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(*E*)-Selective Horner–Wadsworth–Emmons reaction of aryl alkyl ketones with bis(2,2,2-trifluoroethyl)phosphonoacetic acid

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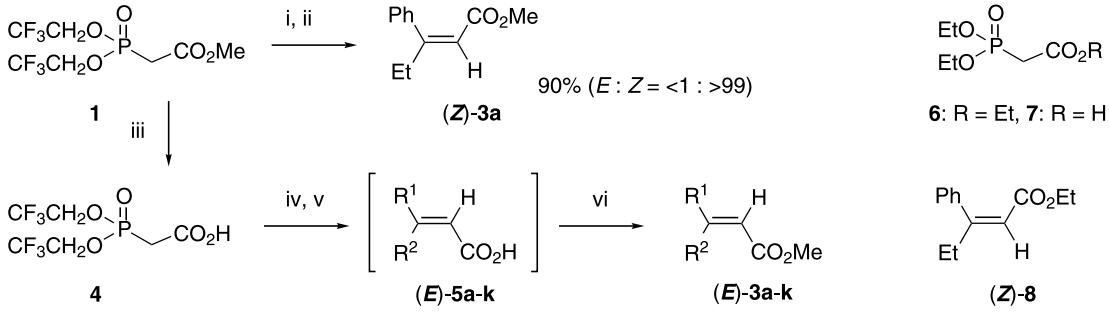
Abstract—The stereoselective Horner–Wadsworth–Emmons reaction of aryl alkyl ketones with bis(2,2,2-trifluoroethyl)phosphonoacetic acid utilizing lithium hexamethyldisilazide in DMF afforded (*E*)-α,β-unsaturated carboxylic acids as the major products.

Recently, a number of studies have attempted to develop a highly stereoselective method for synthesizing trisubstituted alkenes.[1–4] Although one such method, the stereoselective Horner–Wadsworth–Emmons (HWE) reaction of aldehydes, has been well established,[5–7] moderate reactivity and selectivity are generally observed in the HWE reactions with ketones.[8,9] We have previously reported a versatile method for the stereoselective HWE reaction with aryl alkyl ketones that can be utilized to prepare (*Z*)-α,β-unsaturated esters.[10,11] For example, an excellent *Z*-selectivity (*E*:*Z* = <1:>99) was observed in the HWE reaction of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**)[12] with phenyl ethyl ketone (**2a**) using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine, as shown in Scheme 1. In this communication, we report a convenient HWE reaction of bis(2,2,2-trifluoroethyl)phosphonoacetic acid (**4**) with various aryl alkyl ketones using lithium hexamethyldisilazide (LHMDS). To the best of our knowledge, this is the first example of an appreciably stereoselective HWE reaction of aryl alkyl ketones for the synthesis of (*E*)-α,β-unsaturated esters (*E*)-**3**.



a: R^1 = Ph, R^2 = Et, **b**: R^1 = Ph, R^2 = Me, **c**: R^1 = Ph, R^2 = *i*-Pr, **d**: R^1 = Ph, R^2 = *t*-Bu, **e**: R^1 = Ph, R^2 = *n*-pentyl, **f**: R^1 = 2-naphthyl, R^2 = Et, **g**: R^1 = *p*-methoxyphenyl, R^2 = Et, **h**: R^1 = *p*-tolyl, R^2 = Et, **i**: R^1 = *p*-chlorophenyl, R^2 = Et, **j**: R^1 = *p*-nitrophenyl, R^2 = Et, **k**: R^1 = $PhCH_2CH_2$, R^2 = Et,

Scheme 1. *Reagents and conditions*: (i) $Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/CH_2Cl_2/0°C/1 h; (ii) PhCOEt (**2a**)/0°C/18 h; (iii) PLE (Sigma, E-2884)/0.1 M phosphate buffer (pH 7.4)–acetone (9:1); (iv) *i*-PrMgBr or LHMDS/THF or DMF/0 °C /1 h; (v) R^1COR^2 (**2**); (vi) $TMSCHN_2$/MeOH–benzene (2:7)/rt/30 min.

Keywords: Horner–Wadsworth–Emmons reactions; olefination; stereoselection; α,β-unsaturated carboxylic acids; α,β-unsaturated esters; Wittig reactions.

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Table 1. Stereoselective HWE reactions of phenyl ethyl ketone (**2a**) with bis(2,2,2-trifluoroethyl)phosphonoacetic acid (**4**)

Entry	Conditions[a]	Solvent[b]	Temperature	Yield (%) of **3a**[c]	(*E*)-**5a**:(*Z*)-**5a**[d]
1	*i*-PrMgBr	THF	Reflux	70	76:24
2	*i*-PrMgBr	THF	rt	42	85:15
3	*i*-PrMgBr	THF	0°C	22	95:5
4	LHMDS	THF	0°C	56	89:11
5	LHMDS	MeCN	0°C	82	88:12
6	LHMDS	DMA	0°C	84	94:6
7	LHMDS	DMF	60°C	87	88:12
8	LHMDS	DMF	0°C	91	93:7
9	LHMDS	DMF	−40°C	50	96:4

[a] *i*-PrMgBr = **4**/*i*-PrMgBr/**2a** (1.2:2.5:1 molar ratio)/25 h; LHMDS = **4**/LHMDS/**2a** (1.2:2.5:1 molar ratio)/25 h.
[b] DMA: *N*,*N*-dimethylacetamide, DMF: *N*,*N*-dimethylformamide.
[c] Isolated yields.
[d] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.

