ORGANIC LETTERS

2012
Vol. 14, No. 16
4206–4209

Novel One-pot Three-component Coupling Reaction with Trimethylsilylmethylphosphonate, Acyl Fluoride, and Aldehyde through the Horner–Wadsworth–Emmons Reaction

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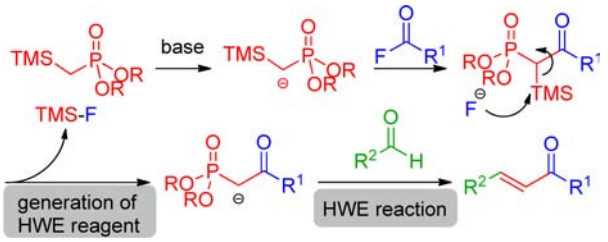
Received July 9, 2012

ABSTRACT



A novel three-component coupling between trimethylsilylmethylphosphonate, acyl fluoride, and aldehyde has been developed. A sequential nucleophilic addition of lithio-trimethylsilylmethylphosphonate to the acyl fluoride and Horner–Wadsworth–Emmons reaction of an aldehyde with the lithio-β-ketophosphonate generated in situ by desilylation at the α-position of the α-silyl-β-ketophosphonate by fluoride took place cleanly in a one-pot operation. Various *E*- and *Z*-enones were obtained in high yields with high stereoselectivities by this one-pot procedure.

The Horner–Wadsworth–Emmons reaction (HWE reaction) is a reliable and powerful method for carbon–carbon bond formation via coupling between a β-ketophosphonate and an aldehyde, giving an α,β-unsaturated compound with high stereoselectivity.[1] The HWE reaction has been broadly utilized for the synthesis of various compounds including natural products. In general, the β-ketophosphonate used as the HWE reaction precursor **A** is synthesized from a readily accessible compound. Representative examples for the synthesis of **A** are shown in Scheme 1. An aldehyde is often transformed into **A** in 2 steps through addition of commercially available methylphosphonate,

(1) Review of HWE reaction: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99.

(2) (a) Traoré, M.; Maynadier, M.; Souard, F.; Choisnard, L.; Vial, H.; Wong, Y.-S. *J. Org. Chem.* **2011**, *76*, 1409–1417. (b) Nicolaou, K. C.; Jiang, X.; Lindsay-Scott, P. J.; Corbu, A.; Yamashiro, S.; Bacconi, A.; Fowler, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1139–1144. (c) Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas, F. *J. Am. Chem. Soc.* **2010**, *132*, 6855–6861. (d) Crimimins, M. T.; Zuccarello, J. L.; McDougall, P. J.; Ellis, J. M. *Chem.—Eur. J.* **2009**, *15*, 9235–9244. (e) Sparling, B. A.; Simpson, G. L.; Jamison, T. F. *Tetrahedron* **2009**, *65*, 3270–3280. (f) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y. J. Aubé *J. Am. Chem. Soc.* **2008**, *130*, 6018–6024. (g) Torihata, M.; Nakahara, T.; Kuwahara, S. *Org. Lett.* **2007**, *9*, 2557–2559. (h) Fujiwara, K.; Aki, Y.; Yamamoto, F.; Kawamura, M.; Kobayashi, M.; Okano, A.; Awakura, D.; Shiga, S.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2007**, *48*, 4523–4527. (i) Yadav, J. S.; Venugopal, C. *Synlett* **2007**, 2262–2266. (j) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6527–6532. (k) Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439–2442.

(3) (a) Coppola, G. M. *Synthesis* **1988**, 81–84. (b) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371–3373. (c) Rodriquez, M.; Bruno, I.; Cini, E.; Marchetti, M.; Taddei, M.; Gomez-Paloma, L. *J. Org. Chem.* **2006**, *71*, 103–107. (d) Milburn, R. R.; McRae, K.; Chan, J.; Tedrow, J.; Larsen, R.; Faul, M. *Tetrahedron Lett.* **2009**, *50*, 870–872. (e) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912–4915.

(4) (a) Ezquerra, J.; Mendoza, J.; Pedregal, C.; Ramírez, C. *Tetrahedron Lett.* **1992**, *33*, 5589–5590. (b) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163–2171. (c) Tchabanenko, K.; Chesworth, R.; Parker, J. S.; Anand, N. K.; Russell, A. T.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron Lett.* **2005**, *61*, 11649–11656.

