn(OSO_2CF_3)_2$ / *N*-ethylpiperidine / **2** (1.4 : 1.68 : 1.54 : 1)
[b] Isolated yield
[c] ^{1}H NMR (400 MHz, $CDCl_3$) analysis
[d] HPLC (TSK-GEL Silica 60, hexane - propan-2-ol) analysis

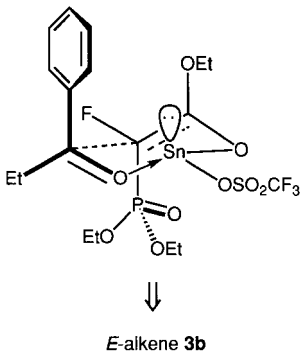
Table 3. $MgBr_2$ / Et_3N / THF or *i*-PrMgBr / THF mediated Horner-Wadsworth-Emmons reactions of **1** with aldehydes **2h**,**i**[a]

Entry	Aldehyde	Conditions	T / °C	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**2h**	(A)	0	89	**3h** (19 : 81)
2	**2h**	(B)	reflux	86	**3h** (25 : 75)
3	**2h**	(B)	40	95	**3h** (26 : 74)
4	**2h**	(B)	0	82	**3h** (23 : 77)
5	**2h**	(B)	-40	43	**3h** (33 : 67)
6	**2h**	(B)	-78	34	**3h** (51 : 49)
7	**2h**	(B)	-100	13	**3h** (64 : 36)
8	**2i**	(A)	0	77	**3i** (53 : 47)
9	**2i**	(B)	reflux	74	**3i** (37 : 63)
10	**2i**	(B)	0	82	**3i** (70 : 30)
11	**2i**	(B)	-78	12	**3i** (95 : 5)

[a] Conditions: (A); THF, 1 h, **1** / $MgBr_2$ / Et_3N / **2** (1.4 : 1.68 : 1.54 : 1), (B); THF, 1 h, **1** /*i*-PrMgBr / **2** (1.7 : 1.5 : 1)
[b] Isolated yield
[c] ^1H NMR (400 MHz, $CDCl_3$) analysis

entries 1,2, and 4-7).[8] The geometry of α-fluoro-α,β-unsaturated esters **3a-g** was assigned on the basis of ^1H-^1H NOE experiments (400 MHz, $CDCl_3$) of the corresponding primary alcohols derived by reduction of **3a-g** with DIBAL-H in CH_2Cl_2 at 0 °C. When THF was employed as the solvent instead of CH_2Cl_2 in the same Sn(II)-promoted reaction of alkyl aryl ketone **2b** with **1**, *E*-selectivity of the alkenic product **3b** decreased from 99 : 1 to 93 : 7. Interestingly, the NaH-promoted reactions of the ketones **2c**,**d** bearing bulky *i*-Pr or *t*-Bu group in THF was hard to obtain the highly *E*-selective products **3c**,**d** (Table 1, entries 3 and 4), while the Sn(II)-promoted reactions of **2c**,**d** in CH_2Cl_2 gave **3c**,**d** in an excellent *E*-selective manner and in good yields (Table 2, entries 4 and 5) as well as those of the ketones **2a**,**b**. Thus, the stereochemical outcome with high *E*-selectivity in the $Sn(OSO_2CF_3)_2$-mediated HWE reactions of ketones **2a-f** with fluorophosphonate **1** can be rationalized in terms of a six-membered transition state as shown in Fig. 1 (*e.g.* **2b**).[7] The stereoselectivity in the NaH-promoted HWE reactions of **2a-g** with **1** seems to depend on the relative bulkiness between both substituents of the ketones in a plausible non-chelation-controlled transition state. Under both reaction conditions as described above, the HWE reactions of ketone **2g** with **1** gave a ca. 1 : 1 mixture of *E*- and *Z*-isomers of **3g** (Table 1, entry 7; Table 2, entry 8), respectively.

