One-pot synthesis of (*E*)-α-chloro-α,β-unsaturated esters

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Chlorination of a phosphonate anion derived *in situ* from methyl bis(2,2,2-trifluoroethoxy)phosphonoacetate **2** followed by the addition of aldehydes constitutes a stereoselective single flask procedure for the preparation of *E*-configured α-chloro-α,β-unsaturated esters.

Keywords: olefination, α-chloro-α,β-unsaturated esters, Horner–Wadsworth–Emmons reaction, methyl bis(2,2,2-trifluoroethoxy) chlorophosphonoacetate

α-Chloro-α,β-unsaturated esters (α-chloroacrylates) are important intermediates in organic synthesis, for example, for the preparation of biologically active compounds.[1] They are useful and versatile building blocks.[2-10] Many methods for the synthesis of α-chloro-α,β-unsaturated esters have been developed.[11-16]

However, most of these methods are limited by their poor stereoselectivity, low yields and the involvement of multisteps transformations. The need for a general and stereoselective method for the efficient synthesis of (*E*)-α-chloroacrylates therefore still remains. In particular, the Horner–Wadsworth–Emmons (HWE) reaction[17,18] is one of the most powerful and attractive methods for this purpose. Tago and Kogen[19,20] reported a synthesis of the novel HWE reagent methyl bis(2,2,2-trifluoroethoxy)bromophosphonoacetate and the condensation of this novel reagent with aldehydes in HWE reactions in the presence of *tert*-BuOK and 18-C-6 to give the corresponding (*E*)-α-bromo-α,β-unsaturated esters with high stereoselectivity. The reagent was prepared in 35% overall yield by treatment of methyl bis(2,2,2-trifluoroethoxy)phosphonoacetate **2** with sodium hypobromite and subsequent reduction of the methyl bis(2,2,2-trifluoroethoxy) dibromophosphonoacetate using 1 equivalent of $SnCl_2$.

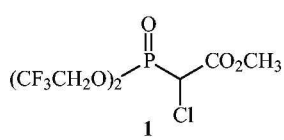
Recently Qing and Zhang[21] reported on the bromination of a phosphonate anion *in situ* (NaH/Br_2) followed by the condensation of aldehydes in presence of NaH to give (*E*)-α-bromo-α,β-unsaturated esters with high stereoselectivity and good yield (87–44%).

I now report the *in situ* preparation of the analogous novel HWE reagent methyl bis(2,2,2-trifluoroethoxy)chlorophosphonoacetate **1** and its condensation with aldehydes in a one-pot procedure to give (*E*)-α-chloro-α,β-unsaturated esters with high stereoselectivity and good yield.

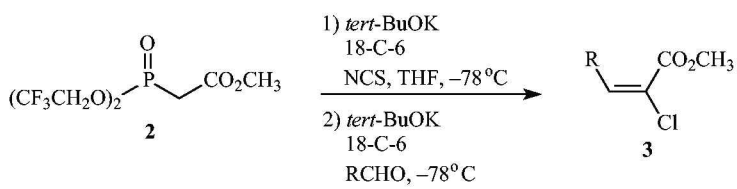
Result and discussion

In view of the above results, I first decided to use Qing and Zhang's procedure, using *N*-chlorosuccinimide (NCS) as chlorinating agent to generate the reagent **1**. However this gave many side products and thereafter we modified Tago and Kogen's methodology by preparing methyl bis(2,2,2-trifluoroethoxy)chlorophosphonoacetate **1** *in situ* from methyl bis (2,2,2-trifluoro ethoxy)phosphonoacetate **2** and NCS in the presence of *tert*-BuOK and 18-C-6 at −78 °C. After 2 hours ^{31}P NMR spectroscopy showed methyl bis(2,2,2-trifluoroethoxy)phosphono acetate to be completely chlorinated. The novel reagent **1** which formed *in situ* was then allowed to react in a HWE reaction with various aldehydes (see Scheme 1). As shown in Table 1, the reaction with aromatic aldehydes gave (*E*)-α-chloro-α,β-unsaturated esters stereoselectively and good yield (87–75%) (entries 1–3). The aromatic aldehyde possessing an electron-donating group (entry 2) was less reactive and less stereoselective. Aliphatic aldehydes and conjugated aldehydes were slightly less reactive but high stereoselectivity still remained. In all reactions, the *E* and *Z* isomers were not separated, but *E*/*Z* ratios were readily determined by ^1H NMR spectroscopy. The vinylic proton of the *Z* isomer was downfield from the signal of the *E* isomer and the methoxy protons of *E* isomer were downfield from the signal of the *Z* isomer. This assignment was confirmed by NOE analysis of the allylic alcohol derived from the corresponding esters by DIBAL reduction.

For further evaluation of the *E*-selectivity reaction methyl bis(2,2,2-trifluoroethoxy)iodophosphonoacetate was prepared by the same procedure by using N-iodosuccinimide NIS as iodination agent. The HWE reaction with various aldehydes gave no selectivity (*E*/*Z* 1 : 1)



1



2 **3**

Scheme 1

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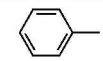
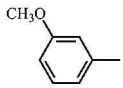
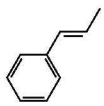
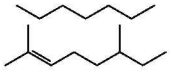
Table 1 One-pot synthesis of (*E*)-α-chloro-α,β-unsaturated esters

Entry	R	Product	Time/h	Yield/%[a]	*E*:*Z*[b]
1		**3a**	2	87	10:1
2		**3b**	4	75	5:1
3		**3c**	2	81	11:1
4		**3d**	4	76	10:1
5		**3e**	2	79	10:1
6		**3f**	2	78	15:1

[a]Yields were based on aldehydes. [b]This ratio was determined by ^{1}H NMR spectroscopy.