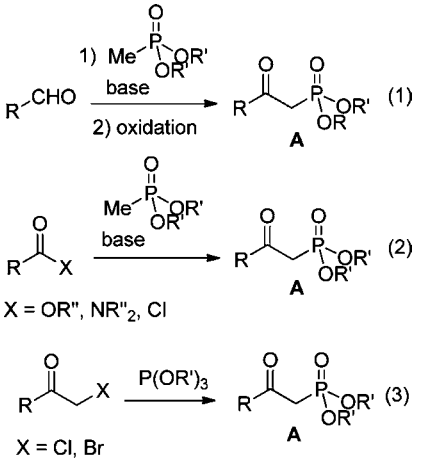
(5) (a) Balczewski, P.; Mikolajczyk, M. *Org. Lett.* **2000**, *2*, 1153–1155. (b) Motoyoshiya, J.; Miyajima, M.; Hirakawa, K.; Kakurai, T. *J. Org. Chem.* **1985**, *50*, 1326–1327. (c) Savignac, P.; Mathey, F. *Tetrahedron Lett.* **1976**, *17*, 2829–2832.

10.1021/ol301879a
Published on Web 07/31/2012

followed by oxidation of the resultant alcohol (eq 1).[2] Carboxylic acid derivatives, such as esters,[3] imides,[4] or acyl chlorides,[5] are also employed as precursors by addition of methylphosphonate (eq 2). The Michaelis–Arbuzov reaction, that is, substitution of an α-halocarbonyl compound by a trialkyl phosphite, also affords **A** (eq 3).[6] However, these procedures sometimes encounter problems in purification due to side products or the high polarity of **A**.

Accordingly, we planned to develop the one-pot synthesis of the α,β-unsaturated ketone through the formation

Scheme 1. Synthesis of β-Ketophosphonates



of **A** accompanied by the instantaneous generation of its enolate and subsequent HWE reaction. We envisioned that the sequential reactions illustrated in Scheme 2 would be suitable for this purpose. The α-silyl-β-ketophosphonate **4** would be formed by the nucleophilic substitution reaction between the acyl fluoride **3** and the enolate **2** produced by treatment of the trimethylsilylmethylphosphonate **1** with a base. The acyl fluoride **3** can be obtained from the corresponding carboxylic acid and (diethylamino)sulfur trifluoride (DAST)[7] with high purity by simple extraction and is stable for several days. We expected that the fluoride ion liberated during the substitution would induce the in situ generation of the corresponding enolate **5** via desilylation at the α-position of **4**.[8] Subsequent addition of the aldehyde **6** to the reaction mixture would afford the HWE product **7**. Herein, we would like to describe the novel one-pot three-component coupling reaction.

(6) (a) Taber, D. F.; Bai, S.; Guo, P. *Tetrahedron Lett.* **2008**, *49*, 6904–6906. (b) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266–4268.

(7) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578. (b) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787–789.

(8) Desilylation from α-silylphosphonate or α-silylester by fluoride, see: (a) Latouche, R.; Texier-Boullet, F.; Harnelin, J. *Tetrahedron Lett.* **1991**, *32*, 1179–1182. (b) Kita, Y.; Sekihachi, J.; Hayashi, Y.; Da, Y.-Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990**, *55*, 1108–1112. (c) Kawashima, T.; Ishii, T.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1831–1837. (d) Kawashima, T.; Ishii, T.; Inamoto, N. *Tetrahedron Lett.* **1983**, *24*, 739–742.

Scheme 2. Proposed One-pot Reaction

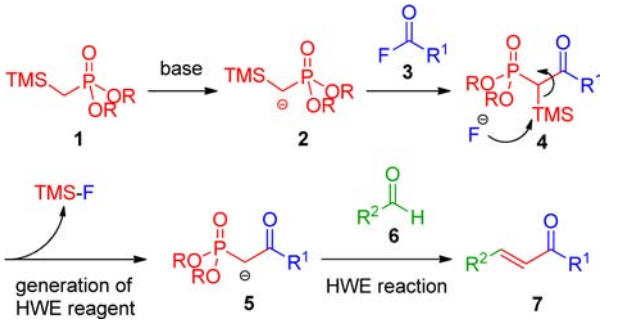
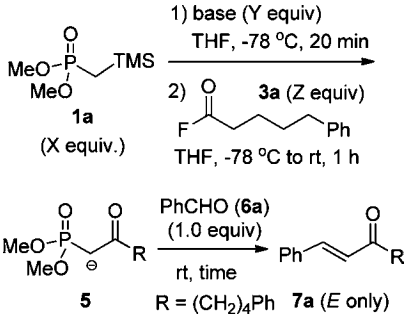


