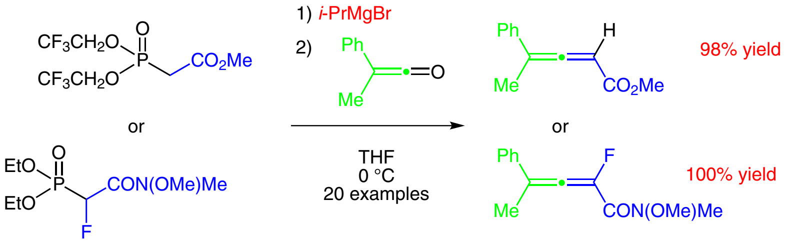
Synthesis of Allenyl Esters by Horner–Wadsworth–Emmons Reactions of Ketenes Mediated by Isopropylmagnesium Bromide

Shigeki Sano*
Tomoya Matsumoto
Teppei Yano
Munehisa Toguchi
Michiyasu Nakao

Graduate School of Pharmaceutical Sciences, Tokushima University, Sho-machi, Tokushima 770-8505, Japan
ssano@tokushima-u.ac.jp



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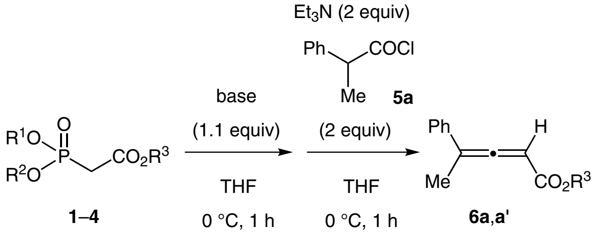
Abstract The synthesis of conjugated allenyl esters (tri-substituted allenes) was achieved by magnesium(II)-mediated Horner–Wadsworth–Emmons reaction of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate with disubstituted ketenes. In addition, a novel access to α-fluorinated allenyl carboxamides (tetrasubstituted allenes) is presented.

Key words Horner–Wadsworth–Emmons reaction, allenes, ketenes, Grignard reagents, fluorine

Since the first synthesis of glutinic acid (allene-1,3-dicarboxylic acid) in 1887,[1] allenes have attracted considerable attention as chemical curiosities.[2] Furthermore, allene derivatives have recently been established as versatile building blocks in organic synthesis, including asymmetric synthesis.[3] Allenic structures are also found in natural products and pharmaceutical agents.[4] We have already established a characteristic method of synthesizing conjugated allenyl esters from diethyl α-alkynyl-α-methoxy malonates through a cascade reaction,[5] and suggested the possibility of developing novel inhibitors of cysteine protease based on several biomimetic reactions by using conjugated allenyl compounds and their precursors.[6] On the other hand, the Horner–Wadsworth–Emmons (HWE) reaction of phosphonoacetates with aldehydes (or ketones) is one of the most useful methods of synthesizing α,β-unsaturated esters.[7] There are, however, only a limited number of reports concerning the HWE reaction of ketene for the preparation of allenyl esters.[8,9] We now describe a facile one-pot synthesis of allenyl esters (tri- or tetra-substituted allenes) by HWE reactions of ketenes using ***i*-PrMgBr** as base.

We first investigated HWE reactions of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent, **1**)[10,11] with a di-substituted ketene, which was prepared in situ from 2-phenylpropionyl chloride (**5a**) and triethylamine,[9g,j] as shown in Table 1. Phosphonoacetate **1** is a typical *Z*-selective HWE reagent due to the electron-withdrawing effect of the two trifluoroethoxy groups on its phosphorus atom. As expected, the desired conjugated allenyl ester **6a** (tri-substituted allene) was obtained by the HWE reaction of **1** in good to excellent yields by using bases such as *n*-BuLi, NaH, and *i*-PrMgBr (entries 1–3). Among these, *i*-

Table 1 HWE Reactions of Phosphonoacetates **1**–**4** with Phenyl Methyl Ketene Prepared In Situ from 2-Phenylpropionyl Chloride (**5a**)



1–4

6a,a'

