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Bis(2,2,2-trifluoroethyl)bromophosphonoacetate, a Novel HWE Reagent for the Preparation of (*E*)-α-Bromoacrylates: A General and Stereoselective Method for the Synthesis of Trisubstituted Alkenes

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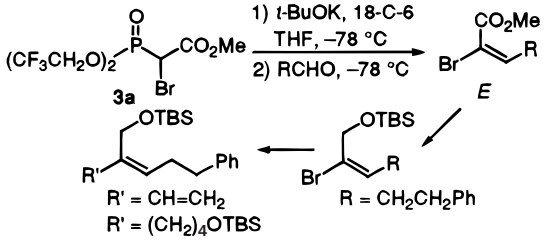
ABSTRACT



A novel reagent, methyl bis(2,2,2-trifluoroethoxy)bromophosphonoacetate (3a), was designed and prepared in order to efficiently synthesize (*E*)-α-bromoacrylates, which are useful precursors for various C–C bond formations. Honer–Wadsworth–Emmons (HWE) reaction of various aldehydes with 3a in the presence of *t*-BuOK and 18-C-6 gave the corresponding (*E*)-α-bromoacrylate derivatives with high stereoselectivity. Using the (*E*)-α-bromoacrylate as a key intermediate, a general stereoselective synthesis of trisubstituted alkenes via Pd-catalyzed cross-coupling was developed.

The highly stereoselective construction of trisubstituted alkenes is one of the most challenging problems in synthetic organic chemistry.[1] Indeed, many skillful and selective synthetic methods for the preparation of this important functional group have been devised for decades.[2] However, the need for a general and stereoselective method for the efficient synthesis of trisubstituted alkenes still remains.[1] At present, vinyl bromides are widely used as precursors for C−C bond formation with conservation of olefin geometry, using reactions such as Suzuki coupling,[3] or Stille coupling.[4] Therefore, we anticipated that a stereoselective construction of trisubstituted bromoalkenes, for example, α-bromoacrylate derivatives, would provide a useful method to synthesize various trisubstituted olefins.

Although there are limitations to the stereoselective construction of tri- and tetrasubstituted alkenes, Wittig and Horner−Wadsworth−Emmons (HWE) reactions are powerful and attractive methods for the construction of various alkenes.[5] This is because they provide a direct introduction of the C−C double bond from carbonyl compounds. It is

(1) Kelly, S. E. In *Comprehensive Organic Synthesis, Additions to C−X π Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon Press: Oxford 1991; Vol. 1, Chapter 3.

(2) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Kocienski, P. J.; Pritchard, M.; Wadman, S. N.; Whitby, R. J.; Yeates, C. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3419. (c) Martin, S. F.; Daniel, D.; Cherney, R. J.; Liras, S. *J. Org. Chem.* **1992**, *57*, 2523 and references therein. (d) Denmark, S. E.; Amburgey, J. *J. Am. Chem. Soc.* **1993**, *115*, 10386. (e) Pelter, A.; Colclough, M. E. *Tetrahedron* **1995**, *51*, 811. (f) Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93. (g) Kawasaki, T.; Ichige, T.; Kitazume, T. *J. Org. Chem.* **1998**, *63*, 7525.

(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(4) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

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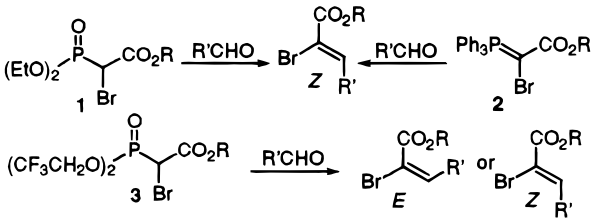
known that the HWE reaction with diethoxybromophosphonoacetate **1** and Wittig reaction with the stabilized ylide **2** gave α-bromoacrylates with slightly predominant *Z*-isomer (Scheme 1).[6,7] On the other hand, only a few procedures for