Table 1. Optimization of Reaction Conditions



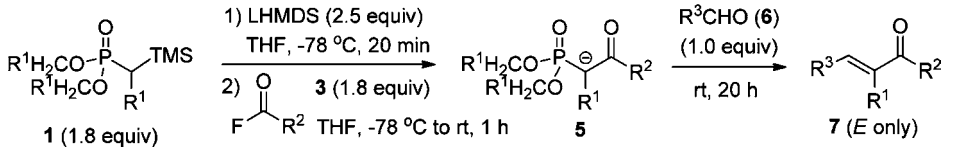
entry	base	time (h)	X	Y	Z	yield[a]
1	*n*-BuLi	2	2.0	2.0	1.8	54%
2	*n*-BuLi	20	2.0	2.0	1.8	57%
3	NaHMDS	20	2.0	2.0	1.8	56%
4	KHMDS	20	2.0	2.0	1.8	76%
5	LHMDS	20	2.0	2.0	1.8	99%
6	LHMDS	2	2.0	2.0	1.8	80%
7	LHMDS	20	1.8	2.5	1.8	99%

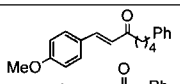
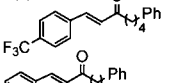
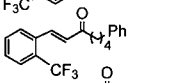
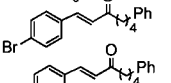
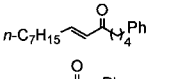
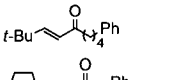
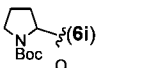
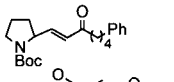
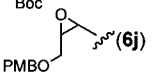
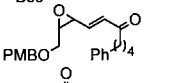
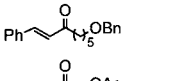
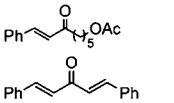
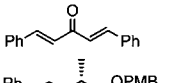
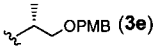
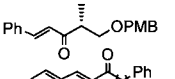
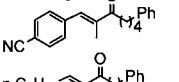
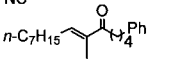
[a] Isolated yield after column chromatography.

Table 1 summarizes the optimization of reaction conditions using dimethyl trimethylsilylmethylphosphonate (**1a**),[9] 5-phenylvaleryl fluoride (**3a**), and benzaldehyde (**6a**). At first, the reactions were carried out by employing 2.0 equiv (to **6a**) of **1a**, 2.0 equiv (to **6a**) of the base, and 1.8 equiv (to **6a**) of **3a**. When *n*-BuLi or NaHMDS was used as the base, the three-component coupling reaction proceeded successfully in one-pot to give the *E*-enone **7a** in 54–57% yields with complete stereoselectivity (entries 1–3). The reaction with KHMDS improved the yield to 76% (entry 4). An almost quantitative yield of **7a** was obtained with LHMDS (entry 5). In the coupling reaction with LHMDS, a shorter reaction time resulted in a decrease in the yield of **7a** (entry 6). When the amount of

(9) (a) Hamada, A.; Braunstein, P. *Organometallics* **2009**, *28*, 1688–1696. (b) Aboujaoude, E. E.; Liétjé, S.; Collignon, N. *Synthesis* **1986**, 934–937.