1: $R^1 = R^2 = CF_3CH_2$, R^3 = Me
2: $R^1 = R^2$ = Ph, R^3 = Et
3: $R^1 = CF_3CH_2$, R^2 = Me, R^3 = Me
4: $R^1 = R^2 = R^3$ = Me

6a: R^3 = Me
6a': R^3 = Et

Entry	HWE reagent	Base	Yield (%)[a]
1	**1**	*n*-BuLi	68 (**6a**)
2	**1**	NaH	5 (**6a**)
3	**1**	*i*-PrMgBr	98 (**6a**)
4	**2**	*i*-PrMgBr	96 (**6a′**)
5	**3**	*i*-PrMgBr	81 (**6a**)
6	**4**	*i*-PrMgBr	72 (**6a**)

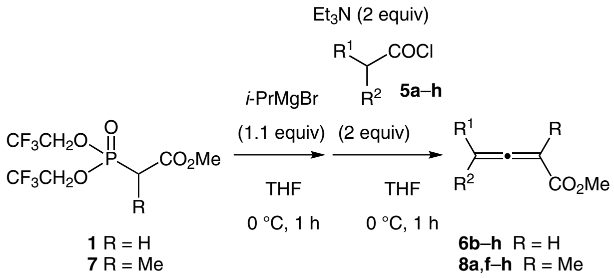
[a] Isolated yield.

PrMgBr afforded allenyl ester **6a** in almost quantitative yield (98%).[12,13] We have reported the use of stereoselective HWE reactions for the preparation of α,β-unsaturated esters by using *i*-PrMgBr.[14] Thus, HWE reagents **2**–**4** were investigated in the HWE reaction mediated by *i*-PrMgBr for the preparation of conjugated allenyl esters **6a** and **6a′** (entries 4–6). As a result, *Z*-selective HWE reagent **2** (Ando reagent)[15,16] also furnished **6a′** in excellent yield (96%). It appears that increasing the *Z*-selectivity of HWE reagents in the reaction with aldehydes and ketones tends to increase the chemical yield of allenyl ester **6a** (entries 3, 5, and 6).

To explore the substrate scope of the HWE reaction, a range of ketenes generated in situ from the corresponding acyl chlorides **5a**–**h** were subjected to reaction with HWE reagent **1** as shown in Table 2. In all cases investigated, HWE reactions of di-substituted ketenes derived from acyl chlorides **5b**–**e** proceeded smoothly to afford 90–100% yields of the desired allenyl esters **6b**–**e** (tri-substituted allenes) (entries 1–4). On the other hand, the HWE reaction of mono-substituted ketenes derived from acyl chlorides **5f**–**h** resulted in the formation of allenyl esters **6f**–**h** (di-substituted allenes) in low yields (entries 5–7). It is interesting to note that a similar HWE reaction of ketenes derived from **5f**–**h** with α-methylated Still–Gennari reagent (**7**)[17] afforded the corresponding allenyl esters **8f**–**h** (tri-substituted allenes) in higher yields than those of **6f**–**h** (entries 8–10). The HWE reaction of **7** with phenyl methyl ketene derived from acyl chloride **5a** furnished allenyl ester **8a** (tetra-substituted allene) in 89% yield (entry 11).

We next investigated the use of ethyl 2-fluoro-2-diethylphosphonoacetate (**9**)[18,19] in place of **1** as the HWE reagent to obtain a fluorinated allenyl ester. There are very few examples of the synthesis of α-fluorinated allenyl esters.[20] As a result, the desired product **12a** (tetra-substituted allene) was obtained in moderate yield (Table 3, entry 1). However, the HWE reaction of phosphonoacetic acid **10** using 2.1 equivalent of *i*-PrMgBr did not proceed (entry 2). Nevertheless, the HWE reaction of Weinreb amide **11**[21] with di-substituted ketenes derived from acyl chlorides **5a**–**c** afforded fluorinated allenyl carboxamides **14a**–**c** (tetra-substituted allenes) in 71–100% yields (entries 3–8).[22] Unfortunately, poor yields of fluorinated allenyl carboxamides

