New reaction mode of the Horner–Wadsworth–Emmons reaction using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine

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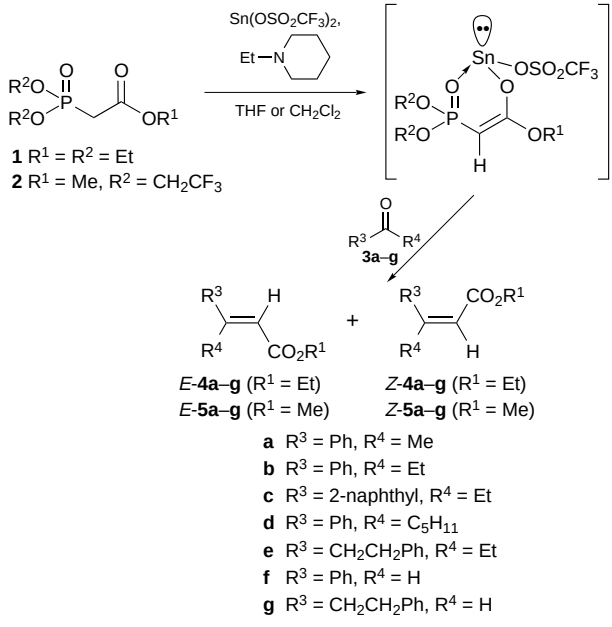
Excellent *Z* or *E* selectivity is observed in the Horner–Wadsworth–Emmons reactions of methyl bis(trifluoroethyl)phosphonoacetate 2 with aryl alkyl ketones 3a–d or aldehydes 3f,g using $Sn(OSO_2CF_3)_2$ in the presence of *N*-ethylpiperidine, which should have a different reaction mode to those using sodium hydride.

The Horner–Wadsworth–Emmons (HWE) reaction is one of the most efficient methods for the preparation of α,β-unsaturated esters.[1] The reactions of aldehydes with phosphonates bearing α-substituents that stabilise the carbanion preferentially furnish the corresponding *E*-alkenes. Various bases such as sodium hydride, butyllithium and sodium ethoxide have been employed in order to generate the phosphonate carbanions. In similar HWE reactions, mild olefination procedures using lithium and magnesium salts[2] in the presence of tertiary amines or with lithium hydroxide[3] are also available. Interestingly, the reactions of methyl bis(trifluoroethyl)phosphonoacetate **2**[4] or ethyl diphenylphosphonoacetate[5] with aldehydes selectively yield *Z*-alkenes. However, the stereoselectivity of their HWE reactions with ketones has never been investigated in detail because of their low reactivity and low stereoselectivity.[6]

Herein we describe the stereochemical outcome in the HWE reactions of ethyl diethylphosphonoacetate **1** and methyl bis(trifluoroethyl)phosphonoacetate **2** with some aryl alkyl ketones **3a**–**e** and aldehydes **3f**,**g** using $Sn(OSO_2CF_3)_2$ in the presence of *N*-ethylpiperidine, as shown in Scheme 1.† The results are shown in Tables 1–3.‡

The conventional HWE reactions of aryl alkyl ketones **3a**–**d** with phosphonate **1** in the presence of sodium hydride in THF at 0 °C and then at room temperature gave the corresponding α,β-unsaturated esters **4a**–**d** with modest *E* selectivity (Table 1, entries 1–4). On the other hand, treatment of **3b**–**d** and **1** with $Sn(OSO_2CF_3)_2$ in the presence of *N*-ethylpiperidine in THF at 0 °C afforded *Z*-alkenes **4b**–**d**, respectively, in a highly selective fashion (Table 2, entries 2–4). Under both sets of reaction conditions described above, the HWE reactions of aldehydes **3f**,**g** with **1** gave **4f**,**g** in the usual highly *E*-selective manner (Table 1, entries 6 and 7; Table 2, entries 6 and 7). Poor stereoselectivity was observed in both reaction systems for ketone **3e** (Table 1, entry 5; Table 2, entry 5). A significant