Subsequently, the similar Sn(II)- and NaH-promoted reactions of aldehydes **2h**,**i** with fluorophosphonate **1** afforded the corresponding α-fluoro-α,β-unsaturated esters **3h**,**i** with a good or excellent *E*-selectivity (Table 1, entries 8 and 9; Table 2, entries 9 and 10). The geometry of **3h**,**i** was determined by the coupling constants between fluorine and the adjacent olefinic proton in their ^1H NMR analysis (400 MHz, $CDCl_3$) as follows; *E*-**3h** ($J_{H\text{-}F}$ = 22.3 Hz, lit.[5] 22 Hz), *Z*-**3h** ($J_{H\text{-}F}$ = 35.1 Hz), *E*-**3i** ($J_{H\text{-}F}$ = 21.4 Hz), and *Z*-**3i** ($J_{H\text{-}F}$ = 32.8 Hz). Previously, we reported a characteristic reaction mode with Mg(II) in the aldol type reactions,



E-alkene **3b**

Figure 1. Plausible six-membered transition state involving Sn(II) chelation

which was quite different from that with Sn(II).[9] Thus, tentative HWE reactions of benzaldehyde **2h** with **1** at various temperatures employing $MgBr_2$-triethylamine or *i*-PrMgBr gave *Z*-selective **3h** (Table 3, entries 1-5), which was contrary to the *E*-selectivity in the cases of Sn(II)- and NaH-promoted reactions at 0 °C (Table 1, entry 8; Table 2 entry 9). The Mg(II)-promoted HWE reaction of **2i** with **1** gave **3i** in the modest *Z*-selective manner (Table 3, entry 9). Interestingly, the stereoselectivity of α-fluoro-α,β-unsaturated esters **3h**,**i** in the Mg(II)-promoted reactions of aldehydes **2h**,**i** with **1** was variable depending on the reaction temperatures. The *Z*-selective manner (Table 3, entries 2-5 and 9) in the Mg(II)-promoted reactions of **2h**,**i** changed to *E*-selective one (Table 3, entries 7, 10, and 11) with decreasing the reaction temperature.[4] These results made it possible to prepare the *Z*-isomers of α-fluoro-α,β-unsaturated esters by exploiting the Mg(II)-promoted HWE reaction.

References and Notes

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(8) A typical procedure is as follows. To a suspension of $Sn(OSO_2CF_3)_2$ (820 mg, 1.97 mmol) and 2-fluoro-2-

diethylphosphonoacetate **1** (330 μL, 1.64 mmol) in anhydrous CH_2Cl_2 (5 mL) was added *N*-ethylpiperidine (247 μL, 1.80 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h under argon, and alkyl aryl ketone **2b** (155 μL, 1.17 mmol) was added. After being stirred at 0 °C for 21 h under argon, the reaction mixture was poured into H_2O (15 mL) and then extracted with $CHCl_3$ (3 x 50 mL). To the $CHCl_3$ extract was added *n*-hexane (300 mL), and the mixture was submitted to filtration through a silica gel short column. The filtrate was evaporated *in vacuo* to afford a crude product **3b** (*E* : *Z* = 99 : 1), which was purified by chromatography on a silica gel column eluting with *n*-hexane/AcOEt (20 : 1) to obtain α-fluoro-α,β-unsaturated esters *E*-**3b** (37.6 mg, 91%) and *Z*-**3b** (2.4 mg, 1%) as a pale yellow oil, respectively. *E*-**3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3 H, t, *J* = 7.3 Hz), 1.00 (3 H, t, *J* = 7.3 Hz), 2.55 (2 H, dq, $^4J_{H,F}$ = 3.6 Hz, *J* = 7.3 Hz), 4.02 (2 H, q, *J* = 7.3 Hz), 7.10-7.17 (2 H, m), 7.30-7.38 (3 H, m); IR (NaCl) 2980, 2937, 1729, 1656, 1444, 1265, 1151, 763, 700 cm^{-1}; HREI-MS calcd for $C_{13}H_{15}O_2F$ MW 222.1056, found *m*/*e* 222.1057 (M^+); Anal. Calcd for $C_{13}H_{15}O_2F$: C, 70.25; H, 6.80. Found: C, 69.96; H, 6.92. *Z*-**3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3 H, t, *J* = 7.3 Hz), 1.37 (3 H, t, *J* = 7.3 Hz), 2.90 (2 H, dq, $^4J_{H,F}$ = 1.8 Hz, *J* = 7.3 Hz), 4.34 (2 H, q, *J* = 7.3 Hz), 7.28-7.43 (5 H, m); IR (NaCl) 2975, 2932, 1725, 1642, 1445, 1247, 1142, 766, 699 cm^{-1}; HREI-MS calcd for $C_{13}H_{15}O_2F$ MW 222.1056, found *m*/*e* 222.1069 (M^+).

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