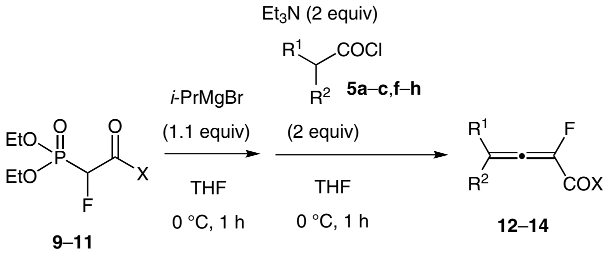
Table 2 HWE Reactions of Phosphonoacetates **1** and **7** with Ketenes Prepared In Situ from Acid Chlorides **5a**–**h**



Entry	HWE reagent	R¹	R²	Yield (%)[a]
1	**1** (R = H)	Ph	Et	100 (**6b**)
2	**1** (R = H)	Ph	Ph	100 (**6c**)
3	**1** (R = H)	4-$O_2NC_6H_4$	Me	90 (**6d**)
4	**1** (R = H)	4-$MeOC_6H_4$	Me	97 (**6e**)
5	**1** (R = H)	Ph	H	29 (**6f**)
6	**1** (R = H)	Bn	H	38 (**6g**)
7	**1** (R = H)	*n*-C_6H_{13}	H	22 (**6h**)
8	**7** (R = Me)	Ph	H	40 (**8f**)
9	**7** (R = Me)	Bn	H	69 (**8g**)
10	**7** (R = Me)	*n*-C_6H_{13}	H	65 (**8h**)
11[b]	**7** (R = Me)	Ph	Me	89 (**8a**)

[a] Isolated yield.
[b] Reaction mixture was stirred for 3 h.

Table 3 HWE Reactions of α-Fluorophosphonoacetates **9**–**11** with Ketenes Prepared In Situ from Acid Chlorides **5a**–**c** and **5f**–**h**



9: X = OEt, **10**: X = OH, **11**: X = N(OMe)Me

Entry	HWE reagent	R¹	R²	Yield (%)[a]
1	**9** (X = OEt)	Ph	Me	ca. 57 (**12a**)[b]
2[c]	**10** (X = OH)	Ph	Me	0 (**13a**)
3	**11** [X = N(OMe)Me]	Ph	Me	71 (**14a**)
4[d]	**11** [X = N(OMe)Me]	Ph	Me	90 (**14a**)
5[e]	**11** [X = N(OMe)Me]	Ph	Me	100 (**14a**)
6	**11** [X = N(OMe)Me]	Ph	Et	71 (**14b**)
7[e]	**11** [X = N(OMe)Me]	Ph	Et	94 (**14b**)
8	**11** [X = N(OMe)Me]	Ph	Ph	92 (**14c**)
9	**11** [X = N(OMe)Me]	Ph	H	0 (**14f**)[f]
10	**11** [X = N(OMe)Me]	Bn	H	0 (**14g**)[g]
11[e]	**11** [X = N(OMe)Me]	Bn	H	ca. 14 (**14g**)[b,h]
12	**11** [X = N(OMe)Me]	*n*-C_6H_{13}	H	0 (**14h**)[i]

[a] Isolated yield.
[b] Containing small amounts of impurities.
[c] *i*-PrMgBr (2.1 equiv) was used.
[d] Reaction mixture was stirred for 3 h.
[e] Reaction mixture was stirred for 18 h.
[f] HWE reagent **11** was recovered (ca. 54%).
[g] HWE reagent **11** was recovered (ca. 40%).
[h] HWE reagent **11** was recovered (ca. 20%).
[i] HWE reagent **11** was not recovered.

14f–**h** (tri-substituted allenes) were obtained in the HWE reaction of Weinreb amide **11** with mono-substituted ketenes derived from acyl chlorides **5f**–**h** (entries 9–12).

In conclusion, we have developed a facile method of synthesizing conjugated allenyl esters **6** and **8** through the magnesium(II)-mediated HWE reaction of **1** and **7** with di-substituted ketenes, which were prepared in situ from the corresponding acid chlorides. For the first time, α-fluorinated allenyl carboxamides **14** have also been prepared by using the magnesium(II)-mediated HWE reaction of **11** with di-substituted ketenes. We believe that the proposed method of synthesizing conjugated allenyl carboxylic acid derivatives is a valuable addition to the chemistry of allenes.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378803.