Table 2. One-pot Reaction with Various Substrates



entry	R^1	R^2	R^3	product	yield[a]
1	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*p*-$OMeC_6H_4$ (**6b**)	 (**7b**)	79%[b]
2	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*p*-$CF_3C_6H_4$ (**6c**)	 (**7c**)	87%
3	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*o*-$CF_3C_6H_4$ (**6d**)	 (**7d**)	94%[b]
4	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*p*-BrC_6H_4 (**6e**)	 (**7e**)	95%
5	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*p*-CNC_6H_4 (**6f**)	(**7f**)	98%
6	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*n*-C_7H_{15} (**6g**)	 (**7g**)	82%
7	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	*t*-Bu (**6h**)	 (**7h**)	61%[b]
8	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	 (**6i**)	 (**7i**)	94%
9	H (**1a**)	$(CH_2)_4Ph$ (**3a**)	 (**6j**)	 (**7j**)	84%
10	H (**1a**)	$(CH_2)_5OBn$ (**3b**)	Ph (**6a**)	 (**7k**)	99%
11	H (**1a**)	$(CH_2)_5OAc$ (**3c**)	Ph (**6a**)	 (**7l**)	74%
12	H (**1a**)	CH=CHPh (**3d**)	Ph (**6a**)	 (**7m**)	54%[b]
13	H (**1a**)	 (**3e**)	Ph (**6a**)	 (**7n**)	97%[c]
14	Me (**1b**)	$(CH_2)_4Ph$ (**3a**)	*p*-CNC_6H_4 (**6f**)	 (**7o**)	82%[d]
15	Me (**1b**)	$(CH_2)_4Ph$ (**3a**)	*n*-C_7H_{15} (**6g**)	 (**7p**)	98%[d]

[a] Isolated yield after column chromatography. [b] Stirred for 48 h. [c] LHMDS (2.0 equiv) was used. [d] Stirred for 48 h; 2.5 equiv each of **1b** and **3a**, and 3.0 equiv of *n*-BuLi as a base were used.

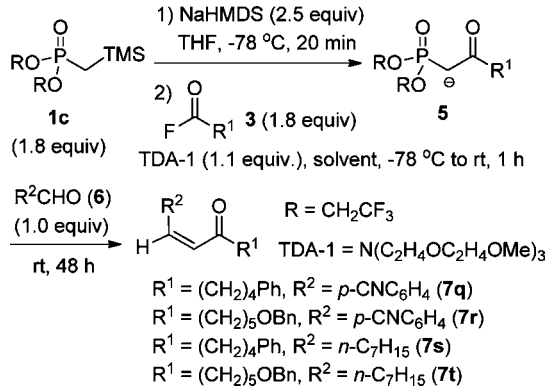
1a was reduced to 1.8 equiv (to **6a**), 2.5 equiv (to **6a**) of LHMDS was necessary to obtain **7a** with excellent yield (entry 7). In stark contrast, the same reaction with the anion generated from LHMDS and dimethyl methylphosphonate [$MeP(O)(OMe)_2$], **3a**, and **6a** did not take place at all and any formation of **7a** or the corresponding β-ketophosphonate was not observed.[10]

As mentioned above, **7a** was quantitatively derived from **6a** with complete stereoselectivity under the optimized conditions (Table 1, entry 7). Next, the scope of substrates for the coupling reaction was examined.[11] As shown in Table 2, a wide variety of aldehydes and acyl fluorides participated in the one-pot procedure, providing the *E*-enones as the sole stereoisomers in high yields. In the coupling reactions of **3a**, the aromatic aldehydes **6b**–**f** with electron-donating or -withdrawing groups on the benzene ring afforded the *E*-enones **7b**–**f** in high yields, although longer reaction times were needed with the electron-donating aldehyde **6b** and sterically demanding aldehyde **6d** (entries 1–5). The alkyl aldehydes, octanal (**6g**) and 2,2-dimethylpropanal (**6h**), were also converted into the *E*-enones **7g** and **7h** (entries 6, 7).

(10) Berté-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 821–824.

(11) To a solution of **1a** (35.3 mg, 0.180 mmol) in THF (1 mL) was added LHMDS (1.0 M in THF, 250 μL, 0.250 mmol) at −78 °C under Ar atmosphere. After 20 min, a solution of **3a** (32.4 mg, 0.180 mmol) in THF (0.5 mL) was added to the mixture. The mixture was warmed to room temperature and stirred for 1 h, after which **6a** (10.2 μL, 0.100 mmol) was added to the mixture. The mixture was stirred for 20 h, quenched with saturated $NaHCO_3$, extracted with AcOEt (×3), washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1:99) to give **7a** (26.0 mg, 0.0990 mmol, 99%) as colorless oil.