Scheme 1

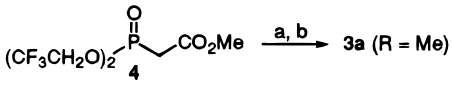


the synthesis of (*E*)-α-bromoacrylates have been reported in the literature.[8] Thus, a general method for the synthesis of (*E*)-α-bromoacrylates would be a beneficial synthetic achievement. (*E*)-α-Fluoroacrylates are synthesized stereoselectively by the HWE reaction of diethoxyfluorophosphonoacetate with lithium base.[9] However, it is apparent that fluoroalkenes cannot be used as precursors for C−C bond formation. Therefore, we investigated HWE reagents and reaction conditions to develop a stereoselective synthetic method for (*E*)-α-bromoacrylates from which precursors for C−C bond formation could be readily synthesized. In this Letter, we describe the preparation of the novel HWE reagent **3** and a general methodology for the construction of trisubstituted alkenes, which involves the stereoselective HWE reaction of **3** followed by stereospecific C−C bond formation by Pd-catalyzed cross-coupling.

While the HWE reaction using diethoxyphosphonoacetate shows a preference for the formation of more stable disubstituted *E*-olefins,[5a,10] Still's electrophilic bis(2,2,2-trifluoroethoxy)phosphonoacetate reacts with aldehydes in the presence of KHMDS and 18-crown-6 ether (18-C-6) to afford *Z*-α,*β*-unsaturated esters selectively.[2a,11,12] In view of the above fact, we designed a novel reagent, bis(2,2,2-trifluoroethyl)bromophosphonoacetate, **3**, anticipating that (*E*)-α-bromoacrylates would be synthesized by the HWE reaction since **3** is thought to be complementary to **1** in the analogous reaction.

The novel reagent **3a** was readily prepared from methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**4**)[2a] using a procedure similar to that reported by McKenna et al. (Scheme 2).[13] Treatment of **4** with freshly prepared sodium hypobromide afforded dibromide, which was subsequently reduced by 1 equiv of $SnCl_2$.[14] A small amount of unreacted dibromide and over-reduced product **4** were removed by flash chromatography (dichloromethane/acetone = 50:1) using silica gel which was pretreated with dichloromethane containing 4 N HCl in ethyl acetate.[15] Finally, the residue was distilled under reduced pressure (bp 85−87 °C, 0.4 mmHg) to give pure **3a** (60% yield from **4**).

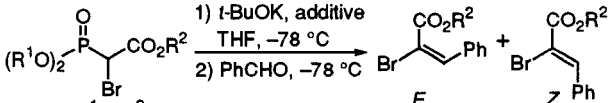
Scheme 2[a]



[a] (a) Aqueous NaOBr 85%; (b) $SnCl_2 \cdot 2H_2O$ (0.96 equiv), EtOH, H_2O, 70%.

The results of the HWE reaction between **1a** or **3a** and aldehydes using potassium *tert*-butoxide (*t*-BuOK) are summarized in Table 1. Excess amounts of *t*-BuOK reduced the yield and stereoselectivity.[16] Therefore, phosphonoacetates were used slightly in excess of *t*-BuOK. As we anticipated, HWE reactions with **3a** proceeded with high *E*-selectivity

Table 1. Results of the HWE Reaction with **1a** or **3a** and Benzaldehyde



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

run[a]	reagent	additive	time	yield, %[b]	*E*/*Z*[c]
1	**1a**[d]	none	16 h	94	1/5
2	**1a**	18-C-6	16 h	93	1/14
3	**3a**	none	2 h	65	10/1
4	**3a**	18-C-6	20 min	94	30/1

[a] 1 equiv of benzaldehyde, 1.1 equiv of **1a** or **3a**, 1.05 equiv of *t*-BuOK, and 1.3 equiv of additive (runs 2 and 4) were used. [b] Isolated yield. [c] Determined by ^1H NMR (400 MHz) analysis of the products. [d] For preparation of **1a**, see ref 13.

(5) For review to see: (a) Wadsworth, W. S. *Org. React*. **1977**, *25*, 73. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 863. (c) Vedejs, E.; Peterson, M. J. *Top. Stereochem*. **1994**, *21*, 1.