Recently, we reported the *Z*-selective HWE reaction of aldehydes with 2-fluoro-2-diethylphosphonoacetic acid, and the *E*-selective HWE reaction of aldehydes with phosphonoacetic acid **4** under *i*-PrMgBr conditions.[13,14] In these and other studies, we have focused our attention on stereoselection of the HWE reaction with aryl alkyl ketones.[10,15,16] Taking into account an electrostatic repulsion between the aromatic moiety of aryl alkyl ketones and the carboxylate anion derived from phosphonoacetic acid **4**, a magnesium salt of the dianion of **4** was treated with phenyl ethyl ketone (**2a**) in THF to yield the α,β-unsaturated carboxylic acid **5a**. Esterification of crude **5a** with an excess amount of trimethylsilyldiazomethane ($TMSCHN_2$)[17] provided the desired α,β-unsaturated esters **3a**, as shown in Scheme 1. Under *i*-PrMgBr conditions in THF, temperature-dependent improvement of *E*-selectivity up to 95:5 (*E*:*Z*) was achieved in the reactions of **4** with **2a** (Table 1, entries 1–3). After optimization of the reaction conditions, we found that LHMDS in DMF was a suitable base for use in this HWE reaction (Table 1, entry 8).[18] A lower reaction temperature was found to lead to an increase in the stereoselectivity of **5a** in the HWE reactions of **4** with **2a** under LHMDS conditions (Table 1, entries 7–9). In the HWE reactions of phosphonoacetate **1** with **2a** employing LHMDS (1.25 mol equiv., DMF, 0°C, 25 h), α,β-unsaturated ester **3a** was scarcely obtained (86% recovery of **2a**). Moderate *Z*-selectivity and yield of **3a** (25%, *E*:*Z* = 35:65, 55% recovery of **2a**) were observed in the HWE reaction of **1** with **2a** by employing LHMDS (1.25 mol equiv., 0°C, 25 h) in THF. The HWE reaction of phosphonoacetate **1** with **2a** by employing NaH (1.5 mol equiv., 0°C, 23 h) in THF also afforded **3a** with moderate *Z*-selectivity (93%, *E*:*Z* = 39:61).[10] On the other hand, the HWE reactions of ethyl diethylphosphonoacetate **6** (1.25 mol equiv. of LHMDS, DMF, 0°C, 25 h) or diethylphosphonoacetic acid **7** (2.5 mol equiv. of LHMDS, DMF, 0°C, 25 h) with **2a** afforded **8** (trace amount) or **5a** (28%, *E*:*Z* = 87:13) with moderate yields and selectivity. Phosphonoacetic acid **4** was prepared in 92% yield by enzymatic hydrolysis of **1** with porcine liver esterase (PLE) in 0.1 M phosphate buffer (pH 7.4)–acetone (9:1).[14] The geometry of **5a** was confirmed by measurement of the ^{1}H–^{1}H nuclear Overhauser effect (NOE) (300 MHz, $CDCl_3$) in **3a**. The *E*:*Z* ratios of **5a** were determined by the integration of appropriate proton absorptions obtained by ^{1}H NMR (400 MHz) analysis.

A fairly good *E*-selectivity was observed in the HWE reaction of **4** with aryl alkyl ketones **2b**,**c**,**e**,**f**, as shown in Table 2. It was hard to obtain a satisfactory yield by the HWE reaction with ketone **2c** bearing the bulky isopropyl group (Table 2, entry 3). No reaction occurred when phenyl *tert*-butyl ketone (**2d**) was used (Table 2, entry 4). We also carried out HWE reactions of **4** with aryl alkyl ketones **2g**–**j** bearing various substituents on the aromatic moiety. In the cases of aromatic compounds **2g**,**h** having an electron-donating methoxy or methyl group, the *E*:*Z* stereoselectivity was good, with ratios of 93:7 and 95:5, respectively (Table 2, entries 7 and 8). In contrast, the similar reactions of ketones **2i**,**j** having an electron-withdrawing chloro or nitro group, resulted in a lower stereoselectivity (Table 2, entries 9–11). The HWE reactions of phenetyl ethyl ketone (**2k**) with **4** gave a 54:46 mixture of *E*- and *Z*-isomers of **5k** (Table 2, entry 12).