Table 3. *Z*-Selective One-pot Reaction



entry	solvent	R^1	R^2	yield[a] (*E*:*Z*)[b]
1	THF	$(CH_2)_4Ph$ (**3a**)	*p*-CNC_6H_4 (**6f**)	84% (7:93)
2	THF	$(CH_2)_5OBn$ (**3b**)	*p*-CNC_6H_4 (**6f**)	65% (16:84)
3	PhMe-HMPA	$(CH_2)_4Ph$ (**3a**)	*n*-C_7H_{15} (**6g**)	67% (25:75)
4	PhMe-HMPA	$(CH_2)_5OBn$ (**3b**)	*n*-C_7H_{15} (**6g**)	95% (37:63)

[a] Isolated yield of *EZ* mixture after column chromatograpohy. [b] Ratio was determined by analysis of crude ^1H NMR spectra.

Functional groups such as carbamate, epoxide, and PMB ether were compatible with the one-pot reaction and the highly functionalized *E*-enones **7i** and **7j** were obtained (entries 8, 9). Various acyl fluorides were also good substrates for the present reaction. Benzyl ether, acetate, and olefin were tolerated to give the *E*-enones **7k**−**m** (entries 10−12). Furthermore, the branched acyl fluoride **3e** bearing a chiral center at the α-position afforded the optically pure *E*-enone **7n** without racemization (entry 13).[12] Trisubstituted *E*-α,*β*-unsaturated ketones were also readily accessed by the one-pot procedure. Attempts to synthesize the trisubstituted olefins were conducted with diethyl 1-trimethylsilylethylphosphonate (**1b**).[9b] The three-component couplings of **3a** with **6f** and **6g** successfully occurred in a completely stereoselective manner using *n*-BuLi as the base instead of LHMDS to yield the trisubstituted *E*-enones **7o** and **7p** (entries 14, 15).

Z-α,*β*-Unsaturated ketones have often been constructed in several steps (e.g., addition of acetylide to aldehyde, partial reduction of triple bond to *Z*-olefin, and oxidation of the resultant alcohol).[13] For rapid access to this unit, the *Z*-selective three-component coupling reaction was examined according to the reports by Still[14a] and Ando.[14b,c] Among the phosphonates and the bases tested, the combination of bis(2,2,2-trifluoroethyl) trimethylsilylmethylphosphonate (**1c**)[15] and NaHMDS in the presence of TDA-1[16] afforded the best selectivity (*E*:*Z* = 7:93) with **3a** and **6f**, giving the *Z*-enone **7q** in good yield (Table 3, entry 1).[17] The acyl fluoride **3b** also reacted with **6f** in high selectivity to afford the *Z*-enone **7r** (entry 2). The coupling reactions of the alkyl aldehyde **6g** with **3a** and **3b** gave the *Z*-enones **7s** and **7t** as the major stereoisomers (entries 3, 4).

In summary, we have developed a novel three-component coupling reaction with trimethylsilylmethylphosphonate, acyl fluoride, and aldehyde. Nucleophilic substitution of lithio-trimethylsilylmethylphosphonate with acyl fluoride and subsequent HWE reaction of the aldehyde with the lithio-*β*-ketophosphonate generated in situ through desilyation of the α-silyl group of the α-silyl-*β*-ketophosphonate by the fluoride ion proceeded smoothly in a one-pot operation. Various substrates participated in the one-pot coupling reaction to give *E*- or *Z*-enones stereoselectively in high yields. To the best of our knowledge, the present reaction is the first example of this type of one-pot coupling reaction. This new synthetic method will allow rapid access to α,*β*-unsaturated ketones with high stereoselectivities.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available. Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Confirmation of optical purity of **7n**, see Supporting Information.

(13) (a) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3021–3025. (b) Bajwa, N.; Jennings, M. P. *J. Org. Chem.* **2008**, *73*, 3638–3641. (c) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Louiseleur, O. *Org. Lett.* **2005**, *7*, 4125–4128. (d) Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. *Tetrahedron Asymmetry* **2003**, *14*, 275–280.

(14) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408. (b) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105–4108. (c) Ando, K. *J. Syn. Org. Chem. Jpn.* **2000**, *58*, 869–876.

(15) Preparation of **1c**, see Supporting Information.

(16) Touchard, F. P. *Tetrahedron Lett.* **2004**, *45*, 5519–5523.

(17) Optimization for *Z*-selective HWE reaction, see Supporting Information.

The authors declare no competing financial interest.