Scheme 1

Table 1 NaH/THF mediated Horner–Wadsworth–Emmons reactions of **1** and **2** with ketones **3a**–**e** and aldehydes **3f**,**g**[a]

Entry	Phosphono-acetate	Ketone or aldehyde	*t*/h	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**1**	**3a**	66	100	**4a** (85:15)
2	**1**	**3b**	72	100	**4b** (62:38)
3	**1**	**3c**	72	86	**4c** (57:43)
4	**1**	**3d**	72	88	**4d** (51:49)
5	**1**	**3e**	72	93	**4e** (53:47)[d]
6	**1**	**3f**	1	100	**4f** (100:0)
7	**1**	**3g**	1	79	**4g** (97:3)
8	**2**	**3a**	23	100	**5a** (45:55)
9	**2**	**3b**	23	93	**5b** (39:61)
10	**2**	**3c**	24	82	**5c** (36:64)
11	**2**	**3d**	24	91	**5d** (35:65)
12	**2**	**3e**	23	52	**5e** (38:62)[d]
13	**2**	**3f**[e]	3	100	**5f** (15:85)
14	**2**	**3g**[e]	3	94	**5g** (8:92)

[a] Conditions: THF, 0 °C to room temp., **1** or **2**/NaH/**3** (1.7 : 1.5 : 1). [b] Isolated yields. [c] ^{1}H NMR (400 MHz, $CDCl_3$) analysis. [d] HPLC analysis (TSK-GEL Silica 60, hexane–propan-2-ol. [e] −78 °C.

Table 2 $Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/THF mediated Horner–Wadsworth–Emmons reactions of **1** and **2** with ketones **3a–e** and aldehydes **3f,g**[a]

Entry	Phosphono-acetate	Ketone or aldehyde	*t*/h	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**1**	**3a**	21	—[d]	—
2	**1**	**3b**	72	44	**4b** (7:93)
3	**1**	**3c**	19	38	**4c** (6:94)
4	**1**	**3d**	80	36	**4d** (6:94)
5	**1**	**3e**	19	4	**4e** (58:42)[e]
6	**1**	**3f**	20	47	**4f** (100:0)
7	**1**	**3g**	18	31	**4g** (100:0)
8	**2**	**3a**	18	95	**5a** (16:84)
9	**2**	**3b**	17	100	**5b** (16:84)
10	**2**	**3c**	16	92	**5c** (13:87)
11	**2**	**3d**	17	95	**5d** (12:88)
12	**2**	**3e**	17	65	**5e** (36:64)[e]
13	**2**	**3f**[f]	20	62	**5f** (89:11)
14	**2**	**3g**[f]	20	44	**5g** (95:5)

[a] Conditions: THF, 0 °C, **1** or **2**/$Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/**3** (1.4 : 1.68 : 1.54 : 1). [b] Isolated yields. [c] ^{1}H NMR (400 MHz, $CDCl_3$) analysis. [d] Aldol product (78% yield). [e] HPLC analysis (TSK-GEL Silica 60, hexane–propan-2-ol. [f] −78 °C.

Fig. 1

Table 3 $Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/CH_2Cl_2 mediated Horner–Wadsworth–Emmons reactions of **2** with ketones **3a–e** and aldehydes **3f,g**[a]

Entry	Ketone or aldehyde	*t*/h	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**3a**	15	84	**5a** (2 : 98)
2	**3b**	18	90	**5b** (< 1 : > 99)
3	**3c**	18	95	**5c** (2 : 98)
4	**3d**	18	98	**5d** (1 : 99)
5	**3e**	15	59	**5e** (40 : 60)[d]
6	**3f**[e]	23	29	**5f** (94 : 6)
7	**3g**[e]	24	—[f]	—

[a] Conditions: CH_2Cl_2, 0 °C, **2**/$Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/**3** (1.4 : 1.68 : 1.54 : 1). [b] Isolated yields. [c] ^1H NMR (400 MHz, $CDCl_3$) analysis. [d] HPLC analysis (TSK-GEL Silica 60, hexane–propan-2-ol. [e] −78 °C. [f] No reaction.