References

(1) (a) Burton, B. S.; von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145. (b) Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3208.

(2) (a) Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 177. (b) Maitland, P.; Mills, W. H. *Nature* **1935**, *135*, 994. (c) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317.

(3) (a) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (b) Kim, H.; Williams, L. J. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 870. (c) Pinho e Melo, T. M. V. D. *Monatsh. Chem.* **2011**, *142*, 681. (d) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384. (e) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. (f) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2014**, *43*, 2886.

(4) Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.

(5) (a) Nagao, Y.; Kim, K.; Sano, S.; Kakegawa, H.; Lee, W. S.; Shimizu, H.; Shiro, M.; Katunuma, N. *Tetrahedron Lett.* **1996**, *37*, 861. (b) Sano, S.; Shimizu, H.; Nagao, Y. *Tetrahedron Lett.* **2005**, *46*, 2883. (c) Sano, S.; Shimizu, H.; Kim, K.; Lee, W. S.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2006**, *54*, 196.

(6) (a) Nagao, Y.; Sano, S.; Morimoto, K.; Kakegawa, H.; Takatani, T.; Shiro, M.; Katunuma, N. *Tetrahedron Lett.* **2000**, *41*, 2419. (b) Takeuchi, Y.; Fujiwara, T.; Shimone, Y.; Miyataka, H.; Satoh, T.; Kirk, K. L.; Hori, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6202.

(7) (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S. Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (d) Bisceglia, J. A.; Orelli, L. R. *Curr. Org. Chem.* **2012**, *16*, 2206. (e) Al Jasem, Y.; El-Esawi, R.; Thiemann, T. *J. Chem. Res.* **2014**, *38*, 453.

(8) For examples of HWE reactions, see: (a) Runge, W.; Kresze, G. *Justus Liebigs Ann. Chem.* **1975**, 1361. (b) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735. (c) Yamazaki, J.; Watanabe, T.; Tanaka, K. *Tetrahedron: Asymmetry* **2001**, *12*, 669. (d) Nagaoka, Y.; Inoue, H.; Tomioka, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1843. (e) Inoue, H.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **2002**, *58*, 83. (f) Huang, X.; Xiong, Z.-C. *Chem. Commun.* **2003**, 1714. (g) Plunkett, S.; Dahms, K.; Senge, M. O. *Eur. J. Org. Chem.* **2013**, 1566.

(9) For examples of Wittig reactions, see: (a) Kresze, G.; Runge, W.; Ruch, E. *Justus Liebigs Ann. Chem.* **1972**, *756*, 112. (b) Bestmann, H.-J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198. (c) Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* **1968**, *22*, 2347. (d) Lang, R. W.; Hansen, H.-J. *Helv. Chim. Acta* **1979**, *62*, 1025. (e) Lang, R. W.; Hansen, H.-J. *Helv. Chim. Acta* **1980**, *63*, 438. (f) Himbert, G.; Fink, D. *J. Prakt. Chem.* **1997**, *339*, 233. (g) Pinho e Melo, T. M. V. D.; Cardoso, A. L.; d'A. Rocha Gonsalves, A. M.; Costa Pessoa, J.; Paixão, J. A.; Beja, A. M. *Eur. J. Org. Chem.* **2004**, 4830. (h) Li, C.-Y.; Sun, X.-L.; Jing, Q.; Tang, Y. *Chem. Commun.* **2006**, 2980. (i) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494. (j) Li, C.-Y.; Zhu, B.-H.; Ye, L.-W.; Jing, Q.; Sun, X.-L.; Tang, Y.; Shen, Q. *Tetrahedron* **2007**, *63*, 8046. (k) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Chem. Eur. J.* **2010**, *16*, 7376.

(10) DeHoff, B.; Roy, M.-N. *Methyl bis(2,2,2-trifluoroethoxy)phosphinylacetate*, In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, **2012**.

(11) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Messik, F.; Oberthür, M. *Synthesis* **2013**, *45*, 167.

