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A one-pot synthesis of (*E*)-α-bromo-α,β-unsaturated esters and their trifluoromethylation: a general and stereoselective route to (*E*)-α-trifluoromethyl-α,β-unsaturated esters

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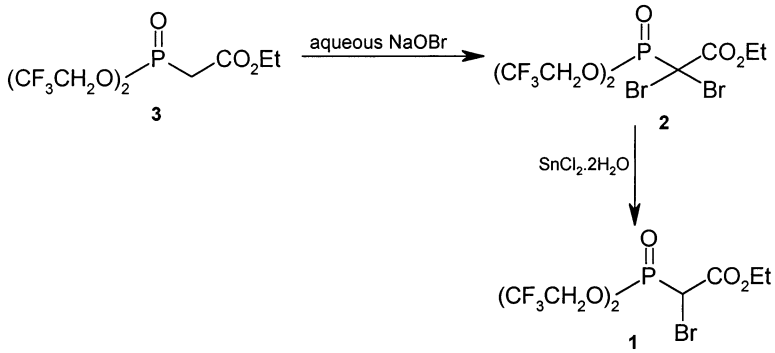
Abstract—Bromination of a phosphonate anion derived in situ from ethyl bis(2,2,2-trifluoroethyl)phosphonoacetate **3** followed by the addition of aldehydes produced (*E*)-α-bromo-α,β-unsaturated esters **5** stereoselectively. The treatment of **5** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA provided (*E*)-α-trifluoromethyl-α,β-unsaturated esters **6**.

Considerable attention has been given to trifluoromethyl-containing organic compounds as agrochemical and pharmaceutical agents due to their unique properties arising from their electron density, acidity, and lipophilicity.[1] Accordingly, the development of newer methods for the synthesis of trifluoromethyl-containing organic compounds continues to be an important area of research in agricultural, medicinal, and organic chemistry.[2] In continuation of our ongoing projects involving the synthesis of trifluoromethyl-containing nucleosides,[3] we required (*E*)-α-trifluoromethyl-α,β-unsaturated esters. We envisaged the preparation of such trifluoromethyl-containing building blocks via the trifluoromethylation of (*E*)-α-bromo-α,β-unsaturated esters. Herein, we wish to report a one-pot synthesis of (*E*)-α-bromo-α,β-unsaturated esters and their trifluoromethylation for the preparation of (*E*)-α-trifluoromethyl-α,β-unsaturated esters.

Although there are some limitations with respect to the stereoselective construction of alkenes, Wittig and Horner–Wadsworth–Emmons (HWE) reactions are powerful and attractive methods for the synthesis of various alkenes.[4] Kogen et al.[5] recently reported a novel reagent, methyl bis(2,2,2-trifluoroethoxy)bromophosphonoacetate, and the HWE reaction of aldehydes with



Scheme 1.

Keywords: α-bromo-α,β-unsaturated esters; trifluoromethylation.

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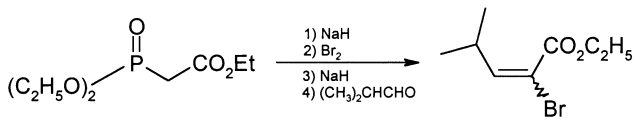
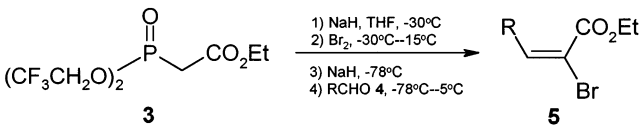
this novel reagent in the presence of *t*-BuOK which gave (*E*)-α-bromo-α,β-unsaturated esters with high stereoselectivity. However, when we attempted to make ethyl bis(2,2,2-trifluoroethyl)bromophonoacetate **1** using Kogen's methodology (Scheme 1), we found that the yield of **1** was low (35% overall yield from **3**), and that during treatment of ethyl bis(2,2,2-trifluoroethyl)-dibromophosphonoacetate **2** with 1 equiv. of $SnCl_2$, some of the over-reduced product **3** appeared and unreacted dibromide **2** remained. The polarity of **1** was very close to that of **2** and **3**, and therefore it was very difficult to separate from them by flash chromatography.