improvement in the selectivity and yield was found when Still's reagent, methyl bis(trifluoroethyl)phosphonoacetate **2**, was used under the Sn^{II}-promoted (Tables 2 and 3). In particular, the reactions of **3a–d** with **2** employing $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in CH_2Cl_2 at 0 °C afforded the corresponding *Z*-alkenes **5a–d** in a more highly selective manner (Table 3, entries 1–4) than those carried out in THF (Table 2, entries 8–11). The reactions using the NaH procedure resulted in low *Z*-selectivity (Table 1, entries 8–11). The HWE reactions of aldehydes **3f,g** with **2** in the presence of NaH in THF at −78 °C gave *Z*-**5f,g** with similar good selectivity to that using Still's reagent (Table 1, entries 13 and 14). The same reactions employing $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in THF or CH_2Cl_2 at −78 °C, on the contrary, gave *E*-**5f,g** with fairly good selectivity, as we anticipated (Table 2, entries 13 and 14; Table 3, entry 6). Surprisingly the stereoselectivity of **5f,g** in the Sn^{II}-promoted reactions of **3f,g** with **2** [THF, 20–22 h, **2**/$Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/**3f** or **3g** (1.4 : 1.68 : 1.54 : 1)] was variable depending on the reaction temperatures as follows; *E* : *Z* ratio (temperature, yield) of **5f** = 33 : 67 (0 °C, 90%), 19 : 81 (−30 °C, 72%), 12 : 88 (−45 °C, 68%), 26 : 74 (−56 °C, 62%), 71 : 29 (−65 °C, 57%) and 89 : 11 (−78 °C, 62%); *E* : *Z* ratio (temperature, yield) of **5g** = 6 : 94 (0 °C, 85%), < 1 : > 99 (−40 °C, 53%) and 95 : 5 (−78 °C, 44%). However, the similar Sn^{II}-promoted reaction of **3f** in CH_2Cl_2 always afforded the *E*-alkene **5f** (*E* : *Z* = 78 : 22 to 94 : 6) irrespective of the reaction temperature (room temperature to −78 °C). The NaH-promoted reactions of **3f,g** in THF also always gave the corresponding *Z*-alkenes **5f** [*E* : *Z* = 28 : 72 (0 °C) and 15 : 85 (−78 °C)] and **5g** [*E* : *Z* = 18 : 82 (0 °C) and 8 : 92 (−78 °C)], respectively.

On the basis of the experimental results described above, the high *Z*-selectivity in the $Sn(OSO_2CF_3)_2$-mediated HWE reactions of ketones **3a–d** with **1** and **2** can be rationalised in terms of six-membered transition state **A** (*e.g.* **3b**) involving Sn^{II} chelation (Fig. 1). Another possible transition state **B** favouring *E*-selectivity will be disadvantageous due to 1,3-diaxial steric repulsion between the ethyl (or other alkyl) group and the R^1O group. This speculative consideration is supported by the fact that 1-methyl-1-phenylcyclohexane exhibits an axial preference for the phenyl group in spite of the relatively large *A* value of the phenyl group (2.87 kcal mol^{-1}) compared with the ethyl group (1.8 kcal mol^{-1}).[7] The *E*-selectivity in the $Sn(OSO_2CF_3)_2$-mediated HWE reactions of aldehydes **3f,g** with **1** in THF at 0 °C, with **2** in THF at −65 to −78 °C and with **2** in CH_2Cl_2 at room temperature to −78 °C may also be explained in terms of six-membered transition state **C** (*e.g.* **3f**). The Sn^{II}-promoted HWE reactions of the reactive reagent **2** with aldehydes **3f,g** in THF at higher reaction temperatures than −65 °C seem to proceed in a non-chelation-controlled manner like the case of NaH.

Footnotes

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‡ Full characterisation will be published as part of a forthcoming paper.

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