(6) (a) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733. (b) Grinev, G. V.; Chervenyuk, G. I.; Dombrovskii, A. V. *J. Gen. Chem. USSR* **1969**, *39*, 1223. (c) Semmelhack, M. F.; Brickner, S. J. *J. Am. Chem. Soc*. **1981**, *103*, 3945. (d) Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Miyamoto, T.; Taniguchi, K.; Hayashi, M. *J. Med. Chem*. **1981**, *24*, 1149. (e) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc*. **1985**, *107*, 2474.

(7) (a) Gonzalez, M. S. P.; Aciego R. M. D.; Herrera, F. J. L. *Tetrahedron* **1988**, *44*, 3715. (b) Sato, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem*. **1991**, *56*, 2278.

(8) (a) Nakamura, I.; Harada, K. *Heterocycles* **1978**, *9*, 473. (b) Kolsaker, P.; Brobakke, K. *Acta Chem. Scand. B* **1981**, *35*, 701. (c) Bestmann, H. J.; Dostalek, R.; Zimmermann, R. *Chem. Ber*. **1992**, *125*, 2081. These procedures generally lack of efficiency because of multiple steps or limitation of substrate.

(9) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev*. **1996**, *96*, 1641 and references therein.

(10) Etemad-Moghadam, G.; Seyden-Penne, J. *Tetrahedron* **1984**, *40*, 5153.

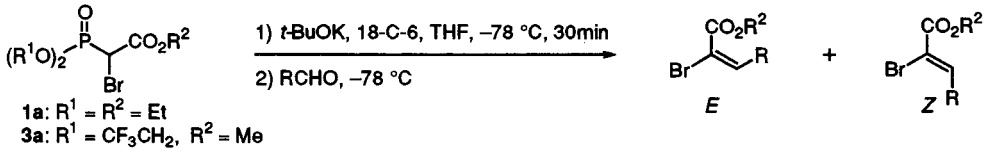
(11) Hensel, M. J.; Fuchs, P. L. *Synth. Commun*. **1986**, *16*, 1285.

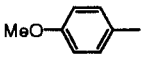
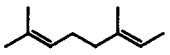
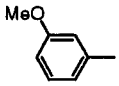
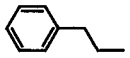
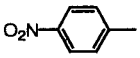
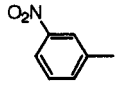
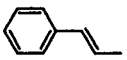
(12) For another *Z*-selective HWE reagent, see: (a) Ando, K. *Tetrahedron Lett*. **1995**, *36*, 4105. (b) Ando, K. *J. Org. Chem*. **1997**, *62*, 1934.

(13) McKenna, C. E.; Khawli, L. A. *J. Org. Chem*. **1986**, *51*, 5467.

(14) $SnCl_2 \cdot 2H_2O$, which was purchased from Aldrich Chemical Co., gave the best result for reduction.

Table 2. Results of the HWE Reaction with **1a** or **3a** and a Range of Aldehydes



Run[a]	R	Reagent	Time (h)	Yield (%)[b]	E : Z[c]	Run[a]	R	Reagent	Time (h)	Yield (%)[b]	E : Z[c]
1		3a	4	94	30 : 1	8		3a	5	84	15 : 1
2		3a	1.5	98	28 : 1	9[e]		3a	3	75	32 : 1
3		3a	1.5	97	19 : 1	10[g]		3a	2	86	>50 : 1
4		3a	1	94	9 : 1	11[f,g]	*n*-Bu	1a	5	80	3 : 1
5		3a	1.5	98	25 : 1	12[f,g,h]		1a	5	72	1 : 3
6		3a	17	quant.	*E* only[d]	13[g]		3a	6.5	64	>50 : 1
7		1a	5	87	1 : 2	14[f,g]		1a	5	47	3 :1
						15		3a	1.5	96	26 : 1

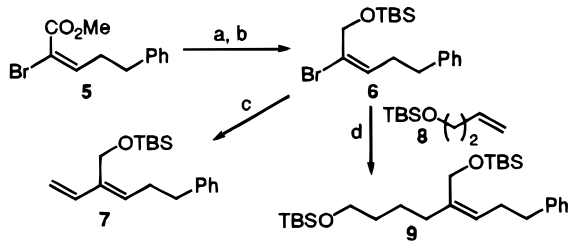
[a] See the corresponding footnotes in Table 1. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the products. [d] *Z*-product cannot be detected by ^{1}H NMR analysis. [e] At −20 °C. [f] At −40 °C. [g] Aldehyde was distilled before use in the reaction. [h] Without 18-C-6.