(12) **Typical Procedure:** To a solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**; 40 μL, 0.188 mmol) in anhydrous THF (1.9 mL) was added *i*-PrMgBr (0.77 mol/L in THF, 269 μL, 0.207 mmol), and the solution was stirred at 0 °C for 1 h under argon. After adding triethylamine (53 μL, 0.377 mmol) and 2-phenylpropionyl chloride (**5a**; 56 μL, 0.377 mmol), the mixture was stirred at 0 °C for 1 h under argon. The reaction mixture was treated with sat. aq NH_4Cl (2 mL) and then extracted with $CHCl_3$ (3 × 20 mL). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 12.5:1 to 11:1) to afford allenyl ester **6a** (34.7 mg, 98%).

(13) Data for **6a**: Pale-yellow oil; IR (neat): 2951, 1948, 1722, 1495, 1437, 1392, 1263, 1209, 1151 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.21$ (d, $J = 2.9$ Hz, 3 H), 3.75 (s, 3 H), 5.90 (q, $J = 2.9$ Hz, 1 H), 7.27–7.28 (m, 1 H), 7.33–7.40 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.2$, 52.1, 89.5, 105.5, 126.2, 127.9, 128.6, 134.3, 166.1, 214.0. MS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{12}NaO_2$: 211.0735; found: 211.0732. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.27; H, 6.54.

(14) (a) Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777. (b) Sano, S.; Teranishi, R.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 9183. (c) Sano, S.; Takemoto, Y.; Nagao, Y. *ARKIVOC* **2003**, *(viii)*, 93. (d) Sano, S.; Takemoto, Y.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 8853. (e) Sano, S.; Matsumoto, T.; Nanataki, H.; Tempaku, S.; Nakao, M. *Tetrahedron Lett.* **2014**, *55*, 6248.

(15) Roy, M.-N. *Ethyl 2-(diphenoxyphosphinyl)acetate*, In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, **2013**.

(16) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934. (c) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411. (d) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406. (e) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745. (f) Ando, K. *Synlett* **2001**, 1272.

(17) (a) Sano, S.; Takehisa, T.; Ogawa, S.; Yokoyama, K.; Nagao, Y. *Chem. Pharm. Bull.* **2002**, *50*, 1300. (b) Sano, S.; Abe, S.; Azetsu, T.; Nakao, M.; Shiro, M.; Nagao, Y. *Lett. Org. Chem.* **2006**, *3*, 798.

(18) Jiang, J. *Triethyl 2-fluoro-2-phosphonoacetate*, In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, **2006**.

(19) (a) Machleidt, H.; Wessendorf, R. *Justus Liebigs Ann. Chem.* **1964**, *674*, 1. (b) Burton, D. J.; Yang, Z.-Y.; Qui, W. *Chem. Rev.* **1996**, *96*, 1641.

(20) Xu, B.; Hammond, G. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 689.

(21) Boumendjel, A.; Nuzillard, J.-M.; Massiot, G. *Tetrahedron Lett.* **1999**, *40*, 9033.

(22) Data for **14a**: Yield: 37.6 mg (quant.); yellow oil. IR (neat): 2937, 1954, 1652, 1462, 1444, 1417, 1386, 1155 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (d, $^5J_{C-F}$ = 8.3 Hz, 3 H), 3.26 (s, 3 H), 3.51 (s, 3 H), 7.31–7.40 (m, 3 H), 7.49–7.53 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 33.7, 61.6, 118.9 (d, $^3J_{C-F}$ = 12.0 Hz), 126.8 (d, $^5J_{C-F}$ = 2.7 Hz), 128.7, 129.1 (d, $^6J_{C-F}$ = 1.7 Hz), 129.6 (d, $^1J_{C-F}$ = 234.8 Hz), 134.4 (d, $^4J_{C-F}$ = 1.7 Hz), 162.0 (d, $^2J_{C-F}$ = 40.1 Hz), 193.2 (d, $^2J_{C-F}$ = 18.7 Hz). MS (ESI): m/z [M + Na]$^+$ calcd for $C_{13}H_{14}FNNaO_2$: 258.0906; found: 258.0896. Anal. Calcd for $C_{13}H_{14}FNO_2$: C, 66.37; H, 6.00; N, 5.95. Found: C, 66.08; H, 6.02; N, 5.89.