Forty years ago, Emmons et al.[6] reported that halogenation of a phosphonate anion in situ followed by the addition of an aldehyde or ketone gave a vinylic halide (Scheme 2). This was a simple procedure (one-pot) for the synthesis of vinylic halides. However, a mixture of *Z*- and *E*-isomers was obtained.

In view of this, we decided to use a one-pot procedure for the preparation of (*E*)-α-bromo-α,β-unsaturated esters **5**. First, the synthesis of **5a** was carried out using Emmons's procedure. Reaction of the aldehyde **4a** with the phosphonate anion prepared in situ from 1 equiv. of **3** in the presence of NaH gave **5a** in only a poor



Scheme 2.



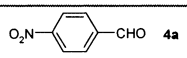
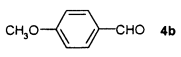
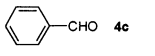
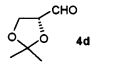
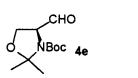
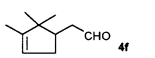
Scheme 3.

yield (10%), along with unreacted **4a**. We were delighted, however, to obtain **5a** in 57% yield and with high *E*-selectivity (*E*:*Z*=24:1) using 2 equiv. of **3**. For further evaluation of this one-pot procedure, we examined the HWE reactions of **3** with various aldehydes. As shown in Scheme 3 and Table 1,[7] the reactions with aromatic aldehydes gave (*E*)-α-bromo-α,β-unsaturated esters stereoselectively with high yields (87–57%) (entries 1–3), branched aliphatic aldehydes were slightly less reactive (59–44%), but high stereoselectivity still remained (entries 4–6). It is worth noting that the yield of **5** obtained by this one-pot procedure was higher than that prepared from **3** in three steps as Kogen et al.[5] reported.

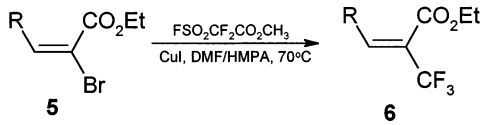
We recently described a novel route to (*Z*)-α-trifluoromethyl-α,β-unsaturated esters by coupling (*Z*)-α-bromo-α,β-unsaturated esters with CF_3Cu generated in situ.[3] Having the (*E*)-α-bromo-α,β-unsaturated esters **5** in hand, we were interested in exploring the feasibility of using **5** in trifluoromethylation reactions for the synthesis of (*E*)-α-trifluoromethyl-α,β-unsaturated esters. The coupling of **5** with CF_3Cu generated in situ from $FSO_2CF_2CO_2Me$ and CuI proceeded readily giving (*E*)-α-trifluoromethyl-α,β-unsaturated esters **6** (Scheme 4).

As shown in Table 2, **5c** and **5a** with an electron-withdrawing nitro group at the *para* position gave **6c** and **6a**, respectively, in high yield (entries 1 and 3). However, **5b** with an electron-donating *para* methoxy group gave **6b** in only a 65% yield, along with unreacted **5b** (entry 2). In addition, branched aliphatic (*E*)-α-bromo-α,β-unsaturated esters were slightly less reactive, although they reacted high stereoselectivity. The following observations are noteworthy: (1) an excess of $FSO_2CF_2CO_2CH_3$ (2.5 equiv.) and CuI (0.8 equiv.) are necessary for the complete conversion of **5**; (2) limited *E*/*Z* isomerization occurred (entries 2–4), but the major products were the *E*-isomers; (3) in the case of compound **5f** (entry 6), the yield was low (46%) because fluoro-containing by-products were produced (detected

Table 1. A one-pot synthesis of (*E*)-α-bromo-α,β-unsaturated esters **5**

Entry	Aldehyde	Product	Yield (%)[a]	*E*:*Z*[b]
1	 4a	**5a**	57	24:1
2	 4b	**5b**	79	25:1
3	 4c	**5c**	87	*E* only
4	 4d	**5d**	59	*E* only
5	 4e	**5e**	52	*E* only
6	 4f	**5f**	44	*E* only

[a] Isolated yield based on aldehyde. [b] Determined by ^1H NMR



Scheme 4.