(runs 3 and 4) in contrast to the same reaction with **1a** (runs 1 and 2). Furthermore, stereoselectivity and/or yield were markedly improved using 1.3 equiv of 18-C-6 as an additive (runs 2 and 4). When using LHMDS as a base, a higher temperature (even at room temperature) was needed for the HWE reaction to proceed with **3a**, and both the yield and stereoselectivity were significantly decreased (38%, *E*/*Z* = 2:1).

For further evaluation of the applicability of this *E*-selective reaction, we examined the HWE reaction using **3a** with various aldehydes. As shown in Table 2, olefination of most aldehydes with **3a** in the presence of *t*-BuOK and 18-C-6 gave (*E*)-α-bromoacrylates[17] with high stereoselectivities and excellent yields. The reaction with aromatic aldehydes proceeded rapidly and gave (*E*)-α-bromoacrylates stereoselectively with high yields (runs 1−5). Conjugated aldehydes and branched aliphatic aldehydes were slightly less reactive, but high stereoselectivity still remained (runs 6, 8, and 13). *E*/*Z* ratio and reactivities were extremely diminished when using **1a** instead of **3a** (runs 7, 11, 12, and 14). This HWE reagent **3a** provides an efficient and highly stereoselective method to obtain various (*E*)-α-bromoacrylates, which are very useful precursors for various C−C bond formations.

To examine the availability of (*E*)-α-bromoacrylates, trisubstituted alkenes **7** and **9** were synthesized as shown in Scheme 3. From acrylate **5**, a precursor for the coupling

Scheme 3[a]



[a] (a) DIBAL-H, CH_2Cl_2, −78 °C, 88%; (b) TBSCl, imidazole, DMF, rt, 96%; (c) *n*-$Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, THF, rt, 66%; (d) **8**, 9-BBN, THF, rt then **6**, $PdCl_2$(dppf), Ph_3As, Cs_2CO_3, DMF, 50 °C, 81%.

reaction was readily synthesized in two steps. **7** was synthesized by Stille coupling of **6** with vinylstannane, and Suzuki coupling of **6** and **8** gave trisubstituted olefin **9** in good yields. The combination of stereoselective bromoolefination and C−C bond formation affords a useful and general synthetic method for a wide range of trisubstituted alkenes. This protocol has considerable potential for the construction of complex molecules.

In conclusion, the novel HWE reagent **3a** was designed and prepared. (*E*)-α-Bromoacrylates were synthesized stereoselectively and efficiently from **3a** with various aldehydes

(15) Reagent **3a** is unstable even under weakly basic conditions. Usual silica gel column chromatography caused decomposition of **3a**. The purified **3a** was enough to stable to be stored in a freezer (−20 °C) over 3 years without decomposition.

(16) Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett*. **1999**, *40*, 6725.

(17) Geometry of α-bromoacrylates were determined by NOE analysis of the allylic alcohol which was derived from DIBAL-H reduction of corresponding ester.

in the presence of *t*-BuOK and 18-C-6. Using the product (*E*)-α-bromoacrylate as a key intermediate, we succeeded in developing a general protocol for the highly stereoselective synthesis of trisubstituted alkenes via Pd-catalyzed cross-coupling.

Supporting Information Available: Experimental details for the preparation of **3a**, the general procedure for the HWE reaction, and the synthesis of **7** and **9** and the characterization of α-bromoacrylates and compounds **6**, **7**, and **9**. This material is available free charge via the Internet at http://pubs.acs.org.

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