Table 2. Stereoselective HWE reactions of ketone **2** with bis(2,2,2-trifluoroethyl)phosphonoacetic acid (**4**)[a]

Entry	Ketone	Temperature	Yield (%)[b]	*E*:*Z*[c]
1	**2b**	0°C	89 (**3b**)	88:12 (**5b**)
2	**2b**	−40°C	45 (**3b**)	91:9 (**5b**)
3	**2c**	0°C	18 (**3c**)	95:5 (**5c**)
4	**2d**	0°C	0 (**3d**)	– (**5d**)
5	**2e**	0°C	85 (**3e**)	92:8 (**5e**)
6	**2f**	0°C	81 (**3f**)	90:10 (**5f**)
7	**2g**	0°C	77 (**3g**)	93:7 (**5g**)
8	**2h**	0°C	94 (**3h**)	95:5 (**5h**)
9	**2i**	0°C	70 (**3i**)	90:10 (**5i**)
10	**2j**	0°C	91 (**3j**)	78:22 (**5j**)
11	**2j**	−40°C	86 (**3j**)	85:15 (**5j**)
12	**2k**	0°C	76 (**3k**)	54:46 (**5k**)[d]

[a] DMF, **4**/LHMDS/**2** (1.2:2.5:1 molar ratio)/25 h.
[b] Isolated yields.
[c] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.
[d] Determined by ^{1}H NMR (400 MHz, CD_3OD) analysis.

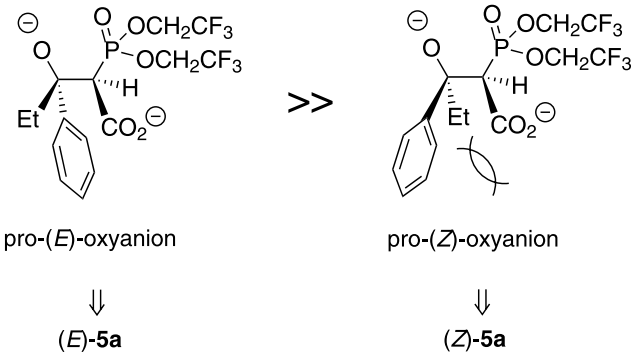

Figure 1. Plausible transition state for the *E*-selective HWE reaction of **4** with **2a** in terms of the electrostatic repulsion between the carboxylate anion and the phenyl group.

A plausible transition state of the *E*-selective HWE reactions of phosphonoacetic acid **4** with phenyl ethyl ketone (**2a**) is shown in Figure 1. The transition state for the formation of (*Z*)-**5a** from pro-(*Z*)-oxyanion may be less favorable than that from pro-(*E*)-oxyanion to (*E*)-**5a** because of an electrostatic repulsion between the carboxylate anion and the phenyl group of the oxyanion intermediate.[13,14,19–21] Consequently, (*E*)-α,β-unsaturated carboxylic acid (*E*)-**5a** was obtained as the major product. In general, decreasing reaction temperature tends to enhance *E*-selection of the HWE reaction of phosphonoacetic acid **4** with aryl alkyl ketone **2**. In the case of *p*-nitrophenyl ethyl ketone (**2j**), such an electrostatic repulsion may not be effective for the *E*-selective HWE reaction at 0°C.[22–26]

In summary, we have developed an improved *E*-selective HWE reaction of phosphonoacetic acid **4** with various aryl alkyl ketones utilizing LHMDS as a base in DMF. In addition to the *Z*-selective HWE reaction of aryl alkyl ketones under $Sn(OSO_2CF_3)_2$ conditions,[10,11] this novel procedure may find application in the organic synthesis of various trisubstituted alkenes.

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18. Typical procedure of *E*-selective HWE reaction: To a stirred solution of phosphonoacetic acid **4** (98 mg, 0.32 mmol) in anhydrous DMF (5 mL) was added a 1.06 mol/L solution of LHMDS (0.63 mL, 0.67 mmol) in *n*-hexane at 0°C under argon. The mixture was stirred at 0°C for 1 h, and phenyl ethyl ketone (**2a**) (35.7 μL, 0.27 mmol) was added to the solution. After being stirred at 0°C for 25 h, the reaction mixture was treated with H_2O (10 mL) and then washed with $CHCl_3$ (20 mL). The water layer was acidified with 10% HCl and extracted with AcOEt (60 mL×3). The extract was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The organic layer was evaporated in vacuo to afford a crude product **5a** (*E*:*Z* = 93:7). To the solution of **5a** in MeOH (2 mL) and benzene (7 mL) was added an excess amount of $TMSCHN_2$ (2.0 mol/L solution in *n*-hexane, ca. 0.5 mL, ca. 1 mmol). After being stirred at room temperature for 30 min, the reaction mixture was evaporated in vacuo to afford a crude product, which was purified by chromatography on a silica gel column eluted with *n*-hexane–AcOEt (10:1), giving a mimxture of α,β-unsaturated esters (*E*)- and (*Z*)-**3a** (46 mg, 91%, *E*:*Z* = 94:6) as a colorless oil.
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