Conclusion

In conclusion, I have described a single flask procedure for the stereoselective and efficient preparation of (*E*)-α-chloro-α,β-unsaturated esters.

Experimental

IR spectra were recorded on a Perkin Elmer 883 and spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a JEOL ECP400 instrument in $CDCl_3$. HRMS and NOE analysis were performed by the Department of Organic Chemistry of the University of Hannover, Germany.

General procedure for the synthesis of (E)-α-chloro-α,β-unsaturated esters **3**. A solution of **2** (1.3 mmol) and 18-C-6 (1.3 mmol) in THF (8 mL) was cooled to −78°C. Then (1.3 mmol) solid potassium *tert*-butoxide was added to the solution. After stirring for 30 min at −78°C, NCS (1.4 mmol) in THF (4 mL) and CH_3CN (4 mL) was added dropwise to the reaction mixture which was then stirred for 2 h at −78°C. Then 18-C-6 (1.3 mmol) and (1.3 mmol) potassium *tert*-butoxide was added to the solution at the reaction mixture was stirred for 30 min at −78°C. The aldehyde (1 mmol) was the added to the reaction mixture and stirring was continued. When the reaction was complete, saturated aqueous NH_4Cl was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chroatography on silica gel (petroleum ether: ethyl acetate = 20:1)

(E)-2-Chloro-3-phenylacrylic acid methyl ester (**3a**): IR ($CDCl_3$) 3018, 2995, 1734, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.28 (m, 6H, aromatic-H, vinylic-H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1, 137.5, 133.8, 129.1, 129.0, 128.4, 122.5, 52.9; MS (EI) *m/z* (%) = 198(20), 196 (64) [M +], 161 (100); HRMS (EI). Calcd for $C_{10}H_9O_2{}^{35}Cl$ (M +) 196.0291. Found: 196.0291.

(E)-2-Chloro-3-(3-methoxyphenyl)acrylic acid methyl ester (**3b**): IR ($CDCl_3$) 3018, 2958, 1751, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.22 (m, 2H, aromatic-H), 7.16 (s, 1H), 6.89–6.85 (m, 2H, aromatic-H), 3.80 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.9, 158.0, 141.7, 135.6, 128.1, 127.7, 121.1, 113.6, 112.4, 53.9, 51.6; MS (EI) *m/z* (%) = 228 (20), 226 (56) [M +], 161 (100); HRMS (EI). Calcd for $C_{11}H_{11}O_3{}^{35}Cl$ (M +) 226.0397. Found: 226.0397.

(E)-2-Chloro-3-furan-2-ylacrylic acid methyl ester (**3c**): IR ($CDCl_3$) 3018, 2956, 1716, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* = 1.5 Hz, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.08 (s, 1H), 6.47 (dd, *J* = 3.6, *J* = 1.5 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 148.5, 144.5, 127.1, 118.3, 116.2, 112.7, 52.9; MS (EI) *m/z* (%) = 188 (19), 186 (57) [M +], 57 (100); HRMS (EI). Calcd for $C_8H_7O_3{}^{35}Cl$ (M +) 186.0084. Found: 186.0084.

(E, E)-2-Chloro-5-phenylpenta-2,4-dienoic acid methyl ester (**3d**): IR ($CDCl_3$) 3018, 2990, 1734, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (dd, *J* = 11.7 Hz, *J* = 15.4 Hz, 1H), 7.54–7.49 (m, 2H, aromatic-H), 7.38–7.33 (m, 3H, aromatic-H), 7.03 (d, *J* = 11.0 Hz, 1H), 6.80 (d, *J* = 15.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 142.6, 141.6, 136.1, 129.3, 128.7, 128.9, 128.8, 127.6, 124.0, 52.8; MS (EI) *m/z* (%) = 224 (10), 222 (24) [M +], 105 (100); HRMS (EI). Calcd for $C_{12}H_{11}O_2{}^{35}Cl$ (M +) 222.0448. Found: 222.0445.

(E)-2-Chloro-nonenoic acid methyl ester (**3e**): IR ($CDCl_3$) 3018, 2976, 1743, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.44 (t, *J* = 7.4 Hz), 3.80 (s, 3H), 2.52 (q, *J* = 7.4 Hz, 2H), 1.42–1.40 (m, 2H), 1.31–1.25 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 145.9, 121.5, 52.7, 31.6, 30.1, 29.1, 28.9, 22.6, 14.1; MS (EI) *m/z* (%) = 205 (6), 203 (14), [M–H], 113 (100); HRMS (EI). Calcd for $C_{10}H_{17}O_2{}^{35}Cl$ (M–H) 203.0838. Found: 203.0838.

(E)-2-Chloro-5,9-dimethyldeca-2,8-dienoic acid methyl ester (**3f**): IR ($CDCl_3$) 3018, 2956, 1718, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.46 (t, *J* = 8.1 Hz, 1H), 5.07 (t, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 2.60–2.49 (m, 2H), 2.04–2.02 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.41–1.39 (m, 1H), 1.28–1.21 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 144.7, 131.5, 124.3, 122.1, 52.6, 37.0, 36.8, 36.7, 25.8, 25.5, 19.5, 17.7; MS (EI) *m/z* (%) = 245 (2.5), 243 (7) [M-H], 59 (100); HRMS (EI). Calcd for $C_{13}H_{21}O_2Cl$ (M-H) 243.1153. Found: 243.1151.

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