Table 2. Synthesis of (*E*)-α-trifluoromethyl-α,β-unsaturated esters **6**

Entry	**5** (*E*:*Z*)	Product	Yield (%)[a]	*E*:*Z*[b]
1	**5a** (24:1)	**6a**	91	24:1
2	**5b** (25:1)	**6b**	65	11:1
3	**5c** (*E* only)	**6c**	92	28:1
4	**5d** (*E* only)	**6d**	61	24:1
5	**5e** (*E* only)	**6e**	56	*E* only
6	**5f** (*E* only)	**6f**	46	*E* only

[a] Isolated yield based on **5**.
[b] Determined by ^{19}F NMR.

by ^{19}F NMR of the reaction mixture). The configuration of the double bond in **6** was determined by the chemical shifts of the alkenyl proton. The alkenyl proton in the *E* isomer appeared at higher field than in the *Z* isomer.[8]

In conclusion, we describe a one-pot methodology for the stereoselective and efficient preparation of (*E*)-α-bromo-α,β-unsaturated esters **5**. Using **5** as the key intermediate, we succeeded in developing a general procedure for the highly stereoselective synthesis of (*E*)-α-trifluoromethyl-α,β-unsaturated esters **6**.

References

1. (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds. ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996; (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; (c) *Synthesis and Chemistry of Agrochemical III*; Baker, D. R.; Fenyes, J. G.; Steffens, J. J., Eds. ACS Symposium Series 504; American Chemical Society: Washington, DC, 1992.
2. (a) *Asymmetric Fluoroorganic Chemistry*; Ramachandran, P. V., Ed. ACS Symposium Series 746; American Chemical Society: Washington, DC, 1999; (b) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Gordon and Breach Science: Amsterdam, 1998; (c) Burton, D. J.; Yang, Z. Y.; Qiu, W. *Chem. Rev*. **1996**, *96*, 1641.
3. Zhang, X.; Qing, F. L.; Yu, Y. *J. Org. Chem*. **2000**, *65*, 7075.
4. (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.
5. (a) Tago, K.; Kogen, H. *Org. Lett*. **2000**, *2*, 1975; (b) Tago, K.; Kogen, H. *Tetrahedron* **2000**, *56*, 8825.
6. Wadsworth, Jr., W. S.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733.
7. Representative procedure for the synthesis of (*E*)-α-bromo-α,β-unsaturated esters **5**. Ethyl bis(trifluoroethyl)phosphonoacetate[9] (664 mg, 2 mmol) in anhydrous THF (2 ml) was added dropwise at −30°C to a slurry of 60% sodium hydride (80 mg, 2 mmol) in anhydrous THF (4 ml). The solution was stirred for 30 min at −30°C until the solution turned clear. Bromine (0.1 ml, 2 mmol) in anhydrous THF (1.5 ml) was added dropwise to the reaction mixture at −30°C. During the addition, the reaction gradually became cloudy. After the addition of bromine, the reaction mixture was warmed briefly at 10–15°C, then cooled to −78°C and 60% sodium hydride (80 mg, 2 mmol) was added all at once. The reaction mixture was stirred for 30 min at −78°C. Then 3-methoxybenzaldehyde **4b** (136 mg, 1 mmol) in anhydrous THF (1.5 ml) was added dropwise to the mixture at such a rate as to maintain the temperature at −78°C. The solution was stirred for about 4–5 h at −78°C. Then the reaction mixture was stirred overnight at 5–10°C. Saturated aqueous NH_4Cl solution was added to the reaction mixture and the aqueous mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 20:1) to give 224 mg (79% yield) of **5b** as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 3H), 6.84 (d, J = 7.7 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); IR (thin film) 1720, 1602, 1512, 1255, 1176 cm^{-1}; MS m/z 286 (M^+, 43), 284 (M^+, 44), 177 (100). Anal. calcd for $C_{12}H_{13}O_3Br$: C, 50.55; H, 4.59. Found: C, 50.36; H, 4.59.
8. Allmendinger, T.; Lang, R. W. *Tetrahedron Lett*. **1991**, *32*, 339